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Boyle C. Cheng
Editor

Handbook of Spine Technology

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With 425 Figures and 94 Tables

Springer

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This book is dedicated to my parents, Samuel and Ruth, who were inspiring from an early age and, moreover, instilled within me the power of harnessing personal talent combined with a strong work ethic to achieve the best of all possible outcomes. In turn, I hope this to be a legacy for my wife, Judy and my two sons, Cooper and Jonathan who have in their own ways, motivated, encouraged, and supported this effort.

Preface

Historically, the excitement generated by a new technology for spine or an innovation in spinal interventions has been followed in relatively short order by sobering patient complications or broad-spectrum failures. Such catastrophes often necessitate salvage procedures and ultimately a dramatic decline in interest that ends in a failed pile of debris with a ruinous perception for the categorical technology that may last a generation or more. The disastrous scenarios have been repeated to the point of becoming frequent in spine technologies with very little evidence of slowing. Accordingly, the spine landscape is littered with the burned-out wreckages of abandoned technologies.

This book documents the fundamentals of spinal treatments, original design intent for spinal devices and the clinical outcomes of spine technologies. Often there is little more than tribal knowledge and even less information documenting the history of surgical approaches and supporting hardware. This is evident by the repeated failure modes for similar devices in databases and registries. The goal of this handbook is to provide a repository of information for both successful spine technologies as well as those with poor clinical outcomes and, moreover, the root cause of the failed spinal implants that contributed to the unsatisfactory results. If nothing else, this will serve the healthcare community by memorializing the history of spine technologies and prevent a repeat of the technological cycle that contributed to problematic patient outcomes. The specific aim of this book is to record from both a clinical and a scientific point of view what we have learned about the human spine and the influence of spine technologies that have contributed to the attempted treatment.

Important devices include those that failed catastrophically, for example, nucleus augmentation devices, to those that were ahead of the times but not necessarily a commercial success including motion preservation devices. Beyond the necessary surgical skills, patient selection has often been cited as essential to the commercialization of a device. Patient reported outcomes are a good proxy to the success of the device as well as a relative metric for regulatory purposes. The systematic diagnosis for patients presenting with back pain requires the most appropriate technology for the patient's symptoms. In one patient, immediate fixation and stabilization is the best solution and, in combination with the appropriate adjuncts to fusion, affords the patient the best opportunity for success. In other segments of the population with different

sets of symptoms, the solution may be a motion-preserving technology. The guidance and design rationale will help the audience understand the premise of each technology and, ultimately, how best the technology may be applied and in which patient population.

It is without fail that the lessons of the past can help mitigate potential disasters and even prevent another timely consuming and financially draining iteration. From engineers to clinical scientists, publications frequently discuss the most successful technologies or the most popular techniques. However, the most valuable lessons may be in failure. Failure may be attributable to the design of the device. It may also be a materials limitation. One failure often not discussed is surgeon error. Regardless, understanding the origin of the failure or root cause analysis is essential to future refinements.

Technologies that cover new materials, design failures, and even technologies developed for the sole purpose of finding an indication are presented. Often, there is no prior art, no reported case studies nor hints of potential complications attributable to a technology. Discovery of this information requires the courage to reflect on such mistakes and the willingness to share them. Documentation can lead to helpful preventative warnings resulting in the potential for reduced iterations and, ideally, failed products resulting in voluntary, or worse, mandated product market withdrawals. It is the goal of this handbook to put on display such failures so that we may advance technology for the patients benefit.

Boyle C. Cheng, Ph.D.

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Part I

Low Back Pain Is a Point of View

Low Back Patterns of Pain: Classification Based on Clinical Presentation

1

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Abstract

The ubiquitous presence of low back pain with its multiple natural histories makes classification difficult. Any categorization begins by defining the essential elements of the problem to build a structure that reflects the values of the organizer, values determined by experience, personal concerns, and a point of view. Although a grouping of back pain patients based on responses to a particular treatment may be as valid as one based upon the varying degrees of socioeconomic impact produced by the pain, any classification's ultimate value depends on the interests of the user. Patterns of pain focuses on the initial presentation delineated by a specific set of questions in the history and confirmed by selected features of the physical examination. History divides mechanical low back pain into four distinct syndromes while the physical examination further delineates two of these patterns. A pattern of mechanical low back pain can be defined by the location of the dominant pain (back or leg), the consistency (constant or truly intermittent), and the effect of flexion on the symptoms. Response to flexion separates two cohorts of intermittent leg dominant pain patients with very different clinical scenarios and treatment demands. The physical examination divides back dominant pain patients needing only a straightforward treatment strategy from those who require more complex supervision. Additional questions and tests highlight or eliminate sinister, nonmechanical pathologies. The classification both directs initial management and provides a reasonable prognosis for speed and completeness of recovery.

Keywords

Mechanical low back pain · History · Physical examination · Classification · Clinical presentation · Patterns of pain · Referred pain · Radicular pain

Introduction

Low back pain is a human condition. Virtually everyone will, at some time in their lives, suffer pain in the lower back. Those that remain permanently pain free are the exception. Numerous studies have reported a lifetime incidence over 80% (Balagué et al. 2012). Nearly all will suffer from symptoms arising from minor mechanical spinal malfunctions associated with aging and natural degeneration. The pain can be intense but the pathology is overwhelmingly benign (Deyo and Weinstein 2001). Emphasizing the nonthreatening nature of the problem, however, belies its massive impact. A study on the global burden of

disease in 2013 found back pain to be the most frequent cause of disability for over half the world's population (Global Burden of Disease Study 2013 Collaborators 2015).

Medicalizing the condition has led to unfortunate consequences, shifting attention from the ubiquitous mechanical causes of pain to rare, albeit more sinister, pathologies. This misdirection is reflected in numerous attempts at a pathology-based classification. How clinicians organize a problem establishes their diagnostic probabilities and assigns priorities for investigations and treatment. To concentrate on the possibility of serious pathology, like malignancy, means screening every back pain sufferer for something present in less than 1% of cases (Henschke et al. 2009). Individual clinical features implying an ominous condition, called Red Flags, have poor accuracy. The Red Flag of night pain, frequent among back pain sufferers, can be raised as a source of concern. In one study of nearly 500 patients, 40% had night pain but not one had serious pathology (Harding et al. 2005). Algorithms beginning with a check for Red Flags are popular and no one can deny the value of a thorough history but that route can lead to unnecessary testing and unwarranted patient anxiety, and may not provide the anticipated certainty (Downie et al. 2013). From a wider perspective, identifying a pathophysiological pain source is possible in only 10–15% of cases, ultimately leading in most cases to the counter-productive diagnosis of "nonspecific" back pain (Krismer et al. 2007).

Classification Options

Treatment Response

Attempts to improve specificity and thereby offer therapeutic guidance have classified low back pain on the patient's reaction to specified mechanical treatments. Results show slight improvement as might be expected from the circular nature of the cohort construction; patients who did well following a particular maneuver were classified, after treatment, as suitable for that category (Fritz et al. 2003). One problem in using this sort of classification in primary care is the requirement that the clinician to be able to properly perform the classifying techniques, direction-specific or trunk-stabilizing exercises or spinal manipulation (Brennan et al. 2006). Even when the determination was made by trained physical therapists, over 30% of the subjects could not be clearly classified (Stanton et al. 2011).

Time Based

Classifications can be time based but even here there remains considerable variability and disagreement. There is no consensus on the length of time back pain must be present before it shifts from acute to chronic and no defined duration for the pain-free interval that distinguishes a new attack from a continuing chronic condition. To address this lack of consistency, the classic designations of acute and chronic have been replaced with more broadly inclusive terms such as "persistent" or "recurrent" (Norton et al. 2016). However, neither set of definitions offers immediate clinical guidance for treating the patients in pain.

Administrative

Administrative classifications typically use the tenth revision of the International Statistical Classification of Diseases and Related Health Problems, Clinical Modification (ICD – 10 – CM) codes to either identify relevant pathologies or support a diagnosis of "nonspecific" back pain. The nonspecific categories include such divergent entities as kissing spines and lumbago, the former a description of putatively abnormal anatomy and the latter an antiquated name for low back pain first used in 1684 to describe "pain in the muscles of the loins" (Oxford English Dictionary 2019). In a comprehensive review of administrative data on health-care utilization, Norton identified and validated four distinct groups of patients: one cohort with immediate total recovery, one with frequent relapses but with little ongoing healthcare utilization, and two groups with high

continuing demand – one for therapeutic interventions and the other for medication (Norton et al. 2016). Significantly the groupings were unrelated to either the patients' demographic or clinical characteristics; the classification had no prognostic value. Retrospectively identifying the amount of resource consumption offers no prediction of that outcome nor identifies those patients at risk.

Risk of Chronicity

STarT Back categorizes patients by predicting their risk of chronicity (Hill et al. 2008). This classification has shown promise in directing primary care by identifying those people most likely to develop persistent problems. It was developed in England and uses a short simple questionnaire that takes into account pertinent physical findings while emphasizing a psychosocial subscale gauging bothersomeness, catastrophizing, fear, anxiety, and depression. It characterizes patients as a low, medium, or high risk of chronicity and recommends appropriate intensive therapy. A study by Foster assessing the results found modest overall improvements in patients' outcomes with a more targeted use of health care resources and without increased costs (Foster et al. 2014). The authors noted that the mean difference in patient disability in their study was less than that in the original trial, a fact they attributed to the higher proportion of low-risk patients and the variability in physician engagement. The magnitude of the second problem, the variability of physician engagement, and its negative impact on generalizability was highlighted by the MATCH study at Kaiser Permanente in Washington State. In spite of extensive training for both the participating primary care physicians and physical therapists the trial showed no statistically significant differences in patient outcomes or health care use between the intervention and control groups (Cherkin et al. 2018). Several factors may account for this lack of success including limited access to suitable treatment for the high-risk patients but, regardless of the reason, using the classification did not alter practice patterns. Further, it was never designed nor intended to direct immediate management.

Anatomic

Many, if not most, clinicians believe initial treatment must be determined by and directed toward the source of pain. A pathoanatomic classification seems obligatory. But, unless that treatment is an invasive procedure, management involves the entire patient not just a local painful structure. In cases where the cause of the pain is obscure and the clinical symptoms raise no concerns for an urgent or serious condition, seeking a structural diagnosis simply to fill a physical or pathological category is heading down the wrong track. It promotes needless investigations and excessive imaging. With current technology it is almost always possible to find an aberration in the spine. Whether the identified pathology is the reason for the patient's back pain is an entirely different question. The false positive rate for MRIs of the spine in middle aged patients approaches 90% (Wnuk et al. 2018). Employing MRI as a screening tool to locate abnormalities without a clinical indication has a strong iatrogenic effect, offers no benefits and degrades the outcome (Webster et al. 2013).

Nonspecific

The prevailing medical paradigm dictates that we must establish a cause before we can treat. In the overwhelming majority of back pain patients, however, no pathoanatomic diagnosis is possible (Koes et al. 2006). This pain, designated as "nonspecific," is neither the product of recognizable structural defects or deformities in the spine nor the result of identifiable pathologies including trauma, tumor, systemic disease, or local infection. It denotes pain arising from spinal structures, not pain referred to the back but arising from known causes in other parts of the body or within a sensitized central nervous system. While there is no agreement on the particular pain generator within the spine, there is widespread consensus among clinicians that "nonspecific" back pain is mechanical back pain produced by nothing more sinister than minor mechanical malfunctions, the inevitable consequence of normal wear and

tear (Maher et al. 2017). The potential severity of the pain does not reflect the benign reality of the underlying problem but the intensity of the problem can justify immediate treatment. Deferring therapy to conduct unnecessary and predictably futile investigations to isolate the site of the pain is ill-advised.

A Syndrome Approach

From the patient's perspective back pain is never nonspecific; the symptoms are never vague and the mechanical characteristics are obvious. Mechanical pain is pain produced by movement or position and relieved by rest or a change in posture. The pain fluctuates with activity. Again from the patient's perspective, the primary reason for seeking professional help is to relieve that pain. With a definitive diagnosis out of reach the clinician's decisions must be rely on something else. There is another option. In 1987 the Quebec Task Force noted, "Distinct patterns of reliable clinical findings are the only logical basis for back pain categorization and subsequent treatment." (Spitzer et al. 1987). The therapy can be built on the patient's clinical presentation, on a mechanical syndrome. A syndrome is a constellation of signs and symptoms that consistently appear together and respond predictably to treatment. Reluctance to base treatment solely on the clinical picture is understandable but, in the case of mechanical back pain, unjustified. A syndrome has an undetermined but definite etiology; its invariable presentation is not random chance. The only difference between a syndrome and a disease is, in fact, the former's lack of an agreed etiology. Once the cause of a condition becomes known the syndrome becomes a disease. For "nonspecific" mechanical back pain, discovering the exact source of the symptoms would obviously not alter the clinical picture nor diminish the value of already proven effective non-surgical treatment.

A classification that can offer clinicians immediate guidance in the initial management of back pain rests on typical mechanical syndromes or patterns drawn from the history and physical examination without additional imaging or investigations. It should identify unusual presentations and highlight potentially serious features. By emphasizing the regular mechanical patterns, which comprise about 90% of the low back pain presentations in a primary care setting, the classification renders the few sinister presentations plainly visible (Chien and Bajwa 2008). Detecting Red Flags becomes a by-product, not the purpose, of the assessment.

This Patterns of Pain classification has been validated and proven successful. For nearly 50 years, it has been the basis of back pain treatment at the CBI Health Group in its more than 170 rehabilitation clinics across Canada (Hall et al. 2009). It is the foundation of the Saskatchewan Spine Pathway. Instituted in 2011 the Pathway has produced substantial cost savings and improved patient satisfaction with spine care across the province (Wilgenbusch et al. 2014). In 2012, the Ontario Ministry of Health and Long-Term Care launched a pilot project, again using this pattern classification of clinical presentation, to develop the Inter-professional Spine Assessment and Education Clinics (ISAEC), a network of spine triage clinics. The program proved so successful that in 2018 the Ministry expanded it across the entire province. The Ontario Ministry also funded an online aid for primary care practitioners, the CORE (**C**linically **O**rganized **R**elevant **E**xam) Back Tool. It offers a concise method of separating patients with back or leg pain into those who require further investigation or referral and those whose straightforward mechanical picture encourages management by the primary care provider. This differentiation is made using the same mechanical syndrome classification (Alleyne et al. 2016).

Four Patterns of Pain

Mechanical back pain can be divided into four, clearly delineated patterns of pain identified on history (see Table 1**)** and confirmed or refuted with the physical examination (see Table 2**)**. Each pattern suggests an initial course of treatment, the outcome of which either supports or rejects the

Table 1 The essential components in a "patterns of pain" history

Number	Category	Question	Objective
1	Pattern	Where is your pain the worst?	Discriminate between back dominant (referred) pain and leg dominant (radicular) pain
2		Is your pain constant or intermittent?	Obtain a precise account of the pain's consistency and whether or not it ever completely disappears
3		Does bending forward make your typical pain worse?	Determine the effect of flexion on the pain given in answer to Question One
4	Mandatory	Since the start of your pain, has there been a change in your bladder or bowel function?	Consider possibility of an acute cauda equina syndrome
5	Function	What can't you do now that you could be before you were in pain and why?	Estimate the required treatment intensity; the reason for the impairment should be the pain given in answer to Question One
6	Additional	What positons or movements relieve your typical pain?	Identify features that may assist with management
7		Have you had this pain before?	Establish context for the current episode and the likelihood of further recurrences
8		What treatment have you had and did it work?	Previous successful treatments for the same pattern should be effective again
9	Inflammatory	If you are under 45 years old do you have periods of morning back stiffness lasting longer than 30 minutes?	Screen for spondyloarthritis

Table 2 The essential components in a "patterns of pain" physical examination

Procedure	Optimum Position	Objective/Technique
Observation		Assess general activity both before and during the examination. Back specific elements: gait, contour, color, surgical scars
Movement	Standing	Observe flexion and extension for rhythm of movement and reproduction of the typical pain
	Lying prone	If the patient reports pain on standing flexion evaluate the response to ten prone passive extensions
Nerve root irritation tests	Lying supine	Examiner lifts the patient's straight leg. Nerve root irritation reproduces or exacerbates the typical leg dominant pain. May be performed with patient sitting
	Lying prone	Femoral stretch reproduces the anterior thigh dominant pain. Examiner extends the patient's straight leg. Perform when indicated by history
Nerve root function tests	Detailed in Table 3	Check muscle power or tendon reflexes involving L3, 4, 5, and S1
Upper motor neuron tests	Sitting	Identify spinal cord involvement by plantar response or sustained ankle/ patellar clonus
Saddle sensation	Lying prone	Screen for cauda equina syndrome with light touch to the S2 dermatome, midline between the upper buttocks

Positive findings may prompt further, more comprehensive testing. When suggested by the history additional investigations can include the hips, abdomen, peripheral pulses, or sensation

pattern diagnosis. The classification is constructed to be integrated into early patient management; inconsistences within the history, between the history and the physical examination or in the anticipated course of treatment for the selected pattern will alert the clinician to potential problems.

History

Question One

The history begins with three pattern questions: questions designed to define the characteristics of the four patterns. The first question is "Where is your pain the worst?" This is not the same as asking the patient "Where do you hurt?" The latter question encourages vague and rambling answers that may not only divert focus from the major symptoms but shift attention to irrelevant details. The important distinction is between back or leg dominant pain. In this classification, back dominant pain is pain felt most intensely in one or more of the following locations: low back, upper buttocks, coccyx, over the greater trochanters (Tortolani et al. 2002). Back dominant pain can occasionally extend to the groin and genitals. This pain is referred pain, pain arising within the musculoskeletal structures of the spine but felt some distance from the source. The concept of referred pain has been recognized for over 100 years but there is still no consensus as to the mechanism by which the pain spreads other than agreement that it does not involve direct irritation of the peripheral nerves (Bogduk 2009).

Back dominant referred pain can radiate into the legs and may extend well below the knee to include the foot (Hill et al. (2011). The clinically important issue is establishing where the patient's pain is most excruciating. Although referred pain can involve the leg, the site of the most severe pain is always somewhere in a band around the lower back, upper buttocks, hips, and groin.

Complicating the recognition of back dominant pain is the fact that areas of referred pain can become locally tender (Smythe 1986). Palpating the trochanteric region may elicit local discomfort misdiagnosed as bursitis. Tenderness over the upper buttock can be falsely attributed to pushing on a painful piriformis muscle. Palpable "trigger points" over the posterior iliac crest are another example of local findings without local pathology. Occasional temporary symptomatic relief following injection of a local anesthetic further compounds the diagnostic confusion.

Leg dominant pain represents radicular pain originating from direct irritation of one of more of the roots of the sciatic or femoral nerves and carried along the nerves into the legs. Radicular pain is pain most intense anywhere at or below the gluteal fold. Pain in the lowest three centimeters of the buttock is considered leg dominant as is pain felt most strongly in the thigh, calf, ankle of foot. Referred back dominant pain can extend to the foot and leg dominant radicular pain may not go below the knee. The demarcation point is the lower buttock, not the knee joint.

Getting a patient to choose the site of the dominant pain can be challenging. Back dominant pain frequently involves the leg and leg dominant pain can be accompanied by pain in the back. Asking the patient to pick only one area when they both hurt may give the erroneous impression that the examiner is not interested in the whole problem and the patient may be unwilling to relinquish any part of the complaint. They refuse to choose or describe them as equally painful. But the pattern of pain classification demands identification of the predominant pain location. The best solution is simply to change the question. Instead of asking, "Where is the pain the worst?" say, "If I could stop only one of your pains, in the back or in the leg, which one would you want me to stop?" The natural reply to this question might be, "I want you to stop them both," but this is a very different conversation from one that tries to determine only which one hurts more. Now the clinician can acknowledge that the patient does indeed have two significant painful areas and that both deserve attention. It is no longer a matter of which pain to treat but merely a decision of which pain to treat first.

In the infrequent situation where the patient still cannot choose between the back and the leg pain, the correct option is to pick the "worst case" scenario. Since leg dominant pain reflects nerve involvement and therefore has the potential, no matter how slight, to be associated with significant neurological impairment leg pain takes precedence. It is prudent throughout the history and physical examination to consider the more serious alternative, bearing in mind that no matter how excruciating the pain, 95% of back pain patients suffer from a benign mechanical condition.

Question Two

The second pattern question in the history addresses consistency. Is the dominant pain constant or intermittent? For fear of minimizing the problem to the examiner, many patients are reluctant to admit the pain ever stops. When asked directly, "Is your pain constant" they respond, "Yes" and once committed patients may be unwilling to change the answer. A correct report of the pain's consistency is essential to assign the pattern. To obtain an accurate report the clinician must give the patient "permission" to relate the all the details, including moments of spontaneous improvement, without appearing to diminish the seriousness of the complaint. The clinician needs to frame the question in a way that does not minimize the patient's concerns. The question is best asked in two parts. The first part lays out the conditions under which the pain might stop: the best time of day or the best situation. These suggestions must be accompanied by a statement that the clinician is fully aware of the severity of the pain and the fact that, even though it may briefly disappear, it will always return. If the patient, however reluctantly, admits the pain does disappear there must be a second follow-up question. "Does that pain disappear completely? Is it totally gone?" There is only one correct answer to describe intermittent pain, "Yes." The patient must state unequivocally that the pain entirely disappears. Any other answer such as "nearly," "almost," "mostly," or "feels much better" is considered as constant pain. The decision to accept the pain as intermittent must take into account the level of analgesic medication; regular narcotic use means the pain must be considered constant. When there is any doubt, the general principle when using this classification is for the clinician to select the more serious option, in this instance constant pain.

This practice is critically important when assessing consistency. Truly intermittent back dominant pain is never the result of spinal malignancy or active spinal infection. Both of these sinister pathologies can produce pain that fluctuates with position or movement but even in the best circumstances, the pain never disappears completely. Whether the pain is constant or intermittent is such an influential factor that the clinician should repeat the patient's words exactly then ask the patient to verify that was what was said. The power of these questions, properly asked and answered, is enormous. At first contact and without any additional investigations, they can eliminate the possibility of two devastating pathologies. Constant pain clearly doesn't confirm malignancy but it does leave the slight possibility of a more serious condition. In this case, it would be appropriate to ask about a history of cancer in the preceding 5 years. Recognizing the fact that the overwhelming majority of back pain whether constant or intermittent is nonthreatening, constant pain still requires further questioning. Truly intermittent back dominant pain permits reassurance that the problem is almost certainly a benign mechanical condition.

Question Three

The third and final pattern question is deliberately direct: "Does bending forward make your typical pain worse?" This is the critical part of the broader open-ended question, "What makes your pain worse?" Understanding the aggravating factors aids planning treatment but knowing the effect of flexion on the typical pain does more. It completes the identification (along with location and consistency) of the principal pain pattern, a pattern which provides direction for the entire therapeutic regimen. The pain under consideration, the typical pain, is the dominant pain given as the answer to the first question. Bending forward may produce discomfort in other areas, like behind the knees from tight hamstrings, but these observations should not distract the examiner from the primary complaint.

Question Four

The fourth question is mandatory since it addresses the only true emergency in low back pain: the acute cauda equina syndrome. Interference with the second, third, and fourth sacral

nerve roots, typically from an acute large central lumbar disc rupture, can lead to denervation of the urinary bladder and the rectal sphincter producing the classic triad of a period of urinary retention with eventual overflow, fecal incontinence, and altered perineal sensation (Fraser et al. 2009). Failure to surgically decompress the sacral nerves within the first 48 hours can lead to permanent loss of normal bowel and bladder function, so early recognition is a crucial part of the back examination and, therefore, of the patterns of pain classification.

To avoid confusion with preexisting genitourinary problems and to retain focus on recent onset back and/or leg pain, the fourth question is framed, "Since the start of your current pain has there been a change in your bowel or bladder function?" The temporal limitation keeps the history centered on recent events and avoids a lengthy discussion about prior problems. Another key is the emphasis on change rather than on symptomatic details. A multiparous woman may have longstanding urinary incontinence but that is not a change and therefore not relevant to the current painful episode. Cauda equina syndrome is an extremely rare condition. Most practitioners will spend their entire careers without seeing one so recalling the clinical picture and remaining vigilant for a cauda equina syndrome with every back patient may be unrealistic. Missing the diagnosis is not a matter of negligence as much as it is a matter of extreme improbability. But routinely asking every back pain sufferer if there has been a change in bowel or bladder activity should become a habit and all the clinician needs to remember is "no change. . .no problem." Any change triggers concern and the opportunity to review the relevant information. Constipation is prevalent and, while distressing, not a sign of ominous pathology. It is, however, a recent change from normal function and so worthy of mention and consideration.

Question Five

Question Five concerns the level of impairment. "What can't you do now that you could do before you were in pain and why?" The degree to which the pain interferes with the patient's daily routine dictates treatment intensity. A pain that occasionally limits a recreational activity does not merit the same degree of medical involvement as one that prevents regular employment. Asking about the reason for the impairment, ". . .and why?," is a check on the validity of the patient's reports. The cause of the functional limitations in the answer to Question Five should be related to the same pain that the patient reported answering Question One. If the reason for the patient's restrictions is not the dominant pain then treatment is likely to be misdirected. If the patient says back pain is the problem but reports that it is the leg pain which prevents activity or a return to work, this inconsistency must be resolved before proceeding. The patient may have misunderstood the question, the clinician may have misinterpreted the answer or the problem may not be a straightforward mechanical complaint.

Question Six

The next question enquires about relieving factors, what the patient does to reduce or stop the typical pain. The options should be compatible with, that is opposite to, those things which make the pain worse. Mechanical pain is predictable and consistent in its reaction to physical stress. A constant level of pain, unaffected by changes in posture or activity, strongly suggests a nonmechanical etiology. Only the effect of flexion is necessary for pattern determination but the response to other movements or positions is always considered in the selecting the appropriate mechanical therapy.

Questions Seven and Eight

The next two questions involve prior episodes of pain. The first asks if there have been any previous attacks of the same pain, the second deals with any earlier treatment. Both relate to the patient's existing pain as identified by Question One. Back pain is a recurrent complaint

and the pattern of pain can change over time (Donelson et al. 2012). Someone suffering a first attack should be cautioned that further episodes are likely. For those with a history of back or leg pain, knowing the outcome of past treatment should influence the current management. If the pattern of pain of a former attack was the same pattern as the present one then treatment that worked in the past will presumably work this time. Conversely if a treatment failed before there is little reason to try it again.

Question Nine

A final question, about unusually prolonged morning back stiffness, addresses the possibility of inflammatory spondyloarthropathies such as ankylosing spondylitis or psoriatic arthritis. This symptom is relevant in young and middle-aged patients but of little significance in the elderly. If the patient is under 40, ask "When you get up in the morning do you have stiffness in your back lasting more than half an hour?" At about 5%, this group of illnesses is the second most frequent cause of back pain after mechanical malfunctions (Weisman et al. 2013). Including a screening question for inflammatory spinal conditions along with the mechanical classification questions encompasses over 95% of patients presenting with back or leg pain.

These nine questions, particularly the first five, are the core of the back assessment. It is not the purpose of this classification to limit the scope of the inquiry but rather to sharpen the evaluation so that the essential elements are not overlooked or obscured by irrelevant detail. The clinician can and will ask for additional information. There are, for example, no questions about potential mechanisms of injury. In a study of over 11,000 patients presenting with nontraumatic, nonspecific back pain two thirds of those without a need to know (claiming worker's compensation or initiating a lawsuit) could not identify any cause for their pain. Spontaneous onset accounted for over 60% of cases (Hall et al. 1998). Moreover, regardless of the purported mechanism, all those with a mechanical presentation could be assigned a pain pattern and it was the pattern, not the precipitating event, that directed treatment. Obviously discovering the mechanism is relevant in situations where liability must be established or where there is a history of significant impact. Supplementary questions should be included whenever the pain is constant and nonmechanical or when there is suspicion of a serious underlying pathology. Progressive neurological deficits, unexplained weight loss, recent infection, disproportionate night pain, or unexplained constitutional symptoms are all reason for concern.

History determines the pattern. The physical examination confirms or refutes the choice. The examination is not an independent activity but rather an integral part of the assessment. It is directed by the information obtained from the history and any inconsistencies between the patient's story and the observed findings, just like inconsistencies within the history, must be resolved in order to clearly establish which pattern will direct treatment. Like the nine points comprising the history, the limited number of tests in the physical examination does not constitute a comprehensive evaluation but are the minimum required to corroborate the selected mechanical pattern while eliminating sinister pathologies. The final examination may incorporate additional steps but must include these components.

Physical Examination

To minimize discomfort and speed the examination, the patient should be assessed in a progression of positions selecting the optimum position for each test. Someone with back pain may take several minutes to lie down. Asking them to get up again for another test prolongs the examination and aggravates the pain. Start with the patient standing then sitting then lying down. Some procedures may be done best with the patient kneeling or sitting on a chair with feet on the floor. Using the chair before sitting on the edge of the examining table is both more efficient and more comfortable.

Observation

The physical examination starts with observation and observation starts before the actual examination. How the patient sits or moves or interacts before the formal assessment starts provides information about normal levels of activity and discomfort. Observe the patient's gait. Inspect the back for deformities, discoloration, and scars from previous surgery. Subtle changes in alignment are generally irrelevant. It is the overall contour or obvious areas of redness and swelling that matter.

Palpating along the spine for areas of tenderness is helpful to elicit sites of acute inflammation but plotting the areas of painful muscle tension is of little diagnostic value. Back dominant pain is referred pain and the location of the muscle tenderness is not necessarily the same as the location of the pathology; a painful L4-5 disc may not hurt at the L4-5 level.

Movement

Assessing spinal movement involves recording the rhythm and the reproduction of the typical pain. The physical examination confirms the history and patients who say that bending forward causes their usual pain should report the same pain when they bend forward for the examiner. The one important exception, which can cause confusion, is the patient who reports back pain only after sitting for a prolonged period. Patients whose pain is produced exclusively by a flexed posture and never by flexion movement should be identified on history and a proper interpretation of the lack of pain with movement on physical examination will support, not contradict, the patient's story.

Normal flexion of the lumbar spine follows a smooth progression cephalad from the pelvis without a catch or hitch. The actual range of movement is less important and, unless the measurement is one of a series, of minimal diagnostic significance. The ability to touch the fingers to the floor has more to do with the length of the arms and the flexibility of the hips than it does with the range of movement in the spine. The range of lumbar extension is similarly inconsequential. The important finding is the exacerbation or relief of the typical pain. To avoid apparent spinal extension produced by bending the knees and to better isolate movement to the low back have the patient stand with the front of the legs against the back of a chair or the examining table. Place the hands on the buttocks and not in the small of the back.

One of the three elements of Pattern recognition is the effect of flexion on the typical pain so the physical examination focuses on sagittal movement. Noting pain on rotation or side-bending (pain which may be present in all four patterns) can be useful in choosing treatment strategies but because these movements do not distinguish between the four mechanical presentations they are not used to establish a pattern.

Prone Passive Extension

When the patient reports feeling the typical pain on bending forward, the physical examination includes prone passive extensions. This maneuver, popularized by physiotherapist Robin McKenzie and referred to as a "sloppy push-up," can have a rapid beneficial effect on flexion-aggravated pain and may ultimately become part of a pain control strategy (Donelson and McKenzie 1992). It has no role in evaluating or treating pain that is not made worse with flexion movement. If used, prone passive extensions are ordinarily carried out at the end of the examination while the patient is lying prone on the examining table. With the hands and palms down and slightly above the head, the patient uses the arms to raise the upper body. The action is passive for the back since all the muscular exertion is in the arms; the paraspinal muscles remain relaxed. At the same time, as the torso is pushed up the hips must remain down on the table. The key to a proper sloppy push-up is to have the elbows fully extended and locked at the same time as the front of the pelvis is in contact with the table. The first error is to allow the hips to stay down by

keeping the arms bent. Raising the head and shoulders but not fully extending the elbows engage the back muscles and negate the passive nature of the technique. The second mistake it to allow the hips to rise as the elbows fully extend, as with the conventional push-up exercise. Keeping the spine straight prevents the necessary low back extension. Modifying the patient's hand placement achieves both objectives simultaneously. The more the hands are advanced above the head, the more the arms can be extended without elevating the trunk to the point where the hips are lifted. The quality of the prone passive extension is gauged by the impact on the level of pain not by the distance the sternum is lifted above the bed. The stiffer the spine, the more the hands must be moved above the head. Although the final location of the hands and the amount of lordosis in lumbar spine of a supple young woman are very different from the hand placement and sag in the rigid spine of an old man, the amount of pain relief may be the same. Once the patient has found the proper starting point, suitable for the degree of spinal mobility, he or she slowly repeats the passive extension, pausing briefly between repetitions but without holding the fully elevated positon. Compare the level of typical pain (usually using an 11 point scale of 0 to 10) before the first sloppy push-up to the level of pain at the end of five repetitions. Depending upon the clinical response, another set of five may be required.

Nerve Root Irritation

Straight leg raising (SLR) is a classic test for sciatic nerve root irritation. Lifting the leg with the knee extended puts tension on the nerve and causes the roots to slide though the intervertebral foramen. SLR is widely employed and surprisingly poorly understood. The test is positive only with the reproduction or exacerbation of the patient's typical leg dominant pain – not any leg pain just the patient's preexisting leg dominant pain. The patterns of pain classification rests on distinguishing back dominant referred pain felt in the leg from leg dominant radicular pain that may have associated but secondary pain in the back. The straight leg raise is a test for radicular pain. A proper interpretation is vital to choosing a correct pattern. If the patient has never had leg dominant pain, the patient cannot have a positive test. You cannot reproduce or exacerbate a pain the patient never had. It is impossible to have a positive straight leg test in a patient with back dominant pain.

Much of the confusion and misapplication of the straight leg raising test arises because the test is interpreted without regard for the history. Because any leg pain is incorrectly taken as a positive finding, posterior leg discomfort from hamstring tightness is misinterpreted as a positive test. To avoid this mistake some physicians consider the SLR to be positive only if pain is produced below 60°, an elevation that does not tense the hamstring muscles. Interpreted correctly the test is positive at any elevation if it reproduces the leg dominant pain identified on the history. The level at which the typical leg pain is produced is a measure of neural irritation. Pain felt at a few degrees of elevation (or even when the knee is extended without lifting the leg) indicates acute inflammation while typical pain that occurs only at 80° or 90° degree, though still a positive test, suggests that the nerve root is well on the way to recovery. SLR is passive; the examiner lifts the patient's extended leg. To minimize confusion with hamstring pain, the contralateral leg can be fully flexed, rotating the pelvis and relaxing the posterior thigh muscles.

A positive SLR indicates radicular, leg dominant pain so the reproduction of back pain cannot be a positive result. Considering both back and leg pain to be a positive test is incompatible with the very definition of the maneuver – a test for nerve root irritation not the presence of mechanical back dominant pain.

The femoral stretch test is designed to assess irritation of the roots of the femoral nerve. It is the reverse of the straight leg raise; the patient lies prone and the examiner lifts the straight leg extending the hip and putting tension on the femoral nerve in the anterior thigh. For most patients, this causes back pain, which is not a positive test. Whether or not to do a femoral stretch depends on the patient's history. Femoral nerve radicular pain

is constant in the lower anterolateral thigh and only when this is the chief complaint is the test necessary.

Conduction Deficit

Patients with purely back dominant pain should not have nerve conduction deficits, but since the purpose of the physical examination is to disprove as well as to support the pattern provided by the history, every patient should have a screen of nerve function (see Table 3). This is not intended as a complete neurological examination but simply a quick check on the roots that supply the lower limbs: L3, L4, L5, and S1. The examiner should select one test for each root. A more comprehensive investigation may be necessary if there is an abnormality in the screening exam or when dictated by the history as in cases of leg dominant pain.

Typical choices include the knee reflex for L3 and L4, strength of great toe extension for L5, and the power of great toe flexion for S1. If these are normal bilaterally, no further tests may be necessary. Additional investigations include quadriceps power for L3 and L4; ankle dorsiflexion strength, hip abduction power, and heel walking for L5; ankle reflex, plantar flexion strength, gluteus maximus muscle tone, and toe walking for S1.

Upper Motor Neuron Involvement

Any evidence of spinal cord involvement negates a mechanical pattern diagnosis. Upper motor neuron tests must be part of every examination. Conditions as diverse as a spinal cord meningioma or multiple sclerosis can present as apparently mechanical patterns in the low back, distinguished only by the findings of upper motor pathology: the upgoing toe of a positive plantar reflex, sustained knee, or ankle clonus. One of the goals of the history in this presentation-based classification is to immediately rule out more ominous causes of back pain. A concordant, properly performed physical examination is an indispensable second step to establish the safety and validity of this approach.

Table 3 Nerve root function tests

Optimum position	Procedure	Roots tested	Technique
Gait	Heel walking	L4, L5	Minimum five steps with maximum forefoot elevation
	Toe walking	S1	Minimum five steps with maximum heel elevation
Standing	Trendelenburg test	L5	Examiner's hands on the patient's iliac crests. Assess hip abductor power for the leg on which the patient stands. Contralateral pelvic elevation is the marker. A normal examination is symmetrical elevation
	Toe raises	S1	Ten times bilaterally, then ten times on each leg. Balance by holding the examiner's hands
Kneeling	Ankle tendon reflex	S1	Patient kneels on the chair seat. Tap ankle tendon. Reinforce by squeezing the chair back
Sitting Feet on floor	Ankle dorsiflexion	L4, L5	Elevate forefoot against resistance from the examiner's hand on the midfoot
	Great toe elevation	L5	Elevate great toe against resistance from the examiner's thumb
	Great toe flexion	S1	Keep the great toe flexed and resist pull from the examiner
Sitting Legs free	Patellar tendon reflex	L3, L4	Tap patellar tendon. Reinforce with the Jendrassik maneuver
	Quadriceps power	L3, L4	Patient extends the knee against resistance
Lying prone	Gluteus maximus tone	S1	Palpate buttocks as patient alternately tenses and relaxes. Repeat ten times

Saddle Sensation

This is particularly true of the test for saddle sensation. Cauda equina syndrome is the only diagnosis associated with low back pain where failed recognition on the initial assessment leading to even a short treatment delay can have devastating consequences. Hence Question Four, "Since the start of your current pain has there been a change in your bowel or bladder function?," is mandatory. Testing light touch in the S2 area, midline between the upper buttocks, not only adds an important physical finding, but, when routinely incorporated into the standard back examination, the test itself becomes a prompt to ask the question. Using a tissue or a cotton swab to judge light touch in one outlying area of the perineum is clearly not definitive, and genuine concern will lead to further investigations including a digital rectal examination. But the test is quickly and easily done, nonintrusive and, perhaps most importantly, focuses on cauda equina syndrome, a rare diagnosis that otherwise might not be considered.

Additional Tests

Beyond the six core components of observation, movement, root irritation, nerve function, upper motor neuron involvement, and saddle sensation, the history may suggest further examinations. Ruling out hip pain, a confounding complaint, or checking peripheral pulses in patients with claudication are familiar examples.

Pattern Identification

Combining the history and the physical examination allows classification into one of four mechanical patterns of pain, two of which are subdivided (see Table 4). The patterns are derived from signs and symptoms arising from the underlying mechanical malfunctions but a pattern diagnosis does not require establishing a specific pathoanatomic diagnosis. In some cases, shifting attention from the clinical syndrome to a putative pain generator misleads treatment. Just recognizing a pattern allows valid predictions about symptom duration and the patient's response to selected mechanical therapy. Failure to follow the anticipated course mandates early reassessment and this rapid appreciation of a negative outcome is one of the merits of the system. Back dominant patients constitute the overwhelming majority of the patient population and Pattern 1 is the most frequent presentation.

Pattern 1

Pattern 1 is back dominant pain with pain felt most intensely in the low back, upper buttocks, coccyx, over the flanks, or in the groin; the exact location of the pain should agree with the history. The pain is increased in flexion and may be constant or intermittent. Pattern 1 is the only pattern where the consistency of the pain can vary. The physical examination should support the history so the patient reports the described dominant pain to be increased pain in flexion. The classification defines Pattern 1 as pain worse **in** flexion not **with** flexion. A few Pattern 1 patients have no pain with flexion movement but have pain only after periods of sustained flexion posture. They experience back dominant pain after prolonged sitting; sitting is a flexed posture. In this situation, unless the clinician is prepared to let the patient sit in the examining room for an hour or two, the physical assessment will be negative. A few forward bends will have no effect. For most Pattern 1 patients, however, the typical back pain will be present with both movement and position.

Because Pattern 1 is referred pain without direct involvement of the peripheral nerves, the physical examination will show no signs of nerve root irritation or a loss of normal nerve function associated with the current pattern. An independent defect, such as an absent Achilles tendon reflex from a previous tendon rupture or a long resolved episode of S1 radiculopathy, should not confuse the pattern designation. Single findings – a change in bladder function, for example – should be noted and may significantly change management but it is the combined results of the

Table 4 Patterns of pain

Pattern number	Dominant site	History	Physical examination	Additional features	Subclassification
1	Back	Pain in flexion Constant/ Intermittent	Pain in flexion Neurologically normal	May have pain with extension May have unrelated neurological findings	**PEP** Decrease pain within ten properly performed prone passive extensions
					PEN No change or increase pain within ten properly performed prone passive extensions
2	Back	No pain in flexion Intermittent	No pain in flexion Neurologically normal	Pain with extension May have pain relief with flexion May have unrelated neurological findings	
3	Leg	Constant	Positive irritative and/or conduction findings	Pain with flexion and other movements or positions	
4	Leg	Intermittent	May have positive irritative and/ or conduction findings		**FA** Flexion aggravated
			Negative irritative findings May have conduction loss	Pain with activity in extension Conduction loss may be transient	**FR** Flexion relieved

entire history and physical, not the individual components, that decide the pattern.

Pattern 1 PEP

The change produced by repeated prone passive extensions (the technique is described in detail as part of the physical examination) separates Pattern 1 into two groups. Patients who experience pain reduction within ten repetitions are considered **P**rone **E**xtension **P**ositive or **PEP** patients. For these patients, prone extension is a positive experience. They demonstrate a clear directional preference for unloaded extension and therefore are an easy population to treat. The maneuver used to assess their pain becomes the mainstay of their self-treatment. A few positively responding PEP patients encounter a phenomenon called "centralization" (Aina et al. 2004). As they repetitively extend the lumbar spine, the site of their dominant pain changes in character and sifts toward the midline of the low back, frequently becoming more intense. The change in location toward the center of the back, in spite of the increased pain, is a positive sign and indicates the sloppy push-ups will shortly begin to reduce the typical symptoms. The new central discomfort is always transient. To properly employ this classification a clinician must recognize the favorable significance of centralization.

Pattern 1 PEN

Patients who fail to improve within ten repetitions of the sloppy push-up or whose increased pain prevents any further attempts are labeled Pattern 1 **PEN**, **P**rone **E**xtension **N**egative. For this cohort, the prone passive extension is a negative event and they have neither an obvious directional preference nor a straight path to pain control. Ten repetitions were picked as the demarcation between PEP and PEN because doing ten sloppy

push-ups or less should be relatively easy physically and the immediate pain relief highly motivating. That number therefore separates those who should have little difficulty maintaining the routine from those who may not be able to engage and would benefit from alternate strategies, supervision and continued encouragement.

History determines the pattern but the distinction between PEP and PEN is made by the physical examination and specifically by the pain response to repeated prone passive extensions. Having pain on standing extension is not diagnostic. Patients with discomfort in both standing flexion (Pattern 1) and standing extension may still readily respond to unloaded passive movements. During the first few attempts, a sloppy push-up can be uncomfortable and questioning patients about their level of pain as they are performing the maneuver may give the wrong answer; arching a stiff spine can be unpleasant. Estimating pain relief should wait until after the first five push-ups. PEP patients may report initial discomfort but experience relief once the first set is completed.

Pattern 2

Pattern 2 is also back dominant pain. The pain is always intermittent and is never worse in flexion. Constant pain or any pain in flexion marks the patient as Pattern 1. It is not a question of the amount of pain but simply whether there is any pain at all. Pattern 1 patients may have more discomfort on standing extension than they do when they bend forward but flexing also causes recognizable typical discomfort. In contrast, Pattern 2 patients like to bend forward since flexing can reduce or even abolish the back pain; in no circumstance does flexion make their typical pain worse. Although extension aggravates the pain, it is the effect of flexion, the fact that bending forward never increases the symptoms, which, along with the pain location and consistency, define Pattern 2.

Physical examination of the Pattern 2 patient shows back dominant pain aggravated on extension and never increased, at least unchanged and sometimes abolished, in flexion. The site of the pain matches that described in the history. As with Pattern 1, the neurological examination is either normal or any findings are unrelated to the current episode of pain.

Pattern 3

Pattern 3 is leg dominant and therefore represents radicular pain. In the patterns of pain classification, leg dominant pain begins in the lower buttock about 3 cm above the gluteal fold and can be worse anywhere from that point downwards in the thigh, calf, ankle, or foot. The pain is constant and even though it may fluctuate it never disappears completely. This pattern covers "sciatica," a label used so indiscriminately that it has lost much of its diagnostic value. True sciatica describes only radicular pain arising from compression/inflammation of the roots of the sciatic nerve: L4, L5, S1. In practice, however, the term is incorrectly used any time a patient complains of leg pain, as when the more frequent mechanical back dominant pain briefly spreads into the lower limbs. One of the advantages of using this classification is the precision of the definitions. Because of the inflammatory etiology, Pattern 3 pain must be constant. Because the pathology lies within the lumbar spine, the leg pain is altered by spinal movement or posture. This pattern also covers the femoral nerve roots (L2, L3, L4) since the resulting constant anterior thigh pain is also radicular.

To support the history and confirm Pattern 3, the physical examination must show evidence of either nerve root irritation or conduction loss (diminished power, reflexes, sensation) or both. A majority of cases will show evidence of irritation – a positive straight leg raise – without localizing signs. Some will have both irritation and a focal loss of nerve function, locating the involved spinal level. Rarely there will be a significant conduction loss without irritative findings. A totally normal physical examination is inconsistent with a diagnosis of Pattern 3.

Pattern 4

The format of Pattern 4 differs slightly from the other three. It uses the same three basic questions but the designation depends on only the first two. Any patient with leg dominant intermittent pain is Pattern 4. The third item, the effect of flexion on the typical pain, subdivides the pattern; it uses the same three features in a different way.

Pattern 4 FA

If the intermittent leg dominant pain is increased by bending forward the patient is classified as Pattern 4 **F**lexion **A**ggravated, Pattern 4 **FA**. This is an unusual clinical picture seen occasionally with a resolving Pattern 3: constant radicular leg pain. Typically as the leg symptoms subside the pain becomes back dominant and the patient reverts to Pattern 1. Presumably, if there has been continued interference with normal nerve function, the leg pain remains the major complaint. Since acute inflammation is no longer the primary cause of pain, the complaints become intermittent. Since a flexed posture raises tension on the exiting roots, bending forward heightens the discomfort. Pattern 4 FA has been attributed to post-inflammatory scarring, an "adherent" nerve root, or to intrinsic damage within the nerve itself but the classification does not demand detailed identification of the pathology. Treatment is chosen according to the clinical presentation and confirmed by the patient's successful achievement of the predicted outcomes.

Findings on the physical examination can vary but, obviously, must include reproduction of the patient's typical leg dominant pain in flexion. There may be indications of residual inflammation or a focal conduction deficit. Since extension minimizes root compression, arching backwards or a gentle sloppy push-up should decease the pain.

Pattern 4 FR

When flexion diminishes the intermittent leg pain, the patient is a Pattern 4 **FR**, **F**lexion **R**elieved. This is the clinical picture of neurogenic claudication, a common diagnosis in the older population. Because the symptoms result from vascular compromise of the nerve roots, they are radicular, that is, leg dominant. Because the impact of ischemia varies with activity and posture, the pain is intermittent. Because flexion increases the available space within the intervertebral foramina allowing improved blood supply, sitting or bending forward can eliminate the symptoms. Again it is location, consistency, and the effect of flexion that dictate the Pattern classification. The symptoms are brought on by walking, which is exercise with the back extended, so the differential diagnosis includes intermittent claudication secondary to impaired peripheral circulation. The conditions can coexist making a definitive diagnosis difficult (Nadeau et al. 2013) There are several distinguishing signs, such as the location of the dominant pain above or below the knee (neurogenic claudication/Pattern 4 FR is usually worse in the thigh) however the most reliable differentiating factor is the neurogenic claudicant's need to flex for symptom relief. This is the reason for the "shopping cart sign," the patient's ability to shop comfortably in a supermarket while being unable to walk any distance outside, because the shopping cart permits ambulation in sustained flexion. The history may include what patients describe as a temporary "loss of balance," which is actually a transient motor weakness disrupting normal gait caused by an ischemic nerve root.

The signs and symptoms of Pattern 4 FR, neurogenic claudication, normally disappear at rest so the physical examination can be normal. This is not an inflammatory pathology so the root irritation tests, like the straight leg raise, will be negative. Infrequently long standing cases with substantial vascular impairment may have a permanent focal motor loss.

Using a syndrome-based classification, Pattern 4 FR, reflecting the patient's clinical findings avoids several diagnostic pitfalls and mistakes. One of the most common is misusing spinal stenosis, a description of spinal anatomy, as a diagnosis. A small spinal canal may be asymptomatic and the

measurements of canal diameter on a CT scan are not indications for surgery. Concentrating on the clinical picture, the signs and symptoms that drive treatment rather than focusing on an anatomical variant that may or may not be problematic, keeps the clinician on the right path. This is especially important when treating the elderly patient where both back pain and spinal stenosis are prevalent and both are the result of progressive facet joint degeneration with boney encroachment into the canal. A history of walking limited by pain that disappears with bending forward suggests neurogenic claudication. This supposition will be reinforced by the inevitable identification of spinal stenosis on imaging. But without knowing the location of the dominant pain that assumption may be incorrect. If leg pain is the reason for the impairment then Pattern 4 FR is a reasonable diagnosis. If, however, the pain is back dominant the problem is not nerve root ischemia from canal stenosis but rather mechanical Pattern 2 pain possibly arising from the facet joints. The former might benefit from surgical decompression. The latter will only be made worse.

Pattern Directed Care

Patterns of Pain is a robust, comprehensive classification. Its permutations cover every possible presentation of mechanical low back pain including those with predominantly neurological symptoms (see Fig. 1). A patient's patterns can change and some patterns may coexist. It is not possible for a patient to have both patterns of back dominant pain at the same time, but someone with Pattern 1 back pain can certainly develop constant leg dominant symptoms from nerve root inflammation following a sudden disc rupture or intermittent leg pain from recurrent root ischemia. The

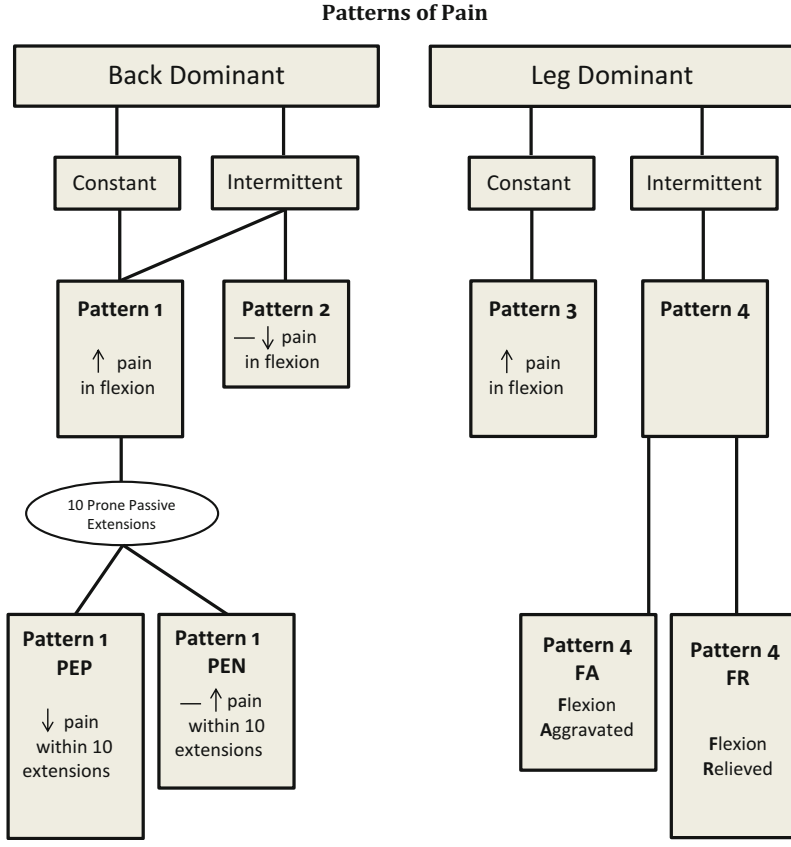

Fig. 1 Patterns of pain

clinical syndromes arise from the underlying pathology but use of the patterns is not tied to a physical diagnosis. Determining a pattern or patterns offers a course of action and usually removes the need for further investigation. Familiarity with the patterns renders the outliers immediately visible and instigates appropriate additional measures. Most mechanical patterns can be managed without recourse to surgery. Noninvasive approaches address the whole patient, not just the pain generator. The anticipated positive response to a therapy chosen by the pattern validates the choice. The goals are pain control and recovery of function not cure. In contrast to nonoperative care, surgery obliges an unequivocally identified, well-defined anatomical target. The aim of an operative intervention is to resolve a local problem, which may be producing widespread symptoms. But in either case, it is the patient's clinical situation, the pattern of the back or leg pain, which shapes treatment.

Principles of Nonsurgical Management

The general principles of nonsurgical management begin with education: advice to the patient about the benign nature of mechanical back pain and the many simple things that can be done every day to reduce the impact of the pain. Patients want to understand the reasons for the pain and need to be reassured that the situation can be controlled. They want assurance that the clinician is capable of successfully managing care and sensing uncertainty in the care provider can make patients less willing to follow sensible recommendations to increase activity in spite of the pain. Offering concrete suggestions related to a recognized pattern rather than resorting to banal platitudes instills confidence in both the patient and the health care provider.

Since the intent is primarily to stop the pain there is a role for purely symptom-relieving procedures. Counter-irritation with heat or cold is hardly a new idea but remains useful. Either modality can be administered professionally as ultrasound or interferential current or self-applied using a hot pack or bag of frozen vegetables. Their application is totally empirical and may be helpful in any pattern.

Correcting posture will change the way the spine is loaded and alter the amount of pain. The correction should be guided by the pattern of pain. Back dominant pain aggravated by flexion will be eased by increasing the lumbar lordosis. Each pattern offers a selection.

Direction-specific movements are at the heart of mechanical therapy. Many are uncomplicated and easily performed, their value determined by their beneficial effect on the pain. Except in Pattern 1 PEN or cases of severe, radicular, leg dominant Pattern 3 pain, pattern-directed repetitive movement should be the first treatment option. Clinicians must prescribe these maneuvers with the same precision and emphasis as they do medicinal remedies. Suggesting they can be done whenever it is convenient or when the patient can find the time belittles their importance and excuses noncompliance.

Analgesic medication should follow not precede mechanical therapy. The pain reduction achieved by changing position or repetitive direction-specific movement usually exceeds that produced by taking a pain pill. Using an analgesic as an adjunct to mechanical treatment is often efficacious but medication should be the second tier. There is no place for opioid medication in the management of Pattern 1 or Pattern 2 pain. No matter how severe, successful control of uncomplicated mechanical back pain can be achieved by physical methods and nonnarcotic analgesia.

Pattern 1 PEP

Patients classified as Pattern 1 PEP (prone extension positive) quickly gain pain control through a variety of activities. Putting one foot up on a footstool arches the low back and reduces the pain. Sitting with a firm foam lumbar roll at about waist level between the spine and the chair back maintains lumbar lordosis. Locating the roll at the correct height places it where it has the most positive influence on the typical pain. The patient is encouraged to make the final adjustments. The

roll must be large enough to change sitting posture and that makes it uncomfortable. The question is not, "Does that feel comfortable?" but "What does that do to your typical pain?" It is not uncommon for patients, at the same time, to complain of the discomfort and report that the typical pain has disappeared. Once the pain has been controlled, comfort follows rapidly. A night roll, a firm foam roll longer than the one used in sitting, can be prescribed to treat morning back pain resulting from sleeping on a poor mattress. Side lying provides no support for the spine between the ribcage and the pelvis. The resultant lateral sag can be painful. Placing the roll at waist level across the line of the body reduces the stress and diminishes the discomfort. Once again patients may initially find the lump uncomfortable so focusing on the typical back pain and setting expectations are important. Placing a pillow between the knees reduces tension on the low back and may ease pain but to do that the pillow must be large enough to influence spinal posture. It requires something thick enough to raise the upper leg to the point that the knee is higher than the hip. A couch cushion can be more effective than a pillow off the bed. If the patient finds that standing extension relieves the back pain, then standing extension can be added to the regimen but the decision to use standing extension must be based on the patient's history and confirmed on the physical examination. Allowing the patient to use ineffective standing extensions rather than the demonstrably helpful prone extensions simply because it is too inconvenient to lie down at work misses the point of mechanical therapy.

The key to treating Pattern 1 PEP is the prone passive extension. By definition, a PEP patient experiences pain relief within ten repetitions. Self-treatment is repeating the same exercise in the same way for the same number of times that produced improvement during the assessment. Sessions are scheduled frequently throughout the day, hourly at first. Putting the activity on a timed basis and recording each result allows the patient to appreciate that it is the prone extensions and not something else producing progress. As pain control is established the number of session decreases. Prone passive extensions are treatment not prophylaxis; when the patient is pain free, there is no reason to continue. A return of the symptoms should trigger a return to the exercise.

Pattern 1 PEN

Pattern 1 PEN (prone extension negative) patients have no direct route to pain control so treatment can be challenging. Because this is Pattern 1, back pain aggravated in flexion, the ultimate goal is pain control through repetitive prone extensions. Because these patients initially have too much pain on extension to do sloppy push-ups their management must begin somewhere else. The same things that work for Patten 1 PEPs, a footstool, lumbar or night rolls, a large pillow between the knees should help here as well but with less benefit.

The best ways to start may be to prescribe periods of scheduled rest. Similar to scheduled movement, the duration, frequency, and positions are clearly stated and based on their effect on the patient's pain in the examining room. The length of the rest period is determined by the amount of time the pain remains reduced and selecting the position simply depends on which one works best. The Z-lie is usually the most effective but that choice and the duration of rest are governed by the patient's reports on the pain. For the Z-lie the patient is supine with the lower legs and feet on the seat of a chair or bench and the buttocks underneath. Both the hips and knees are flexed more than 90° so that the thighs are drawn up over the abdomen; generally the greater the tuck the greater the pain relief. Adding a pillow under the head and/or the buttocks may further improve the result. The clinician should experiment with all the factors – the feet on the chair, the distance the buttocks are under the sear, the height of the pillows – to find the best combination. At each modification, the patient is quizzed about the level of pain.

Another useful maneuver is having the patient lie prone over three or four pillows. They are placed in front of the pelvis and adjusted up or down to the most efficacious location. This is, obviously, very different for the Z-lie but can be

equally advantageous. The optimum posture depends on the amount of pain reduction but pain control usually improves as the number of pillows increases. As the pain subsides the pillows are sequentially removed.

Managing Pattern 1 PEN is a continuum from rest, typically in flexion, to movement in extension, to a Pattern 1 PEP routine. For the patient with constant back dominant pain where all movement hurts, rest in the way that affords the greatest amount of pain relief is the sensible place to begin. This is frequently the Z-lie. As the symptoms subside movement can be introduced. This can be an unloaded flexion such as knees-to-chest stretches. Paradoxically, although Pattern 1 is aggravated in flexion, most Pattern 1 PEN patients find when starting treatment that unloaded flexion is more comfortable than bending backwards. With increased mobility, treatment progresses to extension: first unmoving, like prone over pillows, then with movement, then the sloppy push-up. The art of managing these patients is choosing how far back along this continuum to begin and how quickly to move forward from static flexion to active extension.

Two other groups qualify as Pattern 1 PEN. The prone passive extension is purely sagittal and involves a full range of movement. Some patients respond only to asymmetrical activity and therefore don't improve with straight line extensions. Others gain relief only with midrange movement and are unable to reach end range. In both instances, ten repetitions of the standard prone passive extension fail to provide pain relief and the patients require modified treatment plans.

Pattern 2

Patients classified as Pattern 2 are never worse in flexion and the back dominant pain is always intermittent. Mechanical therapy is flexion. Except for using a large pillow between the knees when the patient lies down to relax the paraspinal muscles, everything else promotes bending forward. This is easily accomplished in sitting. The patient sits with the knees more that shoulder width apart and bends forward lowering the upper body between the legs. Flexion can be increased by grabbing the ankles and pulling down. To return to an upright posture the patient places the hands on the knees and pushes, using the arms, not the back muscles, to raise the torso. For standing flexion, the patient places one foot up on a bench or chair seat, puts the hands on the elevated thigh, and bends forward to rest the chest on the hands. To straighten up the patient pushes with the arms keeping the back relaxed. The mechanical prescription describes the technique, gives the number of repetitions and specifies the frequency during the day. Pattern 2 responds rapidly and the pain relief is sustained.

Pattern 3

Constant leg dominant pain is managed without movement. Pattern 3 radicular pain results from nerve root inflammation so in the acute phase scheduled rest is most appropriate. Similar to Pattern 1 PEN, the other pattern where scheduled rest is the logical first step, the duration and the spacing of the rest periods are dictated by the patient's pain. Unlike Pattern 1 PEN, the patient with severe radicular pain may need to spend much of time, 30 minutes out of each hour, resting. Several positions can decrease the pain. The Z-lie is the best choice. The setup is the same as described for Pattern 1 PEN, but the deciding factor is now the level of leg pain. The constant leg pain cannot be abolished but the amount can be substantially reduced by slight changes in alignment. Providing precise instructions for a method to achieve some relief also gives the patient a sense of control over a frightening situation, control that can be as beneficial as the mechanical changes. Lying prone over pillows may ease the leg pain. The amount of pain reduction governs the number of pillows; there is no progression to lying flat. The decision to use a Z-lie or to rest prone over pillows is purely pragmatic; the patient is encouraged to experiment. Other options include lying prone on the elbows or even on the hands and knees. Whatever works best is the preferred selection.

As the inflammation and the leg dominant pain subside patients can begin a movement-based routine either as a Pattern 1 PEP or PEN or as a Pattern 4 FA, flexion aggravated.

Pattern 4 FA

The two Pattern 4 categories represent two very different pathologies. The intermittent leg dominant pain of Pattern 4 FA, possibly from residual root impairment or scarring, responds to mechanical treatment. Because the pain increases with flexion, treatment resembles that for Pattern 1, but since the source of the pain is neurogenic rather than purely mechanical, the approach is gentler. The footstool, lumbar roll, and large pillow between the knees can all reduce the leg symptoms. Unloaded back extension, prone over pillows, or extension movements like the sloppy push-ups, may offer relief. The aim of treatment is to diminish the intensity and/or the frequency of the recurrent leg pain so whichever combination works is the best one to use. As with all mechanical therapy, sessions should be specific and repeated frequently during the day.

Pattern 4 FR

The key to managing the symptoms of neurogenic claudication, Pattern 4 FR (flexion relieved), is posture. Flexion increases access to the exiting nerve roots, improving circulation to limit or prevent the symptoms. Maintaining spinal flexion requires strong abdominal muscles so therapy is directed at improving core strength and function. A pelvic tilt is the foundational exercise. Tightening the abdomen rotates the pelvis forward, flattens the lumbar spine, and increases the size of the intervertebral foramina. Performing a pelvic tilt lying down with the knees bent and the feet planted firmly on the floor is relatively easy; maintaining the tilt while walking takes endurance. Core strengthening programs often incorporate using equipment like the Swiss exercise ball or techniques like the one-arm dumbbell bench press, things that are well beyond the ability of the average octogenarian. Pattern 4 FR is most commonly an affliction of the elderly, and although core fitness is a valid principle, in practice it may be impossible to achieve. The affected patient population may not be able to make the long-term commitment to exercise necessary to gain improvement. It is for this reason, not because of a lack of understanding of what mechanical therapy is required to improve function in neurogenic claudication that surgical decompression may be the preferred treatment option.

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Back Pain: The Classic Surgeon's View

2

Neil Berrington

Contents

Abstract

Low back pain is a major cause of disability worldwide and is a major burden on healthcare systems. Treatment strategies are varied and the role of surgery is under constant scrutiny. Many patients benefit from spinal surgery aimed at relieving back pain, radicular symptoms, and neurogenic claudication.

The initial evaluation of patients with categorization into clinical groups may help in appropriately assigning patients to consideration for surgery. Patients presenting with radicular syndromes (radicular pain, radiculopathy, and neurogenic claudication) are widely regarded as potential surgical candidates. Aside from certain distinct groups, non-specific back pain is, as a rule, not regarded as benefiting greatly from surgery. Specific disease entities (such as central disc

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prolapse and spondylolysis) might be the exception and should be considered potential surgical candidates.

Patients presenting with radicular syndromes frequently have disc prolapse or spinal stenosis (with or without spondylolisthesis.) After a period of conservative treatment (cognitive behavioral therapy and exercise), surgery may indeed play a major role in treating these patients. Surgical strategies might vary from simple discectomy to complex lumbar decompression and fusions. Outcomes comparable to major joint arthroplasty are sustained for prolonged periods postoperatively.

Careful patient selection and the adoption of less invasive techniques and enhanced recovery after surgery protocols may reduce morbidity and opiate usage in the long run. Surgery remains a valuable and viable option for selected patients presenting with low back pain and associated syndromes.

Keywords

Non-specific back pain · Disc arthroplasty · Spinal fusion · Spondylolisthesis · Guidelines · Opiates · ERAS

Introduction

The almost ubiquitous occurrence of low back pain in the general population makes the symptom a major burden on healthcare systems worldwide. The rising cost of provision of care, the current opiate crisis in North America, and the vast array of less than scientific opinions offered in the popular media have made the condition a major political issue.

In countries with a significant state contribution to healthcare, governments are placing increased scrutiny of healthcare providers to provide cost-effective treatments for spinal conditions. Universal healthcare systems have become bogged down with long wait times for both assessments and treatment of spinal pathology.

It is estimated that the global prevalence of activity limiting low back pain is 7.2% of the population (540 million people). It is now regarded as the single biggest cause of disability worldwide, with the greatest occurrence of disability in lower-income countries (Hartvigsen et al. 2018).

Aside from the cost of care provision, the problem is further compounded by the emergence of a virtual epidemic of opioid use. In Canada alone, the volume of opioid prescriptions has increased by a factor of 3000% since the 1980s (Belzak and Halverson2018) with a prevalence of opioid-related deaths exceeding accident mortalities (CIHI 2018). As many as 2% of US adult report the regular prescription for opioids with about half of these prescribed for low back pain (Deyo et al. 2011). A recent meta-analysis has shown that prescribing opioids for low back pain is significantly associated with ongoing long-term use (Sanger et al. 2019).

Surgical strategies to alleviate low back pain have become increasingly adopted in North America, with the rates of spinal surgery in the USA now being the highest in the world (Chou et al. 2009). The evidence for surgical efficacy has been inconsistent, and recent critiques have labelled surgery as costly and not providing outcomes any better than intensive multidisciplinary rehabilitation (Foster et al. 2018).

Most spinal surgeons would however contend that the role for surgery in the management of many of the causes of spinal disabilities is clear, and confounding statistics and public opinion with undifferentiated data do a large number of patients a huge disservice.

Successful spinal surgery, like much of medicine, is reliant on the thorough clinical evaluation of a patient, a thoughtful analysis of special investigations and an understanding of the best evidence available in modern literature.

The Traditional Approach

Classical teaching has to date held firm that surgery is key in the successful management of many radicular syndromes, cauda equina syndrome and neurogenic claudication. The role for surgery in treating “undifferentiated back pain” and degenerative disc disease is much less clear. As a consequence of this understanding, many referral

pathways are designed such as to direct patients with undifferentiated back pain away from interventional trajectories of care.

The general approach to assessing low back pain is well laid out by a group of Australian primary care providers (Bardin et al. 2017). The initial assessment of a patient with low back pain is contingent on an accurate and thorough history and clinical examination. In this manner, non-spinal pathology can be, for the most part, excluded. Hip pathology, kidney stones, urinary tract infections, and abdominal pathology can then be appropriately directed. The remaining patients are then triaged into three categories:

Specific Spinal Pathology

Fractures, infections, tumors, and cauda equina syndrome should be, for the most part, apparent with a clinical evaluation. This category of patient frequently falls into the realm of spinal surgery as a means to address the spine pathology, relieve neural compression, alleviate pain, and prevent progressive deformity.

Radicular Syndromes

Patients manifesting *radicular pain* account for about 60% of the low back pain population (Hill et al. 2011). Patients with *radiculopathy* on the other hand present with a syndrome characterized by dermatomal sensory loss, myotomal muscle weakness, or absent deep tendon reflexes. Patients with classic spinal stenosis in turn might present with *neurogenic claudication*. Common practice in the treatment of radicular syndromes is a trial of conservative treatment, and surgery is only considered if symptoms extend beyond 6 weeks. The surgical treatment of radicular syndromes remains highly controversial.

Non-specific Low Back Pain

This undifferentiated catch all includes a number of diverse pathologies, mostly regarded as "musculoskeletal." This would include disc prolapse, facet arthropathy, degenerative disc disease, annulus tears, spondylolisthesis, and muscle injuries. The diverse nature of this group makes a universal recommendation (or condemnation) of surgery inappropriate.

Categorizing patients in this manner does help identify a large portion of surgical candidates. Unfortunately a large degree of overlap in symptoms occurs, and patients presenting with a radicular syndrome might have coexisting non-specific low back pain. Attempting to ascribe some degree of dominance to a particular symptom might assist a surgeon in navigating the next course of action.

In healthcare systems with constrained resources, this can aid in identifying patients who might most readily benefit from a surgical consultation or special investigations. A triage pathway has been implemented in Saskatchewan, Canada. The Canadian group was able to demonstrate considerable reductions in wait times and MRI utilization within a universal healthcare system (Fourney et al. 2011). The group regards patients as having syndromes of back pain that are either *leg-dominant* (i.e., radicular syndromes) or *back-dominant*, with an implicit understanding that back-dominant pain represents the non-specific low back pain group and is diverted along a pathway of conservative management.

Surgical Treatment of Specific Spinal Pathology

Much of this tome is devoted to the management of what would seem to be clear-cut indications for spinal surgery. The patient selection and technique adopted will vary widely according to the associated pathology. These conditions are beyond the scope of the discussion in this chapter.

Surgical Treatment of Radicular Syndromes

Lumbar Disc Prolapse

Lumbar disc prolapse is the commonest cause of radicular syndromes, and microdiscectomy is, as a result, the most common neurosurgical procedure

in North America. Despite this, the optimal treatment of lumbar disc prolapse remains highly controversial.

Lumbar disc prolapse is the displacement of intervertebral disc material beyond the normal margins of the disc space and might include disc nucleus and or annulus. The prolapse might be contained within the limits of a bulging annulus and posterior longitudinal ligament or be sequestrated from the ligamentous confines above. On rare occasion, sequestrated disc material can even extrude into the dural tube.

Laterally placed prolapse might account for a radicular syndrome, while large central prolapses can cause profound low back pain. Severe compression of neural elements can manifest as *cauda equina syndrome*.

The decision regarding treatment rests with a well-executed physical examination, as special investigations might not be required, and MRI findings can be misleading. Disc prolapses are frequently noted on MRI scans in asymptomatic patients (Brinjikji et al. 2015). The accuracy of findings on clinical evaluation is somewhat variable but taken as a whole can guide initial treatment options.

A history of leg-dominant pain with a typical dermatomal distribution of pain and positive straight leg raising test is sensitive for diagnosing lumbar disc prolapse, while crossed straight leg raising, paresis, muscle atrophy, and loss of deep tendon reflexes are highly specific for disc prolapse (Deyo and Mirza 2016). The presence of psychological distress, depression, and somatization should be sought, as these symptoms are associated with less than ideal surgical outcomes (Kreiner et al. 2014).

It is critical to exclude any suggestion of a cauda equina syndrome – a history and physical examination reflecting saddle anesthesia, incontinence or urine retention, and poor anal sphincter tone establish this syndrome clinically. The duration of symptoms prior to surgical treatment is a determinant of outcome, and the rates of permanent urinary incontinence increase dramatically over time (Qureshi and Sell 2007).

The natural history of lumbar disc prolapse is generally favorable, with up to 87% of patients reporting a reduction in analgesic use at 3 months and 81% of patients with motor deficit reporting improvement at 1 year (Deyo and Mirza 2016).

Attempts at randomized trials comparing surgery to conservative treatment are confounded by a lack of standardization of treatment arms and considerable crossover. The most robust and frequently sited study on the subject, the multicenter Spine Outcomes Research Trial (SPORT), had such a high crossover of subjects that it is difficult to deduce much at all other than patients will make appropriate choices as their symptoms dictate. As many as 60% of patients left the surgical arm as their symptoms were improving spontaneously (Birkmeyer et al. 2002.) Systematic review of the literature does however support the notion of discectomy favoring nonsurgical treatment for the short-term resolution of symptoms (Gibson 2007).

The ideal approach to preforming a discectomy has not been clearly defined, although a tendency toward less invasive strategies has been associated with shorter hospital stay and shorter periods of absence from work. A recent study on endoscopic discectomy demonstrated this effect, although outcomes at 12 months post-surgery are identical to a standard microdiscectomy (Ruetten et al. 2008).

Discectomy procedures have a relatively low complication rate, and surgery is associated with a quicker return to work than conservative treatment (Deyo and Mirza 2016). Surgery is thus an effective treatment for disc prolapse where symptoms have persisted beyond 6 weeks. Considering the benefits of reducing the use of analgesics (particularly opioids), discectomy remains a highly relevant treatment strategy for well-selected cases.

Spinal Stenosis

A radiological or pathological finding of *spinal stenosis* is universal in older patients, although the relationship between the anatomical diagnosis of stenosis is a tenuous one. Many clinicians prefer to regard symptomatic stenosis as an entity defined by the symptom complex, i.e., radiculopathy or

neurogenic claudication (Backstrom et al. 2011). An entity of claudicant back pain is seen from time to time. These are patients who seem to have a back-dominant pattern of pain, which is aggravated by walking and relieved by sitting down. Selecting this group of patients for surgery does require considerable deliberation. Further complicating the heterogeneity of this group are the entities of stenosis associated degenerative spondylolisthesis and degenerative kyphoscoliosis.

Due to the diversity of pathology accounting for the symptoms and the lack of uniform terminology in describing what is being treated, studies comparing surgery with conservative treatment are clouded with interfering variables and a heterogeneity of patients.

The commonly cited large, multicenter Spine Patient Outcomes Research Trial (SPORT trial) attempted to analyze stenosis in isolation, excluding patients with degenerative spondylolisthesis. In this study, surgery for stenosis had statistically better outcomes for the surgical group for radicular pain, back pain, function, and patient satisfaction (Weinstein et al. 2010). The favorable outcomes were sustained 4 years post-surgery. The outcome of the SPORT trial seems to be validated by data generated by the Canadian Spine Society "Canadian Spine Surgery Outcomes Network" (CSORN) database. Interestingly these data seem to support a contention that both radicular and back pain improvement is sustained postoperatively (Srinivas et al. 2019).

Although the benefit of surgical treatment would appear to be clear, the choice of intervention is less so. Several trials have attempted to compare decompression alone versus decompression and fusion. Although outcomes appear to be comparable in terms of long-term relief of symptoms, the complication rate of decompression with fusion is somewhat higher (Chou et al. 2009). Most recently it has been proposed that instrumented fusion without decompression might even be appropriate (Goel et al. 2019).

What has become evident of late is that less invasive surgical techniques are associated with a shorter duration of absence from work. In a systematic review, the authors found the predictors of delayed return to work which included age, comorbidities, duration and severity of symptoms, depression, mental stress, lateral disc prolapse, and more invasive surgical techniques (Huysmans et al. 2018). Minimally invasive techniques augmented by Enhanced Recovery After Surgery (ERAS) protocols have been shown to reduce perioperative opiate use (Brusko et al. 2019), which in turn might reduce the burden of opiate abuse in this patient population (Berrington 2019).

Surgical Treatment of Non-specific Back Pain

Of all surgically treated conditions, non-radicular back pain remains the most controversial. The Lancet medical journal featured a series of articles focused on the problem of low back pain. Much of the debate generated by the series related to the efficacy (or lack of) in treating low back pain as group. Arguably one of the most influential journals, the publication found surgery to have "insufficient evidence" of efficacy and the role of spinal fusion to be uncertain (Foster et al. 2018). Spinal surgeons however continue to maintain there are certain groups of patients who benefit from surgical intervention.

Degenerative Disc Disease

Maintaining an active lifestyle, exercise therapy, and cognitive behavioral therapy is likely the most appropriate first-line treatment for low back pain (Foster et al. 2018). Studies on the surgical management of degenerative disc disease have yielded somewhat unimpressive results. Naturally not all procedures are equally as effective, and nor are all patients burdened with equivalent pathology.

Spinal fusion is the most commonly performed surgical procedure for this condition, and whether executed via the use of pedicle screws or augmented with some form of anterior stabilization, surgical strategies yield results not much better than the natural history of the condition.

A commonly quoted trial that proponents of surgery would site is the Swedish Lumbar Spine

Study. The study won the Volvo Award in 2001 and is used as evidence of the efficacy of the surgery (Fritzell et al. 2001). In their study the outcomes were favorable in 46% surgical of cases and 18% of nonsurgical cases. Although statistically different, the net overall benefit of surgery is thus only felt in less than 30% of cases. The conclusion of the article (recommending spinal fusion in this condition) is at odds with the results.

Most trials studying spinal fusion outcomes in degenerative disc disease are inconsistent in outcomes, and the role is indeed uncertain (Chou et al. 2009).

Lumbar disc arthroplasty procedures have been touted as the solution to the marginal gains observed in fusion patients. The two major North American trials studying the efficacy of arthroplasty used fusion patients as their control groups. The Charite artificial disc which was compared to a stand-alone interbody cage failed to demonstrate any significant difference in patient outcomes (Blumenthal et al. 2005), while the ProDisc-L trial showed equivalence with 360 degree fusion (Zigler et al. 2007).

The Charite trial in particular is problematic to interpret as it attempted to demonstrate non-inferiority to what was, even at that time, not regarded as the standard surgical treatment for degenerative disc disease (a stand-alone interbody cage). Complications associated with the anterior approach have also led to a slow uptake of the procedure. To what extent lumbar arthroplasty will contribute to treating this group thus remains uncertain.

Emerging technologies attempting to provide motion preservation with a degree of stabilization continue however to intrigue investigators (De Muelenaere and Berrington 2015), but to date the role of any surgery to alter the natural course of degenerative disc disease remains uncertain.

Prolapsed Lumbar Disc

Anecdotal reports of patients with large central herniation of a lumbar disc have indicated a simple discectomy that might improve back-dominant symptoms in selected cases. The mechanism proposed is that dural tension from the disc mass is the meteor for local pain and muscle spasm in the absence of radicular symptoms (Adams 1998; Fig. 1).

Spondylolisthesis

Spondylolisthesis refers to anterior displacement of the vertebral body in reference to the bordering vertebral bodies (Gagnet et al. 2018). Spondylolysis in turn refers to a defect or fracture in the pars interarticularis. Spondylolysis can occur with or without spondylolisthesis.

Five forms of spondylolisthesis are identified (Wiltse et al. 1976):

Type I – Dysplastic: congenital dysplasia and malformation of the first sacral vertebra, resulting in slippage of the L5 vertebra anteriorly

Type II – Isthmic – a defect in the pars interarticularis (IIA) or lengthening of the pars interarticularis due to repetitive fracturing and healing (IIB)

Type III – Degenerative – degenerative failure of the facet joints and ligamentum flavum allowing slippage of the vertebrae anteriorly

Type IV – Traumatic – secondary to trauma to the spine

Type V – Pathologic – lytic tumors, osteopetrosis and osteoporosis resulting in pars defects and subsequent slippage

Spondylolytic spondylolisthesis is the commonest cause of back pain in adolescents and young adults, and conservative management is usually advocated. This takes the form of rest, bracing, and physiotherapy (Blanda et al. 1993). Healing of the pars defect is expected in most early stage cases (Gagnet et al. 2018). When the defect is progressive, success of conservative treatment drops off drastically and generally does not occur once sclerotic change is noted (terminal stage).

Surgical repair of pars defects has taken a number of forms, including screw hook constructs and direct grafting. Where conservative treatments have failed, pars repair remains a viable option. Once a listhesis occurs, most surgeons opt for more substantial implants.

Although a number of procedures have been used to address spondylolytic spondylolisthesis,

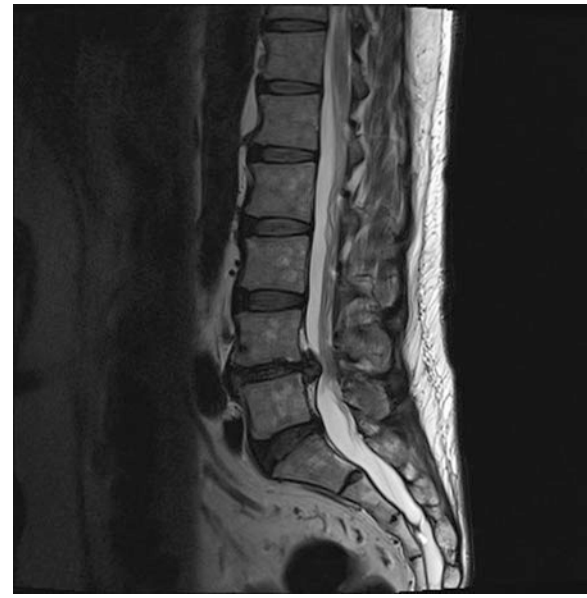

Fig. 1 T2-weighted sagittal MRI scan of a patient with non-specific low back pain and a large central disc herniation. This patient experienced resolution of pain with a simple microdiscectomy

pedicle screw fixation with decompression is generally regarded as the surgical treatment of choice (Violas and Lucas 2016; Gagnet et al. 2018). Lumbar decompression and fusion for degenerative listhesis has been shown to demonstrate sustained improvement comparable to hip and knee arthroplasty (Rampersaud et al. 2014).

Degenerative spondylolisthesis, on the other hand, remains a contested topic with conflicting outcomes in several well-constructed trials. A Scandinavian group showed equivalent outcomes of decompression only when compared to decompression and fusion surgery for stenosis with and without listhesis (Försth et al. 2016), while in the same journal, the frequently cited *Spinal Laminectomy* versus *Instrumented Pedicle Screw* (SLIP) trial demonstrated superiority of outcome at 4 years for the fusion group (Ghogawala et al. 2016).

Both the above studies do show significant and sustained improvement of surgery in patients with spinal stenosis with degenerative listhesis. While it would appear an instrumented fusion that might provide longer term relief, uninstrumented decompression is still clearly a viable option. Careful patient selection might dictate the nature of the surgery, particularly since decompression alone seems to provide meaningful relief of quality of life data.

Conclusions

When confronted with an array of pathology and multiple treatment options, maintaining a clear perspective is difficult. Attempts to offer guidance have been forthcoming from both the North American Spine Society and the Canadian Spine Society.

Choosing Wisely Canada has attempted to provide a consensus opinion of the spine community to allow physicians to make appropriate decisions in this complicated and controversial field. The guidelines are based on both a thorough literature review and expert opinion of the Society members. Their recommendations (1) and (7) are the most relevant to this particular topic. The recommendations follow in Fig. 2.

Patients with low back pain represent a diverse group of pathology, and treatment modalities remain controversial. Identifying which patients are best suited to which type of surgery becomes an art, as it represents the surgeons understanding of the clinical presentation and one's knowledge

1. Don't perform fusion surgery to treat patients with mechanical axial low back pain from multilevel spine degeneration in the absence of: (a) leg pain with or without neurologic symptoms and/or signs of concordant neurologic compression, and (b) structural pathology such as spondylolisthesis or deformity.
2. Don't routinely image patients with low back pain regardless of the duration of symptoms unless: (a) there are clinical reasons to suspect serious underlying pathology (i.e., red flags), or (b) imaging is necessary for the planning and/or execution of a particular evidenced-based therapeutic intervention on a specific spinal condition.
3. Don't use epidural steroid injections (ESI) for patients with axial low back pain who do not have leg dominant symptoms originating in the nerve roots.
4. Don't miss the opportunity to brace the skeletally immature patient with adolescent idiopathic scoliosis (AIS) who has more than one year of growth remaining and a curve magnitude greater than 20 degrees.
5. Don't order peri-operative antibiotics beyond a 24-hour post-operative period for non-complicated instrumented cases in patients who are not at high risk for infection or wound contamination. Administration of a single pre-operative dose for spine cases without instrumentation is adequate.
6. Don't use an opioid analgesic medication as first-line treatment for acute, uncomplicated, mechanical, back-dominant pain.
7. Don't treat post-operative back pain with opioid analgesic medication unless it is functionally directed and strictly time limited.
8. Don't use opioid analgesic medication in the ongoing treatment of chronic, non-malignant back pain.

Fig. 2 Recommendations of *Chooseing Wisely Canada* for patients with spinal symptoms (Choosing Wisely Canada 2019)

of the literature as a whole. As will be seen in this handbook, there are numerous options available to the surgeon.

Certain patients will be identifiable as patients with specific spinal pathology that would potentially require surgical correction ("red flag" patients). Identifying patients with persistent radicular syndromes or claudication will aid in the selection of patients who might benefit from surgery. At that point treatment is individualized, based on which symptoms dominate, the nature of the underlying pathology, and the suitability of the patient for surgery based on comorbid or psychological factors.

Although patients with non-specific low back are usually diverted away from a surgical stream, there might be patients who would benefit from surgery in certain instances, and a blanket condemnation of this form of surgery would seem inappropriate. As technology advances and out understanding of spinal biomechanics changes, hopefully greater numbers of patients will derive benefit form appropriately tailored interventions.

Overall, the modification of surgical stress through the adoption of ERAS and other quality improvement protocols may also in the long run improve outcomes and reduce the use of opiate drugs.

Cross-References

- ▶ Biological Treatment Approaches for Degenerative Disc Disease: Injectable Biomaterials and Bioartificial Disc Replacement
- ▶ Posterior Dynamic Stabilization

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Back Pain: Chiropractor's View

3

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Abstract

In educating engineering students about geology, the advice given to the geology tutors is your job is to convince the engineers that when they need a geologist they should send for one. That might also be a good advice now to those in the medical professions treating patients with non-specific back pain: when you need a chiropractor, send for one or at least talk to one. In the face of the escalating opioid deaths from prescription drugs, there is a compelling, and ethical, obligation for health providers to consider non-pharmacological therapies for treating pain. These therapies have evidence for efficacy and safety, are not addictive, and are associated with a very low rate of adverse events. Chiropractic falls squarely within the framework of these therapies. In most jurisdictions chiropractic is defined as the treatment of musculoskeletal conditions *without the use of drugs or surgery.* As with all the complementary and alternative medicine (CAM) professions, pain is the number one condition that drives patients to CAM providers and specifically low back pain in the case of chiropractors. It is estimated that one in five of all adults in the United States and Canada will use chiropractic care at some time in their life. The purpose of this chapter is to provide information that can help medical practitioners in deciding when to refer to chiropractors. This requires some knowledge about chiropractic education and training, the thinking and practice behind chiropractic care, the different views about back pain and health generally, and the different types of management of back pain arising from that point of view.

Keywords

Chiropractic · Non-pharmacological · Complementary and alternative medicine · Spinal manipulation · Primary spine care

Introduction

There are currently several compelling reasons supporting the need for medicine to change its historical stance toward chiropractic. To use the cliché, “times have changed.” Among the compelling reasons are the following.

The Opioid Crisis

A total of 70,237 Americans died from drug overdose in 2017, and synthetic opioids are the main contributor, accounting for 47,600 of those deaths. From 1991 until 2017, almost 400,000 people died from an overdose involving any

opioid. Of these, from 1991 to 2017, 218,000 people died from overdoses of prescription opioids. Opioids are now the third leading cause of death after heart disease and cancer (https://www.cdc.gov/drugoverdose/data/prescribing/overview.html).

The figures are similar for most western countries. While much of the blame can and should be laid at the feet of drug companies, this crisis is also a medically induced iatrogenic crisis. During an age of evidence-based medicine, it is difficult to understand how new drugs with so little evidence about their addictive nature or associated adverse effects could be so widely prescribed for a common condition like low back pain (Coulter 2018). Systematic reviews of the literature have shown that opioids are actually not very useful in controlling low back pain and are associated with high rates of adverse events (Tucker et al. 2019; Sanger et al. 2019).

There are multiple components to this tragedy, and death is only one part of the picture. Other negative consequences include addiction, lives ruined, crime, and the economic cost to society. The human suffering and social costs are almost incomprehensible. The fact that the crisis came from a desire in medicine to help patients deal effectively with pain adds an element of tragic irony to the crisis. This is somewhat akin to Oedipus declaring he will find and punish the man who caused the plague when Oedipus himself is the cause. But one of the saddest parts of the opioid crisis is that there exists a whole range of non-pharmacological therapies for treating pain. These include such therapies as the chiropractic profession's manipulation, acupuncture, massage therapy, and a whole range of complementary and alternative medicine (CAM) treatments that are available and already treating pain. Estimates from the National Health Survey show that around 38% of the population is using some type of CAM therapy (Clarke et al. 2015).

Of all the available alternative professions, the chiropractic profession is the one most utilized by Americans and Canadians. Low back pain is by far the largest condition category for which CAM therapies are most frequently used, followed by neck pain as the second most common condition (Beliveau et al. 2017). In addition, chiropractic care is rated higher in terms of patient satisfaction (Hertzman-Miller et al. 2002; Yu et al. 2002; Beattie et al. 2011; Herman et al. 2018) as compared to medical care, physical therapy, and osteopathy for low back pain. There is also evidence from one study that initial visits to chiropractors or physical therapists are associated with substantially decreased early and long-term use of opioids. Patients who received initial treatment from chiropractors or physical therapists had decreased odds of short-term and long-term opioid use compared with those who received initial treatment from primary care physicians (Kazis et al. 2019). In the Herman et al. 2019a, observational study, 1,835 chronic back pain patients rated their chiropractic provider at the top of the patient satisfaction scale, and 90% reported that they were extremely confident that their chiropractor would be very or extremely successful in reducing their pain, and over 90% would recommend chiropractic to a friend (Herman et al. 2019a). In the same study (Herman et al. 2018), using 2,024 patients at baseline, over 90% reported high satisfaction with their care, and very few used narcotics. Patients have also stated that avoiding surgery and medications were the most important reasons they chose chiropractic. They also reported high levels of belief in the success of chiropractic in reducing their pain (Hays et al. 2019).

In 2019, UnitedHealthcare was the largest provider of health insurance in the United States. They just announced an innovative new benefit plan for patients in employer-sponsored plans that cover physical therapy and chiropractic services. There will be $0 out-of-pocket cost to patients with low back pain if they choose to see a chiropractor or physical therapist as the first-contact provider, instead of seeing a primary care physician or specialist. To quote from this new benefit plan: "Based on a UnitedHealthcare analysis, by 2021 this benefit design has the potential to reduce the number of spinal imaging tests by 22%, spinal surgeries by 21%, opioid use by 19%, and lower the total cost of care for eligible plan participants and employers." They also note that opioids were

still being prescribed to 9% of patients with low back pain and that this condition is the most common reason for giving opioids (https://www.fiercehealthcare.com/payer/unitedhealth-introduces-new-benefit-for-treating-low-back-pain-for-employer-plans? Nov 1st 2019).

Widespread Use of Chiropractic for Spinal Care

The second compelling reason to talk to a chiropractor is the high probability that your patients are already utilizing their services. There are more than 103,000 chiropractors practicing in 90 countries, with the largest number of chiropractors per capita found in the United States (Stochkendahl et al. 2019). Chiropractic care is one of the most commonly used CAM therapies in Europe, Canada, and the United States (Beliveau et al. 2017; Canizares et al. 2017). As noted above (Clarke et al. 2015), chiropractic is the fourth most used CAM therapy in the United States, but if we exclude natural products, deep breathing, and meditation (all non-provider-based therapies), chiropractic is the most used therapy. Globally, the median 12-month utilization of chiropractic services is 9.1% (IQR, 6.7–13.1%) and lifetime utilization of 22.2% (IQR, 12.8–40.0%) (Beliveau et al. 2017). At least 8–14% of the population in the United States seeks chiropractic care each year, there are 190 million patient visits annually, and there are 70,000 actively licensed chiropractors. A Gallup survey in 2015 showed that more than 50% of US adults have previously sought care from a Doctor of Chiropractic (DC) at some point in their lives (Weeks et al. 2015), while 14% had done so within the previous year. Chiropractors can now be found in private practice, multidisciplinary health treatment facilities, professional athletic teams including olympic teams, military health facilities, and the Veterans Affairs (VA) health facilities (Lisi et al. 2009; Green et al. 2009). More than 100 VA healthcare facilities in the United States currently have chiropractic clinics staffed by DCs. In fiscal year 2018, there were 50,000 veterans receiving in-house chiropractic care and another 80,000 veterans referred to community care programs for chiropractic services. The number of veterans receiving care has more than doubled since 2015 with similar future growth expected due to veteran demand, expansion and success of VA chiropractic services, and a shift in healthcare resources to evidenced-based non-pharmacological options for spine-related conditions and chronic pain (Lisi and Brandt 2016; Dunn et al. 2009).

While chiropractors and medical doctors were always linked through their patients, if surreptitiously, the lack of communication between medical and chiropractic providers has not been in the patient's best interest. It behooves any provider to be informed about the remedies patients take for their health, in addition to those provided by the physician. Clearly a physician cannot advise a patient about the interactive effects of combining therapies if the physician does not know about them. In a groundbreaking study on the use of CAM therapies, one of the most striking results was the finding that patients did not inform their medical doctors about their use of CAM therapies. The chief reasons given were they did not need to know, they never asked, and that they would not understand. In addition, patients expressed concerns that their doctor would disapprove and discourage them from using CAM therapies and/or stop being their provider (Eisenberg et al. 2001).

Mounting Evidence About the Efficacy and Safety of Chiropractic Care

A third compelling reason to work with chiropractors is that there is now a strong evidence base for the safety and effectiveness of chiropractic manipulation, which should allay any concerns about vicarious liability (Nahin et al. 2016). As the level of evidence of safety and effectiveness increases and referrals are more common, the threat of direct liability also decreases (Gilmour et al. 2011a). There are some 100 published randomized clinical trials (RCTs) on the effectiveness of spinal manipulation for acute and chronic low back and neck pain (Shekelle and Coulter 1997; Coulter et al. 2018, 2019a; Qaseem et al. 2017). In a recently published systematic review (SR) and

meta-analysis of RCTs and other SRs involving spinal manipulative therapy (SMT), the conclusion was that SMT is associated with modest improvements in pain and function and only transient minor musculoskeletal side effects (Paige et al. 2017). Spinal manipulation is now recommended as a frontline treatment in the most current American College of Physicians (ACP) clinical practice guideline as an evidence-based treatment for both acute and chronic back pain (Qaseem et al. 2017). In addition to the ACP guideline, the Veterans Affairs (VA) and Department of Defense (DoD) have created a clinical practice guideline (Provider Summary. Department of Veterans Affairs/Department of Defense 2017; Version 2.0) for the diagnosis and treatment of low back pain, with a major concern about reducing the routine use of opioid medications. This joint VA/DoD guideline also recommends SMT as an important non-pharmacological treatment for low back pain.

The totality of the evidence, although there is some variation, is that for low back and neck pain, chiropractic manipulation has clinical efficacy and a very low rate of adverse events (Shekelle and Coulter 1997; Coulter 1998; Swait and Finch 2017). Serious adverse events were almost unheard in the RAND studies of RCTs for manipulation. The RAND Corporation's groundbreaking study of the appropriateness of chiropractic manipulation for acute low back pain (Shekelle and Coulter 1997), used both RCTs and 135 reported case reports for acute low back pain to estimate there was one serious adverse event (such as cauda equina syndrome) per 100 million manipulations. For their study on cervical manipulation where 110 case studies were deemed acceptable, they estimated the rate of serious complications at 6.39 per 10 million manipulations (Coulter 1998). The difficulty in calculating the risk for an event this rare is that it requires a very large database and huge sample sizes that are simply not provided by clinical trials.

It is no longer legitimate to claim that there is no evidentiary base for the safety of chiropractic manipulation. A systematic review of adverse events reported in spinal manipulation RCTs (Gorrell et al. 2016) that reviewed 368 articles found that adverse events were reported in only 38% of the articles and that there were only 2 major adverse events reported in all of those studies. It is interesting to note that only 22 articles reported adverse events in the abstract. Chiropractors accounted for 55% of the SMT provided and physiotherapists 30%. Rubinstein et al. (2019) reviewed the benefits and harms of SMT based on 47 RCTs for chronic LBP and found that found only 1 serious adverse event possibly attributed to the SMT. Another SR of RCTS involving SMT found that most of the observed adverse events were mild to moderate, transient musculoskeletal symptoms. Rubinstein et al. (2019) in one study, the Data Safety Monitoring Board judged only one serious adverse event to be possibly related to SMT. In two recently published clinical trials of older patients with lumbar spinal stenosis treated with spinal manipulation, no serious adverse events were reported (Schneider et al. 2019). Similar conclusions were recently reached by an independent report commissioned by the Victorian State Government in Australia related to the safety of chiropractic manipulation in children under the age of 12 years. After an extensive review of the literature, regulatory complaints, and stakeholder feedback, the report concluded there was little evidence of harm in Australia (Safe Care Victoria 2019). A scoping review of the risks of manipulation by Swait and Finch (2017) of 250 articles that included RCTs, observational studies, and SRs found that estimates of serious adverse events ranged from 1 per 2 million manipulations to 13 per 10,000. Benign and transient minor adverse events following manipulation were common, but serious adverse events were rare.

To put this in context, in the NIH consensus conference for the diagnosis, treatment, and prevention of dental caries (Coulter 2001), only seven RCTs were found in which it was possible to prove that the patient actually had dental caries. This resulted in an inability of the panel of experts to make any recommendations based on the trial literature for the diagnosis, treatment, or prevention of caries. Even the Cochrane Collaboration was unable to provide substantial evidence for

most dental procedures, exemplified by this quote:

> Many standard dental treatments—to say nothing of all the recent innovations and cosmetic extravagances—are likewise not well substantiated by research. Many have never been tested in meticulous clinical trials. Most of the Cochrane reviews reach one of two disheartening conclusions: Either the available evidence fails to confirm the purported benefits of a given dental intervention, or there is simply not enough research to say anything substantive one way or another. (Jabr 2019)

Their conclusion was that dentistry was much less scientific and more prone to gratuitous procedures than the public thinks. Under the standards that are set for evidenced-based practice, this would mean chiropractic is much more evidenced-based than dentistry.

Seeing a chiropractor as first contact has also been shown to decrease duration of episodes (Blanchette et al. 2017) and decrease the likelihood of undergoing surgery, even controlling for severity (Keeney et al. 2013). In addition, an injured worker seeing a chiropractor for low back pain is less likely to experience recurrence of disability (Cifuentes et al. 2011). A recent clinical trial conducted within a military population showed that chiropractic plus medical care for low back pain produced better outcomes than medical care alone (Goertz et al. 2018). Therefore it is clear that if physicians have no qualms about referring patients to dentists despite its lack of evidence about efficacy and safety, the reluctant stance taken toward chiropractic is inconsistent, at the very least. However, such reluctance is diminishing as more patients are asking and seeking referrals for CAM therapies and governments are encouraging collaborative or shared care among healthcare professions (Gilmour et al. 2011a). In Canada, a national survey of family physicians reported that about 12% offer CAM services; however, significant regional variations were noted with higher use in western provinces (Hirschkorn et al. 2009). Others have reported referral rates to chiropractors of about 40% for chronic pain and back problems (Austin et al. 1998). In addition to the availability of a much greater body of evidence on chiropractic, there is a cadre of chiropractic researchers (those with dual DC and PhD degrees) conducting research within prestigious universities both in North America and internationally.

Evidence for Outcomes for Medical Therapies for Spinal Problems

At the same time as this body of positive research on chiropractic is increasing, there is an associated increasing body of literature on the questionable efficacy, effectiveness, and safety of many of the medical procedures for low back pain such as surgery, epidural injections, and even NSAIDs (Bally et al. 2017). This has led to recognition of the over treatment of back pain (Deyo et al. 2009). The questionable results and complications from back surgery have been well documented (Fineberg et al. 2014; Marquez-Lara et al. 2014; Martin et al. 2013), as well as for epidural injections (Manchikanti et al. 2016) and drugs (Machado et al. 2017). Not the least is the evidence for the use of opioids following surgery (Brummett et al. 2017). Increasingly we see in the literature (Chou et al. 2016) calls for noninvasive treatments for low back pain and for non-pharmacological therapies (Chou et al. 2017).

Removal of Legal and Ethical Barriers

Last but not least, in North America there are no longer any legal or ethical barriers for a physician to collaborate with a chiropractor. Until the Wilk et al. versus AMA antitrust trial (Agocs 2011), the AMA stated that it was considered unethical for a physician or hospital to associate in any way with chiropractors, who were considered to be "quacks." While this policy was portrayed as acting in the public interest and protecting the patient from unfounded claims for unscrupulous health practices, the Wilk trial established that the AMA Committee on Quackery was actually a self-serving front for attacking the chiropractic profession. The underlying and stated purpose of this Committee was to first contain and then to eventually eliminate the entire chiropractic profession.

The result of this landmark decision was that CAM providers in general (who were also considered quacks) and chiropractors in particular could now form professional relationships with MDs. This can be seen in the emergence of complementary and integrative medicine clinics in which these inter-professional partnerships were being established (Coulter 2012; Coulter et al. 2008, 2010; Baer and Coulter 2008; Hsiao et al. 2005). It also opened the door for hospitals and the Veterans Administration to include chiropractic services. Prior to this court decision, hospitals could lose their accreditation for accepting referrals from chiropractors. It is ironic that The Joint Commission (2018) (accrediting organization for US hospitals) has published an Advisory Policy on non-pharmacological options for pain management. This Advisory Policy requires that all accredited hospitals include evidence-based, non-opioid treatment options including spinal manipulation, acupuncture, and massage therapy.

One issue at the heart of the Wilk trial (Agocs 2011) was the medical profession's understanding of the legal status and rights of chiropractors, their scope of practice, and what they were licensed to perform. Historically, medicine has frequently questioned the legitimacy of chiropractic, despite the fact that those statements had no basis in law. The state does not give any one profession the legal power to decide who is, or who is not, a legitimate health profession. That power belongs only to the state and once conferred should be recognized. But the health professions as a group and individually have often acted to limit the legal rights of other professions. While this can be seen in conflicts such as optometry and ophthalmology, physical therapy and chiropractic, midwives and nurses, midwives and obstetricians, nurse practitioners and physician assistants, and dentist and denturists, the most extreme case can be seen in medicine and chiropractic. But in all cases, recognizing a scope of practice invariably means confronting other groups' claims for the same scope, either sharing the scope or trying to win exclusivity. Since by definition the scope of medicine is any act carried out by a medical physician, for any other profession to gain a scope of practice, it will be in confrontation with medicine. In some very rare cases, medicine will give over the scope to another profession as in dentistry and the oral cavity, but in most cases, it will be contested as in the case of midwifery, optometry, chiropractic, and, outside of America, osteopathy. As we noted earlier in the Wilk trial, the extent to which organized medicine acted to limit the rights of the chiropractic profession was extreme. The AMA conspired to keep chiropractors out of the military, veterans organizations, hospitals, universities, and the NIH, from access to such things as laboratories, X-rays, and MRI scans. The extent to which this was done can seem staggering and petty to independent observers and is often totally unknown to individual medical doctors.

In 1980, the AMA revised its Principles of Medical Ethics to reflect this new position, allowing medical doctors to be free to choose the patients they served, the environment they served in, and the other types of practitioners they associated with (Agocs 2011). In 1987, US District Judge Susan Getzendanner found the AMA and its co-defendants guilty of violating the Sherman Antitrust Act. In her decision, Getzendanner asserted that "the AMA decided to contain and eliminate chiropractic as a profession" and that it was the AMA's intent "to destroy a competitor" (Getzendanner 1988).

So what is the current legal status of chiropractic in North America? Chiropractic care is licensed and regulated in every state (Lamm et al. 1995; Mootz and Coulter 2002; Sandefur and Coulter 1997) and province and the Yukon Territory, except the Northwest Territories and Nunavut (Boucher et al. 2016) in North America. The legislation for chiropractic covers six dimensions: licensure, the scope of practice, titles, clinical authority (e.g., prescribing authority), self-regulating authority, and reimbursement. In particular, legislation covering chiropractors may include a definition of the scope of practice, specific license to practice as a first-contact provider, title exclusivity, a section on limitations to chiropractic practice, and the specific agency that regulates chiropractors. Legislation is also likely to specify the range of clinical authority for chiropractors, along with reimbursement policies (especially for government schemes such as

Medicare and Medicaid and provincial and federal public funding). Each province or state can be classified according to the nature of the six dimensions mentioned above, so there is a continuum of legal environments under which chiropractors practice ranging from restrictive to expansive. Therefore, the legislation may state: (1) license to practice as a primary provider (primary contact, portal-of-entry, etc.); (2) scope of practice (can be hands only spine only); (3) clinical authority (right to diagnose); (4) reimbursement for services rendered; (5) self-regulatory authority (right to discipline its own members); and (6) exclusive use of the title "Doctor of Chiropractor."

In most jurisdictions, the scope of chiropractic practice will also be influenced by policies or guidelines issued by the regulatory agency responsible for licensing or by court decisions (Sandefur and Coulter 1997). That is, either the licensing agency or the courts may have interpreted the applicable state legislation in ways that affect chiropractic behavior. In particular, most legislation authorizing the licensing of chiropractors provides considerable discretion to the applicable regulatory agency to define the scope of practice. In addition, courts may interpret the standard of care for primary care in a way that would increase or decrease the potential liability exposure for chiropractors who practice primary care. A court may hold a chiropractor to the same standard of care or similar terms that apply to a medical physician, including the principles applied in determining liability (Gilmour et al. 2011b). In Canada, mandated by provincial legislation through enactment of specific chiropractic acts or general health professions/treatment acts, chiropractors must obtain informed consent, written or verbal depending on the jurisdiction, prior to providing care, especially manipulation therapy (Boucher et al. 2016). The courts might also hold chiropractors responsible for performing tasks, such as laboratory tests, traditionally thought to be exclusively a part of primary medical care.

In summary, the legal status may be a restrictive scope of practice, an expansive scope, or a scope that is somewhat ambiguous. For example, California law appears to define the practice of chiropractic very narrowly, seemingly prohibiting the practice of primary care (Deering's California Code Annotated, Business and Professions, Appendix I, Section 7, Chiropractic Act). In Oregon, however, chiropractors have a broad scope, where some forms of primary care (Oregon Revised Statutes Annotated, Vol. 45, Chapter 684.010 and 684.015) such as the practice of obstetrics are permissible. Similarly in Canada, statutes may vary from province to territory because health regulation is a matter of provincial/territorial jurisdiction. So, while all chiropractors in North America have legal status, they vary as to how broad their scope of practice has been defined. However, in all jurisdictions they have the legal right to manipulate the spine and perform diagnosis and to be a primary contact provider. In no jurisdictions is chiropractic restricted by a requirement of referral from the medical professions, as was until recently the case historically with the physical therapy and nursing professions. Both of these professions may now practice as independent, first-contact providers in many jurisdictions.

Insurance Coverage

One of the compelling reasons to recommend chiropractic care in the United States and Canada is the wide coverage of chiropractic care by various types of health insurance. In the recent RAND study in the United States, 68.8% of the patients had some type of health insurance coverage (Herman et al. 2019a). In the United States, chiropractic care is covered by almost all private insurance plans, and chiropractors utilize a majority of the standard diagnostic (ICD-9 and ICD-10) and procedural (CPT) billing codes as other healthcare professionals. Medicare and Medicaid programs as well as most state worker's compensation systems also provide coverage for chiropractic treatment.

Doctors of chiropractic are fully integrated within both the Military Health System and the Veterans Health Administration, caring for patients in healthcare teams, participating in research, training students, and serving in leadership roles (Green et al. 2009). Both active duty

and veterans clinics are staffed by doctors of chiropractic who are hired as federal employees or as contractors, depending on each site's needs and structure.

In Canada, coverage for chiropractic services is provided through provincial and federal public funding, extended healthcare (EHC) plans, or out-of-pocket payments. The amount of and access to provincial public funding has varied by province over the years. Such funding has ranged from complete unlimited funding to limited payment for specific subgroups to no coverage at all. Today, only select provinces provide partial coverage for chiropractic services ranging in British Columbia of a limit of ten visits each calendar year for any allied health treatments, including chiropractic, for those eligible for Medical Services Plan Premium Assistance (seniors and low-income citizens) to Alberta where only seniors have access to a government-sponsored health benefit plan with a maximum yearly amount to Manitoba where all have access to a limited number of visits and costs per calendar year (www.chiropractic.ca/about-chiropractic/chiropractic-coverage/). Accident benefits are also provided to those injured at work and in a motor vehicle collision, but coverage may vary by province and nature of injury. In addition, federal government workers (Royal Canadian Mounted Police, Veterans Affairs Canada, Canadian Forces) have access to funded chiropractic services that is limited by either total annual amount or a set number of visits. First Nations have access to the First Nations Non-Insured Health Benefits which may cover chiropractic services that vary from between regional office and by year (www.chiropractic.ca/about-chiropractic/chiropractic-coverage/).

However, for most chiropractic patients, insurance coverage is most likely provided by an EHC. EHC is a supplementary health and medical plan used to complement provincial health coverage and paid by the patient and/or employer. It is estimated that more than 70% of Canadians have EHC coverage. In Canada, national health expenditures are paid by either public (70%) or private sector spending. Of the 30% private sector spending, out-of-pocket spending accounts for about 15%, EHC plans about 12%, and others about 3% (CIHI 2019). In a recent study of Ontario chiropractors, they reported most patient encounters (68%) were paid out of pocket, with about 31% and 1% paid by EHC or work injury plans (Mior et al. 2019).

What You Need to Know Before Talking to a Chiropractor

Given these compelling reasons for talking to and/or referring your patients to a chiropractor, what is it that a physician might need to know to determine if a given patient is an appropriate candidate for seeing a chiropractor. The first is gaining an appreciation for educational background of chiropractors. What do they study, how much do they study it, and how does it compare to the education of a medical physician and other health professions? Do they study pathology, can they determine if a problem is outside their scope of practice, and do they know how to refer such a patient to the relevant healthcare provider or service? Can they perform differential diagnosis? Do they know what is contraindicated for their care? Can they function as primary contact back specialists? Can they function as gatekeepers for back pain patients to enter the healthcare system?

Secondly what does the research show about the outcomes for chiropractic care, and where can I access it? Are there guidelines that are readily available to assist in making a referral decision? How would I know if something is not appropriate for manipulation? Do chiropractors themselves follow guidelines for practice? What are the quality controls for professional practice in chiropractic? How can I advise my patients about the risk and benefits of chiropractic care to meet my obligations for informing them?

Thirdly, if I send a patient to a chiropractor, how will the case be managed? What are the protocols? How do chiropractors view back pain? What do they offer to patients with spine-related conditions? For acute problems is there some rule of thumb about response rates, the number of visits? How do they decide when to terminate care? For chronic patients is this likely to be

lifetime care? Is there some way of identifying overutilization by the chiropractor? How will this care differ from medical care of back pain? How might surgeons and chiropractors work together? What would be value-added care from using chiropractic?

Education and Training of Chiropractic

In order to be licensed in most jurisdictions, chiropractors must graduate from an accredited teaching institution. Institutions with university status that grant degrees in chiropractic must be accredited by at least two accrediting bodies: a professional or programmatic accreditor and a regional accreditor.

In the United States, programmatic accreditation is awarded through the Council on Chiropractic Education (CCE) (Council on Chiropractic Education 2018). CCE is itself recognized as an accrediting body by the Council for Higher Education Accreditation (CHEA). CHEA recognizes the accrediting bodies for medical education (Liaison Committee for Medical Education) and education of other health professions that have programmatic accreditation (https://www.chea.org/chea-and-usde-recognized-accrediting-organizations). CCE sets the educational standards and outcomes that each college must meet within their respective chiropractic educational curriculum. In chiropractic, these accreditation standards have been rather prescriptive, though there has been a pronounced shift toward demonstration of student competence in recent chiropractic accreditation standards. All American chiropractic programs that desire programmatic accreditation must be reviewed by CCE. Presently, there are 16 doctors of chiropractic programs in 19 locations in the United States accredited by CCE.

(Note: CCE is also a member of the Association of Specialized and Professional Accreditors (ASPA), whose membership also includes LCME, the accrediting body for medical education.) (https://www.aspa-usa.org/our-members/)

In the United States, universities must also undergo regional accreditation by one of six regional accrediting bodies. In California, for example, universities with chiropractic programs are regionally accredited by the Western Association of Schools and Colleges (WASC) and the Western Senior College and University Commission (WSCUC). In Canada, chiropractic programs are accredited by CCE Canada, and in Ontario the Doctor of Chiropractic degree, a second entry baccalaureate honors degree, is offered under the written consent of the Minister of Training, Colleges and Universities (https://www.cmcc.ca/about-cmcc/accreditation).

The net effect of these dual processes is that though the accrediting bodies vary, universities with chiropractic programs in the United States undergo both programmatic and regional accreditation, just as medical programs do for medical education. In countries like Canada, the same process is followed.

To obtain a chiropractic license in the United States, all states require that graduates of accredited chiropractic programs must pass Parts I, II, III, and IV of the National Board of Chiropractic Examiners (NBCE) examinations (http://directory.fclb.org/Statistics/EducationTesting-US.aspx). One state does not require Part III, and most states require a fifth examination in physiotherapy. Part I is taken during the second year of education and focuses on the basic sciences. Part II is taken in the third year of chiropractic education and focuses on diagnosis and chiropractic practice. Part III is taken in the fourth year of chiropractic education and focuses on clinical practice, diagnosis, and management. Part IV is taken in the fifth year of education and is a practical examination. Examinees work with standardized patients and demonstrate examination, diagnosis, and treatment skills and also interpret imaging as part of a radiology examination (https://mynbce.org).

In addition to these NBCE requirements, each state may have additional requirements for licensure, often including successful completion of a state-specific jurisprudence examination. In Canada, candidates seeking registration in individual provinces must first pass examinations offered by the Canadian Chiropractic Education Board (CCEB) (https://www.cceb.ca/home/).

While undergoing training, chiropractic students receive a biomedical education similar to

medical education in many respects. There are some key differences between chiropractic and medical education, particularly in the amount and location of clinical training. A rigorous study comparing the topical content and hours allocated in medical and chiropractic education was published in 1998 (Coulter et al. 1998). That study compared national data for chiropractic and medical curricula and involved site visits and interviews at three chiropractic colleges and three medical schools.

At that time, the basic science programs of medicine and chiropractic were found to be similar, averaging 1,200 h for medical education and 1,420 h for chiropractic education. Chiropractic programs had significantly more anatomy (perhaps not unexpected for practitioners with a neuromuscular and musculoskeletal focus) and physiology instruction. Chiropractors even had more pathology instructional hours than medical education, but this was presumed to be because chiropractic did not have a postgraduate residency program. That is, chiropractors had "lecture learning" in a wide variety of pathologies, where medical education exposes physicians in training to a wider variety of patients and pathologies *clinically*. Medical education also included significantly more training in public health. The type of clinical education varied between the two programs, though the total hours of training were similar when the chiropractic clerkship period (before completing the chiropractic program) is included.

In total, chiropractic and medical education each had curricula of approximately 5,000 h (5,200 for medicine, 4,860 for chiropractic). The most significant difference in the educational programs of the two healthcare disciplines was the medical postgraduate residency. Here, as Coulter et al. (1998) noted, "the difference is drastic, resulting in medical students receiving much more practical clinical education" (p. 73). The other difference was *where* the clinical training occurred – chiropractic's year of clinical training occurred in ambulatory care settings.

Therefore, prior to the postgraduate residency, the education of the two healthcare professions had surprising similarities in 1998 – with the key difference being the presence of the postgraduate residency in medical education. Chiropractic education still resembles dental education (and that of most health professions) in that it does not include a required postgraduate residency. This reflects a funding issue as much as anything else in that residency stipends are rarely available outside of medicine. When osteopathy became recognized in the United States on a par with medicine, it also obtained access to the residencies in medicine. In the United States, the osteopathic academic program mirrors that of medicine. In other countries it more closely mirrors that of chiropractic (Baer 2006).

Since the publication of the 1998 study (Coulter et al. 1998) of chiropractic and medical education, how have things changed? How do chiropractic and medical education compare at present? The Association of American Medical Colleges (AAMC) reported (Association of American Medical Colleges 2019) that the year 1 and year 2 curricula of medical school totaled 1,448.9 h in 2013 (AAMC 2019). The corresponding total was 1,815 in the 1998 study. CCE currently requires that chiropractic programs include a minimum of 4,200 h of education, including the clinical clerkship (CCE 2018). Some states require lengthier programs; for example, California requires 4,400 h (Board of Chiropractic Examiners 2018). In 1998, the total program length of chiropractic programs averaged 4,860 h. Both medical and chiropractic curricula appear to have shortened somewhat since the 1998 study.

The other differences in 1998 between chiropractic and medical education related to the location and amount of postgraduate clinical training. Since 1998, a few chiropractic academic programs have offered limited postgraduate paid residencies in fields such as radiology, sports medicine, primary spine care, and geriatrics. To the authors' knowledge and per recent communication with CCE, none of the above postgraduate residencies have CCE accreditation. However, CCE-accredited residencies have opened on a limited basis within the US Department of Veterans Affairs (VA) (CCE 2017; VA/DoD 2017). Taken together, all of these residencies still impact

a small number of chiropractors. On the other hand, since 1998, residency training in medicine has continued to be a central and distinguishing feature of medical education.

In summary, chiropractic education offers comparable training to medical education *in total hours* prior to graduation. Medical education continues to offer much more extensive postgraduate residency hours with a wider variety of patients and patient care settings. Chiropractic clinical training, which occurs over 1 year, is almost exclusively in ambulatory settings, with limited postgraduate residency positions available.

Medical doctors can be reasonably assured that chiropractic education in the basic sciences (anatomy, physiology, etc.) has been similar in total hours and that chiropractors have had a year of clinical training to prepare them for the historic case mix and case complexity which chiropractors typically see – largely, spine-related disorders and musculoskeletal complaints. Chiropractic programs at universities maintain regional and programmatic accreditation. Chiropractors obtain licensure after passing a series of licensure examinations and meeting other state requirements. Medical doctors and chiropractors still have little opportunity to train together outside of the VA residency programs. These VA residencies offer an excellent opportunity to show what may be possible in further improving chiropractic education and building bridges between chiropractic and medicine.

Overall, the objective of chiropractic education is to prepare the student to become a primary contact health professional, a Doctor of Chiropractic (DC). DCs are capable of diagnosing and deciding what is indicated or contraindicated for chiropractic care, who can manage musculoskeletal conditions within a broad-based wellness paradigm that focuses on the whole person and who knows (and is legally obligated to distinguish) when and how to refer patients to other healthcare providers when necessary.

DCs are licensed healthcare professionals who provide non-pharmacological, conservative care focused on the diagnosis, treatment, co-management, or referral for musculoskeletal conditions (most frequently), including back pain, neck pain, headache, and muscle strains or sprains. Some states and provinces have different scopes of practice, and some chiropractors focus on conditions beyond the musculoskeletal or peripheral nervous system.

The modern DC may or may not manipulate or mobilize joints and soft tissues, employ modalities, supervise and prescribe exercise, and counsel lifestyle changes (sleep hygiene, nutrition, etc.). The primary therapeutic procedure used by DCs is spinal manipulation, and chiropractors perform most of the spinal manipulations rendered annually in the United States. However, chiropractors may use a wide range of therapies and may also contribute to treatment of health problems outside musculoskeletal conditions, though this may often be as adjunctive care.

It is important to note that chiropractors are educated to be doctors and members of a profession. Chiropractic is the name of a profession, not a procedure (Herman and Coulter 2015). While manipulation is the skill for which chiropractors are often best known, it is erroneous to equate the word "chiropractic" with "manipulation." Further, joint manipulation is not a skill that is unique to chiropractors, because at least the professions of physical therapy and osteopathy also include manipulation in their treatment tool boxes. Manipulation and manual therapy skills are also taught in some acupuncture, massage therapy, naturopathy, and other programs. Manipulation is not what makes chiropractic unique.

What does make chiropractic unique? How do chiropractors see it differently?

To answer that question, we need to look at the constellation of elements that make up the chiropractic paradigm, and it is the totality of these that distinguishes chiropractic as a profession.

The Chiropractic Treatment of the Spine

Chiropractic is a system of diagnosis and non-pharmacological therapy focused on the neuromusculoskeletal structures of the human body, particularly the spine and nervous system. The mainstay of chiropractic care is spinal

manipulation and other manual therapies to improve joint motion, in order to relieve pain, improve function, and help the body heal itself. In addition to manual treatment, chiropractic care may also include other treatments such as postural education and therapeutic exercise, as well as the use of adjunctive modalities such as traction, ultrasound, electrical stimulation, and hot/cold packs.

In the early days of chiropractic, subluxations – defined at the time as a misalignment of one or more vertebrae (Wardwell 1992) – were seen as a cause of "disease" as a result of interruption of afferent and efferent neurological signals. This naturally evolved into chiropractors viewing spine-related disorders primarily in a biomechanical and neurological context, with neurological processes being central to the development and perpetuation of these disorders. Emerging evidence largely supports this viewpoint (Seaman and Winterstein 1998; Reichling and Levine 2009; Ischebeck et al. 2017; Panjabi 2003; Garcia-Larrea and Peyron 2013; Henry et al. 2011; Wenngren et al. 2002).

Increasingly, the biopsychosocial model of back pain is being emphasized by chiropractors (Murphy and Hurwitz 2011a, b; Stilwell and Harman 2017) and incorporated into chiropractic training (Murphy 2013, 2016). In this model, chiropractors recognize the important and interrelated roles that biological (somatic, neurophysiological), psychological (fear, catastrophizing, perceived injustice, etc.), and social (socioeconomic status, home life, work disability, etc.) phenomena play in back pain. Given the chiropractic traditions that focus on holism versus reductionism (see below), the biopsychosocial model is a natural fit in the chiropractic approach.

The Perspective

The best way to understand the chiropractic perspective is through the biopsychosocial paradigm prosed by Engel (Engel 1989). Since this is a paradigm widely used in medical education, it provides a perspective for understanding chiropractic in terms that are common to both groups. In this paradigm, health is a complex mix of body, mind, and society. Clearly it is a paradigm that gives attention to cultural, social, and psychological aspects of health and the health encounter. Therefore, the focus is always on the whole patient (holism) rather than a focus on the individual components. Reductionism, which is a hallmark of modern medicine, focuses on the individual components of health: biological systems (such as the cardiovascular system), disease states (such as cancer), and disrupted function (such as a collapsed disk) from either a disordered pathology or trauma. This reductionistic paradigm, which has been very powerful when we are dealing with disease and trauma, differs considerably from how chiropractors view back pain within a holistic paradigm.

Chiropractors do not view diseases as simply disordered pathology (which in the case of back pain there is frequently no identifiable etiology of disease, i.e., non-specific pain) but as dis-ease, a body at lack of ease. The object is to promote normal physiology as opposed to fighting abnormal physiology. For this reason, although chiropractors disagree among themselves about the philosophical basis of their approach, they do tend to subscribe to the belief that the body largely heals itself (*vis mediatrix naturae*), and the role of the chiropractor is to help the body do that. The chiropractor is a facilitator of health, not a giver of health. To that extent they share two maxims of Andrew Still, the founder of osteopathy: "health comes from within or not at all" and "I can no more give you health than I can give you honesty" (Coulter 1999).

This "vitalistic" concept was historically part of medicine but got lost with the emergence of scientific medicine in the nineteenth and twentieth centuries (Reiser 1979). It was present in the ancient Hygieian philosophy, which focused on the person and on the inherent health-maintaining and health-restoring abilities within the person as the source of recovery and health. Many medical commentators have bemoaned the loss of philosophy in modern medicine (Cassell and Siegler 1979; McWhinney 1986; Gordon 1980; Capra 1986; Pellegrino 1979; Cluff 1987).

It is important to understand, therefore, that the chiropractic paradigm sees health somewhat differently from medicine (not just the absence of disease), sees healthcare somewhat differently (helping the body to restore itself), and sees the health provider somewhat differently (as a facilitator and educator not as a curer) (Coulter 2005). Because of these paradigm differences, MDs and DCs practice somewhat differently. No patient mistakes a chiropractic practice as a medical practice. In numerous studies, patients have commented on the differences in experience between MDs and DCs. This is somewhat surprising because they bring the same health problem to both providers and the therapy may not be radically different (there are MDs who manipulate) but the patients report that the health encounter is very different (Coulter 2018).

To see chiropractic as simply a modality – manipulation or mobilization of the spine – is to do a dis-service to chiropractic and may result in those who suffer spinal complaints being underserved. It is manipulation given within a broad-based paradigm. While other professions also perform manipulation, that does not automatically mean they are practicing chiropractic. Chiropractors provide manipulation within what we might term a wellness paradigm (Coulter 1990, 1996a). That is, while the focus might be on back pain, the chiropractor will be exploring a holistic approach and also focus on the lifestyle of their patients. This might include nutrition, diet, weight, exercise, stress, posture, sleeping habits, alcohol consumption, use of drugs, supplements, and therapeutic/rehabilitative exercise. In addition to manipulation, chiropractic care may also involve a range of adjunctive therapy which may include:

> cryotherapy, trigger point therapy, nutritional counseling, and bracing. The majority of practitioners also use massage, heat, traction and electrical muscle stimulation modalities. Acupressure and meridian therapy are used by about 66% of practitioners with less than 10% reporting that they use acupuncture. (Christensen et al. 2015)

An observational RAND study was conducted to determine treatment utilization patterns based on the records of patient in chiropractic offices with low back pain. This study found the following utilization patterns: 84% of the patients received spinal manipulation, 79% received non-thrust manual therapies such as mobilization, massage, and heat packs, 31% received education, and 5% received other forms of therapy such as acupuncture (Coulter et al. 2002). Similar patterns were reported in a recent scoping review, where median and IQR of treatments provided by chiropractors included spinal manipulation (79.3% (55.4–91.3)), soft tissue therapy (35.1% (16.5–52.0)), formal patient education (31.3% (22.6–65.6)), exercise instruction (26.0% (9.0–68.1)), mobilization/traction (17.2% (12.4–32.0)), and to a less extent physical modalities such as supports, electrical stimulation, ultrasound, and acupuncture (Beliveau et al. 2017). The use of these and other modalities is included in the chiropractic scopes of practice in most jurisdictions.

Coulter (2004) has noted that the story one gets about chiropractic from ethnographic studies of the actual encounter shows a quite different picture than what is obtained from health services research using clinical records. Chiropractic is unique in that there are several ethnographic observation studies of the health encounter (Coulter 2004). As he notes, the view from health services research would seem to depict chiropractic care as a narrow-based, sub-speciality dealing overwhelmingly with back pain and chiefly using spinal manipulation. But those who have done the ethnographic observation studies come to slightly different view and conclusion. In this literature (Kelner et al. 1980; Jamison 1994; Coulehan (1995; Coulter et al. 2019), chiropractic is seen as a broad-based, distinct alternative health paradigm, with its own metaphysic, philosophy, language, therapies, and health practices, and as one providing a unique health encounter. Numerous names have been used to describe this paradigm (patient centered, holistic, a wellness paradigm), but it suggests that chiropractic cannot be reduced simply to the manipulation of the spine and other joints. Coulter suggests it is as though the studies are describing two completely different animals.

One of the more interesting studies was published by a medical physician Coulehan

(1995). He concluded that "Chiropractic care, as opposed to spinal adjustment as an isolated treatment, must be viewed as a process or interaction" (Coulehan 1995). He characterized the chiropractor's view as "the faith that heals." That is, chiropractors use explanations that are understandable, that are both mechanical and holistic, that appeal to the patient in that the person is not subtracted from the encounter, and that are positive and drug free. "The net effect is a logical set of beliefs which appeal to common sense, use scientific terminology, yet promote a holistic approach rather than a biomedical approach" (Coulehan 1995). In addition to the laying on of hands, chiropractic care often includes a program of exercise, nutritional counseling, stress management techniques, and behavioral change. Jamison (1993) writes that chiropractic care involves manual, emotional, and psychosocial contact. Chiropractic care is cooperative and focused on the well-being of the patient; uses a low level of technology; is focused on objective, subjective, and effective data; is directed at understanding the whole person; and is personalized (Jamison 1993).

There is an increasing interest in various components of the entire health encounter, with broad consensus that the health encounter is a social encounter that occurs within cultural, social, and individual history (Coulter et al. 2019c). This includes the content of the doctor-patient communication in the encounter (Van Dulmen and Bensing 2002) and interpersonal elements of the encounter (affective communication and instrumental communication), investigating how the patient and the provider perceive the communication (Adams et al. 2012) by using self-reports or analyzing recorded narratives between the provider and the patient (Tarn et al. 2013). Others have studied the cognitive, psychological, and emotional element of the health encounter (Di Blasi et al. 2001).

Last but not least, studies have focused on the belief and expectations of patients and the impact these have on clinical outcomes (Wirth 1995). It is by focusing on the totality of the elements in the health encounter that we can start to distinguish what is different and unique about the chiropractic approach to healthcare. It is not that any one of these elements is unique but the constellation of all the elements as a whole. As Coulter et al. (2019) have shown in their observation of the health encounter in chiropractic, there is nothing non-specific because it is deliberately constructed. The chiropractors and their staff create a style of practice within which the encounters are quite structured and consistent. They found that not only was the nature of the encounter important to the patients; they can delineate and distinguish chiropractic care as distinct from other health encounters, particularly medical encounters.

In summary, there are two views of chiropractic, even within the profession: one view sees chiropractic as back pain specialists, i.e., spine doctors, while the view sees chiropractors as broad-based "wellness" primary care practitioners (Coulter 1983).

The Clinical Encounter

The clinical diagnosis in chiropractic is similar to that used in all health professions, beginning with a patient history and physical examination. Central to the latter will be a neuromusculoskeletal examination (Haldeman et al. 1993). A study of 4,000 randomly chosen chiropractors in the United States, Christensen et al. (2015) found that a case history and physical examination are routinely performed by most chiropractors. One key objective of the diagnostic procedures is to determine whether the problem is contraindicated for chiropractic – requiring a medical referral – or whether it is within the scope of chiropractic and what type of treatment is indicated. Therefore, taking a case history and performing a physical examination are basic elements of chiropractic practice (Cherkin and Mootz 1997). But as noted earlier, chiropractors also pay attention to the psychosocial aspects of their patients. While the patient history will resemble that performed by a medical physician, the chiropractic musculoskeletal examination will be more extensive and comprehensive than that performed in a general medical practice. The reason for this difference is that historically chiropractors were excluded

from the elaborate diagnostic facilities available to MDs; hence they learned to rely more on the history and physical exam findings and less on diagnostic imaging. In this respect, a chiropractor resembles the old-time general practitioner who made house calls where they had to depend on their knowledge of the biological systems, neurological deficits associated with particular diseases, and their palpatory skills, which were all they had to make the diagnosis. Palpation remains a key clinical and low-tech diagnostic skill for chiropractors, where median proportion of use during the assessment is about 90% (Beliveau et al. 2017). While most contemporary chiropractors have access to X-rays, MRIs, CT scans, electromyography, lab tests, etc., they retain the emphasis on physical diagnosis in practice. The sort of physical tests the chiropractor will use may include pain provocation, static palpation, motion palpation, range of motion measurements, observation of postural symmetry, dynamic spinal loading, tissue compliance, gait analysis, muscle strength, and functional capacity (Cherkin and Mootz 1997; Mootz and Coulter 2002; Beliveau et al. 2017).

Another feature of chiropractic care frequently mentioned by patients is their approach to dealing with pain. Kelner et al. (1980) conducted a study of 770 randomly chosen patients, including an ethnographic study of 70 clinics in Canada and interviews of 350 randomly chosen chiropractors. They noted that the majority of patients had tried other types of healthcare for their back problem – usually medicine – before going to the chiropractor. Since their problem was non-specific back pain, they were left without a definitive diagnosis, often with a feeling of rejection with the implied accusation that their problem is all in their head. As noted by Coulehan (1995), the chiropractor not only legitimizes them as a patient; they welcome the opportunity to treat back pain patients. In contrast, the patients reported that in medical encounters their pain was treated almost as a secondary consequence of their being ill.

This has been part of a general cultural belief in western society about being stoic about hardships and pain. There is an assumption that patients are in pain because they are sick. By finding out what is causing the pain and by removing the cause, the assumption is the pain will go away. Alternatively, use drugs to relieve the pain. Patients report that in chiropractic encounters, the pain is not seen as secondary but primary, and the objective of the care immediately, even when the cause is not known definitively, is to target the pain. Having their pain seen as a legitimate focus has a very powerful psychological impact on the patient. This combined with a belief in a positive outcome might be one of the most important predictors of outcomes for chiropractic patients.

The chiropractic clinical encounter may vary for any of the following reasons:

- State or provincial chiropractic statutes
- The philosophical predilection of the individual provider (whether broad-based or focused only on the spine)
- Advanced training the provider may have had in specialized topics such as rehabilitation or sports therapy
- The education the chiropractor had both in chiropractic college and postgraduate education
- The adjunctive therapies/modalities that they might use
- The manipulation system the chiropractor may follow

Manipulation systems are probably the least understood by those outside the chiropractic profession and will be expanded on in the following section. Different systems often have associated with them, specific diagnostic approaches, as in motion palpation or McKenzie technique. The variation in system approach will also include variation in the type of equipment and specialized treatment tables used for the manipulation.

Chiropractic Manual Therapy

Overwhelmingly the main therapy used by chiropractors will be spinal manipulation. In the RAND study (Hurwitz et al. 1998), 84% of patients received manipulation, 79% received non-thrust manual therapies such as joint/soft

tissue mobilization and massage, 31% received education, and 5% received other forms of therapy. In addition, most chiropractors incorporate some type of therapeutic or rehabilitative exercise with spinal manipulation (Christensen et al. 2015; Beliveau et al. 2017; Mior et al. 2019). Manipulation is defined as the use of a manual thrust procedure to move joints into the paraphysiological range, without exceeding the anatomical range of motion. Mobilization involves various grades of manual non-thrust oscillatory movements within the physiological range of motion of a joint. This range of motion is the range a joint can be moved into with the application of external force but not exceeding the anatomical limitation of the joints intrinsic connective tissue (e.g., ligaments, joint capsule, tendons, musculature). In chiropractic, manipulation is generally referred to as an "adjustment." However, for the purpose of this chapter, we prefer to use the term "manipulation," as it is more commonly used in medicine and the other health sciences.

The term "manipulation" does not refer to a single procedure. In fact, there are many different types of chiropractic manipulation techniques that have been developed over the years, although Coulter and Shekelle (2005) in their study of chiropractors in North American identified 14 technique systems used routinely or daily in practice. The National Board of Chiropractic Examiners has conducted practice surveys of the chiropractic profession and found that a similar variety of manipulation techniques were regularly used by chiropractors. The most common types of manipulation utilized routinely by chiropractors include standard thrust spinal manipulation procedures ("diversified"); manipulation/mobilization of extremity joints; the use of specialized treatment tables that introduce axial traction or a drop mechanism during the mobilization ("Cox" or "Thompson"); and handheld devices that deliver a mechanical impulse (aka "activator").

The complexity in applying manipulation techniques can best be delineated by examining the variations technique used with respect to cervical manipulation (Bergmann and Peterson 2011). First, the position of the patient during the manipulation can vary. They can be standing, sitting, or lying on a treatment table, while the chiropractor delivers the manipulation procedure. If lying on a treatment table, the patient can be placed on their back (supine), on their front (prone), or on either side. The position of the chiropractor during the manipulation will also vary. The position used will be determined by the size of the patient, the size of the chiropractor, the location of the area to be manipulated, and the direction/vector of the intended manipulation. Secondly, the contact point of the chiropractor's hand will vary. The manipulation can be performed with the side of the hand, with the heal of the hand, or with crossed hands. Thirdly, the speed, angle, and depth of the manipulation will vary. Chiropractors are experts in controlling the thrust, and what is delivered is a highly specific thrust to a specific part of the joint (Triano et al. 2015). Fourthly, the table being used if the patient is prone may have features that are used in the manipulation such as a drop table. The point is there is a wide variation for any type of manipulation used by individual practitioners (Cherkin and Mootz 1997). The chiropractors can also manipulate other joints such as extremities and use soft tissue therapies. As noted previously, in addition to the manipulation or mobilization, chiropractors may use a variety of ancillary therapies such as mechanotherapy, ultrasound, hydrotherapy, electrical therapies, trigger point therapy, acupressure, acupuncture, massage, heat, ice, traction, muscle stimulation therapy, and vibrators. For example, Christensen et al. (2015) reported that 66% of chiropractic practitioners used acupressure and meridian therapy.

The Coulter-Shekelle study (2005) also documented the daily use of some 23 non-manipulative techniques. The most commonly ranked in terms of use were patient education, exercise (both used by over 80% of the chiropractors on a daily basis), physical therapy, ice therapy, ultrasound, massage therapy, electrical therapy (all over 60%), and traction, orthopedic appliances, nutrition supplements, therapeutic supports (all over 40%) and athletic supports, occupational health, orthotics, and vibratory therapy (all over 20%). Acupuncture was used by 10% of

the chiropractors along with homeopathy. Therefore, chiropractic care should not be considered consisting exclusively of spinal manipulation.

While most chiropractic patients will receive spinal manipulation, the chiropractor will also promote wellness and lifestyle management by counseling. In Christensen's et al. (2015) study, two-thirds of the chiropractors report using nutritional counseling in practice. He reports that the conditions seen by chiropractors mostly fall into the neuromusculoskeletal category but chiropractors also reported such things as obesity, hypertension, and osteoporosis.

In the Kelner et al. (1980) study, the patients reported lifestyle advice that appears simple, but because a lot of it is achievable, the patients find it very useful. This may be as simple as not sleeping on your stomach with a pillow under you face, not driving with a wallet in your rear pocket, and use the correct chair to sit at a computer. Coulter et al. (1996) examined provider and patient reports for 18 preventive behaviors the chiropractor could counsel patients about. Most of the recommendations that the chiropractors report as giving to at least 25% of their patients can be conceived as recommendations closely related to neuromusculoskeletal complaints and involve active remedies (as opposed to bed rest which is recommended for less than 25% of the patients). As might be expected, given that chiropractic is defined as a drugless therapy, the lowest rated recommendation is for medications. Relaxation techniques are also recommended for relatively few patients (37% of the doctors recommend it for more than 25% of the patients), while reducing stress is recommended by 65% of the chiropractors for less than 50% of the patients. Last, but not least, the results for therapeutic supports indicate that the largest category of the chiropractors (43%) recommend them for less than 25% of the patients. Christensen et al. (2015) summarized several early surveys from 2003, 2009, and 2014. The results show 76% used full spine and extremity manipulations and 96% used diversified technique. Virtually all provided health promotion and wellness care. Three quarters used adjunctive procedures such as ice packs, trigger point therapy, braces, electrical stimulation, and two-thirds of hot packs, massage, and heel lifts. Almost all used corrective and spinal rehabilitation exercises, and over 80% included extremity rehabilitative exercises and advice and training for daily living.

What Do Chiropractors Treat?

There is considerable variation in what chiropractors will sometimes claim to treat. But if we confine the claims for those things for which there is either evidence or a reasonable amount of clinical experience to substantiate treating the condition, it would include the following: acute, subacute, and chronic low back pain (Shekelle and Coulter 1997) as well acute neck pain (Coulter et al. 1996; Shekelle and Coulter 1997), chronic low back pain, and neck pain (Coulter et al. 2019a, b). Christensen et al. (2015) reported that joint dysfunction, headaches, degenerative joint disease, muscular strains, spinal disk problems, myofascitis, radiculopathies, spinal curvatures, tendonitis/tenosynovitis, and peripheral neuralgias are often diagnosed and managed in their practices. They also report that patients with tumors, infectious disease, hereditary disease, and other systemic disorders are virtually never or only rarely evaluated and managed in their practices. About two-thirds of diagnoses recorded in chiropractors practices are for musculoskeletal problems (Hurwitz et al. 1998).

A recent large scoping review of the chiropractic profession reported that almost 50% of patients attending for chiropractic did so for low back/back pain, 22.5% for neck pain, 10% for extremity problems, 7.5% for wellness/maintenance, and 5.5% for headaches. Only 3.1% of reported reasons for seeking chiropractic care was for visceral/non-musculoskeletal problems (Beliveau et al. 2017). Therefore, it appears that chiropractors are treating predominantly spine and other musculoskeletal conditions (Christensen et al. 2015).

Who Do They Treat

Much of the medical concern about chiropractic focuses not on what they are treating but on what they *might be* treating outside their scope of

practice. Seldom is this concern based on any data about who constitutes the patient population (Coulter et al. 2002).

Studies of patients using chiropractic care show a prevalence of women (about 60%), whites, those with mid-high levels of income and education with a median age of about 44 years (18–64 years of age primarily (Christensen et al. 2015; Beliveau et al. 2017). Those under 17 years represent 17% of the patients (Christensen et al. 2015) and the over 64, 15%, and with at least partial insurance coverage for care (Coulter and Shekelle 2005; Hurwitz et al. 1998; Mootz et al. 2005). The Coulter-Shekelle study (2005) reported data on 1,275 patients from across the United States and Canada on data collected from three major sources, patient files, practitioner interviews, and patient interviews. The patients were largely white (83%), with an average age of 42 years, predominantly female (61%) and married (57%). The Canadian and US samples were either identical or very similar, but they differed in terms of education. In the American sample, 54% had a degree compared to 38% in Canada, and a further 33% had some college education in the United States compared to 15% in Canada. The patients mostly reported being treated for a back-related problem (76%). When asked to specify their illness or injury, 27% reported it as a neck/cervical problem, 22% as a low back problem, and 21% as a back/spine problem. Extremities accounted for 13% of the health problems. Most had had the symptoms for <3 weeks (45%), but one sizeable group had had them for >6 months (21%). Just over half of the patients (53%) reported having an injury, and the most common reported source for an injury was for nonwork-related events (43%) with work-related accounting for only 16%.

The patients with a back problem (Coulter and Shekelle 2005) were asked to complete a functional self-report questionnaire, the Roland Morris Disability Questionnaire (RMDQ) (Roland and Fairbank 2000). The RMDQ consists of 23 items, and the average score of this sample was 9.7, where a higher value indicates more disability. This sample compares to acute low back pain patients presenting to MDs during the same period, with average RMDQ scores of 10.3 for urban primary care, 12.7 for rural primary care, 11.7 for urban chiropractic, and 9.9 for rural chiropractic (Carey et al. 1995). The patients in this study were asked to complete the Short Form 36 health survey questionnaire (SF 36) to assess their general health status (Jenkinson et al. 1993). The overall results from the SF 36 were compared to age/sex matched norms and to sciatica patients seeing surgeons. Chiropractic patients had values midway between normals and patients with sciatica on physical functioning, role-physical, social functioning, and pain. However for role-emotional, emotional health, and vitality, the chiropractic patients report worse health status than those with sciatica seeking surgery. Compared to the matched norms, the greatest relative difference is for role-limitations physical and pain. The majority of patients (61%) reported that during the last 30 days their pain had been moderate to severe with 33% reporting that the worst bodily pain in the last 30 days was severe to very severe. However, only 8% reported that the pain interfered extremely with their normal work. The majority of patients (58%) reported having no care for the current injury/illness prior to chiropractic. For the majority of these patients, therefore, chiropractors are the primary point of entry for care of these conditions. However, 3% reported having had surgery prior to chiropractic care, 20% reported having medical care other than surgery, and 18% reported having physical therapy. Few patients reported using other forms of "alternative" therapy. They also reported having the current problem for less than 3 months (30%), 6 months to a year (18%), or greater than 1 year (49%).

The mean level of patient satisfaction was quite high (87.4 out of 100). On a scale from 1–10 where 1 represents not confident at all about the treatment and 10 represents very confident, 42% rated the treatment as a 10, and 78% rated it as an 8 or better. Ninety percent would definitely recommend it for their family and friends, and 93% were sure they would return for care.

The results of surveys of acute back pain patients (Herman et al. 2018) show that chiropractic draws the majority of its patients from mainstream healthcare, mostly from medical care. For a majority of patients, the chiropractor is the

primary contact provider for the condition being treated by the chiropractor. The patient clientele is largely white, and based on their education and income, middle class. While the patients report considerable pain from their problems, and some limitations, most appear to remain ambulatory and working. These results suggest that, on average, chiropractic patients with acute back problems are similar to those attending other providers.

With regard to **chronic back problems** in a recent observational study (Herman et al. 2018) of 2,024 current chiropractic patients, the mean age was 48 years, 72% were female, 92% were white, 56% had a professional or bachelor's degree or better, 60% were working full time, 16% were retired, and 68% had some form of insurance coverage. Of those who did the screening questionnaire, 23% had chronic low back pain, 15% had chronic neck pain, and 47% had both conditions. The average amount of time for having pain was 14 years and for seeing a chiropractor was 11 years. They have been seeing their current chiropractor for 5 years on average. The sample is composed chiefly of highly educated, white females, with at least partial insurance coverage for chiropractic and who have been in pain and using chiropractic care for many years. The patients who had both chronic neck and low back pain report more pain and disability for more years and have been seeing a chiropractor for more visits.

The patients reported seeing another health provider before seeing their chiropractor (76%) – usually a primary medical care provider (56%) – followed by massage therapist (41%) and physical therapist (28%). But only 32% see another provider concurrently for their back problem. Only 10% had taken prescription drugs in the last 6 months, but 45% had taken over the counter pain medication, and 24% had taken supplements or herbs. Sixty six percent had used exercise in the last 6 months, but only 5% used psychological counseling. Five percent had taken a narcotic, and 2% had injections in the last 6 months. In this sample of chronic patients, the pain and disability scores were low. The average for the chronic low back pain (CLBP) only group was a numeric pain score of 2.8 (0–10 scale) and an Oswestry score of 19.1 points and for the chronic neck pain (CNP) only group was a pain score of 2.8 and a Neck Disability Index (Vernon and Mior 1991) score of 21.4 points, which were all, as would be expected, closer to previous studies' posttreatment values than baseline values. However this may reflect the fact they have been in continuous chiropractic care for an average of 11 years. Again the satisfaction level for these patients was very high. When asked "how confident are you in recommending chiropractic to a friend," 93% answered extremely or very confident. With regard to the question "how successful do you think chiropractic will be in reducing your pain," 72% said very or extremely successful. This is partly because those with chronic back pain have come to see it as a lifelong condition. They reported that their initial pain scores were very high (8 out of 10) and their motivation for continuing chiropractic is pain avoidance, i.e., to make sure that the pain initial level does not return and they credited regular chiropractic care with making sure it does not occur. Only one-third of the patients endorsed a treatment goal of having their pain go away permanently that is of being cured. The rest had goals of preventing their pain from coming back (22% CLBP, 16% CNP), preventing their pain from getting worse (14% CLBP, 12% CNP), or temporarily relieving their pain (31% CLBP, 41% CNP) (Herman et al. 2019b).

Outcomes of Chiropractic Care

The evidence basis for chiropractic care now includes a wide range of studies including long-term clinical experience, observational studies, randomized clinical trials, meta-analyses, systematic literature reviews, formal expert consensus panels, and government reports and guidelines. The type of outcome measures used also covers the gamut and resembles those used in medicine. Among outcomes assessed in manipulation studies, pain level, physical function, and patient satisfaction have all rated highly. A systematic review by Khorsan et al. (2008) reviewed 629 studies on chiropractic. The most common patient-reported outcomes and instruments

identified were the Oswestry Disability Index, visual analog scale, and Short Form 36. The most common clinician-reported measures were range of motion (i.e., goniometer, lumbar flexion, and inclinometer), motion palpation, and pain threshold (i.e., total tenderness score, tender joint count, current perception threshold, and algometer). Health service measures used included healthcare consumption (i.e., resource utilization and hospitalization), as well as direct and indirect costs. Therefore, while pain is a major outcome measured, it is not the only outcome that is important to either chiropractors or patients.

In clinical trials, chiropractic has been compared to placebo, exercise and advice, no treatment (natural progression), back school, analgesics and NSAIDs, infrared, shortwave diathermy, ultrasound, flexion exercises, massage, electrical stimulation, and various combinations of these comparators, as well as to usual medical care and physical therapy (Mootz and Coulter 2002; Goertz et al. 2018). In a systematic review of manipulation trials published from 2011 to 2017 for adults with low back pain treated in ambulatory settings, Paige et al. (2017) reported that spinal manipulative therapy was associated with modest improvements in pain and function. These studies included measurements of pain (measured by either the 100-mm visual analog scale, 11-point numeric rating scale, or other numeric pain scale), function (measured by the 24-point Roland Morris Disability Questionnaire or Oswestry Disability Index (range, 0–100)), or any harms measured within 6 weeks. No RCT reported any serious adverse event. Minor transient adverse events such as increased pain, muscle stiffness, and headache were reported 50–67% of the time in large case series of patients treated with SMT.

A systematic review was published by Bronfort et al. (2010) which summarized the scientific evidence regarding the effectiveness of manual treatment for the management of a variety of musculoskeletal and non-musculoskeletal conditions. They found 26 categories of conditions containing randomized controlled trial (RCT) evidence for the use of manual therapy: 13 musculoskeletal conditions, 4 types of chronic headache, and 9 non-musculoskeletal conditions. They also identified 49 recent relevant systematic reviews and 16 evidence-based clinical guidelines, plus an additional 46 RCTs not included in the systematic reviews and guidelines.

They concluded that spinal manipulation/mobilization is effective in adults for acute, subacute, and chronic low back pain, migraine and cervicogenic headache, and cervicogenic dizziness; manipulation/mobilization is effective for several extremity joint conditions; and thoracic manipulation/mobilization is effective for acute/subacute neck pain. They found that the evidence was inconclusive for the use of spinal manipulation for the treatment of various non-musculoskeletal conditions in adults and children.

Several other recent systematic reviews of spinal manipulation have all concluded that manipulation produces modest clinical effects that are similar in effectiveness to other recommended therapies for low back pain and neck pain and that serious adverse events are extremely rare. Also, as noted previously, the most current American College of Physicians guideline for the non-pharmacological management of low back pain recommends spinal manipulation as one of the frontline treatments for low back pain (Rubenstein et al. 2019; Masaracchio et al. 2019).

Can the Elderly Benefit from Chiropractic Care?

Older patients make up approximately 15% of chiropractic patient populations (Coulter 1996a). Of patients between 65 and 75 years of age, 14% report using chiropractic services, but that drops off to 6% among those over the age of 75. However, access issues may account for these numbers. There is great regional variation, and one study examining two rural Midwestern communities found that two-thirds of individuals over the age of 65 used chiropractic care (Lavsky-Shulan et al. 1985). That number is increasing substantially among men over 70 years old. Overall, chiropractic utilization by the elderly mirrors that of the general population. Those that do use chiropractic services tend to be in good health,

less likely to use nursing home or hospital services and use fewer prescription drugs, but more over-the-counter medications (Coulter 1996b).

Reliance on clinical experience in the care of elderly patients is the norm within chiropractic, and a great deal of qualitative attention to geriatric care issues can be found in chiropractic training and clinical literature (Killinger 2004; McCarthy 1996). Manipulation techniques are frequently modified to suit the exigencies and tolerances of patients, and specific considerations have been reported in chiropractic literature (Bergmann 1993). Age-appropriate modifications to chiropractic evaluation protocols may also be warranted and have been described as well. Chiropractors also report providing an eclectic host of interventions beyond manipulation for elderly patients including exercise, nutrition, relaxation, and physical therapy (Rupert 2000).

The number of older adults in the United States is increasing yearly, with projections that 20% of the US population will be 65 years of age or older by 2030. Considering the high prevalence of spinal pain and other degenerative musculoskeletal conditions in older adults, chiropractic care should be considered as an option for older adults. Offering nonsurgical, non-pharmacological treatment options to older adults is important, due to the risks associated with opioid medications in this population. It is also important to recognize that chiropractors may incorporate multiple types of manual techniques with older patients. These techniques will be tailored to the individual needs of the patient, with the application of varying levels of biomechanical force and amplitude. Chiropractors also incorporate posture education, health promotion, and therapeutic exercises into multimodal treatment strategies with older adults.

Recently, two large clinical trials were published that involved chiropractic spinal manipulation and exercises provided to older adults with lumbar spinal stenosis (Schneider et al. 2019; Ammendolia et al. 2018). In both of these trials, patients had significant improvements in their walking performance (neurogenic claudication symptoms). Also, it is important to note that no serious adverse events were reported in either trial, which provides evidence that these procedures are relatively safe for use in the older adult population. Dougherty et al. have reported on the safety of SMT in the older adult population, specifically in osteoporosis, anticoagulation therapy, and spinal stenosis. These data are from two randomized controlled trials and also from retrospective data from a chiropractic clinic in a long-term care facility (Dougherty and Killinger 2005; Dougherty et al. 2009).

Therefore, spine surgeons should consider a trial of chiropractic care for patients with mild to moderate levels lumbar spinal stenosis as a reasonable treatment and "screening strategy" before considering decompressive surgery. Failure to respond favorably to chiropractic care would suggest that the patient was more likely to be a proper candidate for surgical decompression.

Hawk et al. (2017) published a systematic review and best practices guideline for chiropractic care of older adults. This document provides a summary of evidence-informed best practices for doctors of chiropractic for the evaluation, management, and manual treatment of older adult patients. This document also provides additional guidance on the importance of tailored approaches to the evaluation of the older adult, specifically in the areas of cognitive impairment and preventive screening. This best practice guideline is an excellent resource for spine surgeons who would like to review an "executive summary" of the literature on the topic of chiropractic care for older adults.

How Does One Find a Good Chiropractor?

The simplest answer is "the same way you find any good doctor." Like any other healthcare practitioner, the expertise, personality, practice style, and availability can all factor into deciding how to find a chiropractor. Different patients may have their own needs and preferences that impact how effective and worthwhile one practitioner might be compared to another. For patients, recommendations of friends or family members are often

the most ready source of information. Internal medicine specialists make up one of the more common interdisciplinary referral sources reported by chiropractors (Christensen et al. 2015). Therefore, asking internists or family practitioners for recommendations may be a good starting place (Curtis and Bove 1992).

Obtaining a list of practitioners in your community from a state licensing board is also a starting point. One can inquire if any chiropractors on the list have had complaints or disciplinary actions upheld against them. In general, when looking to establish an inter-referral relationship, it may be worthwhile to meet with and interview a number of chiropractors to get a sense of their educational background and practice style. Asking questions like "how do you determine how much care someone needs?" and "how do you work and communicate with other providers?" can give insight into clinical styles and preferences that can be compared with your own. Will the chiropractor provide written reports and updates of findings, recommendations, and progress? Additionally, asking a chiropractor about what they do when patient progress is slower than expected and what they do to cultivate a patient's own self-reliance may be important to know.

Last, but not least, the extent to which the chiropractor takes care of his/her own health might be an important consideration. Since much of chiropractic care is about increasing the patient's knowledge and behavior modification for self-care and prevention, it seems reasonable to expect the chiropractor to live by the same standards. If the chiropractor's knowledge does not lead to appropriate healthy behaviors for the chiropractor, it seems difficult to believe it will do so for the patient.

Conclusion

We have attempted to show that there is considerable benefit to back pain patients by visiting chiropractors. For back surgeons, and medical physicians generally, chiropractors offer an alternative form of noninvasive, conservative care that does not involve drugs nor opioids. Increasingly this is the recommendation as a first-line option in spine care guidelines. It would also constitute an evidence-based informed choice with regard to spinal care. One overwhelming reason for referring to chiropractors is the fact the patients are not going to be prescribed drugs. This removes the danger of interactive effects (especially important for the elderly), drug addiction, and overdosing (especially important for pain patients).

For non-musculoskeletal problems, the jury is still very much out for two possible reasons. The first reason is that manipulation may have little or no efficacy/effectiveness with such conditions or that the body of research in this area is currently too sparse to come to any conclusion. While impotence and abstinence may have the same clinical outcome – the failure to reproduce – they have very different causes. The best we can say here is that for non-musculoskeletal problems, there are anecdotal reports from patients about the effectiveness of chiropractic care and a body of anecdotal claims made by chiropractors. Since chiropractic patients tend to be well educated and since people do not usually pay for services that are of no value to them, retaining an open mind here may be the best option. However, it is unacceptable for chiropractors to make health claims about conditions for which they have no evidence.

In conclusion, we have discussed in this chapter the limitations of viewing chiropractic care as simply a modality – i.e., manipulation – which misses the contribution that chiropractors make to the overall wellness of patients. In the case of chiropractors, we now have a substantial body of evidence from Health Services Research on the effectiveness of chiropractic care and a substantial body of trial evidence about its efficacy and safety. Chiropractors are also rather unique among the CAM professions by being extensively studied by the use of ethnographic observation so that the health encounter has been well documented. We can close by quoting three such studies: one from the Faculty of Medicine, University of Toronto, by three sociologists, the second by

a medical epidemiologist, and the third by an anthropologist.

Kelner, Hall, and Coulter (1980) state:

> It offers intelligible care; the chiropractors try to provide their patients with an understanding of their injury or illness, using a language which patients can comprehend. They explain the plan of treatment, the progress of the case, and the relation of their illness to environmental conditions. Finally, they try to make patients aware of their personal role and responsibility in the maintenance of their health. Chiropractic is co-operative care-patients participate as partners in the treatment and enhancing of their own health. (p. 260)

Coulehan (1995) concludes:

> Physicians can learn from the success of the clinical art in chiropractic. This art begins with "the faith that heals", and it involves an interaction that may well function as a positive feedback system to promote healing. By healing, I mean a satisfactory outcome for the patient: relief of pain, diminished anxiety, acceptance of one's lot in life, less disability, a positive mental attitude. (p. 389)

Finally Oths and Hinojosa (2004) makes the following conclusion:

> Given chiropractic's unified theory of disease etiology, which provides a rational interpretation of a patient's problem and an unambiguous method for treating it, the practitioner and the patient can reach a common level of understanding. The end result is most often a patient highly satisfied with the care received. From the observations made in this study, one might be inclined to agree with Kleinman et al. that the chiropractor is "more interested and skilled in handling illness problems than the M.D."

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Chiropractors See It Differently: A Surgeon's Observations

4

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Contents

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Abstract

The practice of physical manipulation and manual therapies as treatment options for low back pain and other spinal problems has been prevalent for thousands of years. Manual therapies in the Western world are often offered by chiropractors as part of alternative medicine. Modern and mainstream health care community has greatly benefited from chiropractic practice, especially in alleviating spinal pain and related injuries. Although chiropractic practice has remained consistent over the years, it has gradually transitioned from craft to profession. However, the profession continues to encounter numerous internal and external challenges that have threatened to curtail its aim of becoming a fully-accepted practice in the mainstream health care industry.

This chapter, researched and written by a spine surgeon, is aimed at providing insight into the role of chiropractors in promoting population health by offering interventions for low back pain. The chapter is based on a wide range of literature on the positive contribution of chiropractors in the promotion of patients' well-being. The author discusses the similarities and differences between chiropractors and other health care professionals in terms of education, training, work philosophy, and treatment mechanisms. Much of the focus on this chapter will be on the extent to which chiropractors view their profession as complementary to rather than contrary to mainstream health care community.

A clear understanding about chiropractic is important because it will see the profession gain full legitimacy in the allied health field. Most importantly, the chapter will help in bridging the conceptual gap that exists between chiropractors and other health care providers. Most importantly, policy makers and the general public will change their skepticism with regards to the crucial profession of chiropractic and begin embracing the concepts of traditional and alternative medicine to improve public health.

Keywords

Chiropractic · Healthcare · Legitimacy · Profession · Mainstream · Medical practice

Introduction

The title of this chapter "Chiropractors see it differently," a priori creates limits and expectations on the perspective of the writer, and a belief that traditional medicine and chiropractic are fundamentally different, with different origins, different beliefs, and different treatment philosophies.

To "see it differently" implies having a different perspective on "it." In order to further elaborate on this statement, we must first define what "it" is, and secondly we must consider what shapes one's views or perspectives. "It" may simply refer to axial low back pain alone, or "It" can encompass as broad a view as illness and disease in general and would thus require that we consider the chiropractic "vitalistic theory" in comparison to "traditional" medicine.

This chapter is probably unlike most others in this book. It has been researched and written by a spine surgeon, attempting to provide an unbiased view of a somewhat unfamiliar topic, in a form

that can be digested by surgeon and nonsurgeon readers alike.

The practice of chiropractic is concerned with the diagnosis, treatment, and prevention of mechanical disorders of the musculoskeletal system. It primarily focuses on the effects of spinal disorders on the normal functioning of the nervous system and the general health of humans. The primary emphasis of chiropractors is on manual treatment, which includes manipulation and adjustment of the spinal column. By restoring the normal function of the musculoskeletal system, chiropractor professionals play a significant role in relieving pain and discomfort arising from accidents, stress, illness, or daily wear and tear that humans are bound to experience. Essentially, chiropractors adopt a holistic approach to health because they tend to evaluate the human body in terms of aspects such as medical history, experience, mental state, hobbies, occupation, and sporting activities. Various forces and pressure that affect the human body are taken into consideration when restoring the normal function of the musculoskeletal system. In broad terms, the goal of chiropractic treatment is to restore the function of the body and assist humans in eradicating the cycle of noxious stimulus, thus promoting self-healing mechanism.

Over the years, chiropractic has sharply divided opinion among health care practitioners from the mainstream medical community as well as the general public. While chiropractors have made positive contribution in the field of medicine, there has been a general reluctance by mainstream medical practitioners to perceive them as bona fide healthcare professionals. Many people are of the opinion that chiropractors do not qualify to be doctors because they do not hold medical degrees. However, they do possess extensive training in chiropractic care, making them licensed practitioners in administering crucial healthcare services.

Numerous intersections do exist between chiropractors and other medical professionals. First, chiropractors, like medical doctors, primarily rely on the medical history of the patient to determine the best approach to therapy. Second, they follow a systematic treatment plan, which is also a common approach among mainstream medical practitioners. Third, they hold practicing licenses, making them bona fide providers of health care services. However, a notable distinction between chiropractors and doctors from the mainstream medical community is the fact that they do not prescribe drugs, perform surgeries, or cure the underlying pathology.

To put the central premise of this chapter in context, and particularly when comparing to the outcomes of "traditional" medical management of low back pain, the following facts must be considered carefully:

1. Musculoskeletal pain, led by spinal disorders, costs the US health care system $874 billion per year and is the most common cause of severe long-term pain and disability (United States Bone and Joint Initiative 2014).
2. Research has found that prescription opioid pain medications are ineffective in the treatment of chronic low back (spinal) pain (Bone and Joint Decade 1998)
3. Chiropractic care offers a nondrug approach to spinal pain and other musculoskeletal conditions that is effective, saves money, and may help some patients avoid the risks of addiction associated with opioid use (Elton 2014).
4. In 2015, two million Americans had a substance use disorder involving prescription pain relievers with 20,101 overdose deaths related to prescription pain relievers (Abdel Shaheed et al. 2016).
5. From 1999 to 2008, overdose death rates and substance use rates quadrupled in parallel to sales of prescription pain relievers (The Center for Behavioral Health Statistics and Quality 2016).
6. The American College of Physicians Clinical Practice Guideline on Low Back Pain recommends the use of nondrug, noninvasive treatments – including spinal manipulation – before moving on to over-the-counter and prescription pain medications (Paulozzi et al. 2011).
7. Among patients with acute low back pain, spinal manipulative therapy was associated

with modest improvements in pain and function at up to 6 weeks with transient minor musculoskeletal harms (Qaseem et al. 2017).

8. Evidence suggests that therapies involving manual therapy and exercise are more effective than alternative strategies for patients with neck pain (Paige et al. 2017).
9. Patients with chronic low back pain treated by chiropractors showed greater improvement and satisfaction at one month than patients treated by family physicians. Satisfaction scores were higher for chiropractic patients. A higher proportion of chiropractic patients (56% vs. 13%) reported that their low back pain was better or much better, whereas nearly one-third of medical patients reported their low back pain was worse or much worse (Hurwitz et al. 2008).
10. It is unlikely that chiropractic care is a significant cause of injury in older adults. Among Medicare beneficiaries aged 66–99 with an office visit risk for a neuromusculoskeletal problem, risk of injury to the head, neck, or trunk within 7 days was 76% lower among subjects with a chiropractic office visit as compared to those who saw a primary care physician (Nyiendo et al. 2000).
11. In one study, the rate of opioid use was lower for recipients of chiropractic services (19%) as compared to nonrecipients (35%). The likelihood of filling a prescription for opioids was also 55% lower in the chiropractic recipient cohort. The average annual per-person charges for opioid prescription fills were 78% lower for recipients of chiropractic services as compared to nonrecipients (Whedon et al. 2015).
12. In addition, average per person charges for clinical services for low back pain were significantly lower for recipients of chiropractic services, $1,513 for chiropractic management vs. $6,766 for medical management (Whedon 2017).
13. Healthcare plans that formally incorporate chiropractic typically realize a 2 to 1 return for every dollar spent (Feldman 2014).
14. Following work-related low back injury, patients who visited a chiropractor were nearly 30 times less likely (1.5 vs. 42.7%) to require surgery as compared to those who chose a surgeon as their first provider (Keeney et al. 2013).
15. Paid costs for episodes of care initiated with a DC were almost 40% less than episodes initiated with an MD. Even after risk adjusting each patient's costs, we found that episodes of care initiated with a DC are 20% less expensive than episodes initiated with an MD (Liliedahl et al. 2010).
16. For Medicare patients with back and/or neck pain, availability of chiropractic care reduces the number of primary care physician visits, resulting in an annual savings of $83.5 million (Davis et al. 2015).

Background of Chiropractic

Manual therapies have been in existence for many centuries. Many cultural communities had practitioners whose primary role was to administer manual therapies to ease musculoskeletal discomforts and pains (Coulter et al. 1998). For example, the "bone setters" of England and Kung Fu masters in Asia are some of the examples of early chiropractic profession in the twentieth century. In the late twentieth century, the Western world saw a rapid emergence of osteopaths, chiropractors, and physiotherapists, thus changing the entire complexion of the manual therapies. From a traditional perspective, manual therapies were transferred from one generation to the other by parents. Fathers and mothers transferred their knowledge to their children, a practice that is still prevalent in some cultures.

The profession of formal chiropractic is around 120 years old, and it has transitioned from a full alternative medicine concept to become part of complementary health care. In fact, chiropractic is considered an integral part of primary care in some jurisdictions. Some scholars have argued that chiropractic includes elements that are consistent with religion and faith healing (Young 2014). Such views make the practice to assume a broader perspective than conventional health care systems. Regardless, it can be argued that the

history of chiropractic and its overall contribution to the health well-being of humans has been checkered by the "good" and by the "bad." From the "good" perspective, the practice has directly contributed to over a century of improvement of public health. Consequently, many people have benefitted from the practice in terms of reduction of suffering caused by low back pain and related disability.

Currently, many countries have streamlined registration and licensing of chiropractors by introducing educational programs aimed at promoting the physical health of populations. The emergence of private colleges and universities is a clear indication that policymakers consider chiropractic as a veritable healthcare alternative. However, there still exists limited private health funding for patient consultations, minimal funding for patients, and little hospital access. The profession graduates competent manual therapists who have excelled in their respective fields and demonstrated their ability to be responsible citizens. However, there have been cases of aberrance, especially when chiropractors have extended their therapies to nonmusculoskeletal areas like ear infections or strabismus. This unwarranted expansion has caused damage not only to the health profession but also to the community at large.

Various scholars have questioned the justification to consider chiropractors as equal and worthy partners in the mainstream health care society. One of the overriding questions has been the ability of chiropractors to command a respect from other practitioners in the health sector, policy makers, and patients. Moreover, there is also the issue of accepting chiropractic professionals as legitimate partners in the national health care industry. To achieve legitimacy in the mainstream health sector, the chiropractors face two critical choices. Practitioners can maintain the status quo and uphold the current practice of "being different" from their counterparts in the mainstream medical profession. Alternatively, they can create a vision in which they endow chiropractors with attributes that make them fit in the mainstream health care community. To advance the chiropract profession globally and achieve the vision of integrating itself fully with the mainstream health industry, it is crucial for stakeholders to consider common grounds between chiropractors and their counterparts, especially in the medical field.

Unlike practitioners in the mainstream medical community, Chiropractic medicine believe that most health problems arise from disturbances in the body's nervous systems. These disturbances, in turn, originate from misalignments or subluxations of the spine. Chiropractic manipulations are aimed at realigning the spinal system and restoring normal function to the nervous system in a self-healing mechanism. The manipulation commonly encompasses a quick thrust of the specific subluxated vertebrae or application of physical pressure, traction, and stretching of the soft tissue attached to the body skeleton (Coulter 1997). Professionals who typically administer the traditional chiropractic medicine and focus entirely on spinal adjustment are referred to as "straights." These professionals have stoked a great deal of controversy, especially among the mainstream medical community because of their unorthodox approach to restoring human health. The main contention is that chiropractors do not belong to the conventional medical realm and thus, should not be considered as bona fide medical practitioners.

Most doctors of chiropractic typically follow traditional approaches when treating their patients. Some of the traditional elements of chiropractic intervention include nutrition and vitamin therapy. These practitioners are referred to as "mixers" because they are inconsistent to the modern medicine practices such as surgery and prescription of drugs. Still, another branch of chiropractic considers the entire musculoskeletal system as a critical determinant of human health. This branch focuses on treating joints and manipulating spinal components. Traditionally, chiropractors have defended their practices against criticism from the medical community and argued that their work is grounded on structural problems. Other than treating lower back pain, some chiropractors intervene in a wide variety of medical problems such as arthritis, asthma, chronic fatigue syndrome, bursitis, headaches, carpal syndrome, menstrual problems, traumatic injuries,

and chronic pain syndrome. Chiropractic remains best known for treating lower back pain.

The distinguishing features of chiropractic's professional identity (WFC 2005) have been described as follows:

(a) Ability to improve function in the neuromusculoskeletal system and overall health and quality of life
(b) Specialized approach to examination, diagnosis, and treatment based on the best available research and clinical evidence and with particular evidence on the relationship between the spine and the nervous system
(c) Tradition of effectiveness and patient satisfaction
(d) Without use of drugs and surgery, enabling patients to avoid these where possible
(e) Expertly qualified providers of spinal adjustment, manipulation and other manual treatments, exercise instruction, and patient education
(f) Collaboration with other health professionals
(g) A patient-centered and biopsychosocial approach, emphasizing the mind-body relationship in health, the self-healing powers of the individual, individual responsibility for health, and encouraging patient independence

In proposing a model for chiropractic as a profession of spine care, Nelson offered a coherent and comprehensive model of professional identity (Nelson et al. 2005). He and his co-authors argue that chiropractic's identity is as a provider of spine care. They argued that such a model is consistent with the best available scientific evidence, is consistent with the current public perception, provides benefit to both the profession and the public, and is capable of gaining for the profession the cultural authority it now lacks. In developing the model, they established a set of criteria that the model must meet:

1. It must be consistent with accepted modes of scientific reasoning and knowledge.
2. It must accommodate future changes in scientific understanding.
3. It must represent a set of clinical competencies within the reach of practicing chiropractors.
4. It must be consistent, credible, and communicable to external constituencies on whom the profession relies.
5. It must represent the evidence of practice experience.
6. It must find a substantial presence within the healthcare marketplace.
7. It must be compatible with the training, licensure, history, and heritage of chiropractic.

Chiropractic Education

Many people are often surprised to discover that the education that chiropractors receive in college is quite similar to that of other medical students. Students attending chiropractic college are required to complete a minimum of 3 years of college-level courses before enrolling in the professional program. In addition, they are expected to complete a doctor of chiropractic degree program, which requires between 4 and 5 years of professional coursework. Researchers have further established that the education of a chiropractor is like that of a medical student to the extent of total classroom hours (Coulter 1997). The following table represents a comparison of the overall curriculum structure of chiropractic schools and medical schools in Kansas City (Table 1).

Typically, chiropractors receive more training in anatomy and physiology than physicians, with many chiropractic colleges focusing on therapeutic principles, diagnosis, orthopedics, and nutrition (Coulter et al. 1998). Three key areas, namely, manipulative/spinal analysis, physical diagnosis, and diagnosis imaging account for more than 50% of the education in clinical sciences (Coulter et al. 1998). Chiropractic interns need to complete 2 years of hands-on clinical experience primarily focusing on manipulation/adjustment as the primary treatment procedure. Researchers have established that chiropractic professionals receive more training in the fields of anatomy, physiology, bacteriology, diagnosis, X-ray, and orthopedics than their medical

Table 1 Comparison of class hours between chiropractic and medical students. (Source: Coulter et al. 1998)

	Chiropractic schools		Medical schools	
Characteristic	Average	Percentage	Average	Percentage
Contact hours	4,826	100	4,667	100
Basic science hours	1,420	29	1,200	26
Clinical science hours	3,406	71	3,467	76
Chiropractic science hours	1,975	41	N/A	N/A
Clerkshp	1,405	29	3,467	76

counterparts (Coulter 1997). Chiropractic institutions typically devote more time teaching students the basics of clinical sciences.

As a healthcare service, chiropractic offers a conservative management approach and does not necessarily require auxiliary staff. It represents a low-cost way of providing important health care services to patients. The World Health Organization encourages and supports countries in the proper use of safe medication and as a result the need to develop guidelines on chiropractic education and safe practice has steadily gained prominence around the world. Regulations for chiropractic practices vary considerably from country to country. In the USA, Canada, and some European countries, chiropractic has been given legal recognition and is being offered as university programs. In these countries, the chiropractic profession is regulated and the prescribed educational qualifications follow the requirements of the respective accrediting agencies. The emphasis on formalizing chiropractic practice in many Western countries is indicative of the fact that the profession possesses the same medical significance as other health care providers such as nurses, doctors, and surgeons.

At the same time, many countries have not yet established a chiropractic educational frameworks or laws to regulate the qualified presence of the profession. Some countries allow qualified health professionals and untrained medical practitioners to use the same techniques of spinal manipulation and claim to provide chiropractic services to patients. However, it is important to note that such physicians rarely receive chiropractic training in accredited programs. It is evident that many countries still regard chiropractic practice as a viable alternative to mainstream medicine for treating spinal injuries.

With the rapid growth in the demand for chiropractic services, health care practitioners may wish to acquire additional chiropractic qualifications. This has led n governments and policy makers to focus on the role of chiropractic practitioners in promoting health care. Many countries have developed conversion programs to enable persons with background in medical training to acquire supplementary education and skills to become chiropractors. Such conversion programs must be flexible. In countries that lack legislation, there may be no educational, professional, or legal framework governing chiropractic practice. The implementation of educational programs relating chiropractic profession depends on the situation in each country.

Although spinal manipulation dates back several thousand years ago, researchers have attributed the foundation of chiropractic to D.D. Palmer in 1895 (Palmer 1967). In 1897, the first school for the training of chiropractors became operation in Davenport, Iowa. Palmer developed the chiropractic theory from several concepts, including medical manipulation, bone setting, and osteopathy. The term "chiropractic" from the Greek and means "done by hand." It was coined by a patient named Reverend Samuel H. Weed and subsequently adopted by Palmer (1967). Chiropractic education initially developed in the USA during a period of significant reformation in the medical field. During this time, people had multiple treatment options not only within conventional medicine but also traditional and alternative health care approaches.

The principles that distinguish and differentiate chiropractic from conventional medical practice have been studied by scholars in the health care field. The different approach to education

between the two fields has influenced chiropractic attitudes. Many professionals from within the profession have maintained principles that include but are not limited to holism, vitalism, naturalism, conservatism, critical rationalism, ethics, and humanism (Coulter 1997). The relationship between structure, especially the spine and musculoskeletal system, and the restoration and preservation of human health is central to the chiropractic approach. Unlike the mainstream medical field, chiropractic focuses on the conservative management of the neuromusculoskeletal system without the need to perform surgery or injections. Biopsychosocial causes and consequences of poor health are also significant factors in the management of patients. When in the best interest of the patient, chiropractic education system emphasizes on the importance of referring to the mainstream health care providers. Medical professionals rarely find the need to refer their patients to chiropractors.

Chiropractic education must involve administrative and academic considerations, including who should be trained, the role and responsibilities of practitioners, the required level of education, the accredited institutions, and the availability of qualified educators. Most countries use national, regional, state, or provincial standards while some authorities delegate to national professional.

The government may wish to evaluate both positive and negative consequences of integrating chiropractic into the mainstream. Many countries have recognized the need to establish "limited" programs as interim measures to establishing full chiropractic educational courses. This approach is deigned to supplement exiting health care education systems rather than replace them. An increased focus on chiropractic indicates that policy makers are recognizing the profession as a viable alternative medicine for promoting the physical wellbeing of citizens. In many countries, chiropractic practitioners who lack formal training are often encouraged to upgrade their education to match the level of their medical counterparts allowing easier integration into the professional workforce.

Chiropractic Profession at a Crossroad with Mainstream Medicine

Chiropractic is an expansive and well-established health care profession in many Western countries, including the United States. The profession is the largest, most regulated, and best recognized practice outside of the mainstream medicine. Research has established that patients seeking alternative health care show great satisfaction with the practice (Coulter et al. 1998). During the past two decades, there has been a drastic change in how medical professionals and learning institution view chiropractic. This change in attitude towards the profession has been partly due to chiropractic's change in its approach to education and treatment.

One point of contention between chiropractic and mainstream medicine is that the former follows a drastically different scientific approach. Chiropractic is an evolving health profession. As envisioned by its originators, the profession is a revolutionary system of healing based on the notion that most of human's suffering and physical discomforts arise from the central nervous system disrupting the healthy expression of life.

From the many schools that were established during the early twentieth century, a stable number of chiropractic training institutions have emerged in many countries around the world. Chiropractic education in the United States, South Africa, Denmark, Canada, and Great Britain is provided in both government-sponsored and private learning institutions and many chiropractic colleges are now accredited by the relevant authorities. For the example, Council of Chiropractic Education is the regulatory agency charged with the responsibility of overseeing all training in the United States (Coulter et al. 1998). In contrast, the mainstream medical practice is regulated by the numerous federal and state laws throughout the country. Each chiropractic college currently requires a minimum of 60 units of prescribed college-level courses – (Coulter 1997). A specialization in the sciences is one prerequisite for enrolling in a chiropractic school.

By the early twenty-first century, chiropractic curricula had an average of 4,820 classroom and clinical hours, with students spending about 30% of these hours in basic science. The rest of the time was spent on clinical work and internships (Coulter et al. 1998). Medical students averaged 4,670 h, with a similar breakdown of subjects. Compared with medical students, chiropractic learners spend more hours focusing on human anatomy and physiology but fewer time on public health (Coulter et al. 1998). They do, however, spend about the same amount of time on important fields such as bio-chemistry, microbiology, and pathology. According to Coulter et al. (1998), chiropractic curricula entails fewer instructions than medical courses in terms of pharmacology, critical/emergency care, and surgery. However, there is a greater emphasis in biomechanics, musculoskeletal function, and manual methods of treatment.

A review of the American medical curriculum indicates that medical students spent more than twice as many hours in clinical experience, but 1,000 fewer hours in didactic and practical clinical courses (Coulter et al. 1998). All chiropractic educational institutions run busy practical clinics to ensure that learners receive training in a chiropractic environment. Specialty programs are available and include 2–3 years' postgraduate residency programs in areas such as radiology, orthopedics, neurology, sports, rehabilitation, and pediatrics. Most states recognize or require students to pass examinations administered by the National Board of Chiropractic Examiners in basic and clinical sciences.

Characteristics of Chiropractic Health Care and Practice

Chiropractic practice has evolved over the years but retains a distinct set of values, traditions, and curricula composition. Modern chiropractic theory has moved away from the original practices envisioned by DD Palmer. Chiropractic practitioners use a novel system of healing based on the premise that neurologic dysfunctions caused by "impinged" nerves at the spinal level is the cause of many human diseases (Coulter et al. 1998). A key belief is that spinal manipulation and adjustment removes the blockage to restore health. Much modern chiropractic theory and practice has moved away from the original mono-causal theory in which practitioners focused on the causes rather than consequences of musculoskeletal injuries. Research is gradually redefining the nature and discipline of chiropractic and its education.

Many observers still associate the practice of chiropractic solely with the practice of spinal manipulation. This is only partly accurate. The modern concept of "complementary and alternative medicine" (CAM) has provided a new meaning and scope to chiropractic practice and many practitioners do not want to be defined by spinal manipulation. Chiropractors perform many of the duties of other primary care providers and often described themselves that way. However, many professionals in health care perceive chiropractic as a profession with limited medical competence, akin to dentistry or podiatry. This is an ongoing debate.

Spinal Manipulation Aspect of Chiropractic

Most chiropractors accept that spinal manipulation is a key element of their practice. Many prefer the term "spinal adjustment" to reflect their belief in the therapeutic and health-enhancing effects of adjusting abnormalities associated with spinal column. There are numerous adjustment techniques but no agreement on the most appropriate or efficacious. Spinal manipulation is the application of a physical force to specific body tissues with therapeutic intent. Traditionally chiropractors applied the external force using their hands, with varying velocity, duration, frequency, and amplitude. Traditional medical practitioners relied on medication, advice, and occasionally surgery to treat spinal problems.

Spinal manipulation is associated with chiropractors, who perform over 90% of the procedures

(Johnson et al. 2012). Additional treatments include heat, cold, TNS, interferential therapy, and active rehabilitation (Johnson et al. 2012). Most chiropractors suggest therapeutic exercises and general physical fitness and combine this with nutritional advice and counseling on weight loss, cessation of smoking, and relaxation techniques (Johnson et al. 2012). Chiropractors also employ massage, acupuncture (and its variants) along with mineral and herb supplements to ease back pain.

Research suggests that for musculoskeletal problems, many patients prefer going to chiropractors than to their family physician with 60% seeking treatment for lower back pain and the remainder for head, neck, and extremity symptoms (Johnson et al. 2012). About 30% of all patients seeking professional intervention for pain in their back consult chiropractors in a primary health care setting. About half of these patients have a chronic musculoskeletal complaint. Studies further indicate that only a very small number of patients – between 2% and 5% – seek care for other conditions (Johnson et al. 2012). A few people visit chiropractors for general health problems, disease prevention, and health advice.

Diagnosis and Assessment Methods in Chiropractic

Chiropractors use a patient-focused diagnostic approach to determine the cause of a problem similar to other health care disciplines. The history, physical examination, and specialty-specific assessments are used by both chiropractors and physicians (Johnson et al. 2012). The Council on Chiropractic Education has specified that institutions must teach basic clinical competencies and that chiropractors are expected to differentiate mechanical musculoskeletal problems from visceral abnormalities. Chiropractic practice guidelines deem obtaining a history, performing a physical examination, and carrying out periodic reassessments are necessary attributes of good practice.

The National Board of Chiropractic Examiners have proposed a framework describing chiropractic practice (Johnson et al. 2012). The emphasis is on arriving at a diagnosis based on information gathered from the patient's history and physical, neurologic, and orthopedic examinations. According to Johnson et al. (2012), chiropractors have the obligation to render "legal and customary" medical diagnoses within the chiropractor's scope of practice. Patients with suspected non-chiropractic diagnoses are referred elsewhere. As distinct from the usual medical primary care physician, the chiropractor frequently does not have the benefit of opinions for practitioners in other specialties.

Unlike medical specialists, chiropractors do not routinely use advanced diagnostic tests. This may reflect their predominantly benign musculoskeletal practice. They do make extensive use of plain-film radiography. Chiropractors spend a considerable amount in their training learning the techniques and interpretation of musculoskeletal radiographs. They typically obtain radiographs of all new patients to diagnose musculoskeletal problems. According to Johnson et al. (2012), chiropractors consider knowledge of normal radiographic procedures to be "extremely important" to an accurate diagnosis.

Clinicians have hotly debated the indications for radiography in chiropractic practice. Its use varies in different regions. A practice-based study comparing chiropractic and physician practices for patients in Oregon hospitals revealed that 26% of patients in both practices had x-rays (Nyiendo et al. 2011). In another study, 67% of chiropractic patients in North Carolina had plain X-rays while 72% of those who saw an orthopedic surgeon were imaged (Johnson et al. 2012). The arrival of Medicare precipitated an increase in ordering radiographs by chiropractic practitioners while subsequent legislation decreased usage.

Chiropractors rely on the patient's medical history to establish the possible etiology of musculoskeletal problems, which can be supplemented by additional studies. Chiropractors are trained to focus on joints, muscle, and soft tissue to determine the potential utility of spinal manipulation. The primary assessment includes palpation, assessing the range and quality of joint motion, and probing for tenderness and inflammations. Based on the findings, chiropractors choose a treatment plan and establish a prognosis. Patients

may receive a trial of chiropractic care, be "co-managed" with a physician or be referred to an appropriate specialist. The chiropractic profession has developed detailed guidelines that govern most aspects of management. These guidelines are part of chiropractic training (Smith 2016).

Chiropractors are trained in a high-touch low-tech health model. The primary concern is the person rather than the disease. Chiropractors believe in the inherent self-healing ability of the body and they are taught to communicate that hope of healing to their patients. Using spinal manipulation combined with other "high-touch" techniques requires a high level of trust between the chiropractor and the patient. Repeated visits allow the relationship between the chiropractor and the patient to thrive. Frequent physical contact between the care giver and the patients communicates confidence on both a social and psychological level (Kent 2018). Chiropractic training emphasizes the physical interaction between the patient and the care giver. The positive outcomes of the relationship demonstrate a more humanistic aspect than is generally seen in mainstream health care. Based on this connection, chiropractors may be better able to offer accepted information and advice than the primary care physician.

Anthropologist and sociologists have suggested that chiropractic treatment for chronic back pain can generate a sense of understanding and trust that mainstream medical professionals cannot match (Lisi et al. 2018). The hands-on and personalized "can-do" approach of the chiropractor seems concrete and reassuring compared to the more scientific, overly cautious, distant, and apparently indifferent approach of the physician. Observational studies have revealed that chiropractic patients are more satisfied with the service they receive compared to those treated by doctors. There is a case for including chiropractic in mainstream health care.

Scientific Rationale of the Chiropractic Profession

Over the last two decades, the chiropractic profession has evoked scientific arguments to justify its treatment of low back pain. Critics in the mainstream health care system have suggested that chiropractors rarely use acceptable and scientifically-proven approaches to treatment. A 2006 Gallup Poll rated chiropractic last among health professionals with regards to using ethical principles (Dynamic Chiropractic 2007). Based on the poll, 84% of patients considered nurses' ethics to be "very high" or "high," while only 36% felt that way about chiropractors (Dynamic Chiropractic 2007, par. 1). Although there may be some scientific support for the chiropractic approach to musculoskeletal dysfunctions, the profession faces difficulties when trying to justify a treatment that is partially rooted in quasi-mythical concepts. Confounding the problem is the fact that the sources of chronic musculoskeletal pain remain controversial so proving any treatment has a scientific basis is difficult.

Numerous studies on the rational for chiropractic care have looked at patients experiencing low back and neck, and headache. They chiefly involved placebo-controlled comparisons with other treatment options. Findings suggest much of the benefit of chiropractic comes from their more holistic approach. The same can be said, however, for many practitioners of alternative medicine.

Bussieres et al. using the Arksey and O'Malley framework reviewed the existing literature to establish current state of knowledge on evidence based practice (EBP), research utilization (RU), and knowledge translation (KT) in chiropractic care (Bussières et al. 2016). Nearly 85% (56/67) of the studies were conducted in Canada, USA, UK, or Australia. EBP included the attitudes and beliefs of chiropractors and the implementation of evidence based treatments. RU involved guideline adherence; frequency and sources of information accessed; and the perceived value of websites and search engines. KT looked at knowledge practice gaps; barriers and facilitators to knowledge use; and selection, tailoring, and implementation of interventions. While most practitioners professed a belief in all three areas, their use varied widely. Gaps existed in areas of assessment of activity limitation, determination of psychosocial factors influencing pain, general health indicators, establishing a prognosis, and exercise prescription. The authors' findings suggested that the majority of chiropractors hold favorable attitudes

and beliefs toward EBP, RU, and KT but rarely put them into practice. They proposed educational strategies aimed at practicing chiropractors to improve patient care. They concluded that the chiropractic profession requires more robust dissemination and implementation research to improve guideline adherence.

Blanchette et al. examined the clinical effectiveness and economic impact of chiropractic care compared to other commonly used approaches to adult patients with nonspecific low back pain (LBP) (Blanchette et al. 2016). They identified randomized controlled trials (RCTs) and/or full economic evaluations of chiropractic care for low back pain compared to standard care by other healthcare providers. Primary outcomes included pain, functional status, and global improvement. Five RCTs compared chiropractic care to exercise therapy (1), physical therapy (3), and medical care (1). The authors found similar effects for all treatments. Three economic evaluations studies (one cost-effectiveness, one cost-minimization, and one cost-benefit) compared chiropractic to medical care. There were divergent conclusions (one favored chiropractic, one favored medical care, one showed equivalent results). Moderate evidence suggests that chiropractic care for LBP appears to be equally effective to physical therapy. Limited evidence suggests the same conclusion when chiropractic care is compared to exercise therapy and medical care.

Classification of Low Back Pain

Hartvigsen and colleagues provide an excellent review of low back pain, its causes, manifestations, and treatments (Hartvigsen et al. 2018). They point out that low back pain is a very common symptom, occurring in all age, socioeconomic, and geographic groups. Globally, years lived with disability caused by low back pain increased by 54% between 1990 and 2015 due largely to population increase and ageing. The biggest increase was in low- and middle-income countries. Low back pain is now the leading cause of disability worldwide. The authors note that it is usually impossible to identify a specific pain generator and that only a small proportion of people have a well understood pathological cause. The data suggest that people with physically demanding jobs, physical and mental comorbidities, smokers, and obese individuals are at greatest risk of low back pain and that it is overrepresented in people with low socioeconomic status. Most people with new episodes of low back pain recover quickly; however, recurrence is common and in a small proportion of people low back pain becomes persistent and disabling. Initial high pain intensity, psychological distress, and accompanying pain at multiple body sites increase the risk of chronicity. Recent research demonstrates that increasing evidence of central pain-modulating mechanisms and pain cognitions have important roles in the development of persistent disabling low back pain. Cost, health-care use, and disability from low back pain vary substantially between countries influenced by local culture and social systems, as well as by beliefs about cause and effect. Disability and costs attributed to low back pain are projected to increase in coming decades, in particular in countries where healthcare systems are fragile and ill-equipped to cope. The authors conclude that intensified research efforts and global initiatives are needed to address the burden of low back pain as a public health problem.

The key messages of their excellent report are:

- Low back pain was responsible for 60.1 million disability-adjusted life-years in 2015, an increase of 54% since 1990, with the biggest increase seen in low and middle-income countries.
- Disability from low back pain is highest in working age groups worldwide, which is especially concerning in countries where informal employment is common and possibilities for job modification are limited.
- Most episodes of low back pain are short-lasting with little or no consequence, but recurrent episodes are common and low back pain is increasingly understood as a long-lasting condition with a variable course rather than episodes of unrelated occurrences

- Low back pain is a complex condition with multiple contributors to both the pain and associated disability, including psychological factors, social factors, biophysical factors, comorbidities, and pain-processing mechanisms.
- For the vast majority of people with low back pain, it is currently not possible to accurately identify the specific nociceptive source.
- Lifestyle factors, such as smoking, obesity, and low levels of physical activity, that relate to poorer general health, are also associated with occurrence of low back pain episodes
- Costs associated with health care and work disability attributed to low back pain vary. considerably between countries, and are influenced by social norms, health-care approaches, and legislation.
- The global burden of low back pain is projected to increase.

Low back pain may occur as a result of a variety of reasons and pathological conditions. Frequently physicians and chiropractors find it difficult to definitively diagnose low back pain and often rely on a description of the symptoms. Chiropractors and physicians should have a classification of low back pain and be aware of those conditions and disease that can produce symptoms. Table 2 highlights the various etiologies of low back pain and the associated diseases.

Treatment of Lower Back Pain in Chiropractic

A plethora of treatment options for lower back pain has not reduced and may have increased the healthcare burden. The traditional chiropractic approach for treating lower back pain, using noninvasive and natural methods, has gained credibility over the years. The practice has gained wider acceptance among patients suffering from lower back problem, and in many instances chiropractors are the first point of contact for individuals suffering from lower back problems.

The lack of consensus of the etiology of mechanical back pain makes it impossible to prove the scientific rigor of most noninvasive treatments. Yet healthcare practitioners are increasingly obliged to claim scientific and evidence-based reasons for treatment. One reason for the acceptability of chiropractors is their focus on demonstrating a scientific rational (LeFebvre et al. 2013). Striving for a scientific approach helps to ensure that health care practitioners are engaged in the best practices (Slaughter et al. 2015). Evidence-based therapy has been strongly promoted yet estimates based on the 2002 National Health Interview Survey revealed that 62.1% of Americans used complementary and alternative medicine (CAM) therapies in 2001 (LeFebvre et al. 2013). Recent data show chiropractic care is the largest CAM in the

Table 2 Etiologies of low back pain and related diseases

Etiology	Associated disease
Psychological	Psychogenic low back pain, in hysteria, and chronic depression/dementia
Trauma	Low back pain associated with fractures
Inflammation	Purulent spondylitis Tuberculous spondylitis Ankylosing spondylitis
Tumors	Spinal metastasis by malignant tumors Multiple myeloma Spinal cord tumors
Degeneration	Spondylosis deformans Intervertebral disc degeneration Intervertebral articular low back pain Lumbar nonspondylolysis spondylolisthesis Ankylosing spinal hyperostosis Lumbar spinal canal stenosis
Abdominal organs	Liver, gallbladder, and pancreatic diseases

United States with approximately 70,000 members (Chapman-Smith 2010).

With regards to lower back disorder, the availability of CAM presents patients with opportunities to explore treatment methods through alternative and personalized approaches. These are typically more attuned to individual preferences. Mainstream medical practitioners tend to employ more use generalized treatment, denying the patience the opportunity to choose.

The personalized approach is consistent with the three major components of evidence-based practice, namely clinician experience and judgment, patient preference and values, and the best available scientific evidence (LeFebvre et al. 2013). In many cases, doctors and spinal specialists do not have enough time or willingness to focus on the nonmedical aspects of the problem.

Doctors of chiropractic use methods that assist patients in self-management including physical exercise, diet, and modification of lifestyle, which improve outcomes and reduce reliance on health care system resources (Johnson et al. 2012). Chiropractors also recognize that a variety of health care providers play a role at various stages. When it is in the patient's best interest, chiropractor consult practitioners in the mainstream health care community for advice (LeFebvre et al. 2013). The goal is to improve patients' functional capacity and educate them on the need to accept responsibility for their own health.

Examination Procedures in Chiropractic

Obtaining a thorough history and carrying out a comprehensive physical examination are critical for the chiropractic management of lower back pain problems. These provide a clinical rationale for appropriate diagnosis and subsequent plan for treatment. Chiropractic assessment includes several steps:

- Obtain the health history of the patient, including information on pain characteristics, red flags, review of previous treatment systems, and risk factors for chronicity
- Identity the specific causes of low back pain
- Conduct a physical examination on the patient for reflexes, dermatomes, myotomes, and orthopedic tests
- Perform a diagnostic testing for red flags

Imaging and other diagnostic tests may be indicated in the presence of severe or progressive neurologic deficits. They can be conducted when the history and physical examination suggest suspicious underlying pathology (Triano et al. 2010). Chiropractors evaluate patients with persistent low back pain and signs of radiculopathy or spinal stenosis to allow for accurate chiropractic intervention and reduce errors during treatment (Chou et al. 2007). A failure to respond may indicate an underlying anatomical anomaly such as spondylolisthesis and indicate imaging. Chiropractors may recommend lateral flexion-extension views to detect excessive intervertebral translation.

Chiropractors classify the conditions of illness and injury in accordance to severity and duration. There are various common descriptions of the illness stages, including acute, subacute, chronic, and recurrent. The acute stage includes symptoms that have been persistent for a period of less than 6 weeks. Subacute stage relates to symptoms that have persisted for a period of between 6 and 12 weeks. Chronic indicated the symptoms have persisted for at least 12 weeks and recurrent defines a return of the original symptoms after a period of complete remission. These symptoms are further subdivided into mild, moderate, and severe, depending on the intensity and the risk they pose to the patient.

Treatment Frequency and Duration in Chiropractic

The frequency and duration of chiropractic treatment is usually dependent on individual patient factors or characteristics. Some of the factors impeding recovery include comorbidities and clinical "yellow flags." Additional treatment visits can give for time to observe therapeutic responses and the clinician should evaluate the treatment outcomes. A typical therapeutic trial of

chiropractic care consists of between 6 and 12 visits over a span of 2–4 weeks (Globe et al. 2016). During these visits, chiropractors monitor their patients' progress to document acceptable gains. Generally acute conditions require fewer treatments.

According to Globe et al. (2016), the initial stages of chiropractic treatment for lower back pain require consistency and clinical methods that reflect the best available evidence. Chiropractors need clinical judgment, experience, and should be aware of the patient's preference. Currently, most literature recommends high-velocity, low amplitude techniques, and mobilizations such as flexion-distraction (Clar et al. 2014).

The initial course of chiropractic treatment typically includes one or more passive, manual therapeutic procedures which require no patient participation. Pain control is achieved with spinal manipulation or mobilization combined with strong reassurance (Globe et al. 2016). As a rule, the chiropractic assessment does not include risk stratification for potential complicating factors.

Clinical judgment and patient preference are important aspects of chiropractic practice and relies on personal assessment of the patient's situation to determine the intervention. Because of the scarcity of definitive evidence about the efficacy of spinal manipulation methods, some researchers have suggested that bracing, taping, and orthoses not be recommended as part of the treatment strategy (Globe et al. 2016). Because so much of chiropractic decision making is highly personal and based on individual experience, however, these options are frequently employed. Such judgments would be less acceptable among medical professionals but are a hallmark of chiropractic care.

Reevaluation and Reexamination in Chiropractic

After concluding the initial phase of treatment, chiropractors re-evaluate the patient's condition. The need for additional treatment is based on the responsiveness to the initial phase of care and the probability achieving additional gains. Patients may plateau in their recovery process necessitating modification or suspension of treatment (Globe et al. 2016). The chiropractor must establish if recovery has paused or if the patient has gained "maximum therapeutic benefit" (Globe et al. 2016). The final treatment visit should provide the necessary education and instructions on effective self-management.

Re-evaluation may suggest continued chiropractic treatment. Chiropractors adopt a proactive system assessing the efficacy of the treatment rather than patient's putative pathology. The chiropractor encourages the patients to resume normal activities while, as much as possible, avoiding aggravating the condition. This advice is consistent with the notion that the human body has an enormous capacity to recover. In cases where the patient plateaus at an unacceptable level of function or pain control, the chiropractor must decide whether to continue treatment or explore for alternative therapeutic interventions. The patients should share in that decision.

Measurement of Health Outcomes in Chiropractic

For a trial of chiropractic care to be considered beneficial, the outcomes must be clinically relevant, the improvement must clearly improve the patient's functional capacity. Some of the observable metrics include pain scales such as the visual analogue and the numeric rating scales, pain diagrams that enable patients to demonstrate the location and character of their conditions and symptoms, an increase in the amount of home and leisure activities such as performing household chores or engaging in physical exercises, an increase in productivity at work, and improvements in validated functional capacity tests such as lifting, flexibility, and endurance.

Benefits and Risk of Chiropractic Care

In comparison to spine surgery, chiropractic care is certainly safe. A 2010 review concluded that the number of serious adverse outcomes among low

back pain patients receiving chiropractic lumbar spine manipulation procedures was less than one per million visits (Bronfort et al. 2010). Other studies indicate that the risk of major adverse outcomes with manual therapy for a variety of conditions is less than with usual medical interventions. The most common complaint after manual treatment was short-lived after-treatment discomforts caused by muscle stiffness (Carnes et al. 2010). Patients judged poor candidates for spinal manipulation are offered alternative treatment choices such as soft-tissue, low-velocity, low-amplitude procedures, and mobilization. There are several clinical situations in which manual manipulation of the spine may be contraindicated and the chiropractor must evaluate the associated risks.

There is a need for flexibility in choosing treatment options. These include co-management with medical doctors. In all cases, full documentation is essential. The chiropractor must remain alert to a change in the patient's symptoms that could indicate a significant deterioration or underlying sinister pathology. These case demand immediate diagnostic workup or referral.

Chiropractic Management of Chronic Lower Back Pain

The management of chronic back pain often includes home-directed self-care and scheduled ongoing care. These are patients for whom self-care measures are insufficient to sustain desirable therapeutic gains. Their condition may progressively deteriorate as demonstrated by previous treatment failures. For these patients, the hands-on therapy or manipulation may produce only short term pain relief that allows compliance with the more important aspects of activity modification and lifestyle adjustment. The role of the chiropractor is to provide direction and reassurance more than mechanical treatment. The connection between the patient and the provider established though physical contact can be used to instill confidence and deal with the overwhelming psychosocial devastation of chronic pain. Any ongoing manual therapy must not interfere with the more essential re-establishment of a normal daily routine and lifestyle.

Biological Rationale for Using Chiropractic

Chiropractors typically direct spinal manipulation at a dysfunctional subluxation. In the current context of chiropractic, a subluxation may connote a functional and not necessarily an anatomic entity. Chiropractic dogma suggests that combination of the initial subluxation and the required manipulation can have important physiological effects on patients including increased motion, changes in facet kinematics, improved tolerance to pain, increased muscle strength, and enhanced proprioception. Much of the chiropractic literature focuses on the physical and long-term well-being of patients. Because the primary aim of chiropractors is to improve the health, the benefits of the professional interaction can override the actual anatomical alterations, if any, produced by the manipulation. The treatment has no significant negative side effects risk and whether any resulting perceived improvement in strength, mobility, or pain relief is the result of resolving a subluxation or providing a strong placebo may be moot.

The Medical Approach to Low Back Pain

Low back pain is a considerable health problem for people in both developed and undeveloped countries. The prevalence of low back pain varies from 49% to 70%, with most of these cases being reported in Western societies (Carnes et al. 2010). Individuals suffering from low back problem typically experience pain, muscle tension, or stiffness localized below the costal margin and just above the gluteal folds, with or without associated leg pain.

The diagnosis process differentiates between patients with specific or nonspecific low back pain. Specific low back pain is defined as symptoms that result from a recognized specific

pathophysiological mechanism such as disc herniation, infection, rheumatoid disease, tumor, or fracture (Carnes et al. 2010). In the United States, some studies suggest that of those suffering from low back pain, 4% have a compression fracture, 3% spondylolisthesis, 0.7% a tumor or metastasis, 0.3% ankylosing spondylitis, and 0.01% an infection (Carnes et al. 2010). According to Koes et al. (2006), 90% of low back pain problems are nonspecific, that is, lacking a defined etiology. Consequently, physicians often diagnose the problem based on the exclusion of specific pathology. Compared to the chiropractic approach, this tactic places the emphasis in the wrong place, stressing rare pathologies over common minor mechanical malfunctions.

Health care professionals employ a variety of diagnostic labels. General practitioners use terms such as lumbago, physical therapists speak of hypomobility, manual therapists refer to joint disorders, and orthopedic surgeons treat degenerative discs (Koes et al. 2006). There is no widely accepted, reliable, and valid classification method for diagnosing nonspecific low back pain. In most cases, it is classified based on duration of the complaints and its severity, acute when it persists for less than 6 weeks, subacute between 6 and 3 months, and chronic when it lasts longer (Koes et al. 2006). These definitions offer no guidance and may be irrelevant.

The clinical course for most episodes of acute low back pain is favorable, with much of the discomforts dissipating within a couple of weeks. This is consistent with findings that indicate that 90% of patients with low back pain in primary care will cease visiting their doctors within 3 months of active treatment. Symptoms fluctuate over time, making it difficult to establish a consistent trend. Most individuals suffer recurrent attacks, with some estimates at about 70% within the first year. The severity and duration of these recurrences frequently do not precipitate need for treatment. Only about 5% of people with low back pain develop chronic problems and related disability.

Many physicians take a narrow view of back pain and overlook nonphysical factors exacerbating the pain. They tend to use a rigid approach to diagnosis and treatment when compared with chiropractors, who interact with patients long enough to identify the more global issues involved.

For nonspecific LBP, numerous studies have shown that surgery does not offer clinically relevant benefits over conservative interventions, including chiropractic treatment (Peul et al. 2014). For degenerative disc disease, a systematic review, including two randomized controlled trials (121 patients), compared intradiscal electrothermal therapy with sham surgery (Helm II et al. 2012). There was no significant difference in outcomes for pain, disability, and quality of life.

In a meta-analysis of four randomized controlled trials (767 patients) comparing spinal fusion surgery with conservative interventions, surgery was not superior in improving back pain, disability, and quality of life (Chou et al. 2009).

A Cochrane review of five randomized controlled trials with 1301 patients evaluated disc replacement for degenerative low back pain (Jacobs et al. 2012). It included one trial (173 patients) that showed a statistically significant but clinical irrelevant difference in VAS favoring disc replacement over nonoperative treatments including chiropractic. When assessing surgical intervention, the potential harms or side effects of surgery have been inconsistently underreported.

The National Institute for Health and Care Excellence (NICE) guidelines on nonspecific low back pain included only one cost effectiveness analysis. This concluded that if decision makers are willing to pay $50,000 per quality adjusted life year (QALY), the chance that surgery is cost effective compared with nonoperative care is only 20% (Savigny et al. 2009).

Surgery does however have a clear role for relief of radicular pain and LBP caused by specific diagnoses. For sciatica due to herniated lumbar disc, a systematic review with five randomized controlled trials (1135 patients) concluded that early surgery leads to short term benefits in function and reduced leg pain (recovery after 4 vs. 12 weeks) but with similar long-term results. (Jacobs et al. 2011). Interestingly, surgery did not provide superior relief of the back pain in these studies.

For neurogenic claudication due to lumbar stenosis, systematic reviews show that surgical decompression (five randomized controlled trials with 918 patients) is superior in improving pain, disability, and quality of life to conservative treatment up to at least 4 years (Kovacs et al. 2011; May and Comer 2013). These studies intentionally excluded patients with predominantly low back pain as their major complaint.

The National Institute for Health and Care Excellence has recently reviewed the surgical treatment of patients with nonspecific low back pain and given guidelines that fusion should only be offered as part of a randomized controlled trial and that lumbar disc replacement should no longer be performed. The NICE guidelines were based on a small number of prospective RCTs, six for lumbar fusion, and five for disc replacement. Each of these trials had difficulties: some involved few patients; some randomized patients to up to three different surgical techniques; there was inconsistent use nonoperative treatment. There were the usual problems of crossover and loss to follow-up. In an excellent commentary in 2017, Todd conclude that what is now urgently required is a high-quality RCT to identify the "ideal" patients with nonspecific back pain for fusion (Todd 2017).

Use of Imaging Technology by Physicians

Physicians often mistakenly use x-ray or magnetic resonance imaging (MRI) trying to diagnose nonspecific low back pain problems. Most of the abnormalities found imaging individuals without low back pain are the same at in patients with the problem. According to Roland and Van Tulder (1998), up to 50% of asymptomatic people have degenerative findings and imaging as a screening tool for back pain may lead to long term health problems. Most people suffering nonspecific low back pain have radiological abnormalities that bear no relationship to the pain. Recognizing the limited value and harmful effects of screening x-rays, clinical guidelines recommend imaging only when a specific diagnosis is being considered and the pictures will have an impact on the treatment decision.

According to Deyo et al. (2010), computed tomography and magnetic resonance imaging are useful and accurate in confirming the diagnoses of lumbar disc herniation and spinal stenosis. Both can be separated from nonspecific low back pain on the basis of the history and physical examination (Deyo et al. 2006). MRI is useful in assessing spinal infections or tumors but only when the diagnosis is already being considered.

Recognizing Chronicity

Early identification of patients with low back pain at risk of long-term disability allows physicians to intervene in a timely manner. The time to recovery increases the longer the pain exists. The transition from acute to chronic pain is complicated by factors, such as the workplace environment or domestic situation, that are outside the individual's control. A focus solely on the physical findings can lead to misdiagnosis. Due to their holistic approach and long association with the patient, the chiropractor may be in good position to recognize the problem.

A recent study indicated that physicians do not consider factors such as distress, depressive mood, and somatization when assessing individuals for low back pain. According to Coulter et al. (1998), these factors are key etiologies for chronicity. If physicians focus on diagnostic tests to the exclusion of a detailed history, they may miss the relevant psychosocial elements. Relying more on the patient's story and having a broader view of the patient's situation can give the chiropractor an advantage.

Treatment Methods for Low Back Pain by Physicians or Chiropractors

The current evidence for treatment of acute and chronic low back pain is given in Table 3.

There are numerous similarities in the way chiropractors and medical doctors treat low back pain, for example, the advice to stay active and

Table 3 Treatment options for acute and chronic back pain. (Source: Koes et al. (2006))

Effectiveness	Acute low back pain	Chronic back pain
Beneficial	Physicians offer advice for patients to remain active Prescription of nonsteroidal anti-inflammatory drugs (NSAIDs)	Exercise therapy Intensive multidisciplinary treatment programs
Trade-off	Prescribe muscle relaxants	Prescribe muscle relaxants
Likely to be beneficial	Spinal manipulation Behavioral therapy Adopt multidisciplinary treatment programs, especially for subacute low back pain	Analgesics Acupuncture Prescribe antidepressants Behavioral therapy Spinal manipulation NSAIDs Back schools
Unknown	Analgesics Acupuncture Back schools Lumbar supports Massaging Multidisciplinary treatment options Tractions Temperature treatment Electromyographical (EMG) biofeedback	Inject patient with epidural steroids EMG biofeedback Lumbar supports Massage Transcutaneous electrical nerve stimulation Traction Local injections
Unbeneficial	Specified back exercises	N/A
Harmful	Extended bed rest	Facet joint injections

avoid prolonged bed rest. There is strong evidence that nonsteroidal anti-inflammatory drugs relieve pain better than chiropractic intervention. According to Koes et al. (2006), muscle relaxants relieve pain more effectively than placebos but significant side effects such as drowsiness limit their use. For many patients, the chiropractic alternative is more attractive.

Research suggests that spinal manipulation and multidisciplinary intervention for subacute low back pain are effective in relieving pain but there is little evidence that medically applied lumbar supports, traction, massage, or acupuncture are more effective than chiropractic adjustment (Deyo et al. 2010). The fact that medical interventions have proven largely ineffective in alleviating low back pain is a reasonable justification to incorporate chiropractic into the management. The techniques are safe and regardless of disputes over the mechanism of action, moderately successful.

The range of treatment options is immense. Studies have supported the use of analgesics, antidepressants, nonsteroidal anti-inflammatory drugs, spinal manipulation, cognitive behavior therapy, and back school. Exercise is the most prescribed form of conservative management for low back pain. According to Koes et al. (2006), exercises and intensive multidisciplinary pain treatment programs prescribed by either chiropractors or physicians are effective for both acute and chronic low back pain. In most cases, treatment effect is limited and short-term and in almost all instances there is no solid scientific rational for the use of a particular modality or approach. The array of choices reflects this lack of evidence. Reports of success are anecdotal and many clinicians, both medical and chiropractic, simply employ those techniques with which they have had personal success. Against this background it is hard to argue against the patient seeking a trial of chiropractic care.

The Place for Surgery

The role of surgery in treating back pain has been the subject of a vast amount of research and, with a few clear indications, its place is still not clear. Studies have look at the effectiveness of surgery and other invasive interventions for low back pain and sciatica (Van Tulder et al. 2006).

Surgical discectomy for sciatica due to lumbar disc prolapse unresponsive to nonoperative management is widely accepted as safe and effective (Koes et al. 2006). Surgical decompression for focal lumbar canal stenosis causing neurogenic claudication achieves functional improvement comparable to total joint replacement. Spine fusion surgery to treat back pain, however, remains the source of aggressive debate (Van Tulder et al. 2006). Randomized controlled trials comparing fusion surgery with conservative and noninvasive intervention methods for back pain have produced conflicting outcomes (Fairbank et al. 2005). No clear, validated criteria exist to guide decision making for operative intervention in patients with back pain but without discrete, identifiable, localized pathology.

When the proper criteria are met, surgical intervention can be effective and is clearly superior to noninvasive treatments including chiropractic manipulation (Kovacs et al. 2011). The problem is both establishing and meeting the indications for a spinal operation. The overwhelming majority of patients are not and never will be surgical candidates and for this group nonoperative therapy remains the correct choice.

Because of the effects of aging and the normal demands of daily life the spine, like the rest of the body, naturally degenerates. Surgery is a one-time event intended to deal with an immediate problem. It is not prophylactic and its benefits may decline over time as the spine grows older. A good example is the decompression for spinal canal stenosis. Narrowing of the canal from boney overgrowth is a natural response to aging. Enlarging a foramen to relieve nerve root compression is typically a successful procedure but it obviously cannot prevent future compromise. Misunderstanding the purpose and the limits of an operation is one reason for apparent surgical failure. The increasing number of spine surgeries and particularly spine fusions is a source of concern (Deyo et al. 2010). An operation is not an alternative to proper spine care, whether by the chiropractor or the family doctor.

Mannion et al. carried out a long-term (average 11 years) follow-up, comparing the outcome of chronic low back pain patients treated with fusion to those managed with multidisciplinary cognitive-behavioral and exercise rehabilitation. They combined the results of three randomized controlled trials conducted in the United Kingdom and Norway and found no statistically significant or clinically relevant differences between the cohorts (Mannion et al. 2013).

There are more questions than answers with regard to spinal fusion for lumbar degenerative disk disease (Deyo 2015). Data from the online Health Care Utilization Project, sponsored by the Agency for Healthcare Research and Quality, showed that the annual number of fusion operations (all indications and spinal levels) in the United States had increased from about 61,000 in 1993 to over 450,000 in 2011, more than a 600% increase (HCUPNet 2014). These procedures accounted for largest bill of any hospital based surgery: over $40 billion. This surge has occurred despite randomized trials suggesting little, if any, advantage of fusion over well-structured rehabilitation for degenerative discs (Mirza and Deyo 2007; Brox et al. 2003; Fairbank et al. 2005) and despite high and increasing rates of revision (Martin et al. 2007). About one in every five patients who undergo lumbar fusion will have revision surgery within 10 years (Fritzell et al. 2002). Fusion for back pain does not seem like a good idea.

Spinal Injections

Injections generally introduce anesthetics, steroids, or sclerosing agents to specific locations in the spine to diagnose or alleviate low back pain. Facet joint injections are a common form of treatment as well as a diagnostic test for "lumbar facet joint syndrome" (Van Tulder et al. 2006). As in so many instances of managing spinal problems, however, there is no clear-cut criterion for diagnosing this condition and treatment is purely empirical.

Compared with chiropractic care, facet injections have proven ineffective in relieving chronic back pain. One study showed no significant difference in low back pain 6 weeks and 6 months after anesthetic facet injection (Gibson and

Waddell 2005). The European low back pain guidelines identified trials with a range of different outcomes. One trial reported that an epidural injection of methylprednisolone was efficacious in alleviating sciatica. Another found that steroid perineural injections were superior to saline injections in patients suffering from "lumbar syndromes" (Koes et al. 2006). Overall the positive results, if any, were short term. In a study showing positive results of epidural corticosteroid injections, 65% of patients reported pain relief lasting between 1 day and 6 weeks. Adding morphine caused unfavorable side effects including drowsiness and dizziness (Koes et al. 2006). None of the trials described long term pain control. The lack of well-designed trials makes a conclusive decision on the effectiveness of injections impossible. Statistically chiropractic interventions were more effective in providing lasting relief.

A similar technique using local penetration is radiofrequency denervation of the facet joints. Trials have produced results similar to the injection of anesthetics. One showed that radiofrequency ablation relieved the intensity of low back pain and improved function for two months (Van Tulder et al. 2006).

Opioids

Prescribing opioids for low back pain has also been common practice by the mainstream medical profession. Evidence clearly shows that opioid analgesics are not superior to nonopioids treatment strategies (Krebs et al. 2018). Further research demonstrates opioids offer no long-term benefits (Cherkin et al. 2016). Long-term opioid therapy is associated with poor patient-reported pain control, reduced quality of life outcomes, diminished function, and psychiatrist disorders (Turner et al. 2016). There are multiple adverse effects including constipation, confusion, increased pain, and respiratory depression (Oderda et al. 2013). According to Vowles et al. (2015), approximately 20% of patients on long-term opioids have an adverse event.

There is no place for opioids in the management of low back pain. The medical profession has created an epidemic of narcotic addiction and overdose deaths.

Adverse Effects of Surgery and Other Invasive Treatment Options

Every invasive procedure used to treat back pain has the potential for adverse side effects. Every operation is a risk/benefit decision. Complications can be intraoperative or occur after the surgery is complete. They range from misadventure to mistake, from unavoidable to preventable, from unfortunate to malpractice.

Some choices should be simple. Routine microdiscectomy, approaching the disc with a minimum of soft tissue disruption, has a lower risk of reoperation than percutaneous laser disk decompression, a largely discredited procedure (Brouwer et al. 2015). Some choices are more complicated. The more extensive the operation the higher the risk of an adverse event but the success of the surgery may require a more complex and therefore a more perilous procedure.

Spine surgery can create its own iatrogenic problems. Decompression may remove too much bone and render the spine unstable causing increased pain and the need for further surgery. Adjacent structures, nerves or blood vessels, may be damaged. Every operation is a chance for infection. No surgical assault on the spine should be casually dismissed. A fully informed consent is mandatory.

Surgery is followed by recovery and that time can vary depending on the nature and the extent of the operation. According to Johns Hopkins Spine Service, individuals who undergo traditional spine surgery for low back pain should expect to miss between 8 and 12 weeks of work (Seladi-Schulman 2017).

Compared to chiropractic manipulation, surgery is a risky proposition but that does not make it the wrong choice. The nature of the treatment depends on the nature of the problem. Most patients with low back pain do not need spine surgery but for those for whom an operation is needed and necessary delaying surgery to receive useless manual therapy is clearly poor patient care.

Rationale for Including Chiropractic Care into Mainstream Medicine

Chiropractic treatment is an excellent example of creating a rick /benefit balance for treating back pain. Most chiropractors rely on manipulating the spine and limit their practice to spinal or, at most, musculoskeletal problems. Although there are numerous theories as to the mechanism of pain relief, there is not scientific validation. Nevertheless, chiropractic care has been shown repeatedly to be more effective in managing back pain than conventional medical methods. Chiropractic techniques for reducing back pain have few if any significant side effects. The benefits clearly outweigh the risks tilting the risk/benefit balance in favor of chiropractic care.

Unfortunately, some chiropractors have chosen to extend their approach to a wide range of unrelated, nonmechanical conditions, creating doubt in the minds of the medical community on the validity of their claims. Incorporating chiropractic into mainstream medicine will require more rigorous analysis and a clear scope of practice.

Clinical practice is complicated and vulnerable to abuse. No treatment no matter how seemly benign is totally without concerns. Risk/benefit is always a tradeoff. The incorporation of chiropractors into a medical healthcare system raises issue of financial incentives, resource allocation, vested interest, and professional jealousy. It will never be as simple as giving patient's free choice. Many patients experience short-term, mild to moderate muscular pain after manipulation. This can be viewed as a harmless event or can be used to raise concerns. Death after chiropractic treatment is extremely rare but not unheard of (Edzard 2016). Failure to recognize an underlying pathology as a source of apparently nonspecific low back pain can have disastrous results. Repeating an adjustment when the previous attempt caused serious problems is both foolishly endangers the patient. Chiropractic manipulation is safe but it is not trivial.

Chiropractors must obtain informed consent from their patients before commencing therapy. This is an ethical imperative. Chiropractors need to inform their patients about the inherent risks of undergoing an adjustment or manipulation. Although the risks may be less, in this regard the chiropractor is not different than the surgeon.

From its inception at the end of the nineteenth century, the chiropractic profession has overcome many of the challenges raised by the medical community. Many medical doctors treat chiropractors with skepticism and reject the concept of alternative medicine. But combining the aspects of chiropractic care that emphasize patient contact, the holistic aspects of healing and the body's ability to repair itself with the diagnostic skills and technology of modern medicine would be to everyone's advantage, primarily the patient's.

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Medical Causes of Back Pain: The Rheumatologist's Perspective

5

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Abstract

Medical causes of back pain include *infection*, *inflammation*, *or malignancy.* These treatable causes of back pain must be recognized by all health providers so that the diagnosis is not missed and appropriate treatments can be started as soon as possible. A medical cause of back pain should be suspected when patients have features of systemic illness – fevers, rash, unexplained weight loss, or joint swelling – or when their medical history contains comorbidities such as psoriasis, inflammatory bowel disease, immunosuppression, or injection drug use. This chapter will focus on how to recognize the clues that will lead to these diagnoses through a series of case studies.

Keywords

Spinal infection · Spondyloarthritis · Osteoporosis · Malignancy · Rheumatology

Case 1

Case Description

A 26-year-old male presents to the emergency department with a 48-h history of worsening back pain. He describes 24 h of fever and chills and is febrile and tachycardic in the emergency room. He is known to be HIV-positive, secondary to intravenous drug use, but has not been taking anti-retroviral therapy for the past several months. His physical exam reveals clear track marks on the upper limbs. The differential diagnosis for suspected spinal infection is listed in Table 1.

Salient Features on History and Physical Exam

Spinal infections present most commonly with acute back pain, fever, and other constitutional symptoms. Limb weakness or other neurologic symptoms are present in less than 50% of cases but, if present, *suggest a surgical emergency.* Patients often have underlying medical comorbidity (diabetes, coronary artery disease, immunosuppression) or use intravenous drugs. The most common sites of *primary* infection are skin and soft tissue, genitourinary, or bacterial endocarditis. Patients with fungal or tuberculous infections are more likely to present with subacute back pain and more prominent constitutional symptoms.Appropriate investigations for suspected spinal infection are outlined in Table 2.

Epidural Abscess

An epidural abscess occurs when pus accumulates between the dural layer of the spinal cord and the spinal ligaments. Over 50% of cases are

Table 1 Differential diagnosis of suspected spinal infection

Condition	Diagnostic clues
Infectious – bacterial (epidural abscess, osteomyelitis, or diskitis)	Acute onset
	History of intravenous drug use
	Recent spinal instrumentation
Infectious – fungal	Subacute presentation
	Immunosuppressed patient
Infectious – tuberculosis	Subacute presentation
	Immunosuppressed patient (particularly HIV+)
	Constitutional symptoms
	Endemic areas – Asia, South America, sub-Saharan Africa; homeless populations

Table 2 Appropriate use of investigations for suspected spinal infection

	Investigation	Relevance
Bloodwork	CBC, electrolytes, creatinine	Leukocytosis in ~60%
	Blood cultures (two sets)	Positive in ~50%
	ESR and CRP	Elevated in >90% of cases
Imaging (Fig. 1)	Plain radiography	Use to Rule out alternative diagnosis
	MRI spine	High sensitivity/ specificity
	Gallium scan	Less sensitive than MRI for abscess
Special tests	TB skin test	If from endemic area
	2D echocardiogram	If *S. aureus* bacteremia
	CT-guided tissue biopsy	If blood cultures negative

due to hematogenous spread of bacteria (most commonly *Staphylococcus aureus*), with at least 40% of cases thought to be due to intravenous drug use. If left untreated, epidural abscesses can lead to permanent neurologic compromise and so should be considered a *medical emergency.*

Diskitis and Osteomyelitis

Osteomyelitis refers to infection of the vertebral body and/or adjacent disk (diskitis). Similar to an epidural abscess, most cases are caused by hematogenous spread. Neurologic complications can occur in up to 40% of patients with vertebral osteomyelitis, and epidural abscesses develop in 15–20%.

MRI is the imaging modality of choice to investigate for spinal infection with high sensitivity and specificity. Although there is concern regarding MRI overuse in the back pain population, a recent study of 167 patients with a history of intravenous drug use and acute back pain found that nearly 40% of patients had evidence of spinal infection on their admission MRI (Colip et al. 2018). Thus, it is reasonable to order an MRI for patients with back pain and a history of intravenous drug use.

Initial Treatment Approach

Epidural Abscess

Any patient with neurologic compromise from an epidural abscess requires urgent surgical decompression. In patients without neurologic symptoms, using medical management alone with intravenous antibiotics is controversial. Patients with leukocytosis, positive blood cultures, or history of diabetes are at a higher risk of failure with medical management, and early surgery should be considered in these patients. Initial antibiotic therapy should be broad-spectrum and then tailored after an organism is identified. Infectious diseases consultation may be warranted.

Diskitis and Osteomyelitis

Antibiotic therapy is the mainstay of treatment for vertebral osteomyelitis; if patients are hemodynamically stable without neurologic symptoms, empiric antibiotics may be delayed until a microbiological specimen can be obtained. Osteomyelitis should be treated with at least 4–6 weeks of intravenous antibiotics, and response to therapy can be monitored by following symptoms (back pain, fever) and acute phase reactants (ESR, CRP). Follow-up imaging is not usually required, but can be considered if patients have ongoing symptoms despite therapy. Surgical treatment should be reserved for those with epidural abscess, spinal implants, or progressive neurological symptoms.

Appropriate Referrals

Any spinal infection should be considered a medical emergency and treated rapidly with broad-spectrum intravenous antibiotics. Patients require admission to hospital and frequent monitoring for sepsis and neurologic deterioration. Consultation from infectious disease specialists may be helpful for making decisions regarding antibiotic choice and duration of therapy. For any patient with ongoing intravenous drug use, referrals to social work and addictions specialists will be vital to prevent recurrence.

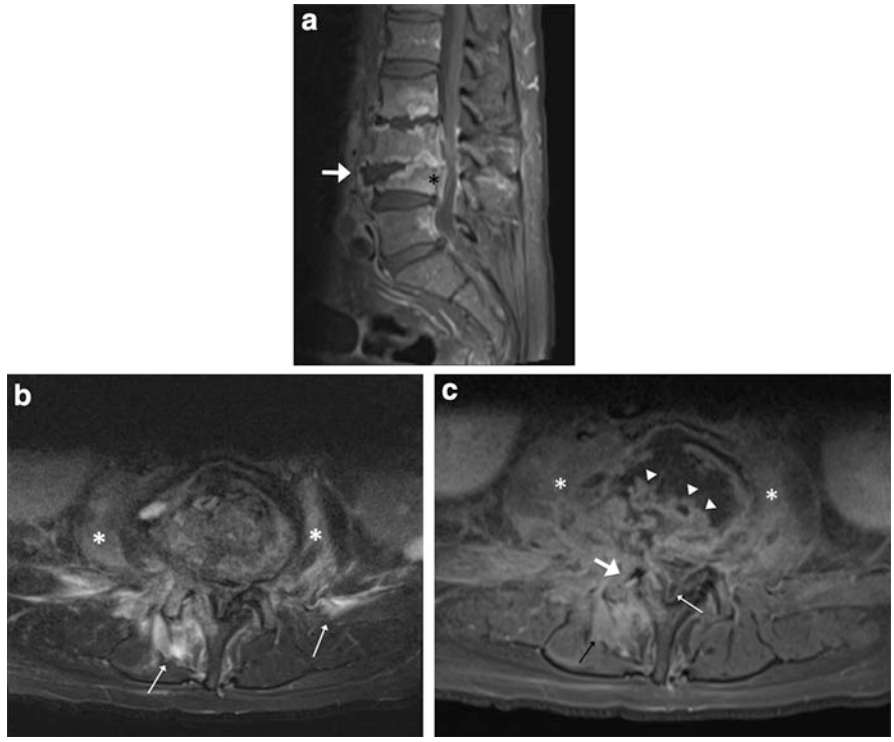

Fig. 1 (**a**) MRI spine showing epidural abscess. Sagittal post-gadolinium T1 FS images of the lumbar spine demonstrate peripherally enhancing intervertebral abscess (white arrow) and significant destruction with loss of height of the L3 and L4 vertebral bodies. Further, endplate destruction is present at L2-3 level. There is intraosseous enhancement in the vertebral bodies from L2 to L5 consistent with osteomyelitis. The enhancing epidural abscess (asterisk) is causing narrowing of the spinal canal. (**b**) MRI spine showing intervertebral discitis. The axial STIR image at the level of L3-4 demonstrates T2-hyperintense intervertebral discitis with significant edema in the posterior elements as well as the paraspinal (white arrows) and psoas muscles (white asterisks). (**c**) MRI spine showing vertebral osteomyelitis. The axial T1 FS post-gadolinium image demonstrates osseous enhancement (thick white arrow) of the posterior elements consistent with vertebral osteomyelitis. There are peripherally enhancing intervertebral (arrowheads) and epidural abscesses (white arrow). There is associated diffuse soft tissue enhancement in the psoas (asterisks) and paraspinal muscles (black arrow)

Case Resolution

This man has a very high pretest probability for spinal infection; he should be admitted to hospital, should have blood cultures drawn, should be treated with broad-spectrum IV antibiotics, and should undergo a spinal MRI to confirm the diagnosis. Careful attention should be paid to his neurological exam, and an infectious diseases consult should also be obtained.

Clinical Pearls and Myths

- Fever with acute back pain is spinal infection until proven otherwise.
- Think of tuberculosis in any patient with fever, weight loss, and subacute back pain, particularly if they are immunosuppressed or from an endemic area.
- Rule out bacterial endocarditis in any patient with S. aureus bacteremia and spinal infection.

Case 2

Case Description

A 35-year-old woman presents with progressive back pain for the past 10 years. The pain localizes to the lower back and radiates down to the buttock, sometimes alternating sides. It is worst during the

night as well as in the morning, where it is associated with significant stiffness. She is referred to a surgical spine clinic after an MRI suggested spinal stenosis at L4–L5; however, the radiologist also describes bone marrow edema in the lumbar spine suggestive of spondyloarthritis.

Differential Diagnosis: Spondyloarthritis

Spondyloarthritis (SpA) refers to a group of related but distinct conditions that can cause inflammation of the sacroiliac joints and spine. SpA can be divided into axial- and peripheral- predominant disorders, depending on which joints are most involved. Axial-predominant SpA includes ankylosing spondylitis; peripheral-predominant SpA includes psoriatic arthritis, inflammatory bowel disease-associated arthritis, and reactive arthritis. The major features of each disorder are listed in Table 3.

Table 3 Classification of spondyloarthritis

Condition	Back involvement	Other features
Ankylosing spondylitis	Bilateral, symmetric sacroiliitis	Associated with peripheral large joint arthritis, acute anterior uveitis, enthesitis, dactylitis
	Spondylitis starts in lumbar spine and progresses upward	
Psoriatic arthritis	Unilateral, asymmetric sacroiliitis	Associated with psoriasis
	Spondylitis less common	Peripheral arthritis common
Reactive arthritis	Unilateral, asymmetric sacroiliitis	History of preceding gastrointestinal or genitourinary infection (within 1–3 weeks)
	Spondylitis less common but can occur in up to 20% of patients	Associated with arthritis, urethritis (sterile), and conjunctivitis
IBD-associated arthritis	Can be unilateral or bilateral	Associated with oral ulcers, acute anterior uveitis, and peripheral arthritis
	Spinal inflammation is often independent of IBD activity	

Clinicians must also be aware of spondyloarthritis mimickers that can also present with similar symptoms. The most common ones are listed in Table 4 below. These conditions can usually be differentiated on the basis of a careful history and physical examination along with imaging. Osteitis condensans ilii (OCI) should be considered in women with postpartum back pain (Fig. 2). Unilateral sacroiliitis without extra-axial features or peripheral arthritis should always raise suspicion for infection and be investigated accordingly (Fig. 3). Diffuse idiopathic skeletal hyperostosis (DISH) can be differentiated from SpA by the lack of SI joint involvement on imaging (Fig. 4).

Table 4 Differential diagnosis of SpA

Condition	Diagnostic clues
Osteitis condensans Ilii (OCI) (Fig. 2)	Female preponderance
	Often presents after pregnancy
	X-ray: associated with sclerosis at inferior SI joint
	No erosions or joint space narrowing
Infectious sacroiliitis (Fig. 3)	Acute or subacute onset
	Almost always unilateral
	Presence of constitutional symptoms
	X-ray: early and extensive erosions on the affected side
Diffuse idiopathic skeletal hyperostosis (DISH) (Fig. 4)	Insidious onset
	Usually starts after age 50
	Associated with diabetes and obesity
	X-ray: flowing, anterior osteophytes but no erosions
	Sacroiliac joints should be normal
Spondyloarthritis (Fig. 5)	Insidious onset
	Usually starts before age 45
	Inflammatory-type back pain (see below)
	Presence of extra-axial features
	Imaging described below

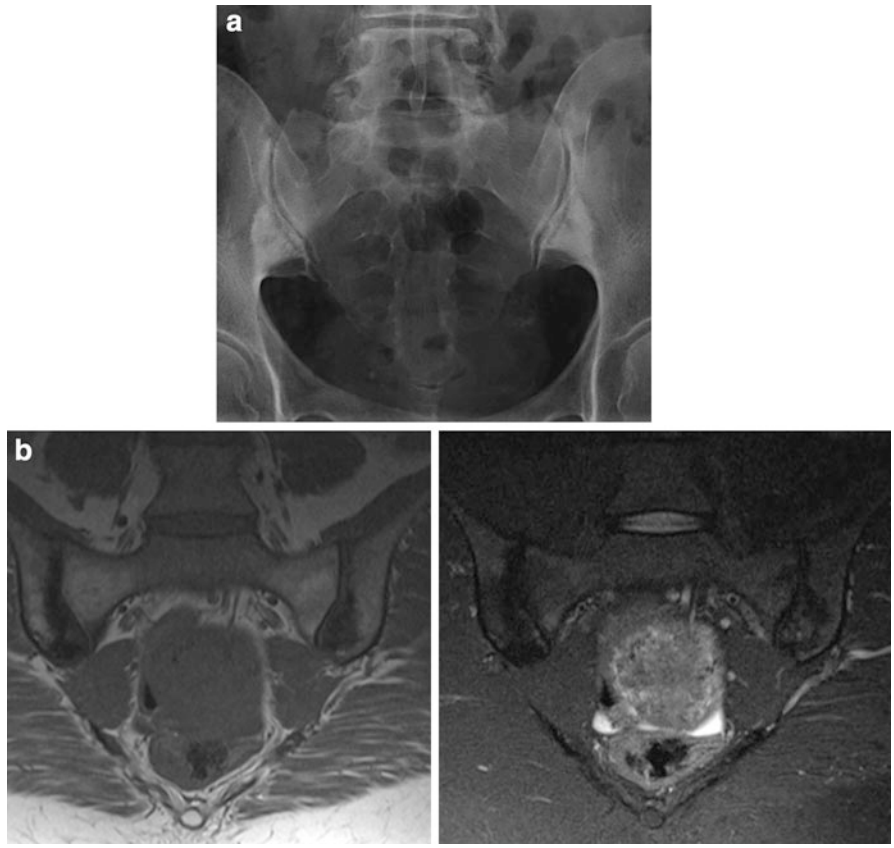

Fig. 2 (**a**) Frontal radiograph showing osteitis condensans ilii. Typical bilateral triangular sclerosis in the ilium adjacent to the sacroiliac joints is depicted. There are no features of erosions or ankylosis. (**b**) MRI showing osteitis condensans ilii. Coronal T1 and STIR images demonstrate signal hypointensity reflecting the sclerosis in the iliac sides of both sacroiliac joints as depicted on the radiographs, in the typical triangular configuration. There are no erosions, ankylosis, or effusion

Salient Features on History and Physical Exam

The history can often be very useful in diagnosing SpA and differentiating it from mimickers. The features of inflammatory back pain can be found in Table 5 and, when present, suggest the need for further investigation. **Extra-axial features**, when present, can help point in the direction of SpA as well: conjunctivitis, uveitis, dactylitis ("sausage" digit), psoriasis, enthesitis (pain at tendon insertion points, commonly the Achilles tendon or plantar fascia), urethritis, peripheral joint arthritis, and inflammatory bowel disease. A family history of psoriasis, Crohn's disease, or ulcerative colitis will also raise the clinical suspicion for SpA.

Physical exam can be helpful in diagnosing SpA and following progression but will often be normal early in the course of disease. The exam should focus on the presence of extra-axial features and measurements of spinal mobility: occiput-to-wall distance, thoracic excursion, lateral spinal flexion, and forward spinal flexion. Abnormalities in spinal mobility may reflect active inflammation and be reversible with treatment, or may reflect chronic damage and be irreversible. Measurement of spinal mobility can be useful to predict disease progression and to follow a patient's response to treatment. The Assessment of SpondyloArthritis International Society (ASAS) handbook is an excellent resource for assessing spinal mobility (Sieper et al.

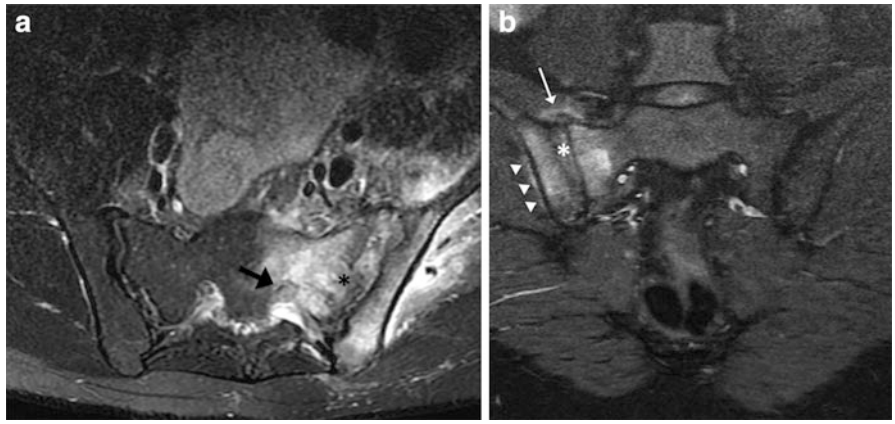

Fig. 3 (**a**) MRI showing infectious sacroiliitis. Axial STIR image shows florid diffuse edema in the sacrum and left ilium as well as in the presacral soft tissues, adjacent gluteal, and iliacus muscles. There is widening of the left sacroiliac joint with an effusion, capsular distension, and cortical destruction (asterisk). The left sacral nerve is thickened (arrow), likely reactive due to the surrounding infective change. (**b**) MRI showing infectious sacroiliitis. The findings on this coronal STIR image are more subtle than the previous example, but the unilateral features of pericapsular edema, effusion with joint distension (arrow) and marrow edema across one sacroiliac joint, are strong indicators of infective sacroiliitis. There is also erosive change with effusion (asterisk) and edema in the adjacent gluteus minimus muscle (arrowheads)

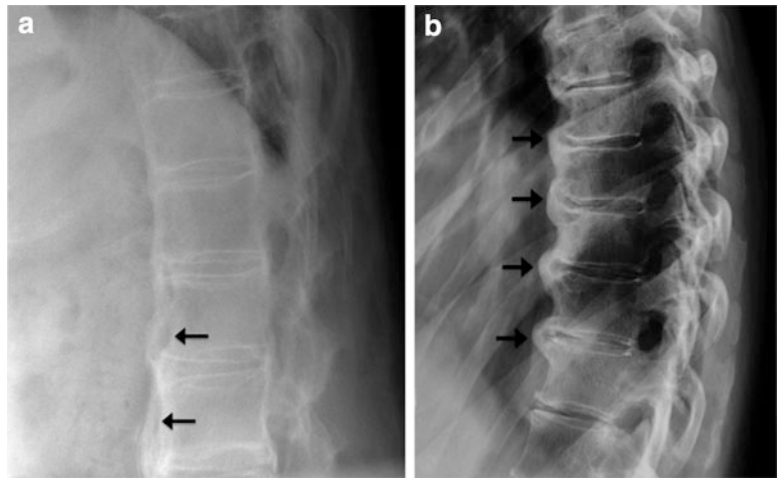

Fig. 4 (**a**) X-ray showing diffuse idiopathic skeletal hyperostosis (DISH). This lateral radiograph of the thoracic spine demonstrates flowing ossification along the anterior longitudinal ligament with radiolucency between the vertebral body and anterior longitudinal ligament (arrow). (**b**) X-ray showing diffuse idiopathic skeletal hyperostosis (DISH). This thoracic radiograph shows exuberant thickening of the anterior longitudinal ligament (black arrows) across contiguous vertebrae. There is only minor endplate degenerative change with preservation of the intervertebral disc heights

2009). Appropriate investigations for suspected SpA are outlined in Table 6.

HLA-B27 positivity is seen frequently in SpA, particularly in ankylosing spondylitis and reactive arthritis. However, it is common enough in the general population (6–8% in North America with significant geographic variation) that its value diagnostically is limited. Only 1 in 50 patients with +HLA-B27 will develop ankylosing spondylitis in their lifetime.

Table 5 Recognizing inflammatory back pain

Insidious onset before age 40
Duration of pain and stiffness at least 3 months
Morning stiffness >30 min
Improvement with exercise but not with rest
Alternating buttock pain
Awakening in second half of the night due to back pain/stiffness
Good response to NSAIDs

Table 6 Appropriate use of investigations for suspected SpA

	Investigation	Relevance
Bloodwork	ESR and CRP	Normal in 30–50% of cases
	HLA-B27	Present in 90% of Caucasians with AS, 50–80% of non-Caucasians
Imaging	Plain radiography	X-ray changes only present in 30% at time of diagnosis
	MRI spine	Highest sensitivity for sacroiliitis

X-ray features of spondyloarthritis include (Figs. 5 and 6):

- Sacroiliac Joints:
  - Joint space narrowing starting at the lower two-thirds of sacroiliac joint
  - Subchondral sclerosis and erosions starting at the iliac side of the sacroiliac joint
  - May see pseudo-widening secondary to erosions
  - Later in disease course will see ankylosis (fusion) of the sacroiliac joint
- Spine:
  - Romanus lesions ("shiny corner sign"): erosions and sclerosis at vertebral body corners
  - Squaring of the vertebral bodies (loss of normal convexity)
  - Syndesmophytes (can be differentiated from osteophytes by the vertical direction of outgrowth and the relative sparing of the disk space)
  - Ossification of the interspinous ligament leading to "dagger spine" appearance

MRI features of spondyloarthritis include (Figs. 5 and 7):

- STIR sequence for active inflammatory lesions:
  - Bone marrow edema
  - Capsulitis
  - Synovitis
  - Enthesitis
- T1-weighted sequence for chronic inflammatory lesions:
  - Subchondral sclerosis
  - Subchondral erosions
  - Syndesmophytes
  - Fat metaplasia
  - Joint space narrowing
  - Ankylosis

Non-radiographic Axial Spondyloarthritis

Axial spondyloarthritis has been divided into "radiographic" (X-ray changes present) and "non-radiographic" (meets diagnostic criteria based on a combination of clinical features, HLAB27 positivity, and/or MRI evidence of sacroiliitis). It is thought that non-radiographic SpA may represent an "early stage" where frank erosions and ankylosis have not yet occurred; however, while some of these patients develop progressive X-ray changes over time, others do not.

Thus, if a patient has a history and physical examination consistent with SpA, or has other suggestive extra-axial manifestations, it is important to consider ordering an MRI, even if plain radiographs are unrevealing. This could also be done in conjunction with a rheumatology consultation.

Subclinical Spondyloarthritis

Recent literature has suggested that MRI changes, particularly bone marrow edema, may be more common in the general population than originally thought. Studies of both elite and recreational athletes without reported back pain have reported rates of sacroiliac joint bone marrow edema up to 30–40% (Lambert et al. 2016). These patients usually do not have axial SpA and do not require treatment. In addition, many patients with

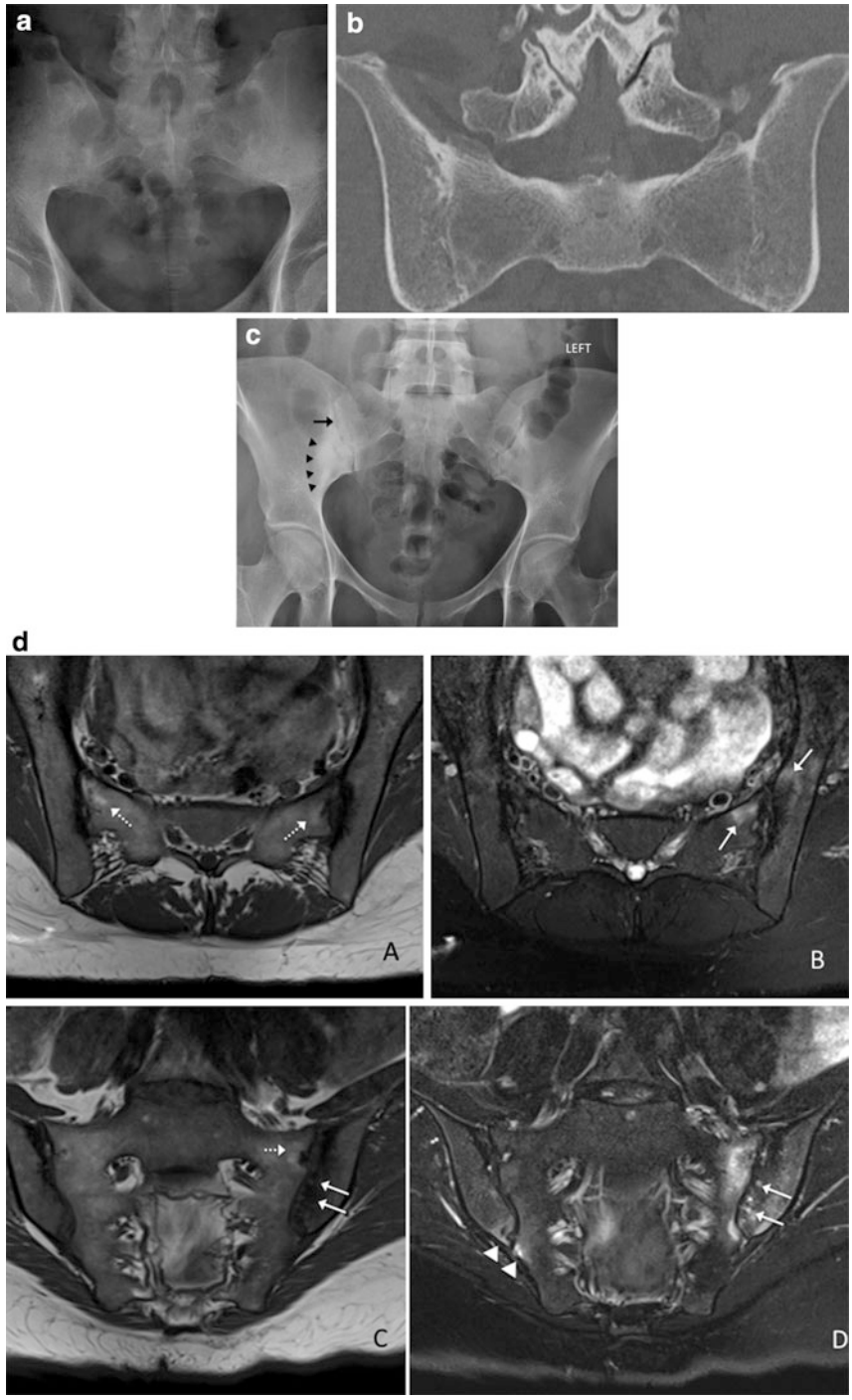

Fig. 5 (**a**) There is complete ankylosis of the sacroiliac joints, in keeping with grade 4 sacroiliitis. (**b**) Coronal image of the CT demonstrates complete ankylosis of the sacroiliac joints, in keeping with grade 4 sacroiliitis. (**c**) Radiograph of the sacroiliac joints demonstrates mild sclerosis in the left sacroiliac joint with minimal erosive change, compatible with grade 2 sacroiliitis. In the right sacroiliac joint, there are erosions (arrow) and marked sclerosis (arrowheads), in keeping with grade 3 sacroiliitis. (**d**) (*A*) Axial T1 and (*B*) STIR images with sclerosis and erosions involving the sacroiliac joints, more prominent on the left. There is multifocal geographic involvement and

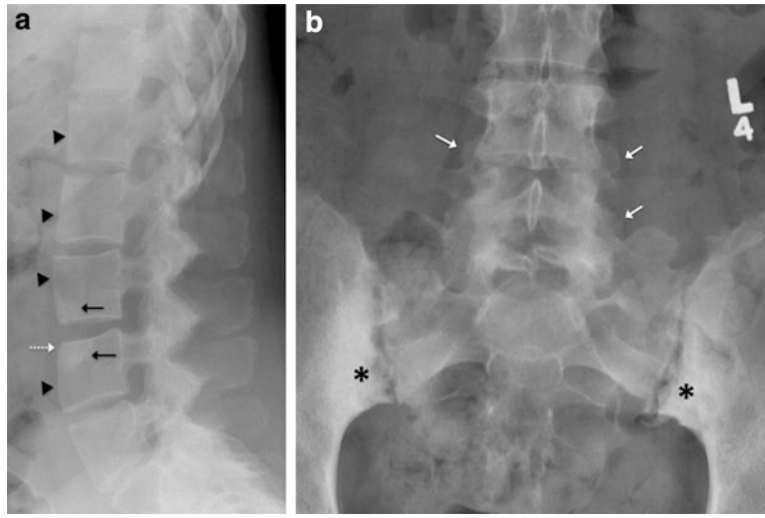

Fig. 6 (**a**) Lateral radiograph of the lumbar spine demonstrates squaring of the vertebral bodies (arrowheads). The irregularity and erosion at the anterior edge of the endplates, known as Romanus lesions (dashed white arrow), are early findings in inflammatory spondyloarthropathies such as ankylosing spondylitis. The "shiny corners" in the anterior aspects of the endplates (black arrows) represent reactive sclerosis and a healing response to the inflammatory erosions. (**b**) Frontal radiograph demonstrates parasyndesmophyte formation (arrows) and features of grade 3 sacroiliitis with erosions and sclerosis (asterisks) involving the sacroiliac joints. Incidental note of spinal dysraphism is present in L5 vertebral body

HLA-B27-related conditions, particularly inflammatory bowel disease, may have radiographic or MRI changes of sacroiliitis without any clinical signs or symptoms (Bandinelli et al. 2016). It is still unclear whether treatment in these patients would lead to improvement in outcomes, but referral to a rheumatologist could be considered for further assessment.

Initial Treatment Approach

All patients with SpA should be counselled on smoking cessation and regular exercise. Appropriate physiotherapy is a cornerstone of management and can help to prevent the restrictions in movement that are common later in the disease course.

Pharmacotherapy has been shown to be effective in symptomatic patients with radiographic and non-radiographic SpA, and the treatment approach is the same. Nonsteroidal anti-inflammatory drugs (NSAIDs) are first-line treatment and can be very effective. There is no evidence that one NSAID is more effective than another. A trial of at least 3 months of daily use is required to determine whether a significant decrease in pain and stiffness has occurred. Switching to a different NSAID is generally indicated if one is unsuccessful. Contraindications to NSAID use include chronic kidney disease, history of gastrointestinal bleeding, and coronary artery disease. Caution

Fig. 5 (continued) subchondral sclerosis with T1-hyperintense regions of sacral fat metaplasia (dashed arrows) on the T1 image. On the STIR image, there is T2-hyperintense edema (solid arrow) around the anterior aspect of the left sacroiliac articulation. (*C*) Coronal T1 and (*D*) STIR images with sclerosis and erosions involving the sacroiliac joints, more prominent on the left. There are erosions (white arrows on both images), more prominent in the iliac side of the left sacroiliac joint where there is also significant edema. In the right sacroiliac joint, there is fat metaplasia (dashed arrow) indicating chronic burnt out inflammatory change on the T1 image. There is a small focus of subchondral edema posteriorly in the right sacroiliac joint

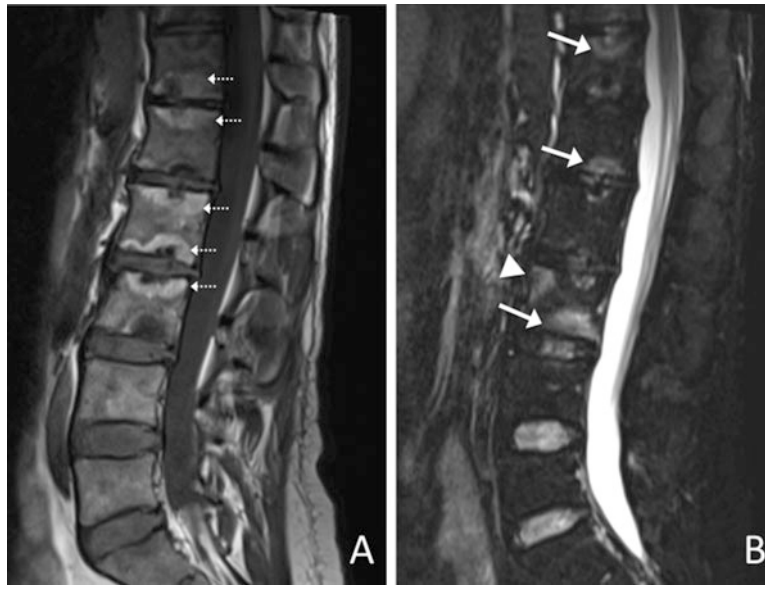

Fig. 7 MRI demonstrating features of spondyloarthritis. (**a**) Sagittal STIR image demonstrates foci of edema at the endplates reflecting inflammatory involvement of the intervertebral discs, described as Andersson lesions (white arrows). The T2-hyperintensities in the anterior corners of the vertebral body (arrowhead) depict "corner inflammatory lesions" in syndesmophyte formation. (**b**) Sagittal T1 image demonstrates T1-hyperintensies surrounding the foci of endplate edema (dashed arrows) depicting fat deposition, reflecting the chronic inflammatory and erosive changes

should be used in the elderly and in those with underlying hypertension or inflammatory bowel disease.

If NSAIDs are unsuccessful, the next treatment option is biological disease-modifying agents. These medications, known as "monoclonal antibodies" or "biologics," are very effective but can be prohibitively expensive for some patients. Common classes of biologics include the anti-TNF antibodies (adalimumab, certolizumab, golimumab, etanercept, and infliximab) as well as an anti-IL-17 antibody, secukinumab. Many other biologic therapies are being developed, and the list of approved medications for SpA is expected to grow. These drugs should be prescribed and monitored by a rheumatologist.

Regular use of NSAIDs and biologics has been shown to improve pain, function, and quality of life and reduce radiographic progression in patients with SpA. Patients are encouraged to remain on therapy long-term, although the optimal treatment duration and approach to tapering or discontinuing medication is still not known.

Appropriate Referrals

All patients with suspected SpA should be referred to rheumatology for further assessment and management. A comprehensive exercise program with involvement of physical therapists should be considered as well.

Case Resolution

This woman's symptoms are classic for inflammatory back pain. She should be investigated for potential spondyloarthritis and treated accordingly; the L4–L5 stenosis is likely incidental.

Clinical Pearls and Myths

- The hallmark of ankylosing spondylitis is a history of inflammatory back pain.
- Myth: ankylosing spondylitis is a male-only disease.

  - In fact, newer cohorts suggest that AS is present in a male: female ratio of 2:1.
- Myth: X-ray findings are required to make a diagnosis of SpA.
  - Non-radiographic SpA can be diagnosed based on clinical features, HLA-B27 positivity, and/or consistent MRI findings.
- Think of SpA in patients with back pain and an underlying diagnosis of inflammatory bowel disease, psoriasis, or uveitis.
- Think of OCI as a common SpA mimicker in women with postpartum back pain.

Case 3

Case Description

A 75-year-old woman presents with severe mid-thoracic back pain for the past 4 weeks. She cannot recall any trauma, although it started after carrying some heavy groceries up the stairs. She has a history of breast cancer and underwent curative surgery 10 years ago. On further questioning, she describes 2 inches of height loss since her mid-20s.

Differential Diagnosis

Severe, acute back pain in an older woman should be investigated for vertebral fracture. Osteoporotic fractures usually occur in postmenopausal women and often with little trauma. Risk factors include low body weight, smoking, excessive alcohol use, long-term corticosteroids, and family history of osteoporosis. Other causes of vertebral fractures are listed in Table 7.

Salient Features on History and Physical Exam

Epidemiological studies suggest that 1–4% of patients presenting to primary care with back pain will be found to have a spinal fracture (Downie et al. 2013). Pain from spinal fractures often occurs acutely and eventually diminishes over time. It is often worse with standing and better lying down due to the force of gravity on the vertebrae. Patients may also notice new loss of height or curvature to the spine.

Table 7 Causes of vertebral compression fracture

Osteoporosis
Trauma
Primary bone tumors (hemangioma, giant cell tumor)
Hematologic malignancies (multiple myeloma, lymphoma)
Solid organ metastases (breast, renal, prostate, lung)

Table 8 Red flags in back pain history

Red flags: spinal fracture	Red flags: malignancy
Prolonged corticosteroid use	History of malignancy
Recent trauma (including fall)	Significant weight loss
Older age (men >65, women >75)	No improvement after 1 month

There are multiple "red flags" that have been identified to predict which patients require imaging to rule out fracture or malignancy (Table 8); however, most of these have a high false positive rate according to a recent Cochrane review (Williams et al. 2013). The only physical exam feature suggestive of fracture was a contusion or abrasion at the site of pain consistent with recent trauma. Patients presenting with any of these features and a history of new back pain likely warrant further imaging.

Appropriate Use of Investigations

The suspicion of a vertebral compression fracture should be confirmed radiographically. The gold standard remains lateral thoracolumbar spine X-rays, which have a high sensitivity and specificity for the diagnosis. More recently, Vertebral Fracture Assessment using bone mineral densitometry has been found to provide similar diagnostic information with less radiation.

If an underlying malignancy is suspected, MRI spine is the investigation of choice. Pathologic fractures and underlying lesions can usually be

Table 9 Investigations after identifying osteoporotic fracture

	Investigation	Relevance
Bloodwork	CBC, creatinine, calcium, 25-OH vitamin D level	>Indicated in preparation for starting anti-osteoporotic therapy
	Phosphate, ALP, TSH, protein electrophoresis	>Indicated to workup for secondary causes of osteoporosis
Imaging (Fig. 8)	Thoracolumbar X-ray	>All patients should be assessed for presence of multiple fractures
	Bone mineral density	>Defines baseline so response to treatment can be monitored
	MRI spine	>If malignancy is suspected
	CT spine	>If MRI is unavailable or contraindicated

identified and differentiated from osteoporotic fractures with this modality. If an osteoporotic fracture is diagnosed, guidelines suggest screening for secondary causes of osteoporosis as listed in Table 9 (Papaioannou et al. 2010).

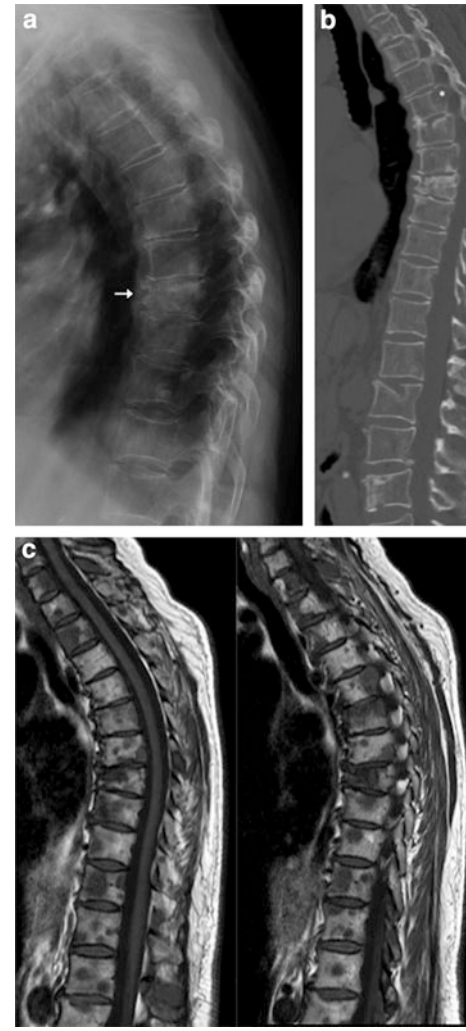

Fig. 8 (**a**) Lateral thoracic radiograph demonstrates a vertebral compression fracture of the T8 vertebral body (arrow). There is mild sclerosis within the fractured vertebral body with questionable sclerotic foci in several of the vertebral bodies and degenerative changes present. (**b**) CT performed to evaluate the thoracic compression fracture shows sclerosis in the vertebral body, with small sclerotic foci in the vertebral endplates in the two levels above and another lumbar vertebral body. There are several hypodense foci in the posterior aspect of the vertebral bodies above the compression fracture with posterior bulging, suspicious for metastases. (**c**) MRI was performed for further evaluation of the compression fractures. Two sagittal T1-weighted images demonstrate multiple foci of low T1 signal intensities in the anterior and posterior columns of the thoracolumbar spine, in keeping with diffuse metastases throughout the spine. The metastatic burden is underestimated on radiographs and CT. There is no spinal stenosis or cord compression on this study

Initial Treatment Approach

Most vertebral fractures can be treated conservatively with adequate analgesia, starting with acetaminophen, as well as rehabilitation. There is also low-quality evidence to support use of calcitonin for management of acute pain from vertebral fractures. When the pain from vertebral fractures does not respond to the above treatments, a trial of opioid therapy may be reasonable; these medications are best prescribed and monitored by the family physician. A subset of patients with vertebral fractures will be severely functionally limited and may benefit from surgical intervention. Surgical procedures for compression fractures will be discussed in more detail later in this volume.

Table 10 Evidence-based management for osteoporosis (Papaioannou et al. 2010)

Non-pharmacologic	Regular, weight-bearing exercise
	Education on fall prevention strategies
	Daily calcium intake of 1200 mg (diet or supplementation)
	Daily vitamin D intake of 800–2000 international units
Pharmacologic	Bisphosphonates: alendronate, risedronate, or zoledronate
	Hormonal therapy: estrogen-containing HRT or raloxifene
	Denosumab
	Teriparatide

Additionally, any patient with a fragility fracture at the spine has osteoporosis by definition, regardless of their bone mineral density (BMD). These patients should be strongly encouraged to follow evidence-based treatment guidelines for osteoporosis, including both pharmacologic and non-pharmacologic measures (Table 10). There is no evidence that use of bisphosphonates impairs healing from vertebral fractures; therefore, they should be started as soon as possible to prevent further fracture events.

Appropriate Referrals

Most family physicians will feel comfortable managing osteoporosis and fragility fractures. However, difficult-to-treat cases, especially patients who fracture while on appropriate therapy, may warrant a referral to specialized osteoporosis clinic for assessment.

Case Resolution

Based on her history of breast cancer, this patient underwent an MRI which did not show any evidence of malignancy. A bone mineral density scan was performed which confirmed low bone mass in the lumbar spine, with a T-score of −2.5. Screening bloodwork did not reveal any secondary causes of osteoporosis. This patient was treated with adequate pain control and started on calcium, vitamin D, and an oral bisphosphonate. Ongoing management will be provided by her family physician.

Clinical Pearls and Myths

- Metastatic disease must be ruled out in patients with new back pain and cancer history.
- Any fragility fracture is an indication for treatment with anti-osteoporotic therapy.
- There is no need to delay initiation of osteoporosis therapy after a fracture.

Conclusion

Investigations to Avoid

While it may sometimes seem that back pain has an infinite number of causes, it is important to remember the list of medical conditions that are *not* a cause of back pain so that investigations can be directed appropriately. Too often, a comprehensive "autoimmune workup" is ordered as an attempt to explain many types of chronic pain; however, ordering these tests without concomitant clinical features leaves both patients and healthcare providers with few satisfying answers.

Autoimmune diseases like rheumatoid arthritis and systemic lupus erythematosus are associated with small and large joint pain and swelling, but as a rule do not affect the lower back. The same principle applies to patients with vasculitis, myositis, and autoimmune thyroid disease. For this reason, ordering the following investigations in the workup of chronic back pain is **unlikely to be useful**: antinuclear antibodies (ANA), rheumatoid factor (RF), thyroid-stimulating hormone (TSH), or antithyroid antibodies.

Similarly, when a patient with a known diagnosis of rheumatoid arthritis or lupus presents with low back pain, their underlying condition should not be blamed and an alternate explanation should be sought. These patients have a higher risk of infection and malignancy compared to the general population and are also more likely to suffer from obesity and low levels of physical activity which may also contribute to chronic back pain.

When to Refer

Rheumatologists have expertise in the diagnosis and management of patients with spondyloarthritis, and any patient with this suspected diagnosis can be referred for further assessment. Inflammatory back pain in a young patient, particularly if they have abnormalities on SI joint imaging and extra-articular features, would be a clear reason for referral. The presence of a positive ANA or HLA-B27 *without* concomitant clinical features does not necessarily require evaluation by a rheumatologist.

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Psychosocial Impact of Chronic Back Pain: Patient and Societal Perspectives

6

Y. Raja Rampersaud

Contents

Abstract

Low back pain (LBP) is a highly prevalent, poorly managed condition that is the number one cause of years lived with disability (YLDs) around the world. It is estimated that one in four prevalent cases of LBP is responsible for 77% of the YLDs. The socioeconomic burden of LBP, particularly in developed countries, is enormous with medical expenditures rivalling that of diabetes or ischemic heart disease. The individual burden of LBP is also tremendous and commonly results in psychosocial distress and dysfunction. The most commonly cited negative prognostic psychological factors are depression, fear-avoidance, and pain catastrophizing. However, pain self-efficacy and patient beliefs have been found to even more strongly associate with actual outcome. Qualitative studies of chronic LBP patients have relieved consistent themes reflecting difficulties in coping with a sense of stigmatization that is associated with an invisible problem, loss of wellness, loss of self, loss of relationships, and loss of the future. For chronic LBP, both exercise therapy and cognitive behavioral therapy (CBT) are now recommended as first-line treatments that should be considered for routine use in addition to providing education regarding the nature of LBP and advice to

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remain active. These recommendations necessitate timely assessment, regardless of duration of symptoms, in LBP patients for the complex biopsychosocial prognostic factors that may impact patient and societal outcome.

Keywords

Chronic low back pain · Biopsychosocial model · Psychological · Social · Socioeconomic · Impact · Individual · Societal

Epidemiology of Chronic Low Back Pain

Burden of Low Back Pain

The Global Burden of Disease Study (Global Burden of Disease, Injury Incidence, Prevalence Collaborators 2016) has demonstrated that the global prevalence of low back pain (LBP) continues to increase. The global point prevalence of LBP in 2015 was 7.3%, and the estimated median 1-year prevalence in adults was 37% (Hartvigsen et al. 2018). LBP is more common in women, and the peak prevalence is in mid-life. LBP is the number one cause of years lived with disability (YLDs) with 77% of the YLDs accounted for by approximately one in four prevalent cases (Global Burden of Disease, Injury Incidence, Prevalence Collaborators 2016). This suggests that although most people experiencing LBP have low levels of disability, the enormous societal impact of LBP is driven by high prevalence and a subgroup of LBP patients with high levels of persistent disability. In 2013, low back and neck pain were globally ranked the fourth leading cause of disability-adjusted life years (DALYs) just after ischemic heart disease, cerebrovascular disease, and lower respiratory infection (Global Burden of Disease 2015 DALYs and HALE Collaborators 2015). This represents an increase over time from being ranked seventh in 1990 and fifth in 2005. Furthermore, low back and neck pain are ranked as the number one cause of DALYs in most high-income countries.

For decades the overarching public and clinical messaging for LBP (e.g., recommendations from clinical practice guidelines) has been that LBP will get better in the majority of patients. Unfortunately, without providing the full context of this message, many patients perceive the term "get better" to mean resolution. However, multiple studies have demonstrated up to 2/3 of individuals with LBP at both the population and primary care level may have recurrent (i.e., episodic) or persistent LBP at 1 year (Hartvigsen et al. 2018). Most of the personal and societal impact of LBP is in those with chronic LBP (CLBP) which is conventionally considered to be LBP symptoms lasting more the 12 weeks. The National Institute of Health (NIH) Pain Consortium Task Force on research standards for CLBP recently defined CLBP as a "back pain problem that has persisted at least 3 months and/or has resulted in pain on at least half the days in the past 6 months" (Deyo et al. 2014). A call for increase in prognostic research to determine which patients will develop CLBP and system-wide strategies for mitigation of chronicity is at the forefront of the paradigm shift in LBP care (Foster et al. 2018).

The discrepancy between favorable natural history and persistence or recurrence is multifactorial and needs to be considered based on two main perspectives. First is the clinical setting that is being studied: the population, primary allied healthcare (e.g., physiotherapy, chiropractic), primary medical care (i.e., family doctor or nurse practitioner), and secondary or tertiary care (e.g., specialized chronic pain clinic, surgical clinic). Each scenario will provide a progressive increasing prevalence or severity of CLBP (persistent or recurrent). Second is most prevalence studies are cross-sectional or of limited duration and thus do not reflect the longitudinal aspects of LBP. Studies assessing the course of LBP over long periods are limited but can provide valuable insight regarding the true nature of LBP. Recent work from our center has demonstrated a sobering picture of the long-term trajectory of LBP in the Canadian population. Canizares et al. (2019) reported on a representative sample ($n = 12{,}782$) of the Canadian population over a 16-year period from 1994 to 2011. Group-based trajectory analysis was used to group participants based on the nature of their back pain over the 16-year follow-up period.

Overall, 45.6% of participants reported back pain at least once during the study period. Of people with back pain, four distinct trajectories were identified: persistent (18.0%), developing (28.1%), recovery (20.5%), and occasional (33.4%). This is consistent with the findings of the Global Burden of Disease Collaboration study that a subgroup(s) of back pain patient (one in four) generates the majority of back pain impact (Global Burden of Disease, Injury Incidence, Prevalence Collaborators 2016). Specifically, the persistent and developing groups, which made up almost half of the patients reporting back pain, were characterized by having more pain-limited activities, disability, depression, and medical comorbidities. Furthermore, only one in five people with back pain recovered over the 16 years, and one in three continued to report occasional back pain. There is substantial literature that the natural history of LBP is not one of resolution in the vast majority of patients, provides a strong rationale for a change in the basic assumptions and approach to the management of LBP. In short LBP should be viewed as a chronic condition.

The Need for a Biopsychosocial Model

A critical part of changing the approach to LBP assessment and management is identification of risk factors for a less then favorable outcome (Hartvigsen et al. 2018). Identifying who is at risk and what factors are potentially modifiable is of paramount importance in CLBP prevention, assessment, and management. Certainly, prognostic research in LBP is by no means novel. The challenge has been the implementation and practice of prognostic care for LBP. Reviewing various multivariate predictive models, Hartvigsen et al. (2018) note several independent risk factors for individuals that are likely to develop a more disabling course of LBP: high pain intensity, psychological distress, accompanying leg pain, and pain at multiple body sites. A wide variety of well-known risk factors associated with poor outcomes have been published. These are nicely summarized by Hartvigsen et al. (2018) and include but are not limited to *symptom-related factors* (previous episode of LBP, higher pain intensity, presence of leg pain), *lifestyle factors* (smoking, higher body mass index, less physical activity), *psychological factors* (depression, catastrophizing, fear-avoidance behavior), and *social factors* (physical work, lower education, compensation claim, poor work satisfaction). However, as noted by Kent and Keating (2008), these predictive studies only explain a small degree of the variance in the outcome of LBP, with most explaining only 30–40%. Thus, despite great advances in identifying risk factors for CLBP, much of what is known to drive poor outcomes has not been comprehensively studied in the same population or remains unknown. Consequently, what factors should be assessed, when they should be assessed, and best practices for assessment and management of LBP remain a source of ongoing tribal like debate.

Despite broad acknowledgment that a biopsychosocial model is critical to advancing LBP care, the majority of LBP assessment and management remain focused on the biomedical model.

This chapter focuses on the psychosocial aspect of CLBP.

Psychosocial Impact of Chronic Low Back Pain

In the broadest sense, CLBP affects all aspects of an individual's life including day-to-day function, mood, social interactions, recreational activities, and work life. I am not aware of any conclusive studies that assess all of these aspects simultaneously. Thus, we are reliant on quantitative and qualitative systematic reviews to inform us of the broader impact of CLBP. Within the psychosocial realm of CLBP, there is typically greater focus on the psychological aspects. However, the social consequences of CLBP are often the primary drivers of secondary psychological cognition and behavior, and therefore these two dimensions should be considered together. The use of psychosocially oriented screening questions, so-called yellow flags, to identify psychosocial barriers to LBP recovery has been noted in many LBP clinical practice guidelines and clinical tools

(Nicholas et al. 2011). Commonly cited "yellow flags" are an individual's belief that pain and activity are harmful leading to fear-avoidance behavior or sickness behavior (e.g., extended rest), low or negative mood, social withdrawal, overprotective family or lack of support, and treatment expectations or beliefs that are against best evidence or are focused on a passive cure. Increased focus on the biopsychosocial approach to LBP has demonstrated that psychosocial risk factors for developing CLBP are much more prevalent than previously thought. In a recent randomized controlled trial, patients presenting to primary care with LBP demonstrated varying degrees of psychological risk factors with 46% rated as moderate risk and 28% being categorized as high risk of chronicity (i.e., persistent LBP) using the Keele StarT Back screening tool (Hill et al. 2011).

Psychological Factors

A large body of evidence confirms that psychological factors, including emotions, beliefs, or avoidance or other maladaptive behaviors, are linked to poor outcomes in low back pain (Chou and Shekelle 2010). While the majority of studies are in the setting of nonsurgical care, it must be noted that psychological factors are also independently associated with poor outcome in surgical intervention for LBP (Wilhelm et al. 2017). A large number of psychological factors have been assessed over the last few decades and most have been found to have a negative association with LBP patient outcomes. However, there are contradicting studies regarding the impact or dominance of one psychological factor over another, whether factors are individually modifiable or not, and whether these factors are mediated by other psychological or non-psychological (e.g., social) factors. The nature and impact of psychological factors in CLBP is an extremely complex issue and thus is often very difficult for both clinicians and their patients to fully understand.

The most commonly cited and clinically assessed psychological factors are depression, fear-avoidance, and pain catastrophizing (Pincus and McCracken 2013). A detailed description of psychological theory is out of scope for this chapter and is not my area of expertise. Pincus and McCracken (2013) provide an excellent review of this topic. Key components of their review are briefly summarized herein to provide a non-psychologist interpretation of the available LBP psychology literature. Depression or low mood is commonly reported in LBP. Depression tends to occur more in the chronic phase and is a commonly identified poor prognostic factor across different key outcomes (i.e., negatively impacts pain, function, and work status). Fear-avoidance covers a broad spectrum of fearful beliefs or cognitions about pain inducing movement, activities, or re-injury and associated patterns of avoidance behavior. The latter can range from simple (e.g., avoiding any lifting) to very elaborate movements or avoidant activity patterns (e.g., bizarre movement patterns or behavioral responses when attempting to do simple task). Fear-avoidance is often a more significant issue when considering work-related factors but can also significantly impact day-to-day function. Pain catastrophizing is the tendency for an individual to describe a pain experience in a more irrational manner than you would expect from an average person. There are often magnification, rumination, and feelings of helplessness regarding the pain experience. Patients also may have maladaptive cognition regarding future events and a relative inability to inhibit pain focused thoughts in anticipation of, during, or following a painful experience.

Another important factor that is receiving more clinical and academic focus is pain self-efficacy. Described by Bandura (1977), self-efficacy is an individual's belief about how well they can cope with difficult situations or their ability to achieve a desired outcome. Higher levels of pain self-efficacy are typically associated with lower levels of disability despite the presence of pain. Lee et al. (2015) performed a systematic review and meta-analysis of which psychological factors are involved in the process of pain leading to disability. Specifically, they reviewed mediation analysis studies. Mediation analysis seeks to identify and explain the mechanism or process that underlies

an observed relationship between an independent variable (e.g., pain) and a dependent variable (e.g., disability) by assessing the influence of the independent variable on a third variable, often termed a mediator variable (e.g., depression), that may influence the dependent variable. Using data from 12 mediation studies, the authors identified self-efficacy, psychological distress (depression/anxiety), and fear were mediators that explained some of the association between LBP pain and developing chronic disability. In a comprehensive study of psychological obstacles to recovery in primary care LBP patients, Foster et al. (2010) assessed the relative strength of 20 different baseline psychological factors to predict patient-reported disability at 6 months. At baseline, most factors were related to degree of disability, with perception of consequences, depression, and pain self-efficacy most strongly associated. However, when considered together, depression, catastrophizing, and fear-avoidance were not independent predictors of outcome. Patients' perceptions regarding the timeline (i.e., belief that their LBP will be chronic), illness identity (i.e., number of symptoms related to their LBP), perception of personal control, and pain self-efficacy were the factors that remained significantly associated with outcome (explaining 56.6% of the variance of outcome). The authors note that patients "who perceive themselves able to exercise control over their back problem, now and in the future, are less likely to develop longer-term disability." I would add that it must be kept in mind that CLBP is a dynamic process; thus psychosocial factors are likely overlapping and/or cumulative to varying degrees over time. Consequently, as much as it is unwise to focus LBP assessment or management on the biomedical model only, focusing on a single psychological factor would likely be equally ineffective.

A patient's acceptance, or lack thereof of chronic pain has been shown to be a significant and independent factor in the outcome of those dealing with CLBP or other types of chronic pain (McCracken and Vowles 2008). Although this may seem intuitive, assessing and managing a patient's ability to accept and deal with chronic pain is not something that is typically addressed in the front-line management of LBP. Similarly, a patient's pain beliefs, and expectations are also independently associated with their recovery from LBP as well as their response to different treatments (Main et al. 2010). In a systematic review by Ramond et al. (2011), the authors found that "depression, psychological distress, passive coping strategies and fear-avoidance beliefs were sometimes found to be independently linked with poor outcome, whereas most social and socio-occupational factors were not." However, a patient's or care provider's perceived beliefs regarding persistent LBP was the factor that was most consistently linked with actual outcome. Although, negative beliefs and expectations are often a part of behavioral/psychological treatment, they are typically not addressed in the early aspects of LBP care and thus may become entrenched (i.e., reinforced) due to persistent or recurrent pain. As noted above, persistence or recurrence is the more likely course of LBP in patients seeking healthcare.

In a Canadian population-based survey of 2400 adults, half of the respondents had pessimistic views of LBP (Gross et al. 2006). Respondents felt that back pain makes "everything in life worse," worsens over time, and eventually will "stop you from working." Interestingly the authors at that time noted: "Contrary to recent evidence-based clinical practice guidelines that advocate that back pain is a benign, self-limiting condition, most subjects in our sample had pessimistic beliefs concerning back pain." The authors concluded: "Public association back pain beliefs in the 2 Canadian provinces sampled are not in harmony with current scientific evidence for this highly prevalent condition. Given the mismatch between public beliefs and current evidence, strategies for re-educating the public are needed." As our knowledge of the natural history of LBP continues to improve, the pateint beliefs reported by Gross et al. (2006) were reflective of the actual experience of many LBP patients. Until recently, the messaging from LBP clinical practice guidelines was in fact misaligned with the reality of LBP patients.

Walker et al. (2004) reported that half of LBP patients do not actually seek healthcare. It is likely

that these patients are the ones who have a favorable natural history. In a systematic review of studies assessing the course of non-specific acute LBP patients seeking treatment in primary care, Itz et al. (2013) found that 65% of patients still report pain at 1 year. The authors concluded: "The findings of this review indicate that the assumption that spontaneous recovery occurs in a large majority of patients is not justified." Similar conclusions can be drawn from the cumulative trajectories of back pain (see above) in the population where almost 50% of individuals experience a persistent or developing trajectory of back pain (Canizares et al. 2019). It is the belief of the author that the decades of clinical practice guideline messaging that LBP is a benign and self-limiting condition, while correct from a medical perspective (i.e., no sinister pathology and typically mild in severity), may have (at least in part) led to some of the more strongly held pessimistic beliefs of patients with CLBP.

The optimistic message of "don't worry it gets better in most people" is still reasonable for public health campaigns. This, however, is not the intended audience of clinical practice guidelines. This message has been delivered for decades by health providers to patients who are seeking healthcare. Given the substantial prevalence data on the transition from acute to chronic LBP (Hartvigsen et al. 2018), this messaging was doomed to fail in the majority rather than a minority of patients as intended. For the large number of patients seeking care who do not "resolve" (whether their beliefs and expectation were falsely set by a well-intended provider or put forth by financially incentivized providers promising a "cure" for LBP), persistent or recurrent pain may lead to a negative perception or belief that something more serious or unmanageable is occurring. This also puts the provider in a difficult position to explain why the pain is not getting better as they said it would. It is the belief of this author that this common scenario leads to the perfect storm of overmedicalization of LBP by the both the patient and healthcare provider(s). This is certainly a multifactorial issue driven by persistent/recurrent symptoms, heightened/worsening symptoms, the potential for loss of or lost patient confidence in the provider(s), clinical uncertainty, and the need/desire to do something.

Social Factors

At a population level, CLBP disproportionately affects people with low education and socioeconomic status association (Shmagel et al. 2016). Possible reasons for this may be related to inadequate health literacy, poor access to healthcare, and greater likelihood of being in labor-intensive work (Hartvigsen et al. 2018). At an individual level, the social implications and interplay of LBP are much more complex and are best understood through qualitative methods of inquiry. Three available systematic reviews and meta-syntheses of the qualitative research on patients' lived experience with LBP provide a deeper understanding of the more complex personal and nuanced aspects of LBP. Interestingly all three were published within a year of each other (Froud et al. 2014; Snelgrove and Liossi 2013; Bunzli et al. 2013) and presented different but interrelated perspectives.

In the study by Froud et al. (2014), the authors reviewed 49 articles from 42 studies. They reported on four first-order themes from the qualitative literature:

Theme 1 – Activities: loss of function, particularly regarding domestic chores, important recreational activities (friends and family), and an inability to plan ahead were consistently found across studies.

Theme 2 – Relationships: significant negative impact on personal relationships was a common impact of CLBP. This occurred from two perspectives. First and more common is being worried about how their inability to participate in activities with family or friends was affecting others (e.g., holding others up or ruining it for others), and second is worrying about the pain that would occur if they participated. However, some felt unsupported in these relationships. Regardless of the perspective, the end result was often social withdrawal and isolation.

Theme 3 – Work: the impact of LBP on work was very prevalent and included the need (and difficulty) to modify work, fear of losing their job, and difficulty navigating disbelief from co-workers.

Theme 4 – Stigma: a very prevalent finding in the qualitative literature pertains to worries of not being believed by others (family, friends, employers, healthcare workers, insurance, etc.) and the need to legitimize or validate that their pain was real.

Froud et al. (2014) provide an excellent summary of the pertinent interpretation of the qualitative literature as follows: "People with low back pain seek to regain their pre-pain healthy, and emotionally robust state. They desire not only diagnoses, treatment and cure, but simultaneously reassurance of the absence of pathology. Practically, although sufferers are often chiefly concerned with (re)engagement in meaningful activities, and attenuation of symptoms, the more experientially-focused literature suggests that the impact of back pain is pervasive, with life-changing effects." Consistent with prevalence of persistent or recurrence LBP, the authors also state the following: "Whilst back pain is not itself life-threatening, it does threaten quality of life. In the absence of diagnosis and effective treatment, complex enmeshment and interactions can ensue between chronic LBP, identity, and social roles, having a diverse and pervasive impact of the condition with life-changing psychological and social consequences."

In the review by Snelgrove and Liossi (2013), the authors assess 33 articles from 28 studies. They summarized the qualitative literature in three interrelated themes similar to those put forth by Froud et al. (2014). **Theme 1- Self:** CLBP leads to "loss of a previous lifestyle and changes in personality." Persistent LBP essentially leads to loss of self (former and future) due to "an incremental rise of functional limitation accompanied by feelings of self-loathing, frustration, anger, negativity towards others, self-denigration and even depression." Furthermore stigmatization (see above), perceived or real, threatens personal integrity. **Theme 2 – Relationships:** Snelgrove and Liossi (2013) divided this into two distinct aspects, (1) relationships with family and friends and (2) relationships with health professionals and the organization of care. The impact of CLBP on relationships with family and friends was noted by Froud et al. (2014). The authors highlighted an important issue of the effect of CLBP on relationships over time: "Participants reported being a burden to their families and 'holding people back' with sympathies lessening as time went on with no diagnosis or formal explanation," the latter being another driver for legitimization and over-medicalization of their CLBP. Negative relationships with health professionals and the organization of care were significant issues. As noted by the authors, "Participants described a good consultation as a partnership enabling a sense of security and belonging; promoting feelings of mutual understanding and recognition, and incorporating individualised care, clear explanations, reassurance, discussing psychosocial issues and future options." In many instances, this does not represent real-world health interactions. As noted by the authors "a lack of diagnosis and ongoing unresponsiveness to treatment invoked perceptions of not being believed, leading to a feeling of stigma and distress," "Participants reported being viewed as culpable; accused of imagining their symptoms; seeking secondary gain; symptoms being 'all in the mind' and laziness." Typically, providers and the system (e.g., disability insurer needs a diagnosis to provide benefits) are biased toward the biomedical approach which often will not provide a specific causation or resolution for most CLBP and further drives these negative psychosocial consequences and loss of faith in healthcare provider(s). **Theme 3 – Coping:** The authors reported coping in the context of individuals' attemps to manage their LBP. Snelgrove and Lossi (2013) note "A number of authors identified biomedical beliefs as a determinant of participants' experiences." "Biomedical beliefs were related to less successful rehabilitation to work and perceptions of reduced well-being; disappointment with the inefficacy of medical treatments; an overall narrow range of behavioural focused coping strategies,

psychological inflexibility and comprehensive enmeshment with pain, with little engagement or acceptance and a loss-orientated focus."

In the third review, Bunzli et al. (2013) reviewed 33 articles representing 28 studies. They also categorized the existing qualitative literature into three interrelated themes similar to those already noted. However, they also provided a provocative conceptualization of CLBP experience as one of "biographical suspension" in which three aspects of suspension were described: "suspended wellness," "suspended self," and "suspended future." **Theme 1 – The Social Construct of CLBP:** This theme emerged based on the highly prevalent biomedical beliefs of back pain patients. This should not be a surprise given the long-standing general biomedical model that is ingrained in both patients and practitioners alike (i.e., "diagnosis-treatment-cure"). As noted by the authors, "A biomedical explanation for the CLBP was critical for an individual to establish their pain as being a legitimate disability, which could then receive the support of the family, workplace, and welfare agencies." "The lack of a satisfactory etiological explanation for their 'invisible' pain meant participants in many studies felt at risk of not being believed." "The participants' experience in the health care system was repeatedly described with feelings of anger and frustration towards professionals who could not fulfill expectations of a diagnosis-treatment-cure pathway." These perceptions were found in most studies to occur with themes of stigmatization as noted above. Even in scenarios where the pain fluctuated, participants reported the need to demonstrate (i.e., sickness/pain behaviors) their pain and its impact all the time as a means of legitimizing their CLBP. The authors put this further into the context of the perceived role of the healthcare provider (HCP), noting that "HCPs were identified as painting an image of the demanding, difficult, and drug-seeking CLBP patient" and "any inference by HCPs of the pain being psychological in origin was felt by participant in several studies to be labeled with the stigma of questionable integrity." **Theme 2 – The psychosocial impact of the nature of CLBP:** The authors noted that "In the studies reviewed, pain was described as omnipresent, salient, and characterized by unpredictable fluctuations in intensity during both waking and sleeping hours"; "studies described participants experiencing disbelief at why they were suffering, prompting feelings of frustration, anger, guilt, and despair"; and "anxiety and distress, in light of an uncertain future, were widely described by study participants." The alterations in mood often resulted in depression. Consistent with the theme of the impact of LBP reported by Snelgrove and Liossi (2013), the authors provide a profound quote that the psychological effects of pain amounted to an "assault on the self." **Theme 3 – Coping with CLBP:** The findings from this theme are consistent with the interpretation of the same theme reported by Snelgrove and Liossi (2013). The authors framed coping strategies that were reflective of a constant fight or struggle to legitimize and control pain and the impact of CLBP in the context of the two other interrelated themes.

It is clear from these qualitative reviews that the biomedical model and practice of medicine are at odds with the lived experience of CLBP patients. The interrelated themes presented by these three reviews certainly resonate with my clinical experience as a spine focused practitioner. For example, the social construct of CLBP noted by Bunzli et al. (2013) is something that I suspect all HCPs dealing with CLBP (or chronic pain of any sort) experience on a regular basis. In my practice, this is a weekly occurrence when attempting to explain to a patient why surgery is not going to fix their pain, a process that takes significantly more time to do than saying "I have a solution that fulfills the biomedical belief and expectation of a given patient." As a strong believer in a holistic approach to CLBP, even under the scenario of a detailed and patient-centric explanation of the nociceptive and centralized mechanisms of pain, explaining the presence of unrelated imaging "abnormalities," etc., patients often simply conclude "so you are saying is this is all in my head" and/or "how is it possible that you cannot fix my – *any given radiographic diagnosis*" (i.e., the highlighted "problem" on their imaging report). As a surgeon in a tertiary-quaternary academic center (i.e., a highly biomedically

focused practice), I find the biomedical belief for a solution so ingrained in some patients that it is at times difficult if not impossible to alter. Another scenario that commonly occurs in my practice and is in keeping with the social implications of CLBP such as legitimization of pain is the need for disability or other insurance companies to have a definitive biomedical diagnosis for an individual who in the eye of the insurer (based on decades of messaging regarding resolution of LBP) should be better. I find this to be a profound source of patient frustration and stigmatization. The resultant stress of financial loss added to the common feeling of stigmatization is a tremendous driver for patients to continue to pursue a biomedical approach to their CLBP. This truly represents a vicious negative feedback loop for a significant proportion of the CLBP population.

Central Sensitization Syndrome

For many years the aforementioned "yellow flags" where thought to be predominantly psychosocially driven and in some cases, particularly where the injury or imaging findings where minor or did not remotely match the degree of symptoms, labelled as malingering behavior. In an excellent review by Nijs et al. (2017), the authors provide an update on how contemporary pain neuroscience is providing evidence of pathophysiological changes in pain processing, termed central sensitization that can occur in approximately 25% of patients with CLBP. Woolf (2011) defined central sensitization as "an amplification of neural signaling within the central nervous system (CNS) that elicits pain hypersensitivity." Individuals with central sensitization can have varying degrees of hypersensitivity; however, patients exhibit increased responsiveness to normal or subthreshold afferent input. Clinical features such as allodynia, pressure hyperalgesia, aftersensations, or temporal summation can be objectively detected. This condition is an important consideration in any individual with chronic pain and in fact has a biomedical explanation; however, it can be very difficult to explain to patients and manage, particularly in later stages. A detailed discussion of the pathophysiology, diagnosis, and management of central sensitization is beyond the scope of this chapter.

Although this chapter focused on psychosocial aspects of CLBP, central sensitization is a pivotal advancement in our understanding of the pain experience and must be considered in the context of those with persistent pain. It is not clear whether certain individuals are prone to developing central sensitization or if the psychosocial consequences noted above in some way lead to central sensitization in certain individuals. For example, in a review by Delpech et al. (2015), the authors surmise that "stress-induced microglia dysfunction may underlie neuroplasticity deficits associated to many mood disorders." In a systematic review of the structural and functional brain changes in CLBP, Kregel et al. (2015) noted consistent finding across studies of increased activation not only in somatosensory-discriminative regions of the brain but also in areas of affective and cognitive processing of pain. In a subsequent review by the same group (Kregel et al. 2017), there is limited evidence suggesting that "maladaptive central neuroplastic changes" may not be permanent and can be improved by targeted interventions. For example, behavioral extinction training was shown to shift pain-induced activation back to sensory discriminative regions from affective brain regions.

Socioeconomic Impact

In a widely cited review, Katz (2006) estimated that the cost of LBP in the United States ranged from $100 to $200 billion (2005 dollars) a year with indirect costs (e.g., lost wages) accounting for up to two-thirds of the cost and direct medical expenditures the rest. Around the same period, the cost of medical expenditure on LBP in Canada was estimated to be $6–$12 billion Canadian dollars per year (Brown et al. 2005). These very broad estimates exemplify the challenges of determining the total cost associated with most chronic health conditions. These challenges are due to a variety of factors including, but not limited to the following: region and country specific economic

factors (e.g., varying cost of healthcare within and among different countries); assessment of specific subpopulations of LBP patients such as primary care (acute or chronic), workers compensation, surgical or chronic pain patients; reporting of direct (healthcare) cost only; and when indirect cost are reported they are limited to individual productivity losses (e.g., time off work) rather than including caregiver cost or the cost of social support (e.g., food or housing). The latter point is relevant to the growing non-working aging population with CLBP.

Indirect Cost

Determining the indirect cost (often referred to as societal cost) of LBP is a resource intense process, and thus there is a limited amount of studies in this domain. Furthermore, indirect cost can vary widely depending on the specific cost variables assessed and which methods are used to determine productivity losses. The latter of which is the main driver of indirect cost. The two main methods used for determining productivity losses are (1) the human-capital method which takes the patient's perspective and tallies loss based on every hour that a individual does not work over the period that they may be eligible to work and (2) the friction-cost method which takes the payer/employer's perspective and only tallies loss based on those hours not worked until another employee takes over the patient's work (Pike and Grosse 2018). The human-capital approach tends to result in estimating significantly greater losses (i.e., higher indirect cost); thus the friction method has become the preferred method of many health economist and countries. Both methods have their merits and limitation, such that combination of methods may be desirable depending on the perspective taken. For example, for a 40-year-old patient who never returns to any form of work, the impact from the perspective of the employer may be relatively small compared to the impact on the disability insurer that has to pay that patient for the next 25 years until retirement age.

Regardless of method used to determine productivity losses, indirect costs are typically responsible for the majority of cost attributed to LBP. In an international review of national cost of illness studies by Dagenais et al. (2008), eight studies looked at both direct and indirect cost. With the exception of one study, indirect costs were responsible for 55–97% of estimated total national cost associated with back pain. Three of the reviewed studies by Dagenais et al. (2008) used both the human capital and friction methods for determining productivity losses. The friction method yielded estimates that were, on average, 56% lower than the human capital approach. In addition to these methodological differences, it is critical to understand whether the estimated cost per patient is being applied to all LBP patients within a representative sample of the population or a specific subgroup recruited from speciality pain or surgical clinics. In this scenario, the cost per patient (both direct and indirect) will likely be grossly different and is not interchangeable between different subpopulations. Consequently, when interpreting cost of illness studies, it is critical that the reader understand the LBP population being studied and the limitations associated with the methods and costing-data sources being used to determine indirect cost. For example, in a more specific CLBP subgroup (discography confirmed discogenic CLBP) of patients referred to four pain clinics in the Netherlands, Geurts et al. (2018) reported total societal cost of €7911.95 per patient (51% direct and 49% indirect cost) using the friction method and €18,940.58 per patient (22% direct and 78% indirect costs) when using the human capital approach. In this example, the human capital approach attributed more than double the cost per patient. Regardless of methods, the cost per patient is this study would be significantly higher than that of a LBP patient who was being managed only in a primary care setting. Thus, it would be erroneous to assign the cost per patient from this study to a different LBP subpopulation or to all LBP patients.

Direct Cost (Healthcare Expenditures)

Relative to older studies reported in the 2008 review by Dagenais et al. (2008), a more contemporaneous study by Dieleman et al. (2016) reports that the US spending for back and neck pain health services continues to increase annually and was estimated to be $87.6 billion in 2013.

Back and neck pain were ranked third, behind diabetes ($101.4 billion) and ischemic heart disease ($88.1 billion), out of all health conditions. The proportion of spending on ambulatory care, emergency care, and pharmaceuticals for back and neck pain was 60.5%, 4.2%, and 4.1%, respectively. Comparatively, the proportion of spending on ambulatory care, emergency care, and pharmaceuticals for diabetes was 23.5%, 0.4%, and 57.6%, respectively. This clearly demonstrates the differential impact on the healthcare system of a predominantly biomedical condition such as diabetes and predominantly non-biomedical condition such as back pain. To gain insight into some of the specific differences in medical expenditure among CLBP patients, Gore et al. (2012) compared a total of 101,294 patients with CLBP to a 1:1 age-, sex-, and region-matched control cohort CLBP. The authors used settled medical and pharmaceutical claims data from more than 98 commercially managed healthcare plans throughout the United States which represented a broader insured adult population. Relative to controls, CLBP patients had a greater number of medical comorbidities, including higher rates of depression (13.0% vs. 6.1%), anxiety (8.0% vs. 3.4%), and sleep disorders (10.0% vs. 3.4%). As expected, patients with CLBP also were more likely to be on opioids (37.0% vs. 14.8) or other analgesic such as nonsteroidal anti-inflammatory drugs (26.2% vs. 9.6%). The study also reported significantly higher estimated total direct medical costs for CLBP patients ($8386 ± $17,507) compared to those without CLBP ($3607 ± $10,845). One notable driver of cost was the almost three times difference in medical expenditures for outpatient investigations (e.g., imaging) in CLBP compared to the control group ($ 3481.65 vs. $1297.47). Overutilization of diagnostic imaging is perhaps the most targeted area of non-guideline concordant care in LBP, particularly the use of more costly imaging such as magnetic resonance imaging (MRI). Inappropriate MRI utilization is not simply a matter of an unnecessary test. The high likelihood of false-positive findings has been shown to lead to a cascade of further investigations and an increased relative risk of invasive treatments including surgery (Webster et al. 2014). Reduction of imaging for LBP is a very prominent part of the global movement Choosing Wisely. However, as noted above, the biomedical approach to LBP is ingrained into patients and providers, and change of behavior in this area has proven to be very difficult. This is highlighted by a 2017 study by Hong et al. (2017) where the authors only found a 4% relative reduction in low-value imaging for LBP 2.5 years into the Choosing Wisely campaign in the United States. Limited studies assessing the impact of alternative models of care using more active care paths and interprofessional delivery have demonstrated greater potential for reduction of unnecessary imaging and associated cost avoidance (Kim et al. 2011; Rampersaud et al. 2016).

As noted at the beginning of this chapter, LBP is the number one cause of years lived with disability (YLDs) with 77% of the YLDs accounted for by approximately one in four of prevalent cases (Global Burden of Disease 2015 DALYs and HALE Collaborators 2015). Although speculative, the evidence presented in this chapter on the psychological and social impact of CLBP would suggest these one and four prevalent cases are likely those with significant psychosocial (including central sensitization) drivers of persistent pain and disability. From a socioeconomic perspective, this subgroup of patients with a disproportionately greater disability burden is also going to be associated with higher medical expenditures and lost productivity (Hartvigsen et al. 2018). In a study by Luo et al. (2004), the authors performed an analysis of the 1998 Medical Expenditure Panel Survey and reported that 25% of patients with LBP were responsible for at least 75% of the healthcare expenditures in those with LBP. Similarly, Katz (2006) noted that 5% of workers (e.g., mostly those that have been off work for more than 1 year and are very unlikely to return to work) are responsible for the 75% of the loss in productivity cost associated to LBP. There is no current national-level evidence to suggest that these findings are not applicable today. In my opinion, although these individual findings have not been comprehensively assessed in the same study, their overarching context

provides a socioeconomic rationale for strategies aimed at prevention or mitigation of CLBP. The early identification of those at risk for persistent pain and disability and implementation of early mitigation strategies to address the psychosocial mediators of persistent pain and disability are clearly the way forward.

Overview of Assessment and Management

A detailed description of the assessment and management of the psychosocial and socioeconomic factors associated with CLBP is not the intended scope of this chapter; however, a brief overview is necessary to provide the clinical implications of the issues outlined in this chapter.

Assessment

A variety of assessment tools as well as integrated model of cares are being developed around the world to address the growing burden of LBP (Foster et al. 2018; Rampersaud et al. 2016). It is clear that the psychosocial impact of CLBP is a principle driver of both patient and societal burden. The paradigm shift in LBP care necessitates primary consideration of psychosocial factors and approaches to care, rather than these being afterthoughts following failure of a primarily biomedical framework. Often, these issues may become ingrained and much more difficult and costly to manage. Consequently, early assessment for psychosocial factors in LBP patients is recommended as part of routine primary care (Foster et al. 2018). Furthermore, the impact of psychosocial factors is not static and thus necessitates prescribed follow-up and reassessment for these barriers to recovery. Incorporating this change enables the move away from a one-size-fits-all approach to a stratified care approach that has been greatly influenced by the literature associated with the use of the Keele STarT Back screening tool in primary care (Hill et al. 2011). The STarT Back screening tool (https://www.keele.ac.uk/sbst/startbacktool/) is a prognostic questionnaire for patients with LBP that aims to identify risk of developing persistent disabling LBP (Hill et al. 2011). It categorizes respondents as low, medium, or high risk of persistent pain/disability (i.e., chronicity) and aims to match treatment to each risk subgroup. Practical tools for primary care are required to enable efficient biopsychosocial assessment and reassessment of LBP in the acute and chronic (persistent or recurrent) scenarios.

In collaboration with interprofessional knowledge experts, front-line primary care providers, and funding from the Ontario Ministry of Health, we have developed the Clinically Organized Relevant Exam (CORE) Tool for the Low Back Pain Toolkit for Primary Care Providers (Alleyne et al. 2016). The CORE Back Tool (https://cep.health/clinical-products/low-back-pain/) provides a primary care toolkit that is evidence informed and interactive and provides a management matrix for early stratified care. It starts with six principle screening questions that allow identification of the biopsychosocial components of a patient presenting with LBP. A response-dependent stepwise progression to more detailed questions and recommended validated tools for more in-depth assessments are also provided. We have had excellent frontline uptake of the CORE Back Tool, and it is now integrated into the medical school curriculum at the University of Toronto. If psychosocial concerns are identified (primary lead question: Is there anything you *can not* do now that you could do before the onset of your low back pain?), then the user is directed to assess for yellow flags and if positive use of a validated prognostic tool such as the STarT Back which has specific questions regarding fear, anxiety, catastrophizing, and low mood (Hill et al. 2011). In addition, I would recommend a brief assessment (Chiarotto et al. 2016) of self-efficacy using the Pain Self-Efficacy Questionnaire – Short Form (PSEQ-4). The PSEQ asks simple questions of patient's confidence in dealing with their LBP such as "I can cope with my pain in most situations" or "I can live a normal lifestyle." Obtaining a basic understanding of a patient's ability to cope or not to cope with a given situation will more broadly help guide the need for psychological as well as social supports as

needed. More intensive psychological assessment and treatment is not within the scope of this chapter and is not typically in the scope of practice of many primary care physicians or medical specialists such as rheumatologist or surgeons that deal with spinal conditions. However, identification of psychosocial issues and referral to appropriate assessment and management should be the responsibility of all practitioners that deal with LBP.

Management

The recently published Lancet series on LBP reflects the paradigm change in messaging and first-line management recommendations for both acute (<6 weeks) and CLBP (Foster et al. 2018). The prioritization of the Lancet Low Back Pain Series Working Group recommendations have only recently begun to surface in clinical practice guidelines. For both acute LBP and CLBP, advice to remain active and education are first-line recommendations. For CLBP both exercise therapy and cognitive behavioral therapy (CBT) are also recommended as first line treatments that should be considered for routine use. Additionally exercise therapy and CBT should also be considered for limited use in selected patients with acute LBP. These recommendations are in line with the need for early assessment of the complex biopsychosocial factors that may negatively impact recovery of LBP patients at any time period from the onset of symptoms. All other treatments such as spinal manipulation, massage, acupuncture, medication, injections, and surgery are to be considered second-line or adjunctive and delivered in a limited fashion in highly selected patients. The goal of these secondary or adjunctive treatments should be to enable functional activities (modified as needed) and optimization of non-pharmaceutical treatment options whenever possible.

For those with or identified as at risk for psychosocial barriers to recovery, CBT is the most commonly recommended treatment (Foster et al. 2018). CBT is a structured, time-limited, problem-focused, and goal-oriented form of psychotherapy. As it pertains to LBP, it has been shown that changing an individual's thoughts about pain and the associated negative emotions or beliefs can change not only how that individual's mind responds to pain but also their body. CBT can be effectively delivered in varying degrees of intensity, by a variety of different types of practitioners (not just psychologist), and in a variety of setting such as one-on-one, group, and even virtually (Vitoula et al. 2018; Bostick 2017). Fundamentally, the goals of CBT are to recognize the negative feelings, thoughts, and behaviors that occur as a result of LBP and use of goal-oriented techniques to incrementally transform negative thoughts (cognitive part) and behaviors (behavioral part) to positive ones that improve an individual's ability to manage their pain (i.e., improve pain self-efficacy) and become more active and engage in healthy behaviors that ultimately reduce their pain. Other adjunctive treatments may be required on a case-by-case basis including medical management of more profound psychological dysfunction (e.g., major depression) to address specific issues that exist or may arise. Just as a one-size-fits-all biomedical approach to LBP does not work, a one-size-fits-all psychosocial approach will also fail. For patients who have not responded to recommended first-line treatments, with ongoing significant pain, functional disability, or psychosocial dysfunction, multidisciplinary rehabilitation programs that individualize and coordinate different types of treatment (e.g., pain management, exercise, and CBT) have been shown to be more effective than standard treatments for pain, disability, and return to work (Kamper et al. 2015). However, it must be noted that multidisciplinary rehabilitation programs can be costly, time-consuming, and resource intensive and may not always be accessible to vulnerable populations (Salathé et al. 2018). Unfortunately, significant changes in policy, system-level clinical pathways, available resources (including first-line management of psychosocial issues such as improvement of self-efficacy), and the mindset of frontline clinicians will be required to see meaningful reduction in the increasing individual and socioeconomic impact of LBP (Foster et al. 2014, 2018).

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Part II

Biomaterials and Biomechanics

Implant Material Bio-compatibility, Sensitivity, and Allergic Reactions

7

Nadim James Hallab, Lauryn Samelko, and Marco Caicedo

Contents

Abstract

Generally biocompatibility to implant-debris governs long-term clinical performance. The following chapter covers: the kinds of implant-debris and the biologic responses to implant-debris. Implants produce debris from wear and corrosion that take the form of particles and ions. Particulate debris generally ranges from 0.01 to 100 s um. Wear rates of articulating bearing such as total hip arthroplasties generally range from 0.1 to 50mm^3/yr. Metal-on-metal total joint replacement components are well known to produce increases in circulating metal in people (>ten-fold that of people without implant, i.e., 2-5parts per billion-Cobalt and 1-3 ppb-Chromiun). Debris bioreactivity is both local and systemic. Local inflammation is primarily mediated by local immune cells called macrophages, which produce pro-inflammatory mediators/cytokines TNFα, IL-1β, IL-6, and PGE2. Although there are many concerns associated with systemic reactivity to implant-debris, to date well-established systemic reactivity has been limited to developed hypersensitivity/allergy reactions. Elevated amounts of in the remote organs such as the liver, spleen of patients with TJA and high levels of circulating metal have not (yet) been associated with remote toxicological or carcinogenic pathologies. Not all implant debris is similarly biocompatible/

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nonbiocompatible. Additionally, the amount of debris-induced-inflammation depends on both the person and amount/kind/size of implant debris. The inflammation and bone loss associated with debris necessitates continued surveillance by physicians to monitor patients/implants over time using traditional physical exams, x-rays, and when appropriate new biological assays such as the testing of metal content and individual biological response such as hypersensitivity metal-LTT assays.

Keywords

Orthopedic implant · Implant-debris · Biologic responses · Particles · Ions · Inflammation · Macrophages · Innate immune resposne · Adaptive immune response · Cytokines · Hypersensitivity · Allergy · Metal-LTT assays

Abbreviations

Al	Aluminum
ALVAL	Aseptic lymphocyte vasculitis associated lesion
Co	Cobalt
Cr	Chromium
$Cr(PO_4)4H_2O$	Chromium orthophosphate
DAMP	Danger associated molecular patterns
DTH	Delayed type hypersensitivity adaptive (lymphocyte mediated) immune response that occurs over days to weeks to years (vs. that of an immediate response).
Hypersensitivity	Adaptive immune responses typically local inflammation mediated by T-cells or B-cells where antigen presenting cells such as macrophages act as gate keepers.
IL-1b	Interleukin 1 almost exclusively produced by inflammasome reaction, such as occurs in a macrophage response to implant debris particles
IL-6	Interleukin 6
IL-18	Interleukin 18
IL-33	Interleukin 33
Inflammasome	Key molecular components of a pro-inflammatory pathway that reacts to danger signals (not pathogens) that are produced when cells are damaged, typically composed of multiprotein oligomers consisting of caspase 1, PYCARD, NALP, and sometimes caspase 5 (also known as caspase 11 or ICH-3).
LALLS	Low angle laser light scattering
metal-LTT	Metal-lymphocyte transformation test (proliferation assay) used as a human diagnostic test for delayed type hypersensitivity responses to implant metals
NALP3/ASC	Inflammasome complex of proteins
PAMP	Pathogen associated molecular pattern
PGE_2	Prostaglandin E2
PMMA	Polymethylmethacrylate
ppb	Parts per billion (ng/mL or ug/L)
PTFE	Teflon (polytetraflouroethylene)
RANKL	Receptor activator of nuclear factor Kappa Beta ligand
ROS	Reactive oxygen species
SEM	Scanning electron microscopy
TEM	Transmission electron microscopy
THA	Total hip arthroplasty
Ti	Titanium
TJA	Total joint arthroplasty
TJR	Total joint replacement

TNF-a	Tumor necrosis factor – alpha
UHMWPE	Ultra high molecular weight polyethylene
V	Vanadium

Introduction

Implant debris and not the implant itself causes slow progressive local inflammation that limits the long term performance of over one million total joint arthroplasties implanted each year in the USA (Charnley 1979, 1970). The direct costs of this slow progressive Adverse Reactivity to Implant Debris (ARID) is approximately $20 billion in the USA per year and is expected to double over the next 10 years (Kurtz et al. 2007a, b, 2009). One of the most important human costs of this bio-implant failure is the increased incidence of death during revision orthopedic surgery which is as high as 13% in people older >75–80 years of age while it is <1% in patients <70 years of age. Biocompatibility mediated implant failures also have elevated complication rates associated with re-operation, with a >20% chance of post-operative dislocation (vs <1% in patients <75 years of age) (Radcliffe et al. 1999). Some designs of orthopedic implants release more bioreactive debris (i.e., metal particles and ions) that result in extraordinarily high failure rates, with levels of failure reported as high as 5% at 6 years post-op, such as some past metal-on-metal total hip arthroplasties designs as well as some types of highly modular implants (i.e., several components that press fit together) (Cooper et al. 2013; Jacobs and Hallab 2006; Korovessis et al. 2006; Milosev et al. 2006). The mechanism of implant debris induced inflammation is best known as an activator of local innate immune responses, i.e., monocytes/macrophages activate NFκβ and secretion of potent inflammatory cytokines such as IL-1β, TNFα, IL-6, and IL-8 (Catelas et al. 1999, 2003; Hallab et al. 2003a; Kaufman et al. 2008; Sethi et al. 2003; Trindade et al. 2001) resulting in localized inflammation (Kaufman et al. 2008; Lewis et al. 2003).

Over the long term all accumulating implant debris and the subsequent slow progressive inflammation results in bone loss and loss of implant fixation (Willert and Semlitsch 1977), termed "aseptic osteolysis," and results in pain and premature loosening of orthopedic implants (Archibeck et al. 2001; Arora et al. 2003a; Jacobs et al. 2001). Clinically, aseptic osteolysis (noninfection related bone loss) generally only refers to measureable bone loss as determined on an x-ray (Fig. 1). It is the particulate and soluble degradation products of orthopedic biomaterials (generated by wear and corrosion) that mediate these Adverse Reactivity to Implant Debris (ARID) effects. Debris may be present as particulate material (i.e., as small colloidal nanometer size complexes or larger >0.3um particles), or soluble products such as free metallic ions which can then react with their proteinaceous and cellular environment. Implant particulate debris can have large specific surface areas by virtue of their small size and large number and thus have a large format for interaction with the surroundings. This chapter will focus on orthopedic implant degradation product bio-compatibility, and ensuing local and systemic consequences of this debris including local inflammatory tissue reactivity and sensitivity and allergic reactions, respectively.

Implant Debris Types: Particles and Ions

All orthopedic implants produce debris of two basic types: particles or soluble debris (e.g., metal ions). The biologic consequences of particles and soluble debris blurs as the size of particles decreases into the nanometer range and become "effectively soluble." Particulate debris (metal, ceramic, or polymers) is generally in the range of 40 nm to 1 mm in size, while so-called common forms of "soluble debris" is currently limited to metal and are quickly bound to serum proteins upon release (such as albumin).

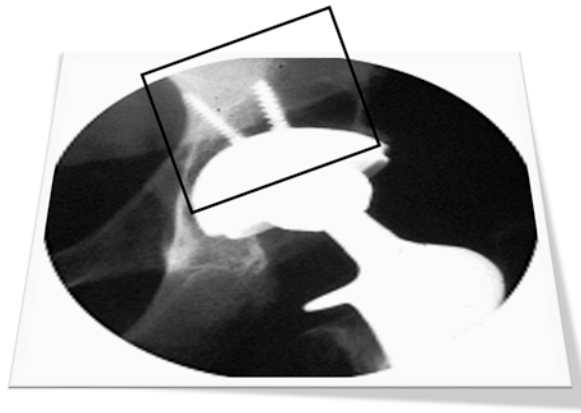

Fig. 1 Peri-implant aseptic osteolysis above the acetabular cup of a metal-on-polymer bearing total hip replacement. Inset shows a granuloma surrounding acetabular fixation screw, which is a common site for bone resorption due to the ease with which particles can migrate and cause inflammatory soft tissue and osteolysis. (Courtesy of Bio-Engineering Solutions Inc.)

Particulate Debris

Different types of orthopedic implants produce different types and amounts of wear debris, with different sizes and shapes of that are generally implant design and material specific. For example, total joint implants with "hard-on-hard" articulating surfaces such as metal-on-metal total hips arthroplasty implants generally produce smaller sized fairly round (submicron), debris. More common metal-on-polymer or ceramic-on-polymer THA bearings produce larger (micron sized) polymeric debris (Fig. 2) that fall into the range of 0.2um to 1um, with little metallic debris. Other sources of metal debris include corrosion and wear at metal-to-metal connections between modular components (Campbell et al. 1995; Jacobs et al. 1994a; Maloney et al. 1993). Highly cross-linked ultrahigh molecular weight polyethylene (X-UMWPE) used in current models of hip replacements provides less war than previous generations of UHMWPE; however, the particle produces are generally smaller (e.g., 0.1microns in size) compared to 0.8–2um of previous generations of UHMWPE (Catelas et al. 2004; Scott et al. 2005). Articulating surfaces comprised of metal and ceramic bearings produce particles that can be an order of magnitude smaller than polymeric particles (at approximately $<$0.05um in diameter, i.e., in the nanometer range).

Histological analysis of peri-implant tissues has identified different types and sizes of particles (Choma et al. 2009; Jacobs et al. 1998a; Punt et al. 2008, 2009; Urban et al. 1998, 2000; van Ooij et al. 2007). However, the sizes of debris in tissues vary dramatically from that identified using simulators and analysis of synovial fluids and tissues. Metal corrosion based stainless steel debris has been found as closely packed, plate-like particle aggregates mostly at steel screw-plate junctions containing particles of chromium compound ranging in size from 0.5 to 5.0 microns (Urban et al. 1996). Similarly large, cobalt alloy corrosion debris has been shown in tissues to be made of a chromium-phosphate ($Cr(PO_4)4H_2O$) hydrate rich material termed "orthophosphate" and ranges in size from $<$1um to $>$500 micrometers (Urban et al. 1996, 1997).

Particle Characterization: Differently than basic histological analysis, more specific means of characterizing implant debris particles include Scanning Electron Microscopy (SEM) or Transmission Electron Microscopy (TEM) techniques. Both of these characterize particles by counting and sizing particles on a number of high, medium, and low power microscopy fields. These techniques are employed for digested tissues and simulator fluids and synovial fluid analysis, after the particulate debris has been isolated and dried on a membrane/mounting media. Because the particles

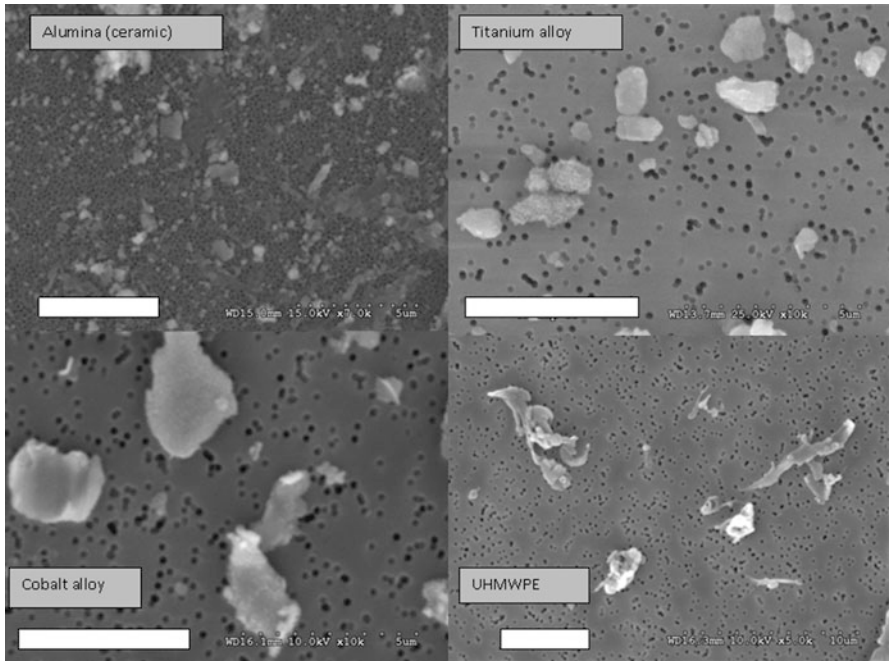

Fig. 2 Implant debris from metal (Cobalt alloy and Titanium) and ceramic (alumina) debris are more rounded in comparison to polymeric (UHMWPE) debris which is more elongated in shape. Note: Bar = 5um. (Courtesy of BioEngineering Solutions Inc.)

observed in the high power fields are over represented when scaled up to the total, these methods have inappropriately biased our understanding that the majority of the wear (mass loss) from an implant is comprised of particles in the nanometer to submicron range. That is while most of the particles identified on a counting (number-based) analysis are in the small ranges (<1um), they do not typically make up the size of debris that is responsible for the majority of the mass loss, i.e., while billions of small particles only add up to 0.01 mg of implant debris it only takes 100's to 1000's of larger particles to equal >10 mg of implant debris. This biased understanding stems from the limited number of particles in tissues and the relatively low numbers of particles (e.g., 100's–1000's) that are counted using image based analysis techniques such as SEM. Other types of analytical techniques, such as low angle laser light scattering (LALLS), have the ability to sample millions to billions of particles, as they pass in front of a laser detection system where the one-in-a-million large particle can be detected and thus provide a more accurate distribution of the total debris.

The ability to comprehensively characterize implant debris is critical to the assessment of consequent biological responses and weigh the effects of new designs and bearing surfaces to older implants. The bias of SEM techniques those of all "number-based" analysis where two very similar number based distributions can look very different when analyzed on a "volume-based" perspective (Fig. 3). Thus for an accurate and comprehensive evaluation of implant debris particulate, both a number and volume based analysis/distribution are required.

Metal Ions (Soluble Debris)

There is continuing clinical concern regarding metal released from orthopedic implant is the form of particles and ions. These ions immediately bind to serum proteins and disseminate into surrounding tissues, bloodstream, and remote organs. Normal

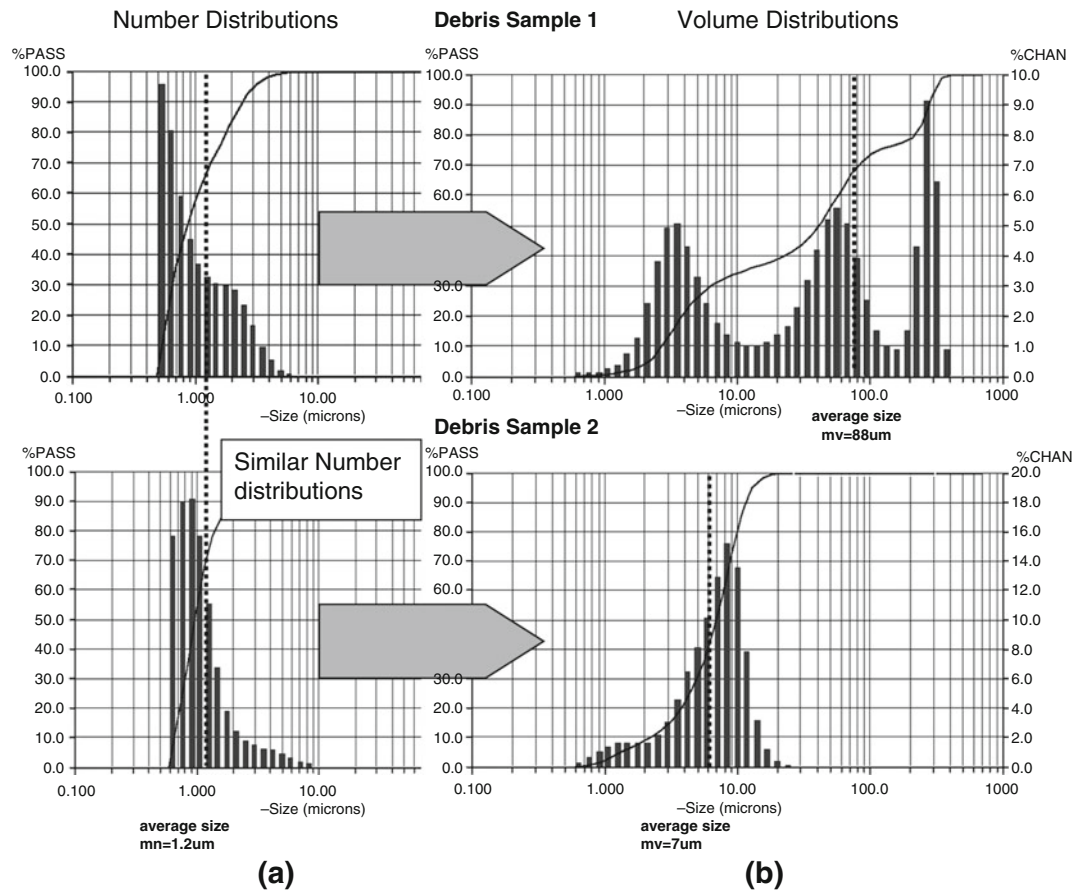

Fig. 3 LALLS analyses of two implant debris samples using a (**a**) volume and (**b**) number distributions demonstrate that similar number distributions and estimates of particle size can result from two very different sizes particles when analyzed using a volume distribution, which shows the size of the particle as a percent of the total volume. Note: The x-axis is particle diameter and the y-axis is (**a**) percentage of total number of particles in each size range and (**b**) the percentage of total mass in each size range. (Courtesy of BioEngineering Solutions Inc)

metal serum levels are generally <1part per billion, ppb (ng/mL): 1–10 ng/ml Al, 0.15 ng/ml Cr, <0.01 ng/ml V, 0.1–0.2 ng/ml Co, and <4.1 ng/ml Ti. Implants do release enough metal to increase these levels systemically following total joint arthroplasty (Table 1). Particles of metal that are released contribute to this increased metal because of the large surface areas available for corrosion (i.e., electrochemical dissolution) (Jacobs et al. 1998a; Urban et al. 1996, 1997, 1998, 2000).

Metal Ion Release: Metal ions released from orthopedic implants have been of concern for over 40 years. Increased levels of systemic circulating Co and Cr are detected following even successful total joint replacements with Co-alloy based components. The same is true of other metal alloy orthopedic implants, e.g., increased serum Ti and Cr concentrations can be found in some individuals with well-functioning Ti and/or Cr containing THR components (Table 1) (Dorr et al. 1990; Jacobs et al. 1994b, 1998a; Michel et al. 1984; Stulberg et al. 1994). Other metals associated with the surgery itself have also been reported where increases in Ni have been noted immediately following surgery, likely related to the use of stainless steel surgical instruments.

Although several factors affect systemic metal ion levels in TJA patients, the most important

Table 1 Approximate concentrations of metal in human body fluids and in human tissue with and without total joint replacements. (Dorr et al. 1990; Jacobs et al. 1994b, 1998a; Michel et al. 1991; Stulberg et al. 1994)

Body fluids (ng/mL or ppb)		Ti	Al	V	Co	Cr	Mo	Ni
Serum	Normal	0.06	0.08	<0.02	0.003	0.001	*	0.007
	TJA	0.09	0.09	0.03	0.007	0.006	*	<0.16
Urine	Normal	<0.04	0.24	0.01	*	0.001	*	*
	TJA	0.07	0.24	<0.01	*	0.009	*	*
Synovial fluid	Normal	0.27	4.0	0.10	0.085	0.058	0.219	0.086
	TJA	11.5	24	1.2	10	7.4	0.604	0.55
Joint capsule	Normal	15.0	35	2.4	0.42	2.6	0.177	69
	TJA-F	399	47	29	14	64	4.65	100
Whole blood	Normal	0.35	0.48	0.12	0.002	0.058	0.009	0.078
	TJA	1.4	8.1	0.45	0.33	2.1	0.104	0.50
Body tissues (µg/g)								
Skeletal muscle	Normal	*	*	*	<12	<12	*	*
	TJA	*	*	*	160	570	*	*
Liver	Normal	100	890	14	120	<14	*	*
	TJA	560	680	22	15,200	1130	*	*
Lung	Normal	710	9830	26	*	*	*	*
	TJA	980	8740	23	*	*	*	*
Spleen	Normal	70	800	<9	30	10	*	*
	TJA	1280	1070	12	1600	180	*	*
Psuedocapsule	Normal	<65	120	<9	50	150	*	*
	TJA	39,400	460	121	5490	3820	*	*
Kidney	Normal	*	*	*	30	<40	*	*
	TJA	*	*	*	60	<40	*	*
Lymphatic	Normal	*	*	*	10	690	*	*
Tissue	TJA	*	*	*	390	690	*	*
Heart	Normal	*	*	*	30	30	*	*
	TJA	*	*	*	280	90	*	*

Normal: Subjects without any metallic prosthesis (not including dental)
TJA: Subjects with total joint arthroplasty
* = Data Not Available

factor is elevated metal implant degradation (wear and/or corrosion). Systemic titanium ion levels up to a hundred times higher than normal have been reported in cases of failed metal-backed patellar components where mechanical implant failures caused high wear such as a wearing through of the polymer liner in a THA and the more wear resistant Co alloy head bores into the titanium alloy acetablular cup. Surprisingly in these cases of excessive Ti-alloy wear and metal release, there was no reported increases in still serum or urine Al, serum or urine V levels, or which are other minor percentages of titanium alloy cups (6% Al and 4% V). Fretting corrosion, of modular implant components has been associated with elevations in serum Co and urine Cr (Jacobs et al. 1998a, b, 1999b). Despite significant increases in Co and Cr concentrations found in the heart, liver, kidney, spleen, and lymphatic tissue from orthopedic implant degradation (Table 1), the majority of metal debris remains local around and in the pseudocapsule that forms around a total joint implant and act much like a joint capsule (Jacobs et al. 1994).

Local Tissue Effects of Wear and Corrosion

The key determining factor of long-term implant performance is implant debris that can trigger a local inflammatory response that causes osteolysis and aseptic implant loosening. Bone homeostasis is dependent upon the intricate balance of bone formation and bone resorption powers which comprises the corresponding function of osteoblasts (bone building cells) vs. osteoclasts (bone resorbing cells) and osteocytes (bone mechanotransduction and signaling network cells). If implant debris induced inflammation causes disruption in bone homeostasis by mitigating osteoblastic bone formation and/or augmenting osteoclastic bone resorption, this will result in a net bone loss (i.e., osteolysis). This osteolysis near the bone-implant interface is the principal pathology associated with the localized effects of TJR degradation. This bone loss happens as a diffuse thinning of the cortical or as focal cyst-like lesions. The first materials to be associated with osteolytic lesions due to massive production amounts of implant debris were particulate polymethylmethacrylate (PMMA) bone cement and old acetabular cups made of PTFE (Teflon). This was based on histological studies showing implant debris associated with macrophages, giant cells, and a vascular granulation tissue. It is now well established that osteolysis in both well-fixed and loose uncemented implants results from the generation of particle debris from any material (Jacobs et al. 2001; Vermes et al. 2001a).

It was first described by Goldring et al. (1983) that the bone-implant interface in patients with loose total hip replacements is comparable to synovial-like membrane and bone resorbing factors such as PGE_2 and collagenase are produced by cells within the membrane. Total hip arthroplasty is more frequently associated with particle induced osteolysis than total knee arthroplasty, and this remains unclear why this is the case. However, it has been postulated that various biomechanical factors such as implant/bone mechanical loading environments, differential mechanisms of hip and knee wear, and differences in interfacial barriers to migration account for this apparent disparity.

All implant debris leads to subtle progressive inflammation that can ultimately result in implant failure. As to exactly how this occurs still remains somewhat contentious, however, increasing evidence continues to indicate that danger signaling by the innate immune system mediates implant debris induced inflammation, which is how the immune system in general detects and reacts to nonpathogen derived biologic stimuli (Caicedo et al. 2008, 2013a; Dostert et al. 2008; Hornung et al. 2008; Naganuma et al. 2016). It has been established over the past 40 years that implant debris induced inflammation is primarily driven by macrophage reactivity to sterile implant debris that results in up-regulation and activation of pro-inflammatory transcription factors (e.g., NFκB) that produce, amplify, and result in the secretion of inflammatory cytokines like IL-1β, TNFα, IL-6, and IL-8 (Jacobs et al. 2001) (Fig. 4). Prostaglandins (e.g., PGE_2) are also involved and mediate implant debris induced inflammation and osteolysis. IL-10 and IL-1Ra are key anti-inflammatory cytokines that act to lessen this inflammatory state induced by implant debris, but it remains less understood the degree which these anti-inflammatory cytokines can decrease the pathology of particle induced osteolysis. Additional factors involved with osteolysis include matrix metalloproteinases collagenase and stromelysin, which are enzymes that mediate the catabolism of the organic component of bone. Also, activated bone and immune cells can generate bone mediators known to play a role in stimulation of osteoclast differentiation and maturation, such as RANKL (also referred to as osteoclast differentiation factor).

Implant debris is sterile and relatively inert and does not have the prototypical molecular characteristics of a pathogen. Therefore, how does implant debris elicit an immune inflammatory response? More specific, how can extra- and intra-cellular mechanisms detect and react to sterile nonbiological material such as implant debris? For the past half century, this question had remained largely unknown. However, new discoveries and advancements in immunology have implicated the NLRP3 inflammasome danger signaling pathway to play a pivotal role in the detection and response to sterile nonbiological stimuli (Fig. 5) (Caicedo et al. 2010).

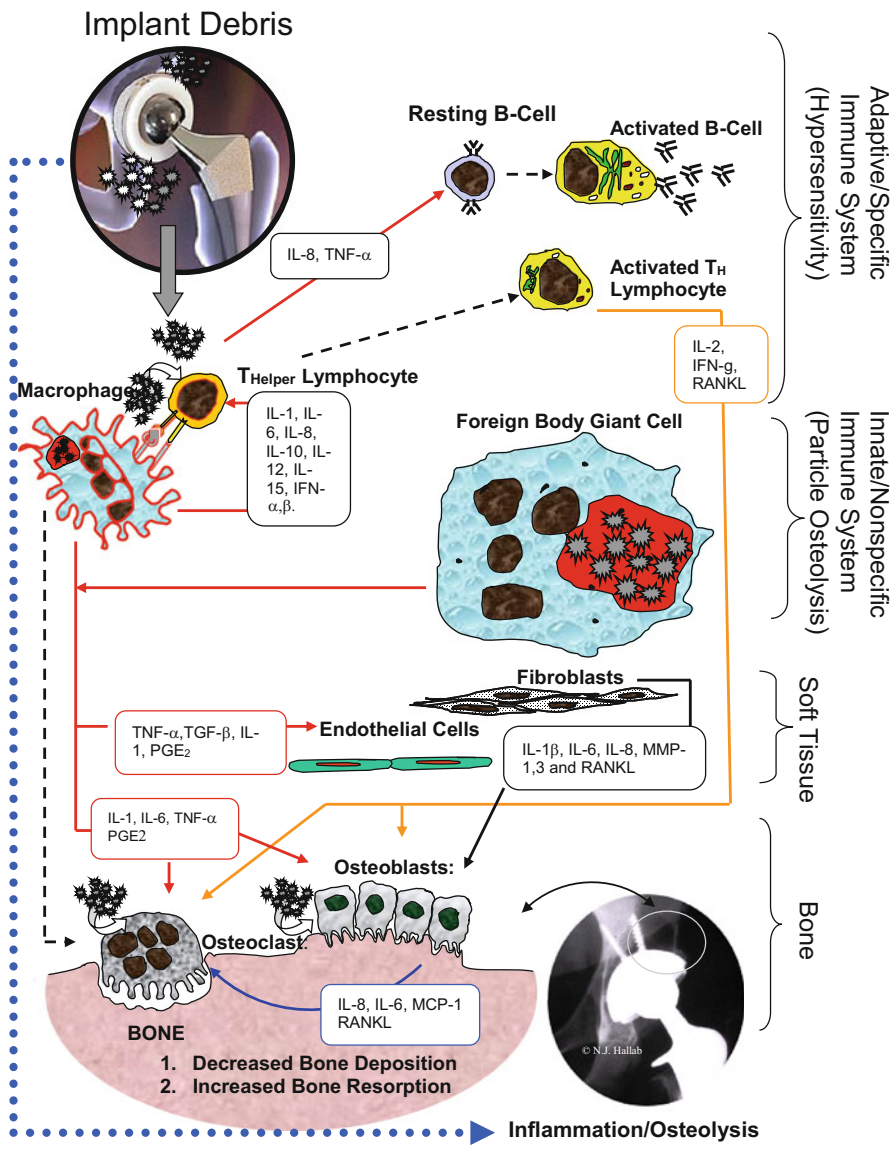

Fig. 4 Numerous cytokines from peri-implant cells reacting to implant debris can negatively affect bone turnover. IL-1, IL-6, and TNF-α are some of the most potent cytokines responsible for increasing bone loss and enhancing pro-inflammatory responses. (Picture courtesy of Bio-Engineering Solutions Inc)

The discovery of the inflammasome danger signaling pathway was pivotal since it was the first biological mechanism to explain how immune cells transduce sterile, nonpathogen derived stimuli (e.g., cell stress and necrosis) into an inflammatory response (Mariathasan et al. 2004; Mariathasan and Monack 2007). Additional nonbiological derived danger signals (e.g., DAMPs) that activate the inflammasome include cell damaging stimuli such as UV light, particulate adjuvants present in modern vaccines (Dostert et al. 2008; Hornung et al. 2008) and, as it turns out, orthopedic implant debris (Caicedo et al. 2008).

When particles activate the inflammasome pathway, immune cells subsequently release

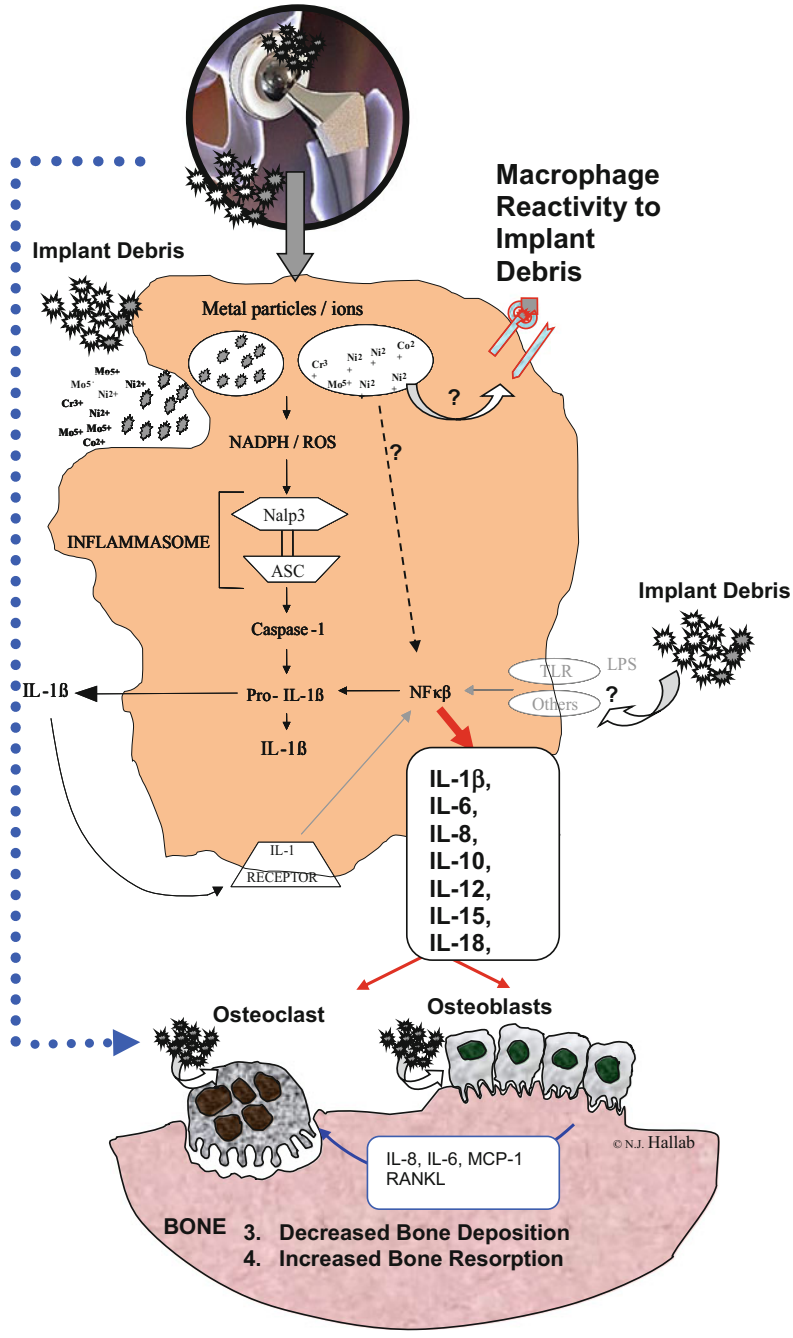

Fig. 5 Metal-induced inflammasome activation occurs when soluble and/or particulate implant debris activate the Nalp3 inflammasome when chemicals inside intracellular compartments used to digest foreign material (such as phagosomal NADPH induced reactive oxygen species and/or Cathepsin B) leaks out of these compartments in an event called phagosomal destabilization. The inflammasome complex Nalp3-ASC then induces the activation of caspase-1, which in turn allows mature IL-1β to be secreted. IL-1β is a very potent pro-inflammatory cytokine that exerts an autocrine and paracrine effect inducing a broader more potent inflammatory response (e.g., activation of NFκβ pro-inflammatory responses). (Courtesy of BioEngineering Solutions Inc)

pro-inflammatory cytokines such as IL-1β, IL-18, IL-33, and a multitude of more. The sequence of events is as follows:

> Implant Debris → Phagocytosis → Lysosomal damage and rupture of protease enzymes (e.g. Cathepsin-B) → ROS (reactive oxygen species) production → Inflammasome (NALP3/ASC) activation → Caspase-1 → Secretion of mature IL-1β (and other IL-1-family dependent cytokines) (Fig. 20).

More specifically, upon ingestion (phagocytosis) of sterile particles by immune cells (or other DAMPs such as asbestos and implant

debris) will cause a degree of lysosomal destabilization. Consequently, lysosomal destabilization will result in the rupture and release of protease enzymes and of the acid rich extreme microenvironment within a lysosome into the cell cytosol, which are used within the lysosome compartment to breakdown ingested DAMPs (e.g., implant debris) and PAMPs. This lysosomal destabilization leads to an increase in NADPH (nicotinamide adenine dinucleotide phosphate-oxidase) and an associated increase in reactive oxygen species (ROS). Subsequently, the release of ROS species leads to the activation of the intracellular multiprotein "inflammasome" complex that is composed of NALP3 (NACHT-, LRR-, and pyrin domain-containing protein 3) in association with ASC (apoptosis-associated speck-like protein containing a CARD domain) (Mariathasan and Monack 2007; Petrilli et al. 2007). Activation of the inflammasome will result in Caspase-1 activation, which then converts cytokines such as pro-IL-1β and pro-IL-18 (and others) into their active mature form. In summary, this illustrates the general numerous steps involved in the activation of the inflammasome danger signaling pathway and the numerous new potential biological points of pharmacologically blocking this response to prevent or mitigate particle induced inflammatory responses and osteolysis.

Systemic Effects of Wear and Corrosion

To some extent, implant surfaces and the implant debris generated are continually releasing chemically active metal ions into the surrounding peri-implant tissues. The released metal ions will bind to serum proteins and may reside in local tissues and also be transported via the bloodstream and the lymphatics to remote organs. This is of concern since it is known the potential toxicity effects of these elements used in modern orthopedic implant alloys: titanium, aluminum, vanadium, cobalt, chromium, and nickel. Metal toxicity can happen by changing: (i) cell/tissue metabolism, (ii) host/parasite interactions, (iii) immunologic interactions, and (iv) by inducing chemical carcinogenesis (Beyersmann 1994; Britton 1996; Goering and Klaasen 1995; Hartwig 1998; Luckey and Venugopal 1979).

Essential trace metals include cobalt and chromium and are necessary for the homeostatic function of various enzyme reactions. However, these elements in excessive quantities can become highly toxic. Accordingly, excessive cobalt can result in heart problems (cardiomyopathy), increased red blood cells (polycythemia), decreased thyroid functions (hypothyroidism), and carcinogenesis, while excessive chromium has been associated to nephropathy, hypersensitivity, and carcinogenesis. Also, metals such as nickel can result in skin rashes (eczematous dermatitis), hypersensitivity reactions, and cancer, and excessive vanadium exposure has been associated to heart and kidney dysfunction, and hypertension and depressive psychosis. Aluminum toxicity can lead to renal failure and blood anemia, bone softening (osteomalacia), and neurological problems. It is important to note, however, that these metal toxicities are generally due to excessively elevated levels of the soluble forms of these elements and most likely do not pertain to the levels of metals released from implant degradation.

Currently, any associated metal toxicity related to metal release from orthopedic implant is conjectural since it has yet to be established the cause and effect of this specific association. It is very difficult, however, to discern any metal toxicity effects related to an implant given the types of health concerns typically associated with the elderly, as well as those expected to occur in any orthopedic patient population (Jacobs et al. 1999a).

Systemic Particle Distribution: It is not well understood as to what determines the amount of implant debris accumulation in remote organs. When the magnitude of particulate debris produced by an implant is augmented, there is a corresponding increase in both the local and systemic burden of implant debris. Mostly, systemic implant debris (located beyond the peri-implant tissue microenvironment) is in the submicron size range. Numerous cases have located metallic, ceramic, or polymeric wear debris from hip and

knee prostheses in regional and pelvic lymph nodes along with the findings of gross dark staining by metallic debris, fibrosis (buildup of fibrous tissue), lymph node necrosis, and histiocytosis (abnormal function of tissue macrophages). Moreover, up to 70% of patients with total joint replacement components had metallic wear particles detected in their para-aortic lymph nodes. The consequences of this occurrence are not clear; however, prototypical immune inflammatory responses in lymph nodes to metallic and polymeric debris involve similar responses seen locally, which include activation of macrophages and associated production of cytokines.

Therefore, lymphatic transport is likely the main course for debris dissemination where particles are transported by perivascular channels as independent particles or as phagocytosed particles within macrophages. Disseminated particles within lymph nodes are primarily submicron in size; however, some metallic particles as large as 50 micrometers and polyethylene particles as large as 30 micrometers have also been detected. Additionally, these particles have been located within macrophages in the liver and spleen and in some instances, in nodules of inflammatory tissue granulomas throughout the organs. Typically, metallic particle size is nearly an order of magnitude less in the liver and spleen, than that in lymph nodes, suggesting there is an additional filtration point that occurs prior to particles culminating in those organs. This is not overly concerning since it is a common function of the cells of the liver, spleen, and lymph nodes to accumulate small quantities of a variety of foreign materials without evident clinical significance. However, nodules of inflammatory tissue (granulomas) or granulomatoid lesions in the liver and spleen can be induced by the accumulation of excessive particle debris. The degree of reaction to particles in the liver, spleen, and lymph nodes is probably modulated, as it is in other tissues by: (1) the dose of particles, (2) their rate of accumulation, (3) the period that they are present, and (4) the biologic reactivity of cells to these particles (size and materials composition). It is not unexpected that metallic particles in the liver or spleen are more common in patients with previously failed implants compared to patients with a primary well-functioning TJR.

It would be expected that in diseases which obstruct the continual lymph flow through lymph nodes, such as a metastatic tumor, or those that disrupt the general flow of circulation, such as chronic heart disease or diabetes, would result in reduced particle migration to remote organs, whereas other pathologies, like acute or chronic-active inflammation, likely augment particle migration (Jacobs et al. 1999a, 2001; Vermes et al. 2001b) via the recruitment of more immune cells to transport the debris away.

Hypersensitivity. In general terms, hypersensitivity responses to metal implants can be defined as an adaptive immune response that is mediated by T cells and typically causes a local inflammatory response around the implant. It is imperative to clarify that "hypersensitivity responses" have a wide range of intensity that can span from mild to severe and need not be on the severe end to be termed "hypersensitivity." Early implant failure (<7 years) that is caused by an exacerbated immune response to otherwise tolerable amounts of implant debris is likely caused and orchestrated by an adaptive immune response. This response is also often termed "metal-allergy," "implant-allergy," or "implant sensitivity." While soluble metals (i.e., metal ions) released from metal prostheses do not act as sensitizers alone, they are able to combine with self-proteins and form metal-protein complexes (haptens) that have the ability to activate the immune system. On the other hand, polymeric wear debris has not been implicated in allergic type immune responses due to its inability to properly degrade in vivo (Hallab et al. 2000a, b, 2001a, b). The most common metals regarded as sensitizers/allergens (metal haptens) include, but are not limited to beryllium, chromium, cobalt, nickel, tantalum, titanium, and vanadium. Nickel, cobalt, and chromium are the most common metal allergens reported in humans and nickel still constitutes 10–16% of medical grade stainless steel (Table 2). In general, the literature exhibits more case reports of hypersensitivity reactions associated with nickel-containing stainless steel and cobalt-alloy implants compared to Titanium-alloy devices (Burt et al. 1998; Cramers and Lucht 1977; Elves et al. 1975; Gordon et al.

Table 2 Approximate weight percent of different metals within popular orthopedic alloys

Alloy	Ni	N	Co	Cr	Ti	Mo	Al	Fe	Mn	Cu	W	C	Si	V
Stainless steel (ASTM F138)	10–15.5	<0.5	*	17–19	*	2–4	*	61–68	*	<0.5	<2.0	<0.06	<1.0	*
CoCrMo alloys (ASTM F75)	<2.0	*	61–66	27–30	*	4.5–7.0	*	<1.5	<1.0	*	*	<0.35	<1.0	*
(ASTM F90)	9–11	*	46–51	19–20	*	*	*	<3.0	<2.5	*	14–16	<0.15	<1.0	*
Ti alloys														
CPTi (ASTM F67)	*	*	*	*	99	*	*	0.2–0.5	*	*	*	<0.1	*	*
Ti-6Al-4 V (ASTM F136)	*	*	*	*	89–91	*	5.5–6.5	*	*	*	*	<0.08	*	3.5–4.5
45TiNi	55	*	*	*	45	*	*	*	*	*	*	*	*	*
Zr alloy (97.5% Zr, 2.5% Nb)	*	*	*	*	*	*	*	*	*	*	*	*	*	*

Note: Alloy compositions are standardized by the American Society for Testing and Materials (ASTM vol. 13.01)
* Indicates less than 0.05%

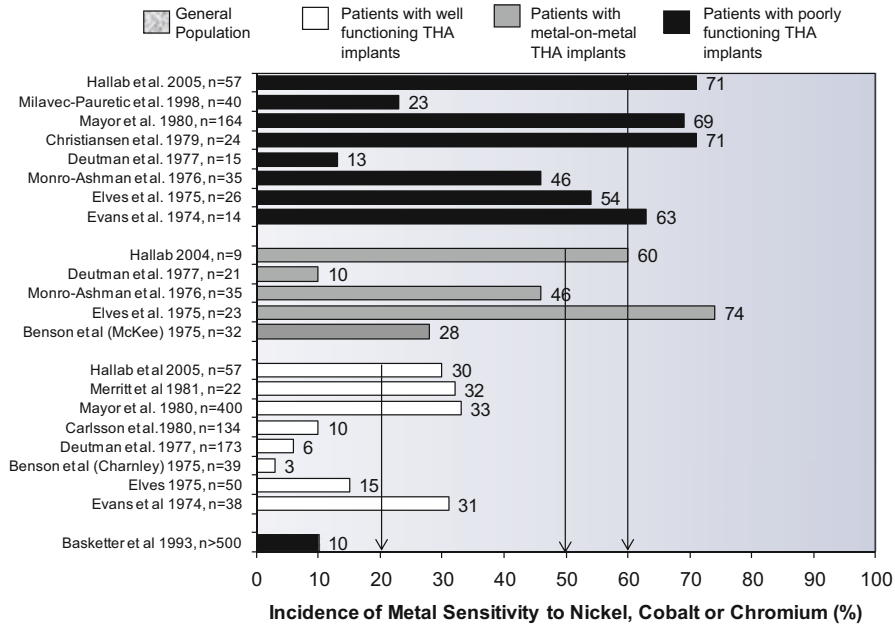

Fig. 6 A compilation of investigations showing the averaged percentage of metal sensitivity among the general population, people with well-functioning implants, people with metal-on-metal implants and people with failing implants (prior to getting them revised). Metal incidence rates include a positive response to allergy testing for nickel, cobalt, and/or chromium. All subjects were tested by means of a patch or metal-LTT (lymphocyte transformation test). (Courtesy of Orthopedic Analysis LLC)

1994; King et al. 1993; Merle et al. 1992; Rostoker et al. 1987; Thomas et al. 1987).

Incidence of Hypersensitivity Responses Among Patients with Metal Implants: People with well-function implants exhibit an incidence of hypersensitivity reactions (25%) twice as high as that of the general population (10%) (Fig. 6). Interestingly, the incidence of metal related hypersensitivity in people with poorly functioning metal prostheses (revision surgery candidates) or well-functioning metal-on-metal hip prostheses is 50–60% (Fig. 6). This higher incidence of metal hypersensitivity in cohorts of patients with metal prostheses has led to speculation that immune reactivity to metal implant components may play a role in implant loosening. Group studies performed over the last three decades have demonstrated a correlation between metal implants and metal sensitization (Hallab et al. 2001a), clearly concluding that metal sensitization can be an important causative factor to implant failure (Merritt and Rodrigo 1996; Rooker and Wilkinson 1980; Rostoker et al. 1987).

Therefore, metal sensitivity testing (metal-LTT) may be beneficial for people with a history of metal allergy before receiving a metal prosthesis. The significance of this line of research cannot be understated, as the use, durability, and performance expectations of metallic spinal implants continue to increase (Black 1996; Jacobs and Goodman 1996).

Metal Sensitivity Mechanism

Generally, metal sensitivity responses can be classified as: 1-Humoral immediate responses that can develop within minutes and are initiated by antibody-antigen complexes (Type I, II, III) and 2-cell-mediated delayed type hypersensitivity responses type IV, which may develop within hours to days (Hensten-Pettersen 1993; Kuby 1991). Immune responses to metal implant degradation products are almost exclusively classified as being delayed type hypersensitivity responses (DTH). This specific type of DTH response has

been predominantly classified as a Th1 type of response, where helper T cells are characterized by the release of a unique signature set of cytokines that include interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), interleukin-1 (IL-1), and interleukin-2 (IL-2). While this specific subset of cells are intended to detect and eradicate intracellular pathogens, they can also potentially induce autoimmune disorders (i.e., Rheumatoid arthritis, Lups, etc.) when mistakenly activated (Arora et al. 2003b; Hallab et al. 2008).

In this manner, activated and primed antigen presenting cells in combination with metal-activated T helper lymphocytes secrete a variety of pro-inflammatory cytokines that effect the recruitment and activation of innate immune cells (i.e., monocytes, macrophages, neutrophils) (Hallab et al. 2013). Some of these cytokines include, but are not limited to IFN-γ and TNF-β, which in turn induce pro-inflammatory physiological changes on local cells (i.e., endothelial cells) to aid the inflammatory response. The main characteristics of a DTH immune response are recruitment, recognition/activation, and migration inhibition of local immune cells (e.g., macrophages, T lymphocytes). Additionally, the release of potent pro-inflammatory cytokines like IL-1β from activated antigen presenting cells effect further recruitment and activation of T cells, which in turn activate additional macrophages exacerbating the immune response. Therefore, in certain types of DTH responses, including those associated with autoimmune diseases, there is a lack of self-regulation (off-switch) that can result in the perpetuation of the inflammatory response resulting in extensive tissue damage. Immunosuppression has been proposed as a strategy to mitigate the effects of the vicious pro-inflammatory cycle of DTH responses in these individuals in order to aid anti-inflammatory immune mechanisms to operate (Looney et al. 2006; Schwarz et al. 2000).

Testing for Metal Sensitivity

At present, there are two modalities accepted for human diagnostic testing for metal sensitivity: 1-patch testing (dermal testing) and 2-blood testing in vitro using a lymphocyte proliferation test (metal-LTT).

Dermal Skin Testing: Commercially available patch testing kits and protocols for the evaluation of metal induced hypersensitivity reactions have been used for over 40 years for purposes of orthopedic implants (Hensten-Pettersen 1993; Rooker and Wilkinson 1980). While patch testing can be a helpful tool in diagnosing dermal sensitivity to several metals, there are important limitations that must be considered when using this modality to assess DTH responses to orthopedic implant degradation products. (1) Primarily, performing patch testing pre-operatively has the potential to pre-sensitize the patient to one or more implant metals (Merritt and Brown 1980). The process of skin patch testing involves mixing metal ion/salts with an organic vehicle (i.e., petroleum Jelly) and the application of this mixture in direct contact with skin for 48 h. The extent to which dermal patch testing induces metal sensitization in humans is not known, but has been well established as a method to induce metal sensitization in animal models (Bonefeld et al. 2015; Vennegaard et al. 2014); therefore, it can potentially be a hazard for the purposes of diagnosing metal DTH responses in future orthopedic implant patients and a significant concern given how routinely this procedure is performed (Granchi et al. 2012). (2) An additional limitation of patch testing is the simulation of immunological potential of metal haptens in a nonsterile dermal environment compared to a significantly different sterile environment found in the peri-implant tissue (Korenblat 1992; Kuby 1991). For example, Langerhans cells – specialized antigen presenting cells of the skin – possess Birbeck granules which are unique antigen-processing/endosomal-processing organelles not found in macrophages/histiocytes in the peri-implant tissue (Mc et al. 2002; Valladeau et al. 2001). (3) Patch testing results are scored subjectively by a healthcare professional (i.e., Allergist) using a 0 to 3+ system, where results may not be easily compared between providers. (4) Immunological responses to patch testing challenge may be severely diminished due to the nature of the site of challenge and inherent

tolerance to environmental factors (i.e., metals) (Benson et al. 1975; Poss et al. 1984; Rooker and Wilkinson 1980; Wang et al. 1997a). The environment of immune challenge during patch testing can be highly variable and is non-standardized as they are usually placed directly on the back of patients (hairless area) for 2 to 3 days and it can be inconsistent from patient to patient. It may also be uncomfortable and the environment under which the test is performed (i.e., cleanliness) cannot controlled or standardized. (5) Lastly, there are no standardized, well-established metal salt concentrations available for patch testing or the availability of all orthopedic implant metals in commercially available patch testing kits (e.g., aluminum, molybdenum, vanadium, and zirconium) (Table 2).

Lymphocyte Transformation Testing (LTT): Also termed lymphocyte proliferation test measures the division/proliferation of peripheral blood T lymphocytes in vitro after exposure to specific antigens during a period of 6 days. Lymphocytes are isolated from a patient's blood sample (simple blood draw) by density gradient separation of mononuclear cells. The proliferation of these lymphocytes is measured 4–6 days (DTH response) after initial antigen exposure using a radiolabeling technique. Radioactive [H^3]-thymidine is incorporated into the DNA of dividing (proliferating) cells and allows for the quantification of actual cell division in response to several metal challenge agents (i.e., Al + 3, Co + 2, Cr + 3, Mo + 5, Ni + 2, V + 3, and Zr + 4) at different concentrations ranging from 0.001 to 0.1 mM. This specific modality of detection of cell proliferation has the ability to detect the specific subset of cells undergoing cell division in response to the antigen challenge. The final amount of proliferation is measured as a Stimulation Index (SI).

> Proliferation Index or Stimulation Index (SI) = (proliferation with treatment, cpms)/(proliferation of equal amount of starting cells of the same individual without treatment, cpms).

Lymphocyte transformation testing (LTT) has gradually become a more widely used and accepted test modality for the diagnosis of orthopedic implant-related metal sensitivity as well as in cohort and basic science studies of metal-induced DTH responses (Everness et al. 1990; Secher et al. 1977; Svejgaard et al. 1976, 1978; Veien and Svejgaard 1978; Veien et al. 1979). LTT testing is performed by isolating mononuclear cells from a patient's peripheral blood sample (i.e., T-cells, B-cells and other lymphocyte populations) and directly exposing them to metal challenge in order to simulate the local peri-implant environment (not possible with dermal patch testing) (Hallab et al. 1998b, 2000, 2000a, b, 2001b, 2013, 2003b). An advantage of LTT testing is that is highly quantitative and not dependent on subjective assessment of results (vs. patch testing) (Thomas et al. 2009). The stimulation Index (SI) is quantified from multiwell replicates of each challenge agent at each concentration tested that allows for the calculation of an average and standard deviation for each antigen tested. This enables assessment of a dose dependent response where a metal sensitive individual may exhibit lymphocyte proliferation at a lower or higher dose of metal challenge (Fig. 2). LTT has also shown to have a greater sensitivity to detect lymphocyte metal sensitization (>80%) compared to patch testing (Carando et al. 1985; Cederbrant et al. 1997; Federmann et al. 1994; Nyfeler and Pichler 1997; Primeau and Adkinson 2001; Torgersen et al. 1993). A recent study performed by Carossino et al. (2016; Innocenti et al. 2014) where patch testing, LTT, and cytokine analysis were performed concluded that "The lymphocyte transformation is the most suitable method for testing systemic allergies." This testing modality is gaining momentum and is increasingly becoming more relevant to the orthopedic community given the growing numbers of TJA performed each year (Kurtz et al. 2009).

Furthermore, other prospective and longitudinal studies as the one discussed in the next section regarding metal-on-metal devices substantiate the concept that LTT or Patch Testing are necessary in a clinical setting, especially for patients receiving specific types of devices that may be more prone to induce metal sensitization. There are also further case and group studies supporting the clinical utility and routine use of metal sensitivity testing for total joint replacement (TJR) patients that have

a history of metal allergy and/or for patients with aseptic/idiopathic implant related pain (Campbell et al. 2010; Hallab et al. 2013; Kwon et al. 2010, 2011; Thomas et al. 2009; Willert et al. 2005; Willert and Semlitsch 1977). Interestingly, while instability and infection are the primary causes of early implant failure, recent reports have put forward algorithms that include metal-induced DTH testing as a possible indication for patients with post-operative pain (Fig. 3) (Park et al. 2016). This specific algorithm suggests that metal-LTT and dermal testing should be performed as a last resort after imaging techniques (MRI, CT) and other infection indications have been ruled out.

Studies of Implant Related Metal Sensitivity Using Diagnostic Testing

Several studies performed over the past four decades have associated metal allergy or metal sensitivity with adverse implant immune responses, where the quantity of implant degradation products has been temporarily linked to symptoms such as severe dermatitis, urticaria, vasculitis (Abdallah et al. 1994; Barranco and Solloman 1972; Halpin 1975; King et al. 1993; Merle et al. 1992; Thomas et al. 1987), and/or nonspecific immune suppression (Bravo et al. 1990; Gillespie et al. 1988; Merritt and Brown 1985; Poss et al. 1984; Wang et al. 1997b). Some case studies have demonstrated cessation of metal sensitivity symptoms after removal of the implant and the reappearance of symptoms once a comparable implant was re-introduced. This agrees with Koch's postulate, an important test for causality in medicine, and demonstrates metal-induced sensitivity responses as causal for early implant failure (Barranco and Solloman 1972). Nevertheless, the majority of the evidence demonstrating the significant clinical utility of metal sensitivity testing can be credited to several retrospective cohort studies that have shown a strong correlation between metal exposure, metal sensitivity, and the performance of metal implants (Benson et al. 1975; Brown et al. 1977; Carlsson et al. 1980; Cramers and Lucht 1977; Deutman et al. 1977; Fischer et al. 1984; Kubba et al. 1981; Mayor et al. 1980; Merritt 1984; Merritt and Brown 1981; Pinkston and Finch 1979; Rooker and Wilkinson 1980). As mentioned previously, these studies demonstrate that people with well performing implants and people with painful/failing implants exhibit rates of metal hypersensitivity two fold or six fold higher compared to the general population, respectively (Caicedo et al. 2013b). It is also clear, based on current and past cohort studies, that specific types of metal implants known to release higher concentrations of ions and/or particles are more likely to induce metal sensitization (Hallab et al. 2013; Kwon et al. 2011).

While metal on metal total hip arthroplasties (MoM THA) provide the advantage of lower implant wear compared to metal-on-polymer (MoP) implants, they are known to release higher concentration of metal ions and particles and thus have a higher incidence of failure attributable to excessive inflammatory responses. Previous studies have shown hypersensitivity-like responses, including histological inflammatory evidence accompanied by severe lymphocyte infiltrates, in as high as 76–100% of patients with poorly performing MoM devices (Korovessis et al. 2006; Milosev et al. 2006). In a prospective study using a cohort of MoM patients, it was shown that in vivo metal sensitivity responses may develop even in well performing (asymptomatic) MoM implants (Hallab et al. 2013) where a significant increase in the rate of diagnosed metal sensitivity increased from 5% preoperatively to 56% within the first 4 years postoperatively (Hallab et al. 2013). In this study increases in serum levels of Co and Cr occurred at early stage, at 3 months postoperatively. However, lymphocyte sensitivity responses only became more evident at 1–4 years post-op. This delay in detection of metal sensitivity responses postoperatively suggests that metal sensitization may develop over-time as exposure to metal ion levels increase. The rates found, while still high compared to conventional implants (25%), are lower than 81% in failing MoM implants previously reported for painful/symptomatic MOM patients by Thomas et al. (2009).

Pain levels have also been shown to correlate with metal sensitivity (Metal-LTT with SI >2) where patients with highly painful implants were

significantly higher compared to patients with nonpainful implants (Caicedo et al. 2013b). Furthermore, TJA patients that reported low implant pain levels also exhibited a relatively lower incidence of metal sensitization further supporting a correlation between aseptic implant pain levels and metal sensitivity. Additionally, not only do TJA female patients referred for metal sensitivity testing exhibit a higher average pain level compared to males, but also show a higher incidence and severity of metal sensitization (Caicedo et al. 2017). This supports the utility of metal DTH testing in patients with aseptic implant-related pain, especially for female orthopedic patients.

Conclusions

Implant degradation and debris is unavoidable and results in activation of the immune system resulting in local inflammation that over time causes more bone loss then homeostatic mechanisms can keep up with, and the result is implant loosening, via aseptic osteolysis. This reactivity may activate the adaptive immune systems and result in allergic type responses involving T-cells. Both innate (macrophage) and adaptive (T lymphocyte) immune system reactivity can act to limit the lifetime of current total joint replacement implants. Advances at the molecular and cellular level continue to increase our understanding of immune reactivity based bone loss. There are a new treatment and diagnostic options available for patients and surgeons ranging from diagnosing preexisting or developed conditions of metal allergy (metal-LTT), general management of inflammation (e.g., NSAIDS) to selective blocking of cellular mediators (e.g., anti-IL-6, anti-TNFα, IL-1β-receptor antagonist). These options should be part of the modern arsenal used to help fight the problem of adverse reactivity to implant debris, i.e., induced inflammatory bone loss. There is increasing need for using patient specific diagnosis and treatment to mitigate the role of metal hypersensitivity and genetic susceptibility to implant debris-induced inflammation.

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8 Mechanical Implant Material Selection, Durability, Strength, and Stiffness

Robert Sommerich, Melissa (Kuhn) DeCelle, and William J. Frasier

Contents

Abstract

Spinal implants are manufactured from a variety of materials to meet user needs as well as the requirements of the physical and environmental demands upon the device. Commonly used materials include titanium, stainless steel, cobalt-chrome, nitinol, carbon fiber reinforced polymer (CFRP), polyetheretherketone (PEEK), silicon nitride, biodegradable polymers, and allograft bone. Material choices can be driven by requirements for strength, biocompatibility, bone ongrowth, flexibility, and radiolucency. Coatings may also be applied to the implants to further enhance physical or biological properties of the implant. These may include

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hydroxyapatite, titanium plasma, or a combination of these two materials. Additionally, implants may have a porous layer or open structure for improvement of osteointegration. Spinal implants are commonly made using conventional manufacturing methods such as machining and injection molding, but additive manufacturing is becoming more commonly used to produce certain implants.

Keywords

Spinal · Implant · Titanium · PEEK · Cobalt-chrome · Interbody · Pedicle screw · Cage · Rod · Hydroxyapatite

Introduction

Modern spinal surgeries use a variety of implants to decompress neural elements, support spinal segments, and stabilize motion segments. This can be achieved by restricting motion through fusion or preserving the natural motion and kinematics of the spine. Fusion occurs through the interbody space from one end plate to another, and the support of this space is provided by an interbody cage, with stability and compression provided by bone screws or hooks and rods. Spinal plates may also be used to provide stability, restore initial bone mechanics, and speed up the healing process after injury (Caspar et al. 1998; Emery et al. 1997). While the implant must withstand anatomical loading, the implant must not result in stress shielding of the surrounding bone which may result in impeding new bone growth. Additional stability may be provided with the use of bone screws or hooks which are connected to the associated rods using set screws. Multiple materials are used to manufacture these implants. These materials need to provide a balance of strength, stiffness, and biocompatibility, as well as manufacturability. In addition to the base materials, there are often surface treatments and coatings applied which are intended to improve implant performance, usually by increasing the screw's resistance to backing out or pulling out from the bone. This increased resistance to removal is achieved by providing surfaces that have improved ingrowth or adhesion of bone to the implant. When fusion is not the desired outcome, clinicians may opt to use implants such as interspinous process devices (IPDs) or artificial discs for spinal segment stabilization and motion preservation. IPDs, for example, provide indirect decompression of spinal nerve roots and canal. Motion preservation devices aim at allowing for load transfer similar to that of the natural kinematics of the spine (Wilke et al. 2008). When selecting an implant material, multiple factors should be considered such as anatomical location, desired clinical outcome, load sharing capability, desired range of motion (ROM), and degree of biocompatibility. This chapter will focus on implant selection based on material properties.

Metallic Implants

(a) **Titanium** – the most commonly used material to produce bone screws, rods, hooks, and set screws is titanium (Ti). Titanium is a popular choice due to its favorable properties of strength, corrosion resistance, and biocompatibility. Compared to stainless steel, titanium produces a less pronounced imaging artifact during X-ray or computed tomography (CT) scans and is less likely to have bacteria adhere to it (Luca et al. 2013). Titanium has also been shown to have a higher rate of bone ongrowth compared to stainless steel, and when used in pedicle screws, to have an increased resistance to backing out, as measured by removal torque in a mini-pig model (Christensen et al. 2000). Implant grade titanium is available primarily in three varieties: titanium-aluminum-vanadium (Ti-6Al-4V), commercially pure (CP), and titanium-molybdenum (Ti-15Mo). Example mechanical properties of these materials are summarized in Table 1. In general, Ti-6Al-4V is the most commonly used of the three options. Ti-6Al-4V is stronger and stiffer than Commercially Pure Titanium, readily available, and easily to machine. After contouring, such as in the case of spinal rods, Ti-6Al-4V also holds its shape

Table 1 Example implant material properties

Material	Tensile strength, ultimate (MPa)	Tensile strength, yield (MPa)	Modulus of elasticity (GPa)	Elongation at break (%)
Ti-6Al-4V ELI	862	786	110	10
Commercially pure Ti (Grade 4)	550	483	102	15
Ti-15Mo (alpha + beta annealed + aged)	900	800	105	10
316L annealed stainless steel	490	190	193	40
Cobalt- chromium	1290	760	235	25
PEEK		80	4	
CFRP		120	18	

Disegi (2009), Zaman et al. (2017), and Najeeb et al. (2016)
Note: Material properties can vary based on processing and should be verified with the selected supplier

better over temperature changes than commercially pure titanium (Noshchenko et al. 2011). Titanium-molybdenum is more difficult and expensive to obtain, and requires advanced expertise in machining, due to its nature of clogging cutting tools. However, when processed to the alpha+beta phase, Ti-15Mo has superior strength properties and a higher resistance to failure in cyclic loading or crack propagation due to stress risers compared to Ti-6Al-4V.

(b) **Stainless steel** – Stainless steel (SS) has been used for bone screws, rods, and hooks as well. Over the past decade this material has fallen out of favor due to patients with nickel allergies. In the past, stainless steel had historically been the material of choice for spinal rods over titanium when a stronger, stiffer construct was required. The use of a stainless steel rod often drove the use of stainless steel screws, hooks, and set screws. This was intended to prevent galvanic corrosion between dissimilar metals, which was a concern when using titanium bone screws with stainless steel rods. These concerns were proved to be generally unfounded (Serhan et al. 2004). The stainless steel grade used for implants is 316L. This material is available in different treatments, providing multiple strengths and stiffnesses. The material properties of 316L stainless steel are summarized in Table 1.

The material of choice for spinal plates has shifted from stainless steel to titanium alloys such as Ti-6Al-4V. A titanium alloy plate can provide sufficient rigidity and stability to allow for arthrodesis, prevent displacement or collapse of the intervertebral grafts, and maintain cervical lordosis to achieve a better prognosis (Chen et al. 2016). Titanium alloy implants are more ductile than stainless steel implants. It is also a proven biocompatible material.

In general, metal implants produce artifacts that make radiologic interpretation more challenging (Aryan et al. 2007). However, titanium and titanium alloys are more MRI (Magnetic Resonance Imaging) compatible than stainless steel due to its lower X-ray beam attenuation coefficients (Lee et al. 2007; Haramati et al. 1994). Another clinical benefit of titanium implants includes its ability to have a modified surface for improved osseointegration. For example, a rough surface can be induced on titanium implants which results in higher osseointegration compared to the smooth surface present on stainless steel implants.

(c) **Cobalt-chrome** – Cobalt-chrome (Co-Cr) is a relatively new entry into the materials available for implants. It is most commonly used for spinal rods, but not necessarily screws or hooks. The advantages of this material over stainless steel or titanium are numerous.

It provides higher strength and stiffness than titanium given the same rod diameter. This allows for the creation of stiffer constructs with stronger correction, or the use of smaller profile implants. Cobalt-chrome rods that are 5.5 mm in diameter have a greater bending stiffness than 6.35 mm diameter titanium rods. Cobalt-chrome also produces less imaging artifact than stainless steel, and can be combined with titanium screws which have better biocompatibility than stainless steel screws. Although mixing of metals in the body (titanium and cobalt-chrome or titanium and stainless steel) may result in galvanic corrosion, the susceptibility of the Ti-Co-Cr construct to this phenomenon is theorized to be less than in a Ti-SS construct (Piazzolla et al. 2013). Additionally, it has been found that the amount of galvanic corrosion evident with two connected stainless-steel implants is actually greater than the corrosion present between a stainless steel and titanium implant (Serhan et al. 2004). Table 1 summarizes example material properties of cobalt-chromium.

(d) **Nitinol** – Nitinol has been used to manufacture spinal rods with the goal of creating a less stiff construct to help reduce adjacent segment disease and provide a more compliant construct. Nitinol is a nickel–titanium alloy, which can be manufactured to produce unique shape-memory effects. Although it contains nickel, animal studies have found that no measurable amounts of nickel are absorbed into the body after implantation (Kok et al. 2013). Although studied in the literature, Nitinol rods have not proven to be particularly popular in the market. Concerns around fretting or wear and corrosion of the nitinol material where it is connected to conventional titanium or stainless steel screws raise concerns around premature implant failure, and thus would require specially treated screws to be used with nitinol rods. This, along with the processing costs and complexity of nitinol may be factors preventing widespread adoption in the market. An additional potential use of nitinol rods is in sliding growth constructs used in the treatment of early onset scoliosis. The sliding rod component allows for less traumatic adjustment of the construct as the patient grows compared to conventional fixed rod constructs. Nitinol has 100 times greater wear resistance than titanium and similar wear resistance as cobalt-chromium. This increased wear resistance would greatly reduce the amount of wear debris produced by the sliding construct over the implantation period, which spans multiple years, greatly reducing the patient's exposure to metallic particles and the potential irritation these could cause (Lukina et al. 2015)

Porous Metals

Materials having a porous structure have been developed in an attempt to increase the physical integration of bone to the implant structure. For example, with interbody cages, this is intended to result in "enhanced fixation of the device, preventing device migration or movement causing abrasive damage to adjacent tissue" and "may provide a transitional zone between the bone and biomaterial to reduce stress-shielding" (Jarman-Smith et al. 2012). Porous metals such as titanium (PlivioPore, Synthes; Tritanium Stryker), Nitinol (Actipore Biorthex), and Tantalum (Trabecular Metal, Zimmer (Hedrocel, Implex)) have been developed and commercialized to address this issue (Jarman-Smith et al. 2012; Lewis 2013). While these materials may address approximating the modulus of bone and the potential for ingrowth for increased stability, the issue with lack of radiolucency and CT/MRI artifact remains.

Polymers

As more metallic devices were implanted, reported issues with subsidence and stress shielding increased. With interbody cages, for example, metallic implants prevented the assessment of fusion due to lack of radiolucency.

Seaman describes "while Ti (titanium) had favorable fusion rates, a noted shortcoming was subsidence or settling into the adjacent vertebral bodies due to the differences in the modulus of elasticity. As a result, polyetheretherketone (PEEK) cages were introduced in the 1990s as an alternative due to their elastic modulus properties" (Seaman et al. 2017). PEEK allows for improved load sharing within the spine while stabilizing the disease segment and reducing stress on adjacent levels comparing to metallic implants, such as Ti.

Additional materials developed during this time including carbon fiber reinforced polymer (CFRP) cages that consisted of PEEK material with carbon fibers. Both PEEK and CFRP implant materials are biocompatible for safe implantation in the spine.

These polymers have clear advantages of reduced modulus, radiolucency, and reduced CT/MRI artifact in comparison to titanium. The PEEK and CFRP implants have elastic modulus characteristics similar to that of natural bone as compared to titanium. The strength of the CFRP material allows for a reduced implant volume and greater graft volumes as compared to implants manufactured from pure PEEK. Brantigan et al. (1991) reported increased pullout forces and similar compressive strengths for the carbon fiber cage as compared to femoral grafts when placed in cadaveric specimens. The reduced elastic modulus and implant design has been shown to potentially load the interbody graft material to allow for a better load sharing environment (Vadapalli et al. 2006; Kanayama et al. 2000).

In addition to the more commonly used metals, there is some use of PEEK or CFRP for both pedicle screws and spinal rods as well. PEEK has generally been used only for spinal rods, while CFRP has been for screws (Ringel et al. 2017). PEEK/CFRP is obviously much weaker and less stiff than the other metallic choices outlined above. The attraction of PEEK rods was the theory that they would flex as the spine moves and would have a similar modulus of elasticity to a PEEK or CFRP interbody spacer, which would also allow for some compliance. This modulus of elasticity is designed to be between that of cortical and cancellous bone, which allows for improved load sharing while still stabilizing the intended segments, but ultimately reducing the chance of adjacent segment degeneration (Athanasakopoulos et al. 2013). This flexible structure, rather than a completely rigid metal one, would be less likely to result in interbody spacers subsiding into the vertebral end plates and pedicle screws plowing out of or fracturing a pedicle when continually loaded, as in normal activities of daily living. However, PEEK rods have limited application to a smaller number of patients because they are not able to be contoured intraoperatively as compared to titanium or stainless steel rods.

PEEK rods and CFRP screws offer a major advantage over metallic implants when being imaged. They are radiolucent and produce no artifact from magnetic resonance imaging. This is especially useful for patients being treated for spinal tumors, where radiation treatment, planning and execution are negatively impacted by titanium or stainless steel screws (Ringel et al. 2017). PEEK rods have also been used successfully in non-fusion procedures. In these procedures, the flexibility of the rods allows for some motion to be maintained in the segment while still offering support and stabilization to the diseased segments. The results of a multi-patient study were an improvement in pain scores and a reduction in range of motion, with an implant failure rate lower than normally reported in the literature (Huang et al. 2016).

However, there remains a potential concern of direct bone ongrowth onto the implant surfaces of PEEK implants. PEEK is a highly inert, hydrophobic thermoplastic polymer that often results in a lack of direct apposition to bone for proper long-term implant performance. The presence of a fibrous tissue layer between the PEEK implant and the adjacent bone has been documented clinically and in animal studies (Phan and Mobbs 2016; Walsh et al. 2015). Phan has described the resulting radiolucent rim at the bone–implant interface due to the fibrous tissue as a "PEEK-Halo" (Phan et al. 2016).

A number of methods have been used to improve the bioactive surfaces of PEEK implants. Implants have been designed with both PEEK and

titanium materials to allow for the titanium surfaces to contact the underlying bone (Rao et al. 2014). Additionally, PEEK implants have been coated with titanium or hydroxyapatite (HA) to improve biocompatibility to increase the resultant direct apposition of bone to the PEEK implant surface (Rao et al. 2014; Robotti and Zappini 2012). However, an early summary of clinical results with the titanium-coated PEEK indicated similar fusion rates as compared to uncoated PEEK (Assem et al. 2015). PEEK is also currently available with HA incorporated into the material (PEEK-OPTIMA HA Enhanced, Invibio) which allows for typical machining of the implant with exposure to HA at the surfaces of the implant. The PEEK HA Enhanced has been shown in animals to result in more direct bone apposition as compared with PEEK bulk material only (Walsh et al. 2016). The addition of bioactive materials to PEEK, surface modification techniques, processing techniques for deposition coating of PEEK implants, and functional and mechanical properties of PEEK are well described (Robotti and Zappini 2012; Roeder and Conrad 2012; Poulsson and Richards 2012). It should be noted that the desire to improve the bone ongrowth onto the PEEK implants must not be at the risk of potential failure of the applied coating during anatomical loading or insertion of the implant. Investigations of coatings have indicated the potential for wear debris or surface damage to occur as a result of procedural impaction to place the implant (Kienle et al. 2016).

Porous PEEK

The solution to the issue of radiopacity that exists with metallic implants may be the development of porous PEEK materials. This may be accomplished through various methods which include particulate leaching, heat sintering, and selective laser sintering. Jarman-Smith describes case studies of porous PEEK that includes mechanical testing and an animal ingrowth in comparison to solid PEEK (Jarman-Smith et al. 2012). In general, bone ingrowth was present in the porous PEEK materials, and more bone ongrowth of the porous PEEK samples which increased at over the 4- to 12-week time periods was demonstrated. Based on the mechanical requirements for a load bearing application a solid–porous PEEK device may be required to meet the functional demands. A solid–porous hybrid has been described using sodium chloride crystals that are leached out to produce a porous surface structure for bone ingrowth. The mechanical properties of the resulting structure have been estimated to support the functional requirements for an interbody device (Torstrick et al. 2016). The mechanical shear properties have been characterized and compared to bulk sintered PEEK in which the surface porous PEEK produced significantly higher results (23.96 MPa vs. 6.81 MPa, for surface porous and bulk porous, respectively). Early clinical results after 1 year with 100 patients have shown no device-related complications (Torstrick et al. 2017) (Fig. 1).

Silicon Nitride

Silicon nitride (Si_3N_4) is a ceramic that has been implanted as an interbody fusion device since 2008 with approximately 25,000 implants up to the year 2015 (McEntire et al. 2015). The materials have also been studied for its characteristics of osteointegration and anti-infection. New bone formation was found to be increased in the absence and presence of a bacterial injection as compared to titanium and PEEK (Webster et al. 2012). However, long-term 10-year clinical history has indicated a potential of adjacent level degeneration that was proposed to be caused by stress shielding due to elastic modulus mismatch (Sorrell et al. 2004). The elastic modulus of silicon nitride is approximately 300 GPa, while that of cortical bone is roughly 10 GPa (Bal and Rahaman 2012).

Biodegradable Polymers

The high stiffness of metallic implants has potential to shield the loading required within the spine to allow for fusion (Chen et al. 2016). This has led

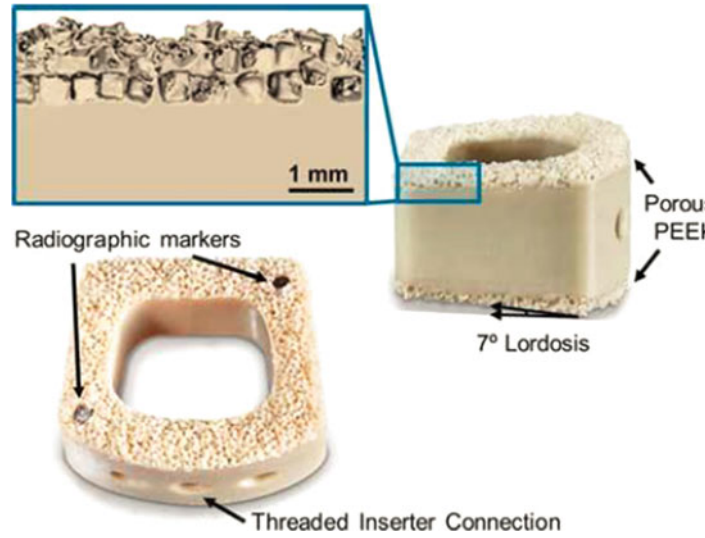

Fig. 1 COHERE implant demonstrating the characteristics of porous PEEK surface (Torstrick et al. 2017)

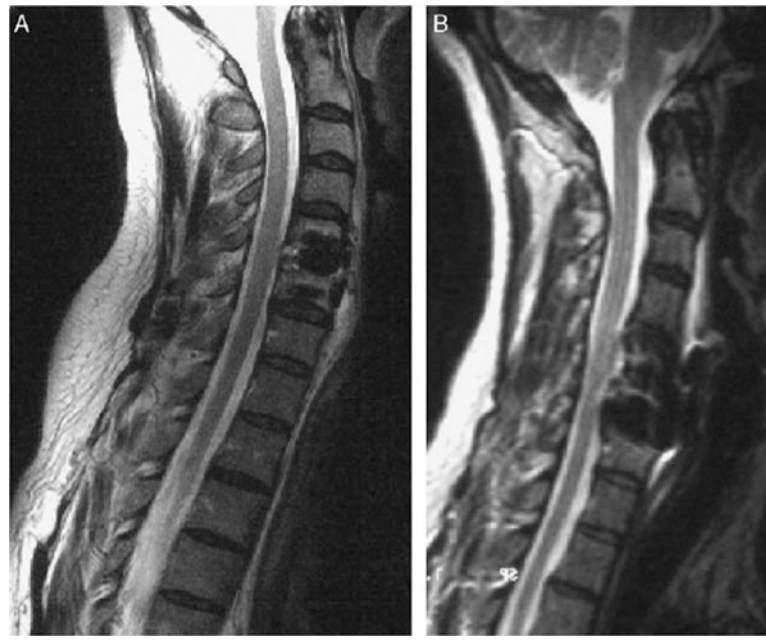

Fig. 2 T2-weighted magnetic resonance imaging of cervical spine showing early postoperative changes after the implantation of bioresorbable plate (**a**) and after implantation of titanium plate (**b**). Notice the obvious imaging artifacts in (**b**) compared with (**a**) (Nabhan et al. 2009)

to the use of biodegradable polymers for use in spine surgery with implants such as cervical plates. The modulus of elasticity of polymers can be altered based on the amount of cross-linking of the polymeric chains present within the material (Cheng et al. 2009). Biodegradable polymers may have lower modulus of elasticity that better represents physiological values when compared to metals (Freeman et al. 2006) which, in turn, can prevent stress shielding. In addition, polymers allow for greater visualization within the interbody space intraoperatively (Aryan et al. 1976) because the material does not produce artifact on MRI or CT scans (Nabhan et al. 2009). This becomes particularly important with specific patient groups, that is, obese patients and patients with shorter necks (Nabhan et al. 2009) (Fig. 2).

One major clinical benefit of biodegradable polymers is the ability of the material to completely hydrolyze within 2 years of initial

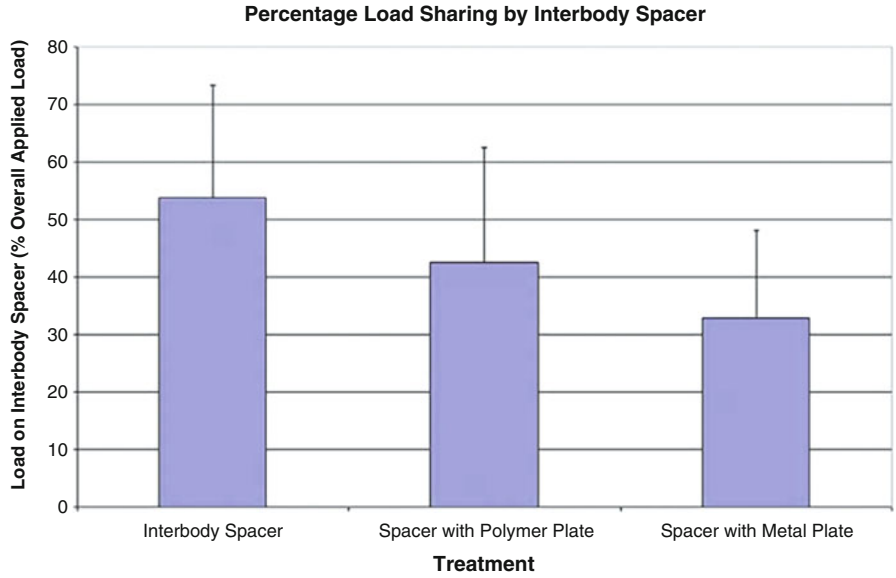

Fig. 3 Graphical representation of percentage load sharing by interbody spacer in the anterior spinal column (Cheng et al. 2009)

surgery. Spinal plates, for example, maintain approximately 90% of its initial strength 6 months post-implantation and approximately 70% of its initial strength 9 months post-implantation. This slow decrease in strength may allow the area of fusion to gradually take more of the load to potentially increase the rate of fusion while reducing stress shielding (Ames et al. 2002; Ciccone et al. 2001). Therefore, there is no need for implant removal in the case of a revision or adjacent segment surgery (Chen et al. 2016). This can reduce the long-term complications that have been historically associated with metallic plating.

In contrast, Boyle et al. compared ROM between an interbody space with a titanium rigid plate and an interbody space fixed with a biodegradable polymer plate (Cheng et al. 2009). They found that the titanium plate in conjunction with the interbody spacer achieved the highest level of motion reduction and also exhibited the lowest mean ROM. In a study by Freeman et al. (2006), the reduction of the ROM for both biodegradable and titanium anterior cervical plates was also compared. The results reported a reduction in the flexion–extension ROM by approximately 50% for a biodegradable plate and approximately 70% with titanium construct.

Boyle et al. also examined the percentage of load sharing with respect to three different conditions:

1. Stand-alone interbody spacer.
2. Spacer with a polymer plate.
3. Spacer with a rigid titanium plate.

The results showed that there was a statistical difference in compressive loading of anterior columns between the stand-alone spacer and the spacer with the Ti plate. However, there was no statistical difference in loading between the stand-alone spacer and the spacer with the polymer plate (see Fig. 3).

Therefore, this study showed that a spacer with a metal plate results in a lower percentage of load shared by the interbody spacer than with a bioresorbable plate. Researchers have reported concerns regarding the reduced rigidity of the biodegradable material and how this will impact its long-term efficacy compared to a rigid metal plate. Brkaric et al. (2007) reported early failure of a bioabsorbable plates, questioning the role of hydrolysis on crack initiation and propagation in polymer plates. In contrast to Boyle's study, there are encouraging clinical results of bioabsorbable

plates (Aryan et al. 1976; Franco et al. 2007; Nabhan et al. 2009; Park et al. 2004; Tomasino et al. 2009; Vaccaro et al. 2002). In regard to imaging, Nabhan et al. (2009) confirmed that a single level bioresorbable plate is MRI and tissue compatible, and shows comparable fusion rates to titanium plate.

Allograft

Allograft is the most commonly used non-autogenous grafting material in spinal surgery (Hamer et al. 1996). Mineralized allograft is primarily osteoconductive, with weak osteoinductive capacity. The majority of allografts are primarily composed of cancellous or cortical bone. Cortical bone allografts provide significant mechanical stability and structural support. Cancellous bone allografts have a faster rate of incorporation. Therefore, the clinical application of an allograft should be considered when selecting graft material. Allografts do not have osteogenic potential because graft cells do not survive the processing/transplantation process. Allograft used for orthopedic applications is fresh frozen, freeze-dried, or demineralized.

One concern with the use of human allograft is the potential of disease transmission from donor to recipient. Donor screening, tissue testing and tissue processing have reduced this risk to less than 1 event per million grafts (Stevenson et al. 1996).

Hydroxyapatite (HA)

HA is composed of calcium phosphate mineral, which has both osteointegrative and osteoconductive properties. Osteointegration results from the formation of a layer of HA shortly after implantation. HA has highly osteoconductive properties, which promote bone growth on a surface (Cook et al. 1994). The material is composed of hydroxylated calcium phosphate and is chemically identical to natural HA of bone (Doria and Gallo 2016). It has the ability to bond directly to bone which reproduces the natural bone-cementing mechanism (Eggli et al. 1988). HA is a very brittle ceramic and is prone to fracture with cyclic loading.

Additive Manufacturing

Currently several manufacturers offer a variety of titanium devices that are produced with additive manufacturing for orthopedic implants. These include porous matrices (Zimmer Biomet OsseoTi Porous Metal, Stryker Tritanium, and Smith & Nephew CONCELOC) and designs with open or porous surfaces (4WEB, Joimax, Renovis, K2M, and Spineart). Lewis published a comparison of commercially available porous metals (Lewis 2013).

The manufacturing technique of additive manufacturing by selective laser sintering (SLS) or electron beam (EB) (termed "powder bed fusion" by ASTM) (ASTM F2792) allows for design options not allowed by subtractive manufacturing methods. An example of this is the truss-based designs (4WEB, Camber Spine) for spinal implants. Due to the variability in processes it is difficult to compare mechanical properties of resultant materials. Some of the available devices incorporate the porous–solid hybrid concept. Since these devices are a continuous structure from the solid to porous structure, the issue of coating delamination should be alleviated.

Additive Manufactured PEKK

An alternative implant material to titanium that is currently used in additive manufacturing for implants is polyetherketoneketone (PEKK) (http://oxfordpm.com/cmf-orthopedics). PEKK is from the same family of polyaryletherketone (PAEK) polymer materials as PEEK (Kurtz and Devine 2007; Kurtz 2012). The material properties are very similar to PEEK. PEKK has been used for cranial repair (FDA 510(k) Feb 2013) and interbody fusion devices (FDA 510(k) July 2015). The PEKK material has recently been investigated for antibacterial properties by Wang et al. The authors concluded from the in vitro testing that

there was "decreased adhesion and growth of *P. aeruginosa* and *S. epidermidis* on nanorough PEKK surface compared with conventional PEEK surfaces" (Wang et al. 2017).

Coatings

In addition to various material choices for implants, there have been attempts made to improve the strength of the interface between the pedicle bone and screw through the use of surface coatings on the threads of the screw. Examples of coatings used include hydroxyapatite (HA) and titanium plasma spray (TPS). Additionally, these coatings have been combined into a composite coating (HA-TPS). Testing of these coating options on a titanium bone screw in a porcine model has shown improvement in screw back out torque compared to an uncoated titanium screw for all 3 of the coating options (Upasani et al. 2009).

Cross-References

- Anterior Lumbar Interbody Fusion and Transforaminal Lumbar Interbody Fusion
- Anterior Spinal Plates: Cervical
- Implant Material Bio-compatibility, Sensitivity, and Allergic Reactions
- Interbody Cages: Cervical
- Interspinous Devices
- Material Selection Impact on Intraoperative Spine Manipulation and Post-op Correction Maintenance
- Pedicle Screw Fixation
- Selection of Implant Material Effect on MRI Interpretation in Patients

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9 Material Selection Impact on Intraoperative Spine Manipulation and Post-op Correction Maintenance

Hesham Mostafa Zakaria and Frank La Marca

Contents

Abstract

As spine surgeons, there are a variety of products and technologies available for application within our discipline. The breadth of variety comes from the diverse materials that are available, each with a unique physical, mechanical, and biological property that gives it advantages and disadvantages. It is fundamentally important for a spine surgeon to understand every facet of these materials, because they will ultimately not only have a unique effect on the body's physiology but will also alter the ability to maintain stabilization while the wound heals and arthrodesis is achieved. This chapter will go over the common commercial materials available for spine stabilization and manipulation. It will discuss in depth the advantages and disadvantages of their specific biomechanical properties and biocompatible. Finally, this chapter will discuss how each material can affect spine stabilization and maintenance of correction.

Keywords

Spine surgery · Spine biotechnology · Spine implants · Metal implants · Metal alloys · Stainless steel · Cobalt chromium · Titanium · Polyetheretherketone · PEEK · Spine manipulation · Deformity correction · Metal implants · Metal alloys · Biomaterials · Biotechnology

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Introduction

It is fundamentally important to understand the mechanical and long term structural properties of spinal implants. Ultimately the goal of spinal instrumentation placement is to provide a transient and load bearing scaffold while wound healing and arthrodesis occurs. Subsequently, implants are required to maintain the biomechanical alignment and correction despite undergoing compressive, torsional, and bending forces. If a selected material is inappropriate for the specific surgery, then it may fail in vivo and thus destabilize the spine and require revision. Failure may be mechanical, or that material itself lacks the tensile strength to maintain correction, or as a result of the material interacting with the local tissue environment, such as corrosion, degradation, or wear. Furthermore, bone remodeling during the healing process as well as over time can affect interaction with the implant material that if not biocompatible could result in inflammatory reaction and/or subsidence of the implant with loss of original corrective alignment results. Tissue reaction to the implant material can also impede bone healing. If bone fusion is not obtained, then all materials may eventually undergo fatigue failure through cyclical force application and loading of the implant. The biomechanical properties of spine alignment correction and how material selection can impact spine manipulation and maintenance of correction will be reviewed.

Biomechanics of Spine Correction

To achieve the required torque for spine manipulation and stabilization, there are a few standard practices: maximum leverage is obtained with fixation of as many possible segments as needed, with rigid rod fixation combined with either pedicle screw fixation, sublaminar hook or wire fixation or anterior vertebral body screw fixation resulting in direct vertebral rotation, distraction and/or compression where needed to restore spinal alignment (Hitchon et al. 2003; Clements et al. 2009; Lee et al. 2004; Bridwell et al. 1993; Bono and Lee 2004; Boos and Webb 1997). The ideal surgical instrumentation will maintain its shape as well as corrective forces at implantation and until arthrodesis occurs. This ability is defined by key mechanical properties, including yield strength (force required to permanently deform the material), stiffness (ability to maintain correction), and fatigue life (how long it can sustain repeated stress).

Young's modulus is the ratio of stress (force per unit area) to strain (deformation of a material), and so it is a measure of the elasticity of a specified material. Ideally, Young's modulus of the implanted material should be similar to bone; differences in elasticity hinder the transfer of forces from the material to the bone tissue, which prevents normal bone remodeling and creates osteopenia, otherwise known as the stress-shielding effect in accordance with Wolf's law (Antunes and de Oliveira 2012; Ebramzadeh et al. 2003; Tahal et al. 2017). Young's modulus of the cortical bone varies depending on bone quality, but it is within the range of 20–30 GPa (El Masri et al. 2012; Dall'Ara et al. 2013). The ultimate and final properties of a construct will depend on the material's diameter, length, and shape. While the minimum parameters required for a given correction is not known, larger and stiffer rods are known to improve deformity correction, and two-rod systems are intuitively stronger than single-rod systems (Fricka et al. 2002; Yoshihara 2013; Abul-Kasim et al. 2011).

An important factor that effects rod fatigue life and a rod's ability to maintain postoperative deformity correction is the intraoperative notching of rods. During normal clinical intraoperative application of rods, straight rods are bent into the required alignment to maintain correction. This is achieved with either a French bender or an in situ bender, which can create a notch in the rod. Notches ultimately weaken the rod by allowing for concentrations of stress at the point of the notch (Shigley 2011; Cook and Young 1985), leading to worsened rod fatigue resistance at that point which can ultimately cause fracture at the point of the notch.

Regardless of the modulus of elasticity of current implant options, there is still a degree of variation between this modulus and that of bone.

Furthermore, the changes occurring during surgery cause for an increased stress riser at the level of transition between fixed spinal segments and those unoperated segments that maintain their physiologic motion. This area of transition and subsequent stress riser is concentrated at the apex of the construct and is known to change the in vivo mechanical properties of the spine, especially fatigue resistance at the transition zone (Yoshihara 2013; Nguyen et al. 2011; Dick and Bourgeault 2001; Lindsey et al. 2006).

Corrosion is material degradation due to reactions with its surrounding environment, which can ultimately lead to hardware failure (Singh and Dahotre 2007; Ratner et al. 2004). As the human body is composed of an aqueous saline solution with numerous cations and anions, it is considered quite corrosive and so corrosion resistance is one of the main features of biocompatibility (Pan et al. 1996; Lin and Bumgardner 2004; Williams and Clark 1982; Hallab et al. 2000; Merritt and Brown 1981, 1985; Baboian 2005). Interaction between different metal implants can also lead to corrosion. Corrosion resistance is impaired passively by the formation of a stable and unreactive surface layer on the material (Gotman 1997); for example, titanium alloys form titanium oxide on their surface which prevents corrosion. For most biomaterials, corrosion progresses by the breakdown of this layer through a variety of means, such as via micro-motions or galvanic processes (Wang et al. 1999; Cunningham et al. 2002, 2013; Hallab et al. 2012). The ability of a material to resist corrosion and failure is one of the main features of biocompatibility, as a corroded material is more likely to fail and corrosive byproducts induce aberrant tissue reactions.

Any foreign material implanted within the human body will produce a reaction in the surrounding tissues. The initial reaction after surgery is always inflammatory, which progresses to fibrosis and scar tissue. At times, this process can become inappropriate for spine surgery. Material selection is important in this regard, as at times, such as in the case where interbody bone tissue formation is required, and not scar tissue. Fibrotic connective tissue growth may supersede bony growth, causing pseudarthrosis. Some materials have been shown to specifically promote bone formation (Matsuno et al. 2001; Blanco et al. 2011). Corrosion and material wear may also produce metallic (nickel, cobalt, and chromium) particulates that form immunogenic metal–protein complexes (Swiontkowski et al. 2001), which can lead to chronic inflammation; chronic inflammation is painful, can affect bone healing (osteolysis), and is more likely to lead to hardware failure by the chronic release of intracellular acids and superoxides (Cook et al. 2000; Gaine et al. 2001; Wang et al. 1997).

Commonly Available Materials for Spine Instrumentation

Stainless Steel Alloys (SSA)

Modern-day surgical grade stainless steel alloys (SSA) are an alloy of iron, nickel, carbon, and molybdenum. SSA are easy to machine, and so they were originally the material of choice for plates and screws. The current practice of surgery seems to be shifting away from the use of SSA, for a variety of reasons; SSA is not corrosive resistant enough for the human body, and so surgical grade alloys require at least 17% chromium to form a stable surface oxide. SSA have the poorest in overall strength of the currently available materials (170 MPa), as well as having a much higher elastic modulus as compared to bone (~200 GPa). It has been shown that SSA have a higher rate of infection than other metals, which may be related to their ability to promote biofilm (Gaine et al. 2001; Soultanis et al. 2008). On MRI, SSA cause a large artifact, which may impair the ability to assess postoperative MRI imaging (Burtscher et al. 1998).

Titanium Alloys (TA)

Titanium naturally forms titanium oxide, making it more corrosive resistant than SSA (Yoshihara 2013; Serhan et al. 2004). Subsequently, titanium alloys are about 90% Ti with the remainder either

aluminum or vanadium. However, there is a wide range of titanium alloys, each with a different atomic configuration causing a unique set of strengths and properties. The most common alloy is Ti-6Al-4V, which is has a higher yield strength (869 GPa) and lower Young's modulus than SSA (114 GPa), and may intrinsically resist biofilms and infection as well as promote bone growth and integration (Gaine et al. 2001; Soultanis et al. 2008; Stambough et al. 1997; Pienkowski et al. 1998; Wedemeyer et al. 2007; Yoon et al. 2008; Banerjee et al. 2004; Christensen et al. 2000; Sun et al. 1999). Unfortunately, it is more expensive, is less stiff, and has overall worse fatigue resistance than SSA (Antunes and de Oliveira 2012; Ghonem 2010; Tahal et al. 2017; Chan 2010), and notching of the rod is known to reduce fatigue resistance even further (Dick and Bourgeault 2001; Lindsey et al. 2006). Newer TAs created from only the beta atomic structure have an even lower Young's modulus at 50 GPa, even closer to that of bone (Antunes and de Oliveira 2012; Brailovski et al. 2011). Further developments in titanium manufacturing have recently produced porous titanium, which preserves its biocompatibility and further decreases its Young's modulus to 2–4 GPa (Wu et al. 2013; Fujibayashi et al. 2011). This new material have been promoted as an interbody device, as it has the strength and osteoinductive capacity of TA with a low enough Young's modulus to prevent the stress-shielding effect. Ultimately, due to its superior mechanical and biological properties, TA has become the standard of care in spine surgery.

Cobalt Chromium Alloys (CCA)

The use of cobalt chromium alloys for spine surgery is a recent introduction. Surgical CCA is a composition of cobalt, chromium, molybdenum, and carbon. Similar to TA, the chromium forms a surface oxide layer that imparts inherent corrosion resistance. CCA have a higher yield strength, stiffer, larger fatigue life span, more resistant to notching, and are less likely to fracture in vivo after scoliosis correction than TA (Nguyen et al. 2011; Doulgeris et al. 2013; Marti 2000; Shinohara et al. 2016; Scheer et al. 2011). However, while CCA is highly biocompatible, the milling of CCA is technically more difficult, making it more expensive, and CCA's Young's modulus is 240, much greater than that of bone. It is highly biocompatible. The stiffness of CCA is an important factor when deciding for which material to be used for some deformity correction, as SSA and TA are known to undergo deformations after deformity correction (Lamerain et al. 2014; Cidambi et al. 2012; Cui et al. 2012). It also produces a large artifact on MRI (Tahal et al. 2017).

Polyetheretherketone

Polyetheretherketone (PEEK) is an organic thermoplastic polymer of bisphenolate salts that was initially created in the 1980s (Panayotov et al. 2016). It has many advantageous biomechanical properties; it is strong, has a low fatigue failure rate, is radiolucent and does not cause a large artifact on MRI (Cho et al. 2002). Perhaps its greatest appeal comes from its biological inertness, resistance to corrosion, and its Young modulus being similar to that of bone (3.6 GPa), which prevents the stress-shielding effect when used as an interbody (Hee and Kundnani 2010). As PEEK is considered biologically inert, the PEEK devices used for implantation are composites of PEEK and 30% chopped carbon, which has been shown to promote osteoblast adherence and bone formation (Jockisch et al. 1992). They are commonly filled with autograft to promote for arthrodesis. It has proven efficacy for anterior cervical spine surgery, with no significant differences with titanium cages (Kasliwal and O'Toole 2014; Kersten et al. 2015). PEEK can create a local inflammatory response which eventually results in a biofilm formation surrounding the implant. However, initial reaction can promote local bone remodeling with subsidence of the implant and loss of disc height correction. Further enhancements to PEEK include plasma coating PEEK with titanium, which introduces some of the osteogenic properties of titanium and further enhances osseous integration (Walsh et al. 2015).

Mixing Metals

In the past, orthopedic implant practices cautioned against mixing dissimilar metals in a biologically active environment due to the fear of galvanic corrosion. Surgeons have therefore shied away from mixing different metal implants. However, orthopedic implant designs, materials and passivation processes have evolved considerably since their inception and there is more interest in combining dissimilar metals among orthopedic surgeons today. In the clinical setting, combinations of titanium and stainless steel most frequently occur in spinal fixation constructs. These metals are generally used together in an attempt to form a construct that takes advantage of the mechanical properties of each component.

Due to better biocompatibility and osseointegration, and lower modulus as well as concerns about late onset infection and the potential need for advanced imaging (CT and MRI), most surgeons have migrated to the use of titanium implants worldwide; therefore, most contemporary spinal implant systems are made of titanium. There are clinical scenarios in which a surgeon may want to use stainless steel or cobalt chrome rods, since, for the same rod diameter, the strength and stiffness properties of titanium are not appropriate. For complex, severe, rigid spinal deformities, titanium rods do not provide sufficient correction and long-term durability. Improper sagittal profile, insufficient correction (coronal and sagittal plane), and rod failure due to pseudarthrosis are the consequence.

For junctional degeneration or deformity at the top of a spinal construct known as proximal junctional kyphosis (PJK), the fusion and instrumentation have to be extended up into the cervical spine, across the cervicothoracic junction, sometimes many years later. Cervical systems traditionally have only been available in titanium, and so surgeons were faced with mixing metals to connect up to previous implants, unless they wanted to open up the entire previous incision, remove the old implants, and replace them at considerable morbidity and cost to the patient. Typically, titanium junctional rod-to-rod connectors are attached to stainless steel screws to create a stable revision construct.

Serhan et al. investigated spinal implant constructs of stainless steel rods with mixed stainless steel and titanium alloy components and implants consisting of titanium alloy rods with mixed stainless steel and titanium alloy components (Serhan et al. 2004). Constructs were immersed in saline and subjected to cyclic bending tests. They were then evaluated visually, with electron microscopy and with spectroscopy for evidence of corrosion. The results indicated that the stainless-steel implant components were less resistant to corrosion than the titanium components. This is partly a result of the strong passivating ability of titanium when compared with stainless steel (Serhan et al. 2004). Based on these results and the clinical use of Ti with SS constructs, the FDA has cleared mixing SS and Ti for the first time in history for the EXPEDIUM Spine System and VIPER and VIPER 2 Systems (K160904) in July 1, 2016.

Surgeons have used stainless steel rods with titanium screws in fusion and non-fusion cases for early-onset scoliosis, adolescent idiopathic scoliosis (AIS), neuromuscular scoliosis, and extension of scoliosis constructs to the cervical spine with excellent clinical results and no sequelae (Zartman et al. 2011; Farnsworth et al. 2014). This comfort with mixing metals in spinal instrumentation constructs came out of necessity and has grown based on published literature and discussions in national and international meetings.

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Biological Treatment Approaches for Degenerative Disc Disease: Injectable Biomaterials and Bioartificial Disc Replacement

10

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Abstract

Degenerative disc disease (DDD) is a major cause of disability in the western world. Current treatment strategies only address the symptoms of DDD. To meet the clinical need of regenerative treatment strategies, biological treatment approaches have become of increasing interest in the past decade. Currently explored treatment strategies involve biomolecular treatments for early-stage degeneration, cell-based therapies involving differentiated cells as well as stem cells for advanced-stage DDD, as well as tissue engineering strategies for total disc replacement in terminal-stage disc degeneration.

The following chapter will provide a comprehensive overview about recent the recent progress in regenerative treatment strategies. This chapter will elucidate experimental in vivo studies as well as published and ongoing clinical trials.

Keywords

Annulus fibrosus repair · AF repair · Intervertebral disc regeneration · Tissue engineering · MSCs · Mesenchymal stem cells · Growth factors · Gene therapy · TE-IVD · Bioartificial disc · Biological IVD treatment

Pathology, Current Treatments, and Resulting Challenges

Low back pain (LBP) is one of the major causes of morbidity that leads to enormous costs for western healthcare systems (Schmidt et al. 2007; Hoy et al. 2010; McBeth and Jones 2007; CDC 2009; Katz 2006). An association between LBP and degenerative disc disease (DDD) has been established by recent studies, accounting DDD for up to 40% of all LBP cases (Pye et al. 2004; MacGregor et al. 2004; Freemont 2009). The intervertebral disc (IVD) contains the soft and gelatinous nucleus pulposus (NP), the surrounding fibrocartilaginous annulus fibrosus (AF), and the cartilaginous endplate (EP) which connects the IVD to the corpus vertebrae. DDD is characterized by extracellular matrix (ECM) degradation, release of proinflammatory cytokines, altered spine biomechanics, angiogenesis, and nerve ingrowth which is associated with increased pain sensation (Le Maitre et al. 2007; Rannou et al. 2003). Factors including mechanical stress, trauma, genetic predisposition, and inflammation can trigger and exacerbate DDD (Podichetty 2007) (Fig. 1).

Among the most commonly performed spinal procedures to treat disc herniation is lumbar discectomy, with an estimated 300,000 cases per year in the United States (Deyo and Weinstein 2001). However, while the neural tissue is decompressed by the discectomy, it leaves the annular defect untreated. Because of this, the risk of recurrent disc herniation through the open defect is elevated, which occurs in 6–23% of patients following discectomy. It is associated with compromised patient outcomes, the need for revision procedures, and increased healthcare costs (Carragee et al. 2003; Swartz and Trost 2003; Bruske-Hohlfeld et al. 1990; Ambrossi et al. 2009; Frymoyer et al. 1978). Aggressive surgical discectomy can reduce the rate of re-herniation, but is associated with more severe disc degeneration and back pain (Frei et al. 2001; Barth et al. 2008; O'Connell et al. 2011). Since the IVD does not possess a sufficient self-repair capacity, current treatment options for DDD range from conservative treatments to invasive therapies for severe and symptomatic courses of DDD, like spinal fusion or total disc replacement (TDR). However, long-term results do not show significant differences between invasive and conservative therapies, and complications are common (Peul et al. 2007; Lequin et al. 2013; Lurie et al. 2014).

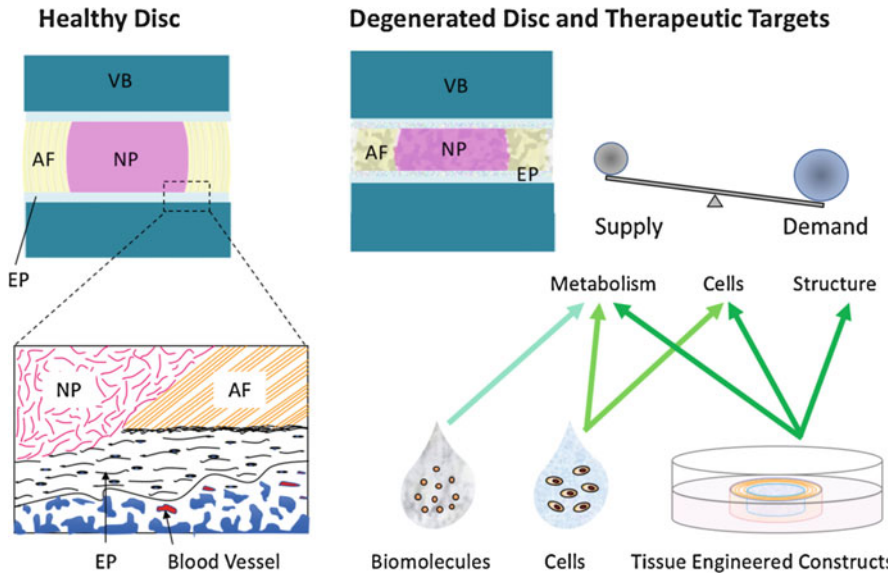

Fig. 1 Schematic pictures of the healthy disc show three components of the disc both macro- and microscopically. In degenerated discs, metabolism, cells, and structure encounter imbalance of supply and demand, one, some, or all of which each strategy will redress. *NP* nucleus pulposus, *AF* annulus fibrosus, *EP* endplate, *VB* vertebral body (Moriguchi et al. 2016)

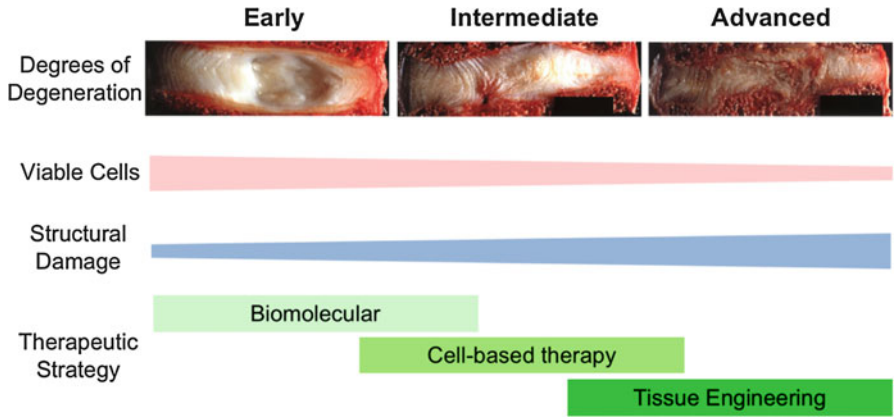

Fig. 2 Treatment strategies for different stages of IVD degeneration (Moriguchi et al. 2016)

To address the limitations of available treatments and enhancing patient outcome, biological approaches to IVD regeneration have become a growing area of interest.

Current strategies for regenerative biological disc treatment can be roughly categorized in three groups: biomolecular therapy, cell therapy, and tissue-engineered IVD construction (An et al. 2011; Zhang et al. 2011a; Maidhof et al. 2012) (Fig. 2).

In the early stage of IVD degeneration, which is defined by beginning structural changes and loss of hydration, a sufficient number of viable cells can still be found.

Thus, these treatment strategies involve recombinant genes, proteins, and stem cell therapies

(Fig. 2). These agents are meant to enhance selective protein expression by stimulating the remaining viable cells in order to promote an intrinsic self-healing within the IVD.

Mid-stage degeneration is characterized by less active and rapidly disappearing viable cells and increasing structural damage. Here, cell transplantations and tissue-engineered biological scaffolds are utilized to recover the damaged IVD.

Finally, the most advanced stage of degeneration is described as severe structural damage to the whole disc and the lack of viable cell activity. For this stage of degeneration, the treatment approaches involve TDR with tissue-engineered constructs.

The following part of this chapter will provide an overview of the current biological treatment approaches for each of the previously described stages, including experimental in vivo studies as well as recent clinical trials.

Biomolecular Treatment (Moriguchi et al. 2016)

A defining compositional change in degenerated discs is the gradual decline of NP water content originating from the loss of proteoglycan. A decrease in swelling pressure within the NP is followed by the reduction of mechanical tension in the AF collagen fibers, resulting in abnormal loading of the spine. The consequence of these alterations often is the instability of segments with subsequent development of neck or back pain and narrowing of the spinal canal, which may induce neurological symptoms. In the early stages of degeneration, the disc undergoes an imbalance of anabolic and catabolic factors that leads to the degradation of extracellular matrix (ECM). Biomolecules such as recombinant proteins and genes can regenerate expression of target molecules through the increase in anabolic or decrease in catabolic factor production, hence facilitating ECM synthesis. The following section will review recent in vivo studies on biomolecules which are used to treat disc degeneration (Table 1).

Recombinant Protein and Growth Factor-Based Therapy

Protein solutions injected directly into discs may have the potential to stimulate cell growth or anabolic response that could reverse disc degeneration. Since the demonstration of the disc's responsiveness to exogenous growth factors in an ex vivo organ culture system (Thompson et al. 1991), various proteins capable of modulating cell growth, differentiation, and ECM synthesis have shown promising for treating DDD. Bone morphogenetic proteins, such as BMP2; BMP7, which is also known as osteogenic protein 1 (OP-1); and BMP14, or growth differentiation factor-5, as well as other transforming growth factor-beta (TGF-β) superfamily such as TGF-beta 1 or 3 have induced bone and cartilage formation. Their usage has been the part of extensive research in cases of spinal arthrodesis and disc regeneration (An et al. 2005, 2011; Imai et al. 2007; Walsh et al. 2004; Masuda et al. 2006; Chujo et al. 2006; Miyamoto et al. 2006; Huang et al. 2007; Chubinskaya et al. 2007; Leckie et al. 2012). In a single in vivo rabbit study by An H. et al., intradiscal OP-1 injection resulted in an increase in proteoglycan content of NP at 2 weeks and disc height at 8 weeks. This treatment has recently been moved on to a clinical trial. Though promising, protein injection is challenged by the short duration of its therapeutic effect. The solution for this may be the development of slow-release carriers or gene-based delivery systems.

Gene Therapy

Gene therapy induces the modification of intradiscal gene expression for a prolonged effect on degenerated discs. Genes that are potentially applicable therefore are delivered through either viral (mostly adenovirus) or non-viral vectors, which are then either directly injected into live tissue (in vivo gene therapy) or transfected into cells cultures in vitro prior to implantation into the IVD (Woods et al. 2011). In one of the pioneering in vivo studies in a rabbit model, NP cells were transfected with TGF-β1 expressing adenovirus vector.

Table 1 Recombinant proteins, growth factors, and gene therapy

Species	Model	Molecules	Dose	Outcome	Refs
Protein injection					
Rat	Compression	IGF-1∗	IGF-1 8 ng/8 ul/disc	GDF-5 and TGF-beta aid in expansion of inner annular fibrochondrocytes into the nucleus	Walsh et al. (2004)
		GDF-5	GDF-5 8 ng/8 ul/disc		
		TGF-beta	TGF-beta 1.6 ng/8 ul/disc		
		bFGF	bFGF 8 ng/8 ul/disc		
Rat	Compression	BMP7 (OP-1)	0.2 ug/uL/disc	OP-1 stimulates anabolic response characterized by the restoration of normal disc morphology	Chubinskaya et al. (2007)
Rabbit	Normal	BMP7 (OP-1)	2 ng/10 ul/disc	Increase in disc height	An et al. (2011)
Rabbit	Chemonucleolysis by C-ABC	OP-1	100 ul/10 ul/disc	Increase in disc height and PG content	Imai et al. (2007)
Rabbit	Needle puncture	BMP7 (OP-1)	100 ug/10 ul/disc	Improvement in disc height and MRI findings	Masuda et al. (2006)
Rabbit	Needle puncture	GDF-5	1100 ng,1, 100 ug/10 ul/disc	Increase in disc height	Chujo et al. (2006)
Rabbit	Needle puncture	OP-1	100 ug/10 ul/disc	Increase in disc height and PG content of the NP	Miyamoto et al. (2006)
Rabbit	Annular tear 5 × 7 mm	BMP2	100 ul/10 ul/disc	Exacerbated degeneration	Huang et al. (2007)
Rabbit	Nucleotomy	PRP	20 ul PRP + microsphere/disc	Less degeneration, more PG	Nagae et al. (2007)
Rabbit	Nucleotomy	PRP	20 ul PRP + microsphere/disc	Improvement in disc height and water content	Sawamura et al. (2009)
Rabbit	Annular puncture	PRP-releasate	20 ul/disc	Better X-ray and MRIs	Obata et al. (2012)
Sheep	Annular incision	BMP 13	300 ug/70 ul saline	BMP 13 prevents loss of hydration	Wei et al. (2009)
Gene therapy					
Rat	Degenerative model induced by unbalanced dynamic and static force	Lentiviral CHOP (C/EBP homologous protein) shRNA	1×10^6 PFU/2 ul/disc	Significant decrease of apoptotic incidence in cells treated with CHOP ShRNA at 7 weeks	Zhang et al. (2011b)
Rat	Normal	Plasmid DNA mixed with microbubbles	2 ug/2 ul/disc	Reported genes were expressed up to 24 weeks	Nishida et al. (2006)
Rabbit	Normal	Ad/CMV-hTGFβ1	6×10^6 PFU/15 ul/disc	Leads to double proteoglycan synthesis	Nishida et al. (1999)
Rabbit	Normal	Ad-LMP1	1×10^7 PFU/10 ul/disc	LMP1 overexpression increases PG, BMP2, and BMP7	Yoon et al. (2004)
Rabbit	Annular puncture	ADAMTS5 siRNA oligonucleotide	10 ug/10 ul/disc	Improvement in MRI and histological scores	Seki et al. (2009)

(continued)

Table 1 (continued)

Species	Model	Molecules	Dose	Outcome	Refs
Rabbit	Annulotomy	AAV2-BMP2 or-TIMP1	6×10^6 virus particles/15 ul/disc	AAV-BMP2 and -TIMP1 delayed degeneration	Leckie et al. (2012)
Rabbit	Post-annulotomy	Ad-Sox9	1×10^9 PFU/10 ul/disc	AdSox9 helped retain chondrocytic appearance, cellular morphology, and ECM at 5 weeks	Paul et al. (2003)

Proteoglycan synthesis showed to be increased by 100% in treated tissue (Nishida et al. 2006).

Since, a variety of proteins were discovered as promising targets for gene therapy: upstream proteins such as LMP-1 which regulates BMP2 and BMP7, ECM-degrading enzymes, disintegrin and metalloproteinase with thrombospondin motifs-5, their inhibitors (tissue inhibitor of metalloproteinase-1, TIMP-1), chondrocyte-specific transcription factors (SRY-box 9, Sox9), and apoptosis inducers (C/EBP homologous protein) (Leckie et al. 2012; Nishida et al. 1999, 2006; Yoon et al. 2004; Seki et al. 2009; Zhang et al. 2011b; Paul et al. 2003).Though gene therapy can be advantageous in its sustained effect, inherent risk of viral gene delivery systems becoming infectious or immunogenic has moved the focus toward non-viral gene delivery systems. The development of microbubble-enhanced ultrasound gene therapy and injection of small interfering RNA (siRNA) have proven to achieve long-standing transgene expression in IVD cells in vivo (Nishida et al. 2006; Zhang et al. 2011b). However, non-viral gene delivery systems are limited by low transfection efficiency, which must be overcome to enhance their clinical applicability. The feasibility of ex vivo gene therapy, which reduces the risks of infection and immunogenicity and plays an important role in the future of tissue engineering technology, has been explored in several studies (Xin et al. 2012; Leo et al. 2004).

Platelet-Rich Plasma

Platelet-rich plasma (PRP), an autologous blood product manufactured by the centrifugation of whole blood, offers a variety of proteins for the treatment of degenerative discs due to its high concentration of platelets. Upon activation, these platelets release a variety of multifunctional growth factors such as PDGF (platelet-derived growth factor), IGF-1 (insulin-like growth factor), TGF-β1, (transforming growth factor-beta 1), VEGF (vascular endothelial growth factor), and bFGF (basic fibroblast growth factor). When used in the early stage of disc degeneration, PRP may enhance disc hydration (Gullung et al. 2011). Various PRP technologies have emerged to retard the degenerative cascade, which include a gelatinous hydrogel scaffold, impregnated with PRP (Nagae et al. 2007; Sawamura et al. 2009; Obata et al. 2012) and soluble releasate derived from activated PRP (Obata et al. 2012). The in vivo efficacy of PRP in improving or maintaining disc height and hydration has facilitated its transition to ongoing clinical trials.

Cell-Based Therapy (Moriguchi et al. 2016)

The efficacy of biomolecules is limited when the degeneration of an IVD is more advanced, since there is a correlation between the progress of the degeneration and the decline of the number of cells responsive to injected genes and proteins (Gruber et al. 2002). Mid-stage degeneration is characterized by a decrease in the number of cells within the IVD tissue. Therefore, cell transplantation is a feasible treatment strategy at this stage. A number of in vivo studies report the efficacy of using a vast array of cell sources (Table 2).

Table 2 Cell therapy

Species	Model	Cell type	Dose	Outcome	Refs
Mouse	Post-annular injury	Allogenic bone marrow MSCs	BMSCs 1.0×10^3	ECM augmented in NP via autonomous differentiation and stimulation of endogenous cells at 12 weeks	Yang et al. (2009)
Mouse	Annular puncture	Multipotent stem cells derived from human umbilical cord blood	1.0×10^3 cells intradiscally, 1.0×10^6 cells intravenously	Unlike intradiscal injection, intravenous injection did not preserve the IVD architecture nor disc height at 14 weeks	Tam et al. (2014)
Sand rat	Discectomy	Autologous disc cells	1.0×10^4 cells/ 5 ul/2-mm^3 Gelfoam	Implanted disc engrafted with the host disc for up to 8 months	Gruber et al. (2002)
Rat	Normal	Bone marrow MSCs	5.0×10^5/50 ul hyaluronan gels	MSCs maintained viability and proliferated over 28 days	Crevensten et al. (2004)
Rat	Post-annular puncture	Human bone marrow MSCs	1.0×10^6/15 ul	Human MSCs survived for 2 weeks post transplantation, increasing disc height and MRI intensity	Jeong et al. (2009)
Rat	Post-annular puncture	Adipose-derived MSCs (ADSCs)	1.0×10^6/50 ul	Discs maintained disc height and restored MRI signal intensity	Jeong et al. (2010)
Rat	Nucleotomy	Co-culture of NP cells and MSCs	2.5×10^5 cells (25% NPCs and 75% MSCs)	Bilaminar co-culture pellet of NP cells and MSCs outperformed solely NP cells or MSCs at 5 weeks	Allon et al. (2010, 2012)
Rabbit	Nucleotomy	Allogenic NP cells	5.0×10^4 cells/ 20 ul	Histology indicated delayed degeneration at 16 weeks	Okuma et al. (2000)
Rabbit	Nucleotomy	Autologous articular chondrocytes	2.0×10^6/ 150 ul	Chondrocytes survived and produced hyaline-like cartilage at 6 months	Gorensek et al. (2004)
Rabbit	Normal	Allogenic bone marrow MSCs	1.0×10^5 cells	MSCs survived and enhanced PG synthesis	Zhang et al. (2005)
Rabbit	Post-nucleotomy	Autologous MSCs	4.0×10^4/40 ul atelocollagen	Improved disc height, MRIs, and histology at 48 weeks	Sakai et al. (2003,2005, 2006)
Rabbit	Post-annular Injury	Autologous bone marrow MSCs	1.0×10^5/25 ul	Injection of MSCs significantly increased PG synthesis in severely degenerated discs at 16 weeks	Ho et al. (2008)
Rabbit	Normal	Allogenic MSCs	1.0 × 105/15 ul	Injected cells engrafted into inner annulus fibrous at 24 weeks	Sobajima et al. (2008)
Rabbit	Post-puncture	Xenogeneic derivatives of embryonic stem cells	1.0 × 106 cells/ 20 ul	New notochordal cells observed; no immune response elicited	Sheikh et al. (2009)
Rabbit	Nucleotomy	Allogenic synovial MSCs	1.0 × 107 cells/ 100 ul PBS	Implanted cells labeled with DiI or GFP detected at 24 weeks. Disc height and MRI signal intensity were maintained	Miyamoto et al. (2010)
Rabbit	Compression	Allogenic bone marrow MSCs	0.08 ml of 1.0 × 106 cells/ ml	Combination of MSC injection and distraction led to better disc height and histology at 8 weeks	Hee et al. (2010)
Rabbit	Post-nucleotomy	Autologous NP cells and allogenic MSCs	1.0 × 106/20 ul	Both NP cells and MSCSs better maintained disc height and GAG content at 16 weeks	Feng et al. (2011)

(continued)

Table 2 (continued)

Species	Model	Cell type	Dose	Outcome	Refs
Canine	Post-nucleotomy	Disc cells	6.0 × 106 cells/1 ml/disc	Disc remained viable, produced ECM, better maintained disc height	Ganey et al. (2003)
Canine	Post-nucleotomy	Autologous MSCs	1.0 × 106/ml stem cells	MSCs led to better disc height, MRI, and histology grading at 12 weeks	Hiyama et al. (2008)
Canine	Post-nucleotomy	Bone marrow MSCs	105, 106, 107 cells	The disc treated with 106 MSCs had more viable cells than 105 and less apoptotic cells than 105 cells at 12 weeks	Serigano et al. (2010)
Porcine	Post-nucleotomy	Human MSCs	0.5 × 106/hydrogel carrier	Implanted cells survived and differentiated into disc-like cells at 6 mos	Henriksson et al. (2009)
Porcine	Nucleotomy	Allogenic juvenile chondrocytes and MSCs	7–10 × 106/0.5–75 ml fibrin carrier	JC outperformed MSCs in proteoglycan synthesis at 12 months	Acosta et al. (2011)

Differentiated Cells

Implanted differentiated disc chondrocytes are meant to produce demanded ECM components such as proteoglycan and collagen types II and I under hypoxia and nutrient stress and can meet the increased cellular and metabolic demands of the disc (Rajpurohit et al. 2002).

Accumulated evidence in an array of animal models demonstrate the viability of autologous or allogenic cells in vivo as well as the integration into the host tissue. Thus, a reduction of ECM degradation, recovery of disc height, and MRI signal intensity can be achieved (Table 2). In fact, the pioneering preclinical study in an injured canine model showed that NP disc chondrocyte implantation contributed to ECM regeneration, retarding further disc degeneration (Ganey et al. 2003).

However favorable, disc cell transplantation showed several challenges: (1) donor site morbidity, (2) difficulty in expanding cells in vitro while maintaining cell phenotype, and (3) paucity of allograft donor tissue. Similar to differentiated disc cells, cultured articular chondrocytes (AC) are a well-established non-disc cell source in regenerative medicine (Brittberg et al. 1994). Their effortless extraction from non-weight-bearing parts of the knee and capacity to produce NP-like ECM when transplanted in vivo makes autologous (Gorensek et al. 2004) or allogenic (Acosta Jr et al. 2011) AC a safe and feasible cell source in IVD regeneration. Furthermore, potential immune evasion by juvenile articular chondrocytes supports their applicability in allogenic cell transplantation.

Stem Cells

Multipotent mesenchymal stem cells (MSCs), which are present in adult bone marrow or adipose tissue, can replicate as undifferentiated cells and then differentiate into lineages of mesenchymal tissue: bone, cartilage, fat, tendon, muscle, and marrow stroma (Pittenger et al. 1999). These somatic stem cells are a potentially ideal option for disc repair due to their accessibility and ability to differentiate along a chondrogenic lineage and produce the required proteoglycan and collagen for the disc ECM. The feasibility of MSCs to facilitate disc repair has been substantiated.

Yet it remains controversial whether differentiated cells or stem cells are superior in terms of regenerative capacity of disc morphology.

A porcine study comparing the utility of different cell sources found that committed articular chondrocytes are more suited for the use in

disc repair than MSCs due to their aptness for survival in the ischemic disc microenvironment (Acosta Jr et al. 2011). Interestingly, a comparative rabbit study found that MSC transplantation can serve as an ideal substitute for differentiated chondrocytes of disc NP owing to better accessibility with equivalent regenerative potential (Feng et al. 2011). Studies assessing the combination of both cells demonstrated that rather in vitro co-culture (Okuma et al. 2000) or co-implantation (Allon et al. 2010) yields better in vivo performance of the implanted cells. Nonetheless, pluripotent embryonic (Evans and Kaufman 1981; Martin 1981) and induced pluripotent stem cells (iPSCs) (Takahashi and Yamanaka 2006), unlike the lower potent MSCs, have unlimited proliferative and differentiate capacities, which can be strategically exploited in cell-based disc repair.

Sheikh H et al. extracted murine embryonic stem cells (ESCs) and differentiated them into chondro-progenitor cells. Upon implantation into rabbit injured discs, these cells induced notochordal cell formation at site of injury without xenograft-associated immune responses (Sheikh et al. 2009). Unstable in vitro differentiation into desired cell lineages and the potential risks of tumor formation in vivo are still major obstacles in the use of ESCs and iPSCs. However, if these issues are overcome, the use of stem cells may offer abundant potential for intervertebral disc repair.

Tissue Engineering Strategies

The implementation of tissue engineering (TE) pioneered by Langer and Vacanti in 1993 (Langer and Vacanti 1993) has fueled the efforts toward constructing functional biological substitutes for TDR as a novel treatment strategy for DDD. Recently, major efforts have been directed toward developing a replacement for either NP or AF using TE technology.

Tissue engineering originally consists of three, and more recently four components (Langer and Vacanti 1993): scaffolds, cells, growth factors, and physical conditioning using electrical or mechanical stimuli (Fig. 3). Since extensive loss of matrix and structural damages are exhibited in

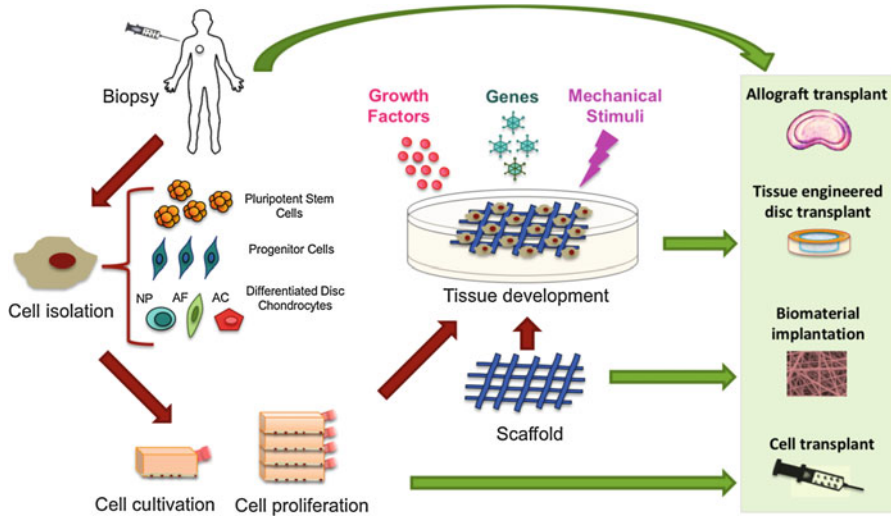

Fig. 3 Cells harvested from different sources can be expanded in vitro and transplanted in vivo in cell transplant for disc regeneration. Scaffolds can be combined with cells, and, if they have bio-mimicking properties, these treatments can be regarded as a part of tissue engineering strategy, which traditionally composes of cells, scaffolds, growth, and factors, but recently including gene treatment and mechanical conditioning. *NP nucleus pulposus cells*, *AF* annulus fibrosus cells, *AC* articular chondrocytes (Moriguchi et al. 2016)

Table 3 Tissue-engineered constructs

Species	Model	Construct	Outcome	Refs
Rat	Subcutaneous implantation	TE-IVD composed of a NP cell-laden alginate surrounded by an AF cell-laden PGL/PLA	Biochemical markers of matrix synthesis, increasing over time, were similar to native tissue at 12 weeks	Mizuno et al. (2004a)
Rat	Subcutaneous implantation	Porous type II collagen/hyaluronate-chondroitin-6-sulfate (CII/HyA-CS)	CII/HyA-CS scaffolds had satisfactory cytocompatibility and histocompatibility, as well as low immunogenicity	Li et al. (2010)
Rat	Subcutaneous implantation	Composite IVD consisting of demineralized bone matrix gelatin and collagen II/hyaluronate/chondroitin-6-sulfate scaffolds seeded AF and NP cells	Implant, similar to native disc in morphology and histology, increased proteoglycan synthesis over 12 weeks	Zhuang et al. (2011)
Rat	Total discectomy	TE-IVD composed of a NP cell-laden alginate surrounded by an AF cell-laden collagen layer	TE-IVD maintained disc space height, produced de novo ECM, and integrated into the spine – yielding intact motion segment with dynamic mechanical properties similar to that of native IVD	Bowles et al. (2011a)
Rat	Subcutaneous implantation	5.0×10^6 cells/ml in pentosan polysulfate-containing polyethylene glycol/hyaluronic acid	MPC/hydrogel composites formed cartilage-like tissue, well tolerated by the host	Frith et al. (2013)
Rabbit	Laser discectomy	2.0×10^6 cells/atelocollagen honeycomb shaped scaffold	AF cells survived and produced hyaline-like cartilage in the disc at 12 weeks	Sato et al. (2003)
Rabbit	Microdiscectomy	Cell-free implant composed of a polyglycolic acid (PGA) felt, hyaluronic acid (HA), and allogenic serum	Implantation of a cell-free PGA-HA implant immersed in serum after discectomy improved disc hydration and preserved disc height 6 months after surgery	Abbushi et al. (2008)
Rabbit	Post-nucleotomy	2.0×10^6 bone marrow MSCs/0.04 ml fibrin glue containing 10-ug/L TGF-β1 (MSC-PFG-TGF-β1)	MSC-PFG-TGF-β1 group had less degeneration and a slower decrease in disc height compared with both degenerative and acellular PFG-TGF-β1 group	Yang et al. (2010)
Rabbit	Nucleotomy	Allogenic NP cell-seeded collagen II/hyaluronan/chondroitin-6-sulfate (CII/HyA/CS) tri-copolymer construct	Viability of allografted NP cells, extracellular matrix deposition, and disc height maintenance; restoration of T2 MRI signal intensity observed at 24 weeks	Huang et al. (2011)
Rabbit	Post-puncture	5.0×10^3 allogenic bone marrow MSCs/10 ul hydrogel	MSCs suppressed collagen I in NP, reduced collagen aggregation, and maintained proper fibrillary properties and function	Leung et al. (2014)
Rabbit	Post-nucleotomy	1.0×10^6 human NP cell line infected with recombinant SV40 adenovirus vector (HNPSV-5) in atelocollagen	Deceleration of disc degeneration was evident after HNPSV-5 transplantation as shown by disc height and histologic examination at 24 weeks	Iwashina et al. (2006)
Canine	Total discectomy	Cell-allograft IVD composites made of allograft and NP cells, with in vitro transduced with recombinant adeno-associated virus (rAAV)-hTERT	The hTERT-loaded NP cells intervention could effectively resist the degeneration of the allogenic transplanted IVD at 12 weeks	Xin et al. (2012)

(continued)

Table 3 (continued)

Species	Model	Construct	Outcome	Refs
Canine	Post-nucleotomy	Autologous adipose tissue-derived stem and regenerative cells in hyaluronic acid carrier (ADRC/HA)	Disc that received ADRC/HA produced matrix and resembled native disc in morphology at 12 months	Ganey et al. (2009)
Canine	Nucleotomy	Cell-scaffold composite made of three-dimensional porous PLGA scaffolds and NP cells	Disc height, segmental stability, and T2-weighted MRI signal intensity were well preserved at 12 weeks	Ruan et al. (2010)
Porcine	Nucleotomy	Cell-scaffold composite made of NP cells and injectable hyaluronan-derived polymeric substitute material HYADDR (1.0 × 105 cells/ml)	Injected discs had a central NP-like region similar to the normal disc biconvex structure and viable chondrocytes forming matrix like that of normal disc at 6 weeks	Revell et al. (2007)
Porcine	Post-annular injury	1.25 × 105 autologous MSCs/ml in either hydrogel PhotoFix or hyaluronic acid	Stem cells in hydrogel treatment had significantly higher T2 MRI intensities and lower degeneration grade at 24 weeks than hydrogel alone treatment	Bendtsen et al. (2011)
Porcine	Partial nucleotomy	5.0 × 105 autologous bone marrow MSCs transduced with retrovirus encoding luciferase in 1 mL hyaluronan-enhanced albumin hydrogel	In vivo 3-day analysis showed persistent metabolically active implanted cells in the disc	Omlor et al. (2014)
Goat	Post-disc injury	2.5 × 105 allogenic bone marrow stromal cells/10 ul PBS + 30 ul chondroitin sulfate-based hydrogel	Significant increase in NP proteoglycan accumulation at 6 months	Zhang et al. (2011c)
Sheep	Total discectomy	Noncrystalline polylactide copolymer interbody cages filled with1.0 × 106 allogenic mesenchymal progenitor cell (MPC)-laden Gelfoam sponge formulated with the chondrogenic agent pentosan polysulfate (PPS)	Biodegradable cage-contained MPCs in combination with PPS produced cartilaginous tissue at 3 months	Goldschlager et al. (2010)
Sheep	Post-chondroitinase-ABC injection	4.0 × 106 or 0.5 × 106 human mesenchymal precursor cells (MPCs) suspended in hyaluronic acid	High-dose injection improved histopathology scores at 3 months, while low dose at 6 months	Ghosh et al. (2012)
Sheep	Nucleotomy	Allogenic or autologous disc cells (0.4–2.0 × 106 cells/0.5–1 ml hydrogel) in hydrogel containing hyaluronic acid and maleolyl-albumin	Biological repair of traumatic damage occurs in sheep discs at 6 months; hydrogel-supported disc cells may be beneficial	Benz et al. (2012)
Canine	Total discectomy	TE-IVD composed of a NP cell-laden alginate surrounded by an AF cell-laden collagen layer	Early displacement in some cases, if stably implanted TE-IVD maintained disc height, produced new ECM, and integrated into host tissue, intact motion segment with dynamic mechanical properties similar to that of native IVD	Moriguchi et al. (2017)

advanced stages of disc degeneration, development of biocompatible and biomimetic scaffolding materials based on engineering innovation can facilitate the recovery of native biological and biomechanical functionality. Numerous studies have assessed tissue-engineered components as well as whole disc constructs of the disc in vivo (Table 3).

Scaffold Development

Numerous scaffold materials, including altinate, silk-fibrin/HA composites, atelocollagen, synthetic polymers, and a collagen 2/hyaluronan/chondroitin-6-sulfate (C2/Hy/CS) composite, which mimic the mechanical and biochemical properties of the native NP, have been part of a study. Extensive research on hyaluronic acid, a native NP extracellular matrix component, has been performed in vivo (Revell et al. 2007; Abbushi et al. 2008; Ganey et al. 2009; Li et al. 2010; Huang et al. 2011). Resorbable cell-free implants consisting of a polyglycolic acid (PGA) felt, hyaluronic acid, and serum were used in a rabbit study. This resulted in improved disc hydration and height 6 months after microdiscectomy (Abbushi et al. 2008). The reason for the frequent use of cells together with bio-mimicking materials is to encourage de novo ECM production. The findings of Ganey T. et al. were that adipose-derived stem cells contribute significantly to the recovery of T2 intensity and disc height in a canine disc injury model. Synthetic polymers such as PGA or poly-L-lactic-co-glycolic acid (PLGA) have also been used either solely or in combination with hydrogels to construct cell-laden TE composites (Abbushi et al. 2008; Ruan et al. 2010).

Biological Annulus Fibrosus Repair

In mid-stage DDD, a commonly occurring pathology is the lumbar disc herniation. Due to the progressive degeneration, the IVD shows reduced hydration. The inadequate hydration of the disc leads to fissure formation, eventually allowing the soft NP to herniate through the defect and thus compress neighboring neural structures (Freemont 2009).

Lumbar discectomy is one of the most commonly performed spinal procedures to treat disc herniation, with an estimated 300,000 cases performed annually in the United States (Deyo and Weinstein 2001). While efficient in relieving acute symptoms by removing the herniated part of the NP and decompressing neural structures, the AF defect typically remains untreated after discectomy. Persistent AF defects increase the risk of re-herniation, which may lead to additional operations including more invasive procedures such as TDR and instrumented fusion (Carragee et al. 2003; Swartz and Trost 2003; Bruske-Hohlfeld et al. 1990; Ambrossi et al. 2009; Frymoyer et al. 1978; Laus et al. 1993).

Previous studies of intervertebral disc repair, which aim to halt, delay, or reverse intervertebral disc degeneration, were primarily focused on NP regeneration (Masuda et al. 2004; Bae and Masuda 2011; Sakai and Grad 2015; Wang et al. 2014; Kepler et al. 2011; Blanquer et al. 2015; Mern et al. 2014). However, the majority of these strategies are delivered through a punctured AF, which can generate a degenerative cascade within the disc affecting IVD biomechanics, cellularity, and biosynthesis even upon modest injury (Elliott et al. 2008; Iatridis et al. 2009; Korecki et al. 2008; Hsieh et al. 2009). Annular defects can emerge not only from needle punctures through the AF to reach the NP but also from the early process of IVD degeneration. Given the sensitivity of the AF, lesions from NP treatment can provoke further degeneration, inducing leakage of the delivered material and eventual failure of the regenerative treatment. In fact, one prospective study with 10-year follow-up found that discography performed with a small needle puncture accelerated disc degeneration rate of same-side disc herniation and changes to the endplate (Carragee et al. 2009). A different study demonstrated that injecting MSCs through the AF into the NP led to cell leakage and augmented osteophyte formation (Vadalà et al. 2012). Combining an injectable NP regenerative strategy with a sealant that repairs annular defects is the optimal strategy that can circumvent leakage of implanted cells or material while enhancing therapeutic outcome. Previous approaches to annular repair have involved mechanical treatments such as suturing and annuloplasty devices, which failed to improve annular healing strength in long-term clinical trials (Ahlgren et al. 2000; Chiang et al. 2011; Bailey et al. 2013). Although several NP regenerative studies and a few in vitro AF studies (Nerurkar et al. 2009) provide critical insight on the

Table 4 Annular repair

Species	Model	Treatment	Outcome	Refs
Rat	Degradation tests with subcutaneous implantation	Fibrin-genipin adhesive hydrogel (fib-gen)	60% of fib-gen remained at 8 weeks and nearly all resorbed at 16 weeks; kinetics show better in vivo longevity compared to fibrin	Likhitpanichkul et al. (2014)
Rat	Needle puncture	Injection of cross-linked high-density collagen (HDC) gels	Cross-liked HDC capable of repairing annular defects most likely due to enhanced stiffness of HDC at 5 weeks	Grunert et al. (2014b)
Porcine	Needle puncture	Injection of Gelfoam, platinum coil, bone cement, and tissue glue	Injection of Gelfoam better improved integrity of punctured disc than the other three to potentially prevent recurrent disc herniation at 2 months	Wang et al. (2007)
Sheep	Box annulotomy	Patch and plug with small intestinal submucosa (SIS) and titanium bone screw	SIS-based treatment led to better maintenance of hydration and intradiscal pressure at 26 weeks after annulotomy	Ledet et al. (2009)
Sheep	Box annulotomy	Triphase AF implant composing two outer phases of absorbable polyglycolic acid (PGA) and a centric phase of a nonabsorbable polyvinylidene fluoride (PVDF) mesh	Implant-treated discs had more reparative tissue. But, contrast media leakage tests under provocative pressure did not show a difference between groups	Hegewald et al. (2015)
Sheep	Microdiscectomy	Allogenic mesenchymal progenitor cells (MPCs) + pentosan polysulfate (PPS) embedded in a gelatin/fibrin scaffold	Discs treated with MPC + PPS showed higher PG content than the untreated or ones treated with solely scaffold at 6 months	Oehme et al. (2014)
Sheep	Box annulotomy	Injection of cross-linked high-density collagen (HDC) gel into annulus defect	IVDs treated with HDC gel showed histologically less degeneration. Imaging difference was not significant	Pennicooke et al. (2017)

reparative process within the AF tissue (Wei et al. 2009; Sakai et al. 2006; Sato et al. 2003; Zhang et al. 2011c), there are a very limited number of in vivo studies focusing primarily on annular repair (Table 4). Current efforts in the biological treatment for in vivo AF repair include either development of injectable material in conjunction with biologics such as biomolecules/cells or construction of rigid implants derived from synthetic polymer or biological tissue.

In order to introduce alternative methods, injectable biomaterials have recently gained further popularity in the field. Injectable genipin cross-linked fibrin collagen gel was suggested to integrate with human AF tissue and presented promising biomechanical and cell-seeding properties in vitro (Schek et al. 2011). Our group successfully tested a high-density collagen gel in vitro and in vivo using a needle puncture rat tail model. Furthermore, we have recently translated this project to a large animal (ovine) model, which demonstrated positive histologic results at 16 weeks following injury (Pennicooke et al. 2017).

Collectively, these studies demonstrate an ability to formulate and deliver injectable biomaterials to the lumbar spine of sheep to seal AF defects, promote sufficient tissue healing, and prevent further disc degeneration.

In another large animal study conducted by Oehme et al., injected mesenchymal progenitor cells combined with chondrogenic agent pentosan

polysulfate maintained disc height, disc morphology, and NP proteoglycan content post microdiscectomy in a sheep model (Oehme et al. 2014). Despite the few studies dedicated to annular repair, more attention is now being paid to this field given its enhancement of even NP-targeted therapy.

Bioartificial Total Disc Replacement Therapies

In advanced stages of DDD with significant structural damage and the absence of viable cell activity, the injection of biomolecules or cell transplantation is no longer a feasible option.

A current surgical treatment strategy for advanced DDD is the total removal of the IVD followed by the fusion of the whole segment including the adjacent vertebrae. However, fusion may result in pseudoarthrosis or adjacent segment disease, which may lead to reoperation and long-distance fusion procedures (Maldonado et al. 2011; Sugawara et al. 2009; Bydon et al. 2013). To prevent these complications and to preserve mobility in the treated segment, TDR by synthetic prosthesis has become an alternative treatment strategy. Yet, current mechanical prosthetic TDR devices have not been able to reproduce the biomechanical properties of the natural IVD. Additionally, recent studies have demonstrated that current TDR devices are not without their disadvantages as they also entail the risk of adjacent segment disease (Maldonado et al. 2011; Kelly et al. 2011).

In this case, the total replacement using a tissue-engineered intervertebral disc with the ability to integrate into the host environment is a promising treatment strategy. The current standard in whole IVD implantation involves NP and AF composites that replace the structurally damaged tissues of a severely degenerated disc.

The first tissue-engineered whole IVD, implanted in vitro within the subcutaneous dorsum of athymic mice, comprised of NP cell-laden polyglycolic and polylactic acid (PGA/PLA) and AF cell-laden alginate (Mizuno et al. 2004a, 2006).

More than a decade ago, our group was the first to develop a tissue-engineered disc, composed of NP cells seeded into an alginate hydrogel, surrounded by a polyglycolic acid and polylactic acid scaffold seeded with AF cells (Mizuno et al. 2004b, 2006). This de novo construct was successfully implanted in the subcutaneous space of the dorsum of athymic mice and demonstrated the feasibility of creating a composite IVD including both AF and NP tissues Several other studies have reported the development of composite tissue-engineered IVD constructs, using combinations of materials such as demineralized bone matrix gelatin with type II collagen, hyaluronate and chondroitin-6-sulfate (C2/HyA-CS) (Zhuang et al. 2011), electrospun polycaprolactone and agarose (Martin et al. 2014), and self-assembled NP cells seeded onto calcium polyphosphate (Hamilton et al. 2006).

More recently, we developed a TE-IVD construct composed of an NP cell-laden alginate nucleus encircled by an AF cell-laden collagen annulus (Bowles et al. 2010, 2012). The efficacy of this construct, namely, maintaining disc height and physiological hydration as well as integrating into the host tissue, has been demonstrated through its implantation in a rat tail in vivo model (Bowles et al. 2011a; Gebhard et al. 2010, 2011; Grunert et al. 2014a; James et al. 2011). Although these results are promising, the rat tail has several dissimilarities with the human spine in terms of anatomy and biomechanical properties (O'Connell et al. 2007, 2011; Lotz 2004). Importantly, the rat tail has a significantly different biomechanical loading profile, as the IVDs of the human spine are exposed to higher axial loads. Furthermore, the rat tail lacks a spinal canal containing nervous tissue as well as posterior bone and joint elements. To move our approach closer toward clinical utilization and to mimic the biomechanical loads and anatomy of a human IVD more accurately, we transitioned to a larger animal model.

In a preliminary study, we performed TDR using TE-IVDs in the cervical spine of skeletally mature beagle dogs. Within this, we demonstrated

the ability of our TE-IVDs to integrate into the host tissue of a larger animal without any signs of inflammatory response (Moriguchi et al. 2017). Notably, these implants performed quite well when stably implanted in the intervertebral space. However, there was a persistent challenge in ensuring that implants remained firmly implanted in the intervertebral space.

Nonetheless, the addition of growth factors or bioactive molecules can encourage de novo ECM deposition. Goldschlager et al. demonstrated that adult allogenic mesenchymal progenitor cells (MPCs) formulated with a chondrogenic agent pentosan polysulfate (PPS) could synthesize a cartilaginous matrix when implanted into a biodegradable carrier and cage and over time might serve as a bioactive interbody spacer following anterior cervical discectomy (Goldschlager et al. 2010). Furthermore, the integration of tissue engineering and gene therapy has been attempted by a Chinese group that developed a tissue-engineered IVD using an allogenic disc transduced with hTERT gene within its NP cells. When implanted in a canine model, the hTERT-loaded NP cells manifested enhanced antidegenerative effect than unloaded NP cell (Xin et al. 2012). Such constructions of whole disc implants, the most ambitious therapeutic strategy yet, are met with extensive biological and functional challenges in vivo. Yet, the progressing field of TE continues to yield promising modifications to meet the higher demands of implanted discs.

Clinical Studies

Several of the above-described regenerative treatment approaches have already been utilized in a clinical setting. However, to date only a few clinical trials have been published on this topic (Table 5).

In the following section, several representative published clinical studies for the different treatment approaches will be presented.

In 2002, Meisel et al. started a multicenter prospective, randomized, controlled, non-blinded EuroDISC study comparing the safety and efficacy of autologous disc chondrocyte transplant (ADCT) implanted 12 weeks post discectomy. The 2-year interim analysis revealed a significant reduction of low back pain as well as retained disc height in the autologous disc cell transplantation (ADCT) group compared to the discectomy only control group (Meisel et al. 2006, 2007). The ADCT product is currently evaluated in a Phase II clinical trial under the product name NOVOCART® Disc (Meisel 2012; Tschugg et al. 2017).

While to date there is no clinical study using tissue-engineered material, efforts have been made to create functional substitutes for NP (Berlemann and Schwarzenbach 2009; Boyd and Carter 2006). Among many clinical studies focusing on NP replacement, a single-center, non-randomized, prospective feasibility study was undertaken to investigate the use of NuCore Injectable Nucleus hydrogel (Spine Wave, Inc., Shelton, CT, USA) post microdiscectomy prevented early disc collapse to potentially slow the degenerative cascade of the spinal segment over time (Berlemann and Schwarzenbach 2009).

The feasibility of a whole allogenic disc transplantation has first been proven by a group in China. Ruan et al. successfully performed transplantation of fresh frozen disc allografts including endplates in five patients. Implants successfully integrated into the host tissue, over the course of 5 years without any inflammatory reaction, although no immunosuppressive therapy was administered (Ruan et al. 2007). The absence of any immunologic response strongly supports the hypothesis that the intervertebral disc space is immunoprivileged tissue. Although promising, the allogenic transplantation of spinal motion segments has several limitations in terms of availability of healthy donor discs and potential disease transmission.

As mentioned in the section above, a frequently discussed treatment strategy is the intradiscal injection of platelet-rich plasma (PRP) for treating DDD. In 2016, Tuakli-Wosornu et al. published the results of a prospective, double-blind, randomized controlled study. Twenty-nine patients with low back pain, refractory to conservative treatment, received intradiscal PRP injections, while 18 patients who received a

Table 5 Published clinical trials

Trial treatment	No. of patients	Study design	Follow-up (m)	Outcome	Refs
Autologous hematopoietic stem cell injection	10	Case series	12	No patients reported any improvement in their discogenic back pain	Haufe and Mork (2006)
Total disc replacement with allogenic IVD	5	Case series	60	Allograft engrafted disc space without apparent immunoreaction; all minus one disc preserved range of motion	Ruan et al. (2007)
Autologous disc chondrocyte transplantation (EuroDisc)	28	Control study	24	ADCT with discectomy shows more pronounced decrease in OPDQ than discectomy alone	Meisel et al. (2006, 2007)
Injectable biomimetic nucleus hydrogel	14	Case series	24	Significant improvement in leg and back pain after micro-discectomy	Berlemann and Schwarzenbach (2009)
Autologous bone marrow mesenchymal cell injection	2	Case series	24	Both patients showed improvements in the vacuum phenomenon as well as signal intensity of T2-weighed MRIs	Yoshikawa et al. (2010)
Autologous bone marrow mesenchymal cell injection	10	Case series	12	Rapid improvement of pain and disability. Disc height was not recovered, but disc hydration was significantly elevated	Orozco et al. (2011)
Allogenic juvenile chondrocytes injection (NuQu)	15	Case series	12	ODI, NRS, SF-36 improved from baseline. 89% of the patients showed improvement on MRI	Coric et al. (2013)
Injection of autologous bone marrow-concentrated cells	26	Case series	12	Statistically significant improvement in pain scores and impairment was demonstrated. Most dramatic improvement seen in patients with higher CFU-F concentrations. Rehydration of the discs observed in 8 of 20 patients	Pettine et al. (2015)
Intradiscal injection of PRP	47	Prospective double-blinded randomized controlled study	12	Significant improvement in pain scales after 2 months, maintained at the 12-month follow-up	Tuakli-Wosornu et al. (2016)
Intradiscal injection of stromal vascular fraction with PRP	15	Case series	12	Significant improvement in VAS, no worsening, no radiographic changes	Comella et al. (2017)

placebo injection with a contrast agent served as a control group. At the 2-month follow-up, the PRP group showed significant improvement in pain scales. Patients maintained these improvements also in the 12-month follow-up (Tuakli-Wosornu et al. 2016).

Recently the utilization of different stem cell lines has found their way to clinical use. In 2006 Haufe et al. was the first to publish clinical results, reporting about intradiscal autologous hematopoietic stem cell injections. However, in the 12-month follow-up, none of

the ten patients reported any improvement in back pain, and 80% of the patients required surgical spinal intervention within a year after injection. Mesenchymal stem cells (MSC) on the other hand showed more promising results in various clinical studies. Due to their relatively easy accessibility and expandability in vivo, the bone marrow has been used as a source for MSCs in several in vitro and in vivo studies. Pettine et al. were the first to utilize bone marrow-concentrated cells (BMCs) as a treatment for discogenic back pain. In 26 patients with chronic low back pain, BMCs harvested from the iliac crest were injected into the IVD. The 1-year follow-up revealed a reduction in pain as well as radiographic improvement in 40% of the patients (Pettine et al. 2015). Yoshikawa et al. reported a case series of two patients who received a collagen sponge soaked with 10^5 cells/mL suspension grafted into a degenerated disc. After 2 years, both patients demonstrated improvement in pain as well as increased hydration on MRI (Yoshikawa et al. 2010). Orozco et al. reported a rapid improvement of pain up to 85% after 3 months in ten patients who underwent intradiscal injection of bone marrow-derived MSCs. Despite the fact that the disc height remained unchanged, an improvement in disc hydration could be observed in the 12-month follow-up MRI (Orozco et al. 2011).

Apart from the bone marrow, the adipose tissue is an abundant source for mesenchymal stem cells (Ganey et al. 2009; Jeong et al. 2010). Due to easier accessibility and less invasive harvest, the utilization of adipose-derived stem cells became more recently of increasing interest. In a recent study, Comella et al. were the first to publish clinical results on the injection of stromal vascular fraction (SVF), containing adipose-derived stem cells as a treatment for low back pain. In this study, SVF was administered along with PRP into lumbar IVDs in15 patients with discogenic back pain. After a 12-month follow-up, patients showed significant improvement in pain scales. However, this study did not provide any radiographic outcome data (Comella et al. 2017).

Unpublished Clinical Trials

Within the last decade, a clear trend toward regenerative treatment approaches is recognizable. This trend is also represented by the increasing number of clinical studies currently emerging aiming to find new biological treatment approaches for DDD. The following will elucidate several promising ongoing clinical studies that are not published yet.

Due to the similar biological profile as disc chondrocytes and potential immunoprivileged property, allogenic juvenile articular chondrocytes are another promising cell source. In a prospective cohort study, Coric et al. demonstrated that NuQu, an injectable percutaneous fibrin-based delivery of juvenile chondrocytes attenuated otherwise medically refractory low back pain (Coric et al. 2013). A class II study has recently been completed. Despite these study's promising results, further investigation with a prospective, randomized, double-blinded, placebo-controlled study is necessary to make cell transplantation a valid therapeutic option for DDD.

Rathmell et al. are currently the first to evaluate the effects and safety of intradiscal injections with recombinant human growth and differentiation factor 5 (rhGDF5) in a clinical trial. GDF-5 belongs to the transforming growth factor-beta (TGF-β) family which is meant to influence the growth and differentiation of various tissues including the intervertebral disc (Xu et al. 2006). The intradiscal administration has shown to improve the reparative capacity of IVDs in a degenerative rabbit model (Chujo et al. 2006). Within a Phase I/II clinical trial, 32 patients receive a single intradiscal injection of rhGDF5 and will be observed over a 36-month follow-up (J R 2008).

Mesoblast Ltd. developed a commercially available lineage of in vitro differentiated allogenic mesenchymal precursor cells (MPCs). Currently, this product is being evaluated under the name Rexlemestrocel-L in a Phase III prospective, multicenter, randomized, double-blind, placebo-controlled study, comparing Rexlemestrocel-L only vs. Rexlemestrocel-L+ hyaluronic acid (Mesoblast Ltd. 2015).

The recently completed Phase II study included 100 patients with chronic low back

pain due to DDD. The outcomes of this study were promising; both treatment groups who received 6 million MPCs and 18 million MPCs, respectively, improved in VAS by 44.4% and 37.9%, whereas the two placebo groups who received saline or hyaluronic acid only improved by 11.8% and 15.8%, respectively. However, no significant improvement in radiographic outcomes could be observed (Mesoblast Ltd. 2019).

The data emerging from these ongoing clinical trials will reinforce findings from published studies and provide new insight for future biological disc repair.

Future Perspective

This present book chapter provides a comprehensive overview on the recent innovations and trends in biological disc repair (Takahashi and Yamanaka 2006). Biomolecular therapies have shown the potential of stimulating the intrinsic healing capacity of the intervertebral discs in early stages (Masuda et al. 2006; Chujo et al. 2006; Huang et al. 2011). In a more advanced setting, cellular therapies are increasingly demonstrating their potential as the understanding of underlying mechanisms of cell differentiation increases (Pittenger et al. 1999; Bernardo et al. 2007; Moroni and Fornasari 2013). A major challenge for cellular therapies remains the determination of the optimal cell type as well as the ideal carrier for application (Acosta Jr et al. 2005).

Another challenge is that all these treatments are inevitably associated with an annular damage caused by the needle puncture, which is necessary for the application of the therapeutic agent. Carragee et al. has shown in a prospective study of notable size that even a small needle puncture may disturb the integrity of the AF enough to accelerate the degeneration of the IVD (Carragee et al. 2009). Therefore, a sufficient annular repair strategy is mandatory in order to seal the defects caused by the necessary needle puncture.

Since the lack of viable cells in advanced DDD makes a stimulating agent, such as growth factors, impossible and the final stages of DDD do not possess enough extracellular matrix to offer an environment for viable cells (Roberts et al. 2006), a replacement will become inevitable. It is known that current mechanical prosthetic devices also involve the risk of adjacent segment disease and thus accelerate further degeneration of the whole spine (Maldonado et al. 2011; Kelly et al. 2011). Therefore, it is inarguable that a biological construct with the ability to integrate into the host tissue will be the better option. Considering the limitations of healthy allogenic transplants (Ruan et al. 2007), tissue engineering will be the best option for end-stage DDD. Although promising, the described in vivo studies for TDR using tissue-engineered constructs (Grunert et al. 2014a; Moriguchi et al. 2017; Bowles et al. 2011b) are still facing challenges that need to be solved before a transition to clinical use will be possible.

Despite all the above-described advances, we still have limited understanding of the physiological concept of a healthy IVD as well as the underlying pathomechanisms of disc degeneration. Also the pathophysiological correlation between back pain and degenerative disc disease is still not entirely explored. Therefore, extensive research about the physiological as well as the pathological processes in intervertebral discs is mandatory before the ideal treatment strategies can be developed.

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Bone Grafts and Bone Graft Substitutes

11

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Abstract

Bone grafting has been uniquely practiced since the early 1600s. Historically, bone grafting includes autologous bone, a variety of allograft bone, and synthetic based-materials utilized in surgical interventions to treat spinal diseases or fractures. One of the most common uses of bone grafts is in spinal surgery to promote fusion between two functional vertebral segments. During a spinal surgery procedure wherein host bone is prepared, bone grafts are employed to optimize the biological environment to augment healing of the bony tissues for a desired outcome of a solid union – successful spinal fusion. State-of-the art bone graft materials have been effectively used to enhance bone induction and healing, providing more predictable outcomes resulting in spinal fusion.

Autograft has traditionally been recognized as the gold standard for bone grafts. However, differing grafting modalities are currently replacing autograft as the standard of care due to patient donor site morbidity, limitation to autograft, and the cessation of training young surgeons in the technique of autograft harvest. This has led to the research and development of various next-generation osteoconductive, osteoinductive, and osteogenic materials. In this chapter, various options to augment or replace autograft bone have been reviewed. Current options for spinal fusion discussed herein include autografts, allografts, and osteoconductive, osteoinductive, osteogenic, and osteostimulative materials. Further, novel materials such as engineered bioactive glass and peptide-based materials are presented. Choice of graft material with consideration of anatomical location, surgical application, spinal fusion technique, and patient characteristics will optimize bone healing and clinical outcomes.

Keywords

Autograft · Allograft · Synthetic bone grafts · Viable bone grafts · Cell-based bone grafts · Bioactive glass · Growth differentiation factors · Bone graft extenders · Substitutes · Combination products · Osteoconductive · Osteoinductive · Osteogenic · Interbody fusion · Posterolateral fusion · Posterior fusion · BMP · rhBMP-2 · rhBMP-7 · P-15

Abbreviations

AATB	American Association of Tissue Bank
ABM	Anorganic bone matrix
ACDF	Anterior cervical discectomy and fusion
ACS	Absorbable collage sponge, used as a carrier
AIBG	Autologous iliac bone graft
ALIF	Anterior lumbar interbody fusion
Allograft	Graft derived from unrelated human donor and transplanted to another person/patient, cadaver via bone bank; live donor patients undergoing removal, i.e., hip replacement

APC, PRP	Autologous platelet concentrate, serum derived from patient himself is concentrated via centrifugation (contains cytokines, growth factors; theorized to promote fusion)
Autograft, Autologous	Bone harvested from patient self from one site of the body and implant to another site of same patient
BAG, BG	Bioactive glass, a ceramic, biologically compatible synthetic material of crystalline components
BCG	Biocompatible glass
BCP	Biphasic calcium phosphate
BIC	Bone-implant contact
BMA	Bone marrow aspirate
BMC	Bone marrow concentrate
BMP, rhBMP-2, rhBMP-7	Bone morphogenetic protein, recombinant human bone morphogenetic protein
βTCP, β-TCP	Beta-tricalcium phosphate
Cage	Cages are cylindrical or square-shaped devices usually threaded. Used as instrumentation/fixation and to hold graft material in a surgical site, employed for interbody fusion, i.e., LT-Cage
Cell-based	Bone grafts with viable cells preserved or substitutes wherein cells are added
CGTP	Current Good Tissue Practice
CHO	Chinese hamster ovary (used to derive rhBMP-2)
Collagen Carrier	ACS, bovine type I collagen matrix
CS	Calcium sulfate, synthetic ceramic material composed of calcium-sulfate (1:1)
DBM powder	Demineralized bone matrix powder (human derived)
DBM, hDBM	Demineralized bone matrix (allograft), bone powder (allograft), hDBM (human derived)
DBM-based product	Demineralized bone matrix-based product, DBM powder (human derived) mixed with other material substances, or carriers
DFBA	Freeze-dried bone allograft
E.BMP, E.BMP-2	Escherichia coli-derived BMP-2 (used to derive rhBMP-2)
ECM	Extracellular matrix
Enhancer	Acts to add properties of osteogenicity or osteoinductivity to a graft material
Extender	Bone graft extender, osteoconductive material, compounds, scaffolds added to other grafting materials (ideally inductive or osteogenic), to increase the volume of graft. May add structural support
FDA CFR	Code of Federal Regulations
FDA, US-FDA	Food and Drug Administration, US FDA

Growth factors/ growth Differentiation factors	BMP, rhBMP-2, rhBMP-7, bone morphogenetic protein, recombinant human bone morphogenetic protein
GvHD	Graft-versus-host disease
h	Human-derived or human-like version
HA	Hydroxyapatite, calcium-containing porous crystal, accounts for a majority of bone natural mineral component
HCO	Bicarbonate (Bae to review)
HCT/P	Human cell and tissue product
ICBG	Iliac crest bone graft, autograft – bone morsels harvested from iliac crest
ISO	International Organization for Standardization
LBG, LAG	Local bone graft, local autograft – bone morsels harvested from the surgical dissection site
LLIF	Lateral lumbar interbody fusion
MED	Minimally effective dose
MIS	Minimally Invasive Surgery
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem cell
ncHA	Nanocrystal hydroxyapatite
OIF	Osteoinductive factor
OLIF	Oblique lumbar interbody fusion
Osteoconductive	Provides structural scaffolding upon which matrix-producing cells deposit new bone
Osteogenic	Presence of osteoblast precursor cells that contribute to new bone growth
Osteoinductive	Presence of molecular growth factors that stimulate precursors cells to migrate to graft site, mature into osteoid-producing cells, increase production of bone matrix
PEEK	Polyetheretherketone synthetic material, hydrophobic material to which cells have a limited ability to bond (polyaryletherketone family colorless organic thermoplastic polymer), used to fabricate spinal devices such as cages
Peptides/growth factors/growth differentiation factors	BMP, rhBMP-2, rhBMP-7 (OP-1 osteogenic protein), bone morphogenetic protein, recombinant human bone morphogenetic protein
rh	Recombinant human form
PLF	Posterolateral fusion
PLIF	Posterior lumbar interbody fusion
PLLF	Posterolateral lumbar fusion
PRP	Platelet-rich plasma (PRP) platelets (thought to have target

	growth factors) from patients' own blood
Segment, spinal segment	Spinal segment of the spine includes a superior vertebral body, disc, inferior vertebral body. Upper vertebral body, target vertebral body, lower vertebral body
Substitute	Graft substitute used instead of autologous bone grafting
TCP	Tricalcium phosphate, synthetic ceramic material composed of calcium and phosphate (3:2)
TI	Titanium (Ti)
TLIF	Transforaminal lumbar interbody fusion
TNF	Tumor necrosis factor
UDI	FDA rule that requires medical device manufacturers to update products with a unique device identifier
Xenograft	Grafted from one species to another species (i.e., bovine to human; porcine to human)

Introduction

Bone grafts and graft substitutes are materials that are used to rapidly induce or support biologic bone remodeling after surgical procedures to reconstruct bony structures and correct deformities and/or to provide initial structural support (Wang and Yeung 2017). In the spine, bone grafts are most often used to support biological healing with bony union of vertebral segments after a spinal fusion surgical procedure.

Bone grafts may come from a patient's own bone (autograft), may come from a human cadaver or living donor via bone bank (allograft), or may be fabricated from a synthetic material such as ceramics or bioactive glass. Furthermore, combination materials including composites of allografts, growth factors, osteogenic cells, synthetic materials of ceramic and/or cements, bioactive glass, and peptide-based materials have been developed and are offered for clinical use in spine fusion. See Table 1 for a description of sources of grafting materials and their associated bone-forming properties.

Design Requirements for Engineered Biomaterials (Table 2)

The selection of bone graft alternatives to be used for spinal fusion should be conducted carefully by considering the different healing environments, reviewing the preclinical and clinical data, and also considering the regulatory burden of proof for products not subjected to high levels of regulation (Boden 2002).

The development of products used for bone regeneration has followed the basic criteria of providing a biocompatible three-dimensional scaffold with controlled architecture capable of stimulating or supporting bone growth in the natural in vivo environment. The ability of the material to be amalgamated with cellular and signal (differentiation/growth factors)-based products is a key strategy in maximizing the efficacy and likely success of fusion. The primary characteristics and significance of bone graft substitutes is shown in Table 2.

Spinal Fusion

Spinal fusion is usually performed to provide stability to the spine when its biomechanics have been disturbed or altered. The surgical concept underlying spinal fusion is to reduce clinically important abnormal motion and add immediate and long-term stability, therefore decreasing or

Table 1 Description of specific graft materials and bone forming properties

Grafting material	Grafting material (typical abbreviation)	Grafting material category and description	Variability	Osteogenic	Osteo inductive	Osteo conductive	Immunogenicity/ disease transmission	Strength (immediate)	Donor site morbidity
Autograft									
Autograft	Iliac crest bone graft (ICBG)	More cancellous (mercerized and/or strut form)	Patients' own bone quality	+++	++	+++	–	+++	++
Autograft	Local bone (LB, LAG)	More cortical (mostly mercerized form)		+/–	+	+	–	+/–	+/–
Autograft	Bone dust (Gao et al. 2018; Street et al. 2017)	Generated via high-speed burr on bone surface		+/– (less than local bone)	+/– (less than local bone)	+/– (less than local bone)	–	–	+/–
Autograft	PRP (platelet-rich plasma) (Elder et al. 2015)	Plasma preparation with increased platelet concentration	Patients' own health status	+/–	++ (Elder et al. 2015) (activation of growth factors)	–	–	–	–
Autograft/bone marrow aspirate (Robbins et al. 2017)	Osteogenic cell with growth factors	Most common source of MSC		+ (variable according to donor's condition)	+ (variable according to donor's condition)	–	–	–	+

Allograft									
Allograft	Fresh (Meyers 1985)	1. Living donor (patient to patient transfer) 2. Cadaveric donor (harvested within 12 h and allotransplantation within 72 h) ➔ Femoral head (as osteochondral form)	Lot-to-lot variability donor's bone condition + sterilization processing techniques	? (no data for osteogenic graft for human)	? (no data for osteogenic graft for human)	? (no data for osteogenic graft for human)	+++ (generally causes an unacceptable host immune reaction as osteogenic graft) ➔ Not used commercially, only animal studies		
Allograft	Fresh (osteochondral graft) (Rauck et al. 2019)	1. Living donor (patient to patient transfer) 2. Cadaveric donor (harvested within 12 h and allotransplantation within 24 h) ➔ Femoral head (as osteochondral form) (Torrie et al. 2015)		+/– (only chondrocyte viability remains)	–	++	+ (reduced/mild immune reaction by cartilaginous portion of graft) + (infection risk due to storage media)	++ (grafted at articular portion for weight supporting)	
Allograft	Fresh-frozen (Kawaguchi and Hart 2015)	From: 1) Living donor 2) Cadaveric donor		–	–	++ (less than autogenous bone) (Miyazaki et al. 2009)	+ (reported cases)	++ (Kawaguchi and Hart 2015)	–
Allograft	Freeze-dried	From: 1) Living donor 2) Cadaveric donor		–	–	++	+/–	+/– (significantly affected by drying process) (Wheeless 2013)	–
Allograft	Gamma sterilization			–	–	++	+/–	+ (by radiation effect) (Hamer et al. 1999)	

(continued)

Table 1 (continued)

Grafting material	Grafting material (typical abbreviation)	Grafting material category and description	Variability	Osteogenic	Osteo inductive	Osteo conductive	Immunogenicity/ disease transmission	Strength (immediate)	Donor site morbidity
Allograft	Demineralized bone matrix (Morris et al. 2018)	Mostly cadaveric donors	Demineralization processes + particle sizes	–	+/–	++	+/–	–	–
Selective cell retained allografts	Osteogenic cell		Patient characteristics	+	+/–	–		–	–
Differentiation factors									
Differentiation/ growth factor (Burke and Dhall 2017)	rhBMP-2	Differentiation/ growth factor	High manufacturing consistency	–	+++	–	–	–	–
	rhBMP-7	Differentiation/ growth factor		–	+++	–	–	–	–
Peptides	B2A (Glazebrook and Young 2016)	Bioactive synthetic peptide		–	–	++	–	–	–
	P15 (Hsu et al. 2017)	Bioactive synthetic peptide		–	–	++	–	–	–
Synthetic ceramics									
Tricalcium phosphate	TCP	Synthetic ceramics		–	–	++	–	–	–
Hydroxy apatite	HA	Synthetic ceramics		–	–	++	–	+/–	–

Biphasic calcium phosphate	BCP	Synthetic ceramics		–	–	++	–	+/–	–
Calcium sulfate	CS	Synthetic ceramics		–	–	++	–	–	–
Synthetic bioactive glasses									
Synthetic bioactive glass	45S5	Bioactive glass with 45% silicate		–	+	++	–	+/– (Hench and Jones 2015)	–
	S53P4	Bioactive glass with 53% silicate			+	+ (less bioactive than 45S5) (Hench and Jones 2015)			
Others									
Xenograft	Xenograft	From nonhuman species, mainly bovine-based bone graft	Donor variability	–	+/– (according to sterilization process)	+	+++ (more than allograft) (Shibuya and Jupiter 2015)	++ (in spine, foot, and ankle and trauma part) (Shibuya and Jupiter 2015)	–
Type I collagen	Xenograft carrier (bovine)	Osteoconductive scaffold/ hemostasis	Anatomic source location and species	–	–	+	–	+/–	–

+++ Characteristic is definitely observed from biologic, clinical, and preclinical studies
++ Characteristic is somewhat observed from biologic, clinical, and preclinical studies
+ Suggested by clinical and preclinical studies. There may be some controversy, or effect is minimal
+/– Debate status
– None/no effect

Table 2 Optimal characteristics of engineered biomaterials (O'Brien 2011)

Characteristic/*sub-characteristic*	Significance
Biocompatibility	The very first criterion of any biomaterials for tissue engineering is biocompatibility. Cells must adhere, function normally, and migrate onto the surface and eventually through the scaffold and begin to proliferate before laying down new matrix. The host's immune reaction to the material must be negligible in order to allow for proper healing
Capacity to bind cells or growth factors	For this purpose, collagen often used as a method to enhance cell and growth factor attachment
Biodegradability	The biomaterials must be biodegradable to allow cells to produce their own extracellular matrix. The by-products of this degradation should also be nontoxic and able to exit the body without interference with other organs
Resorption rate balanced with rate of bone formation	The biomaterials must resorb and allow formation of new bone. Otherwise material may remain and become an inert obstacle to fusion or healing
Mechanical properties	The biomaterials should have mechanical properties consistent with the anatomical site into which it is to be implanted
Intraoperative handling	From a practical perspective, it must be strong enough to allow surgical handling during implantation
Ability to visualize by fluorography intraoperatively	Radio-density important to visualize location and to determine healing with subsequent x-rays
Biomaterials architecture	The biomaterials should have an interconnected pore structure and high porosity to ensure cellular penetration and adequate diffusion of nutrients to cells and of waste products out of the scaffold
Controlled architecture, i.e.*, porosity, interconnected pores, and pore size that permits cell ingrowth*	Cells need to be allowed to interact with each other and have continuity
Promotes revascularization and bone ingrowth	Essential in aiding bone healing
Manufacturing technology	In order for a particular tissue-engineered construct to become clinically and commercially available, it should be safe and cost-effective, manufactured following GMP, GLP, US-FDA, EU-EMA, and WHO International Conference of Harmonization technology standards (ISO) for scale-up from research laboratory-based small batch to large scale production lot reproducibility, maintaining reliability, stability, with optimized production processes meeting manufacturing requirements of country of manufacture and distribution

For the USA, PHS Act (Public Health Service Act), FDA-established regulations for Human Cells, Tissues, and Cellular and Tissue-Based Products (HCT/Ps), set forth in Title 21, Code of Federal Regulations, Part 1271 (21 CFR 1271), Public Health Service Act (42 USC 264), Good Manufacturing Practices (GMP), Good Laboratory Practices (GLP), GTP, Minimal Manipulation of Human Cells, Tissues, and Cellular and Tissue-Based Products etc. HCT/Ps to prevent the introduction, transmission, and spread of communicable diseases. These regulations can be found in 21 CFR Part 1271, section 361 (US FDA 2017, 2018)

eliminating pain thought to be aggravated by the abnormal motion (Herkowitz et al. 2004; Adams 2013). Spinal fusion is performed in patients with degenerative diseases like spinal instability, vertebral fractures, degenerative disc disease, and scoliosis. After a surgical decompression procedure has been performed to relieve pressure on the nerve roots or spinal cord, a fusion procedure may be completed as well to address the instability and provide long-term bony stability and structural reinforcement. The two main types of spinal fusion procedures are posterolateral fusion (PLF) and interbody fusion (IBF) performed from among a large variety of surgical approaches and techniques (Makanji et al. 2018; Morris et al. 2018).

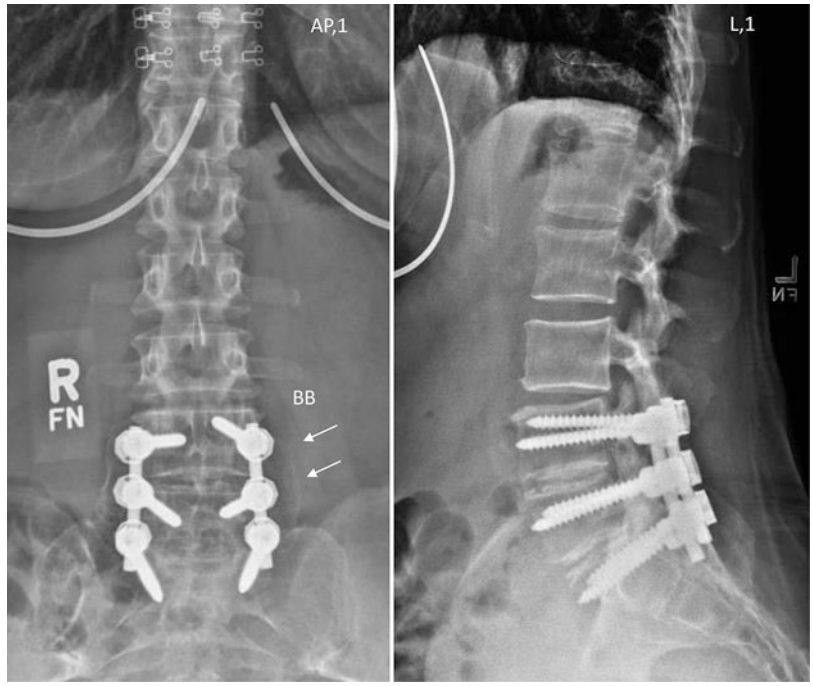

Fig. 1 Example of posterolateral fusion with consolidated bone mass (BB) approximately 1 year after spinal fusion procedure with instrumentation and autograft placed in the posterolateral bed

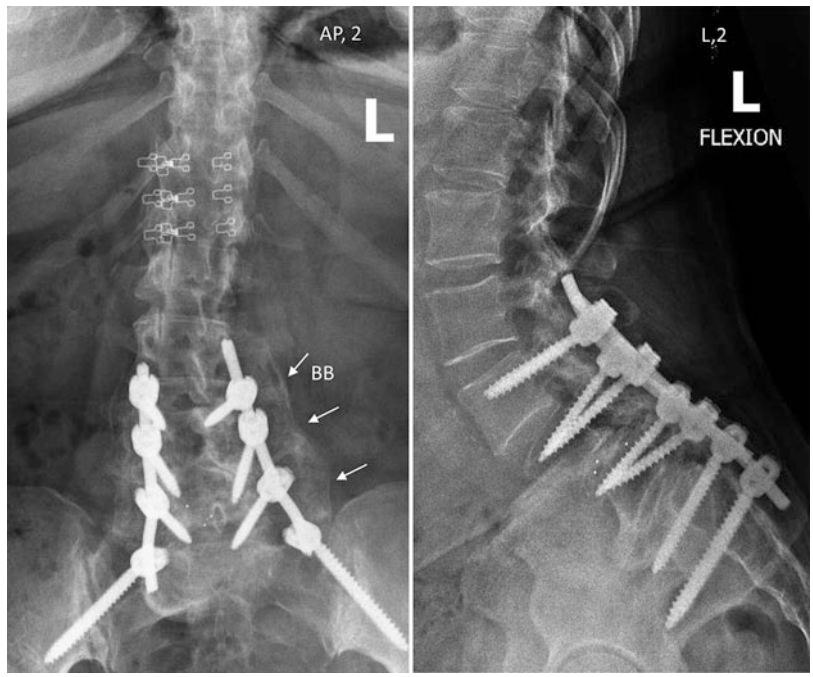

Fig. 2 Example of four-level posterolateral fusion with dense solid bone mass (BB) bilaterally at 1 year after posterior spinal fusion procedure with instrumentation and grafting with Fibergraft (Prosidyan), allografts, and bone marrow aspirate (BMA)

Radiographic images of example patients after surgical fusion procedures in lumbar and cervical spine are provided (Figs. 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, and 11).

In posterolateral fusion (PLF), the bone graft or bone graft substitute is surgically placed between the transverse processes, lateral to the side of the superior vertebral body and inferior vertebral

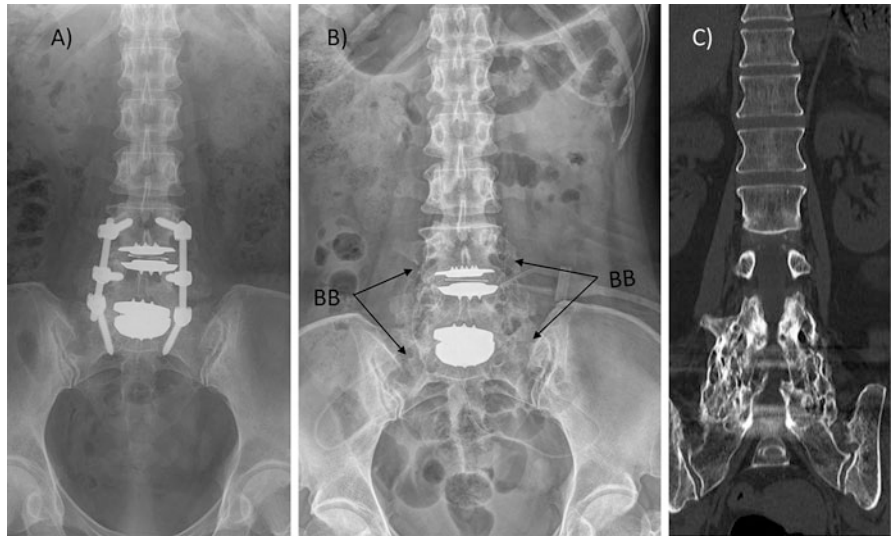

Fig. 3 A 59-year-old female patient was surgically treated for failed artificial disc in the lumbar spine. For treatment, a posterolateral fixation was performed with allograft cancellous chip bone (Medtronic) mixed with autologous local bone and pedicle screw fixation device (Medtronic). A radio-dense bone bridge *was not* observed between transverse process between L3 and S1 on the initial postoperative anterior-posterior radiographs (A). On radiographs taken at 3-year follow-up after removal of pedicle screws, there was a radio-dense bone bridge (BB black arrows) on anterior-posterior (AP) radiographs. On CT image (C), definitive radio-dense bone (BB) was observed with contact between transverse process, facet joint, and grafted bone

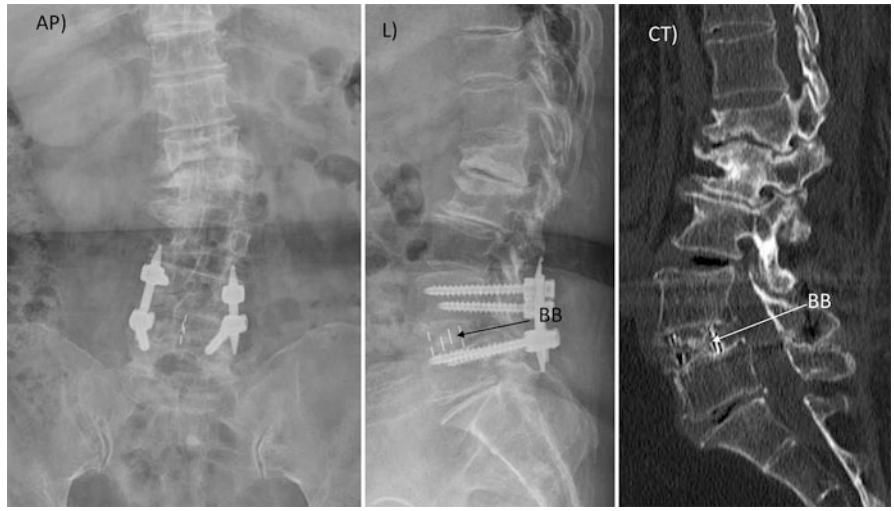

Fig. 4 A 60-year-old female patient was surgically treated with a diagnosis of spinal-stenosis L4-L5. Surgery: an indirect decompression of spinal nerve and fusion via oblique interbody fusion (OLIF) technique with PEEK cage containing DBM-based product (Medtronic). A hemilaminectomy via MIS surgery technique was performed using percutaneous screw fixation. On anterior-posterior (AP), lateral (L) radiographs taken at 1.5-year follow-up, a radio-dense bony line was observed between upper and lower vertebral body through the inserted cage. On sagittal CT view, a dense bridge (bony incorporation) was formed at fusion site. Wedge-shaped vertebral deformation of L1 and L2 compression fracture was observed. L2 fracture was treated with PMMA bone cement

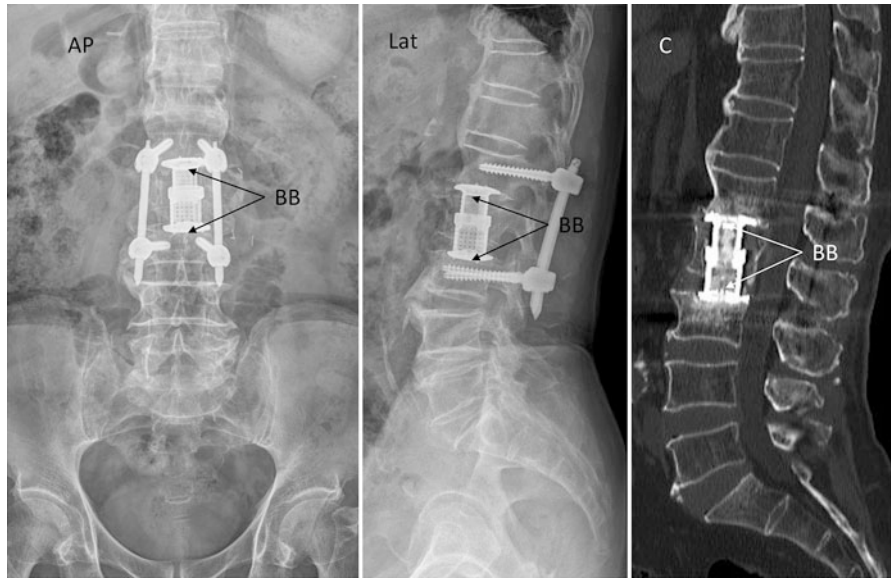

Fig. 5 A 78-year-old male patient was surgically treated for TB spondylitis in L2. The infected vertebrae were removed through corpectomy process. Fusion procedures were performed using a distractible cage (DePuy Synthes) with allograft cancellous chip bone (Medtronic) mixed with autologous local bone and a percutaneous pedicle screw fixation device (Medtronic). Titanium distractible cage with keel on contact surface with vertebral endplate was used for load bearing architecture. On anterior-posterior (AP), lateral (L) radiographs taken at 2-year follow-up, a radio-dense bone bridge (black BB) was observed between upper and lower vertebral body. On CT image (C), definitive radio-dense bone (white BB) was observed connecting through the cage between the two vertebral endplates (white arrows indicate endplates)

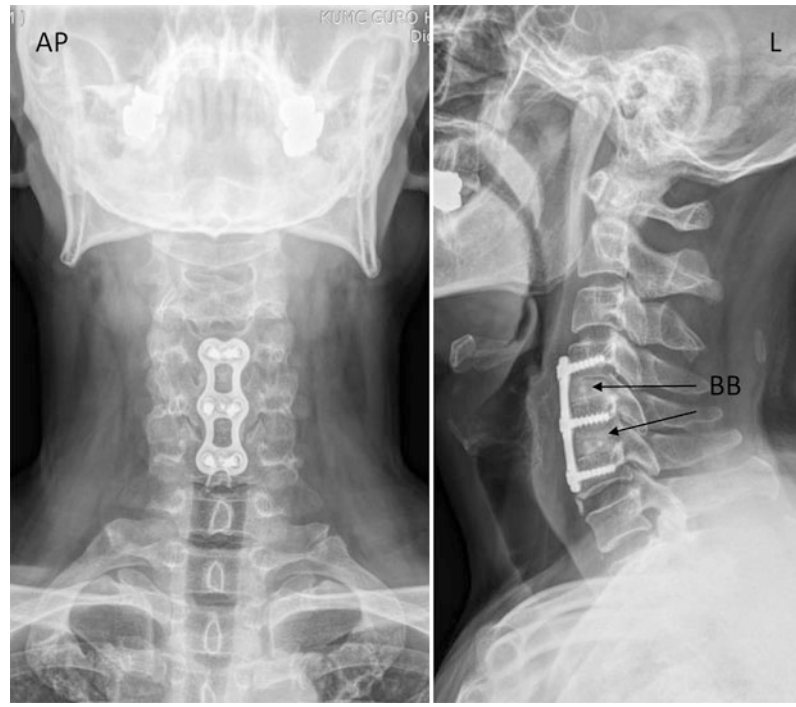

Fig. 6 A 49-year-old male patient was surgically treated for herniated intervertebral disc C4–C5, C5–C6. A total discectomy was performed for decompression through an anterior surgical approach. A machined cortico-cancellous allograft (Medtronic) and cervical plate (Medtronic) were used in the fusion procedure. On anterior-posterior (AP), lateral (L) radiographs taken at 1-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral bodies though the inserted machined cortico-cancellous allograft

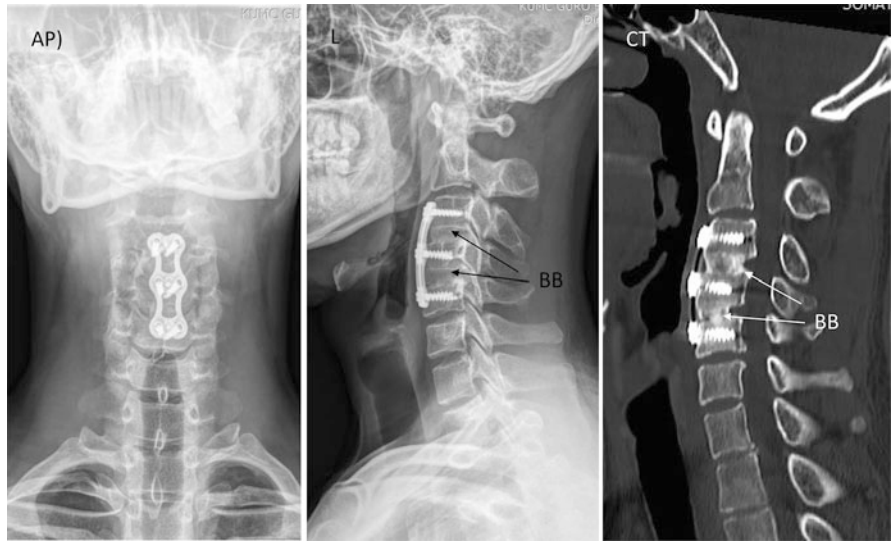

Fig. 7 A 34-year-old male patient was surgically treated for two-level herniated intervertebral disc C3–C4, C4–C5. A total discectomy was performed for decompression through an anterior approach. For the fusion procedure, iliac autogenous bone graft and a cervical plate (Medtronic) were used. On anterior-posterior (AP), lateral (L) radiographs taken at 1-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral body through the inserted iliac autogenous bone graft. On sagittal CT view, there is bone formed and complete incorporation of C3–C4–C5 (BB) at the fusion site

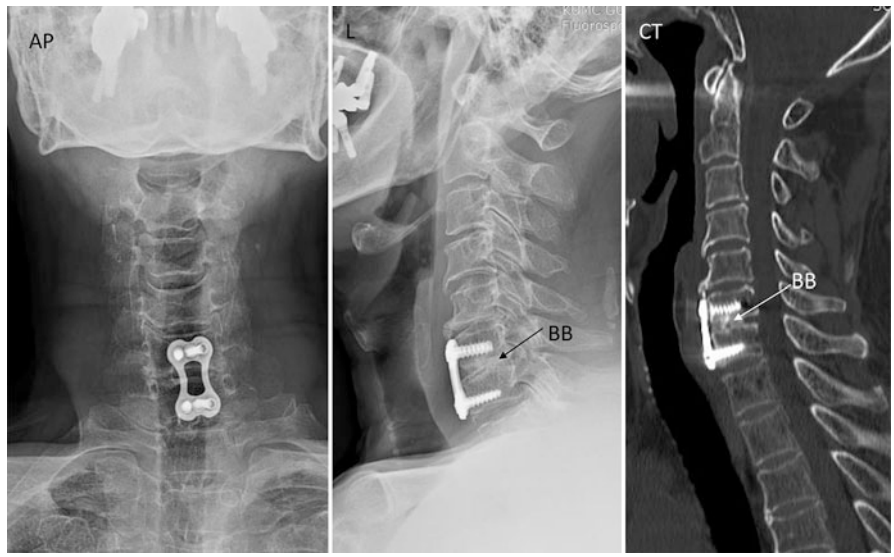

Fig. 8 A 64-year-old male patient was surgically treated for herniated intervertebral disc C6–C7. A total discectomy was performed for decompression through an anterior surgical approach. For fusion procedure, a machined corticocancellous allograft (Medtronic) and a cervical plate (Medtronic) were used. On anterior-posterior (AP), lateral (L) radiographs taken at 1.5-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral body through the inserted machined corticocancellous allograft. On sagittal CT view, a bone bridge (BB, complete bony incorporation) was formed at fusion site

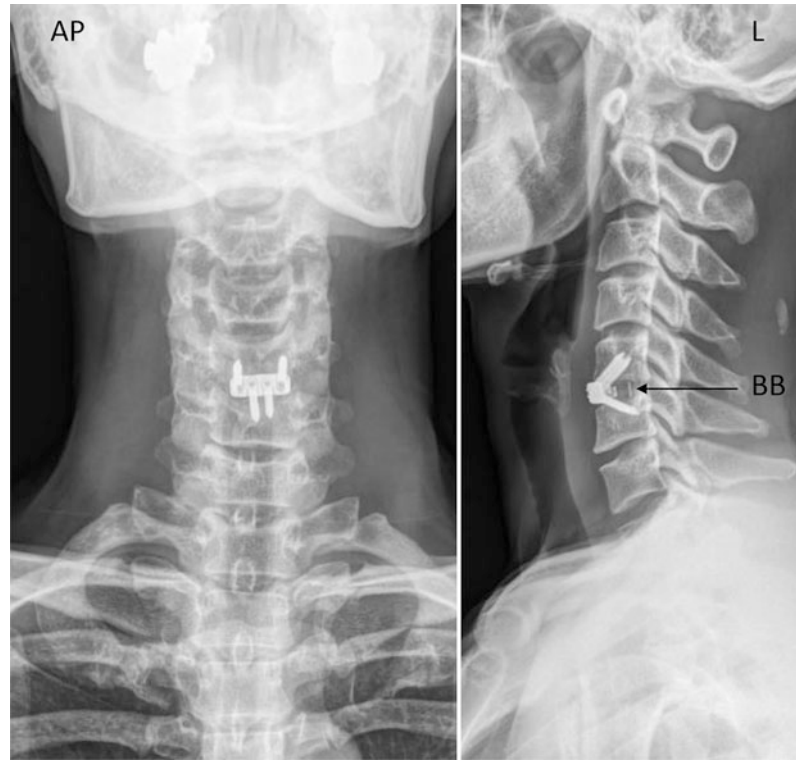

Fig. 9 A 49-year-old female patient was surgically treated for herniated intervertebral disc at C5–C6. A total discectomy was performed for decompression through the anterior approach. For the fusion procedure, a Zero-p system (DePuy Synthes) and DBM-based putty (DBX, DePuy Synthes) were used. On anterior-posterior (AP) and lateral (L) radiographs taken at 2-year follow-up, a radio-dense bone bridge (BB) was observed between upper and lower vertebral body

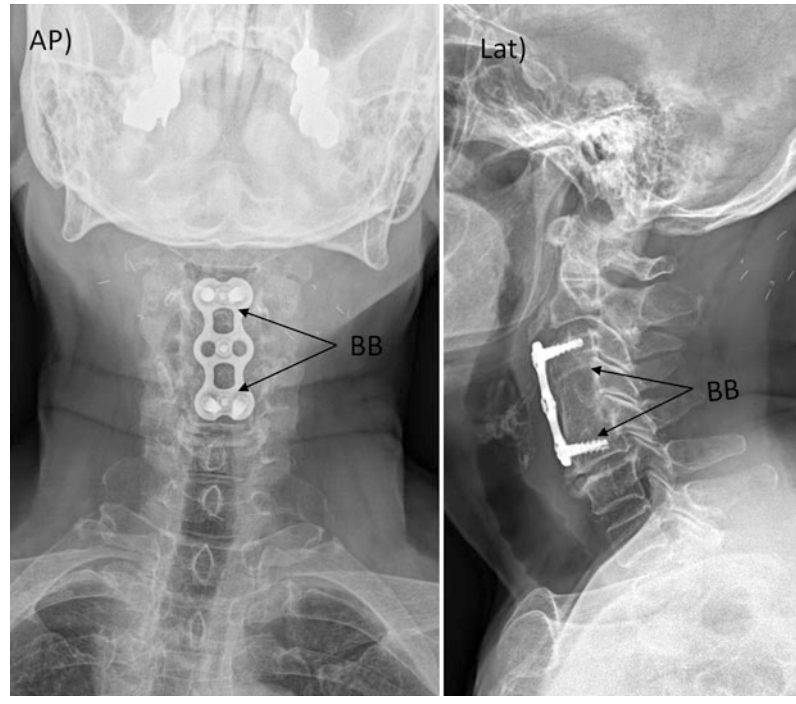

Fig. 10 A 59-year old patient was surgically treated for fracture dislocation injury at C3 vertebrae after fall from height. Treatment of fracture was performed by a decompression through corpectomy and fusion using auto-iliac crest strut bone graft with cervical metal plate fixation spanning C3–4–5). On anterior-posterior (AP), lateral (L) radiographs taken at 3-year follow-up, a radio-dense bone bridge (black BB) was observed between upper and lower vertebral bodies (C3–C5 a solid bone unit). Note no radio-opaque gap between graft material and endplate of adjacent vertebral bodies

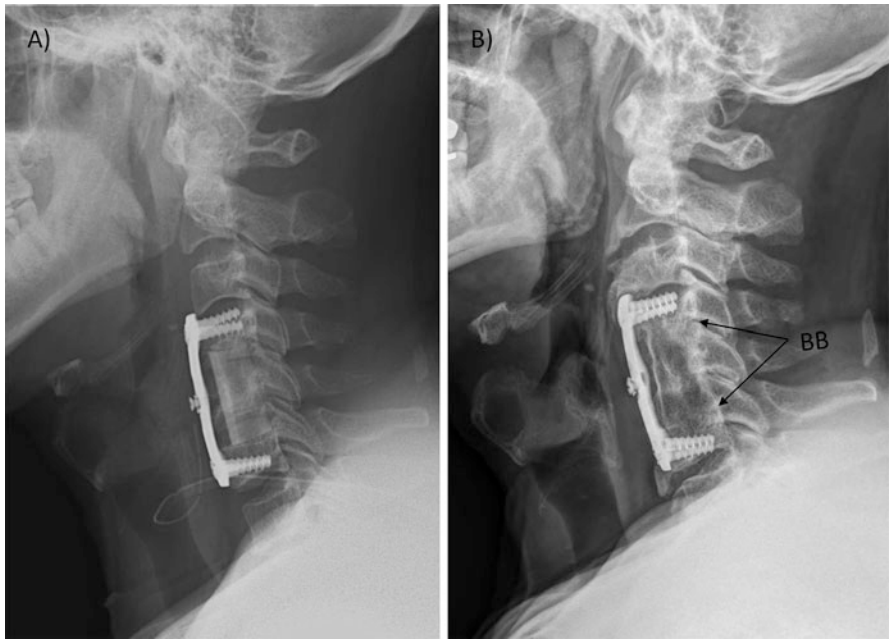

Fig. 11 A 62-year-old male patient was surgically treated for OPLL from C4 to C6 cervical spine. Decompression of the spinal cord was performed through removal of vertebral body of C5 and C6. Fusion was performed using allograft strut fibula bone with a cervical metal plate (Medtronic). After initial postoperative radiography, a radio-opaque gap is seen between grafted material and endplate vertebral body. At 1-year follow-up, a complete incorporation between allograft and host bone is observed as a solid bone unit – no radio-opaque gap between grafted material and vertebral endplates. There is radio-density of grafted material indicating bony consolidation and incorporation with fusion from C4-C7

body. During the healing process, the graft material is remodeled and incorporated into a solid bony "bridge" (BB) between the transverse processes and lamina. Once healed, the spine segment is stabilized, and motion between vertebral functional segments is eliminated or reduced (Fig. 1, example lumbar spine).

In interbody spinal fusion, compared to PLF, the bone grafts or bone graft substitutes are placed between the endplates of two adjacent vertebrae (e.g., Figs. 4 and 5, lumbar spine; Figs. 6, 7, 8, 9, 10, and 11, cervical spine). The bone graft's and/or instrument with graft's contact with the endplates of the adjacent vertebral bodies resists relatively high loading forces.

Due to these biomechanical differences in graft sites, interbody fusion bone grafts are commonly placed with cages that hold the graft in place and are designed to withstand the compressive forces of the vertebrae. When the bone graft or bone graft in a cage is placed between the endplates of the vertebral body, it creates a framework of mechanical support during the early time of graft incorporation. This mechanical fixation and support eventually aids in the biologic bony union connecting one vertebral body to the other. Similarly to posterolateral fusion, once the vertebrae are fused, the spine is stabilized, and movement between operated spine segments should disappear. A systematic recent review of 12 studies (565 IBF-treated patients) by Baker et al. (2017) concluded that interbody fusion was a good surgical option in spondylolisthesis patients with instability. Interbody fusion can be performed by several different surgical approaches and techniques such as anterior (anterior lumbar interbody fusion (ALIF)), posterior (posterior lumbar interbody fusion (PLIF)), transforaminal (transforaminal lumbar interbody fusion (TLIF)), and lateral (lateral lumbar interbody fusion (LLIF)).

After a fusion procedure, the bone healing process occurs in different phases: inflammation,

soft callus formation, hard callus formation, and bone remodeling.

This includes hematoma formation, release of native growth factors/cytokines, and recruitment of inflammatory cells (e.g., macrophages and bone-forming cells); cell differentiation to bone-forming cells and mineralization of the extracellular matrix (ECM); bone resorption and remodeling; and formation of lamellar bone and hematopoietic marrow cavities (Rausch et al. 2017). These complex biologic processes of consolidation of grafted materials into new bone and remodeled into mature bone can be negatively affected by various systemic and local factors. Typical host or patient-based negative factors are advanced age (Ajiboye et al. 2017), concomitant use of tobacco or other drugs, poor nutritional status, and metabolic comorbidities (e.g., diabetes or osteoporosis) (Campbell et al. 2012; Ajiboye et al. 2017). Negative local factors are remaining structural instability, poor vascularity around surgical site, revision surgery, previous or current infection, and other local/surgical site considerations including surgical technical factors such as inadequate preparation of host bone, lack of fixation, inadequate bone graft volume and preparation, and improper use of graft materials (Yoo et al. 2015). Critical challenges for both interbody and posterolateral fusion are the excessive distances for the cells to migrate within and between host bone beds in order to attach to targeted neighboring anatomic bony structures; the limited durability of concentrations of growth factors, peptides, exogenous cells, biochemical, and other agents; and the biomechanical stability. These biologic challenges are particularly deterring in geriatric spine patients with severe osteoporosis.

To achieve successful bone fusion in the spine, surgeons vigilantly adhere to the requirements of bone regeneration and fracture healing mentioned above in deciding use of grafting materials. Bone formation requires three critical elements: osteoconduction, osteoinduction, and osteogenesis. *Osteoconduction* relies on a scaffold that supports cell ingrowth, facilitates vascularization, and provides a network for cells to attach. *Osteoinduction* relies on the provision of signals that act on the precursor cells and encourage cell migration, proliferation, and differentiation into bone-forming cells leading to rapid bone formation. *Osteogenesis* relies on the immediate provision of viable cells emanating from the host to the defect site differentiating into bone-forming cells. Autograft or autogenous bone possesses all three properties essential for bone formation and is therefore considered to be the gold standard graft material for inducing bone healing, consolidation, and fusion of the spine.

Current Materials for Spinal Fusion

The graft material used in spinal fusion procedures can be generally categorized into three main types of materials: autogenous bone graft (autograft) from the patient's own body, allograft from human cadavers and/or living donors, and synthetic bone graft or substitutes (Table 1).

The use of autogenous bone graft has been a standard practice in spine surgery for over a century. The first reported use of autogenous bone graft for spine fusion was reported in 1911 when Fred Albee, MD, placed a tibia between spinal lamina in order to fuse and stabilize the spine (Albee 2007). Autograft has been considered the "gold standard" of bone grafting primarily because it contains all the elements required for successful fusion mentioned above: osteoconductive matrix, osteoinductive factors, and pluripotent bone-forming cells (Gupta and Maitra 2002; Whang and Wang 2003).

Autografts

Autograft for spinal fusion can be obtained via different surgical approaches and dissection methods. Firstly, resected lamina, spinous process, facet, and osteophytes during the surgical decompression process yield bone graft which is then morselized – "local bone graft" (LBG). Local bone is commonly limited in amount and quality as mixture consists of mostly cortical bone vs. cancellous bone (Tuchman et al. 2016). Secondly, a bone graft can be obtained from iliac crest

using a separate surgical incision and various dissections (White and Hirsch 1971), which then can be used as strut or morselized bone. Iliac crest bone graft (ICBG) is relatively abundant, providing good-quality graft (mainly cancellous bone). However, iliac bone and local bone autografts have similar effectiveness in terms of fusion rates, pain scores, and functional outcomes in view of lumbar spine fusion (Tuchman et al. 2016).

Autograft bone is safe to use due to the low risk of disease transmission and offers the optimal chance of acceptance and effectiveness in the transplant site without immune reaction (Campana et al. 2014). However, the limitations with autogenous iliac bone graft such as relatively limited quantity, increased surgical time, and donor site morbidity are well recognized (Vaccaro et al. 2002). Due to these limitations, the use of autograft has declined.

The reduction in the use of autograft from the iliac crest in the recent practice has led to the increase in the use of local bone graft and has created new demands for the identification of cost-effective biologic materials that will "extend" the bone healing effects of local autograft (Ito et al. 2013). To achieve optimal outcomes, these materials should be biocompatible and biodegradable and have beneficial mechanical properties and microarchitecture that facilitates the biological healing process (Table 2).

Allografts

Allografts are primarily osteoconductive with minimal osteoinductive potential and traditionally not osteogenic because the donor cells are eradicated during processing (Campana et al. 2014; Duarte et al. 2017). Allografts have the advantage for a surgeon of easy procurement (off-the-shelf), availability (commercially available), and many varieties of structural and non-structural form. However, allografts consist of nonviable tissue and cannot stimulate bone formation without the addition of bone-stimulating factors and cells (Goldberg and Stevenson 1993; Garbuz et al. 1998; Stevenson 1999). These limitations lead to slower and less complete incorporation with native bone. Additionally, allografts have potential risk of disease transmission even if the incidence is very low and the risk can be controlled during procurement and sterilization process (Campana et al. 2014).

Allo-bone Graft: Cortico-cancellous Allograft (Table 3)

Allograft bone obtained from cadaver sources is added to the most widely used substitute or extender for autogenous bone graft. In the 1980s, femoral head from living donors (after total hip replacement surgery) was also introduced as another form of allograft and has demonstrated good clinical results in lumbar spine fusion (Urrutia and Molina 2013).

Allograft bone may be morselized to various sizes of particulate (i.e., chip bone) formed or machined to create structural spacers and then applied to site of desired bone formation. Cortical allograft is most often used as mechanical strut graft and is suited for interbody fusion, while cancellous allograft serves as a useful osteoconductive scaffold for bone formation.

The efficacy of allograft alone has been shown to have more clinical variability and lower fusion rates in challenging animal models and human studies of spinal fusion (Morris et al. 2018). These overall clinical results suggest that allograft be cautiously used in conjunction with either autograft or osteogenic material (e.g., bone marrow aspiration) to achieve good fusion rates and clinical outcomes (Morris et al. 2018). However, while the actual risk of transmission is negligible, issues of immunogenicity are present (Manyalich et al. 2009).

Allo-bone Graft: Demineralized Bone Matrix (DBM)-Based Product (Table 4)

The DBM technology is based on the observation by Urist MR (Urist 1965) that soluble signals contained within the organic phase of bone were capable of promoting bone formation. The processing of transforming ground cortical bone into DBM powder base involves the use of hydrochloric acid to progressively remove mineral while attempting to preserve the organic phase containing type 1 collagen, non-collagenous

Table 3 Commercially available structural and/or nonstructural allograftsural[a]

Company	Allograft spinal graft products	Formulation product composition		Clinical evidence ClinicalTrials.gov ongoing study	Regulatory clearance/approvals US by FDA registered tissue bank establishments 21CFR1270, CFR 1271 AATB; US; Pharmacopoeia USP standard 71
AlloSource®, Centennial, Co, USA, 1995 Allosource.org	AlloFuse®		Cortical/cancellous spacers Cancellous cervical spacers Cortical cervical spacers	n/a	Regulated human tissue CFR 1270, 1271
	Spinal grafts freeze-dried		Bicortical blocks Dowel Patella wedge Cervical spacers, parallel spacer/textured lordotic Femoral rings Fibular rings, radial rings, ulna rings	n/a	Regulated human tissue CFR 1270, 1271
	Spinal grafts freeze-dried/frozen		Cortical strut TriCortical Ilium Wedges, Strips	n/a	Regulated under CFR 1270, 1271 as a human tissue http://activize.com/wp-content/uploads/2014/05/Allograft-Catalog.pdf
ATEC, Carlsbad, CA	AlphaGRAFT® structural allografts		Vacuum level allograft designed to hydrate	n/a	AATB standards and Good Tissue Practices
Aziyo, Richmond, CA	OsteSpine		Structural cortical (femur, tibia, cortical shafts/struts)/cancellous spacers, (OsteSpine) precision-machined allografts	n/a	Regulated under CFR 1270, 1271 as a human tissue
Bone Bank Allografts, Texas, USA	SteriSorb™	[a]	Osteoconductive Sponge Allografts (100% cancellous bone) Characteristics of a sponge by absorbing saline, blood, or bone marrow aspirate	n/a	Bone Bank Allografts Registration – FDA BBA Manufacturing Registration – FDA (previously THB) Bone Bank Allografts – Accreditation American Association of Tissue Banks (AATB) CTO Registration Certificate – Bone Bank Allografts (International Registration)
	SteriFlex™		Wrappable Bone Allografts (100% cortical bone) Can be bent, contoured, rolled, trimmed, molded, or sewn, making this flexible bone material	n/a	

(continued)

Table 3 (continued)

Company	Allograft spinal graft products	Formulation product composition	Clinical evidence ClinicalTrials.gov ongoing study	Regulatory clearance/approvals US by FDA registered tissue bank establishments 21CFR1270, CFR 1271 AATB; US; Pharmacopoeia USP standard 71
	SteriGraft™ – Cervical ACF SteriGraft™ – ACF Cortical-Cancellous Spacer SteriGraft™ – ALIF SteriGraft™ – PLIF SteriGraft™ – Unicortical Dense Cancellous Block SteriGraft™ – Dense Cancellous Block	Fully machined. Constructed of 100% human cortical bone (femur or tibia) Fully machined. Constructed of 100% human cortical bone with an internal cancellous plug (femur or tibia) Fully machined. Constructed of 100% human cortical bone (femur) Fully machined. Constructed of 100% human cortical bone (femur or tibia) Unicortical Dense Cancellous Block (femoral head, patella, distal tibia, talus, or calcaneus) Dense Cancellous Block (femoral head, patella, distal tibia, talus, or calcaneus)	n/a	
	Traditional bone/ cancellous bone allografts Traditional bone/ cortical-cancellous bone allografts	Traditional-type cancellous bone chip or tricortical allo-iliac bone	n/a	
DePuy Synthes Spine	Zero-P Natural Plate System	Zero-Profile Plate with Allograft Spacer (cervical spine)	n/a	21 CFR 888.3060, K152239, 2015 Dec FDA 510(k) cleared
Hospital Innovations Ltd. Pontyclum, Wales, UK	Ilium Tricortical strips Bone blocks Whole and hemi shaft	Traditional cortical/cancellous bone graft Available freeze-dried (FD) or frozen (FZ) Sterilized SAL 10^{-6}	n/a	#22512, CF729FG, 2014 Jul [Regulation 7(1) Schedule 2 of Human Tissue Authority (Quality and Safety for Human Application (non-departmental public body, Department of Health and Social Care, UK) Regulations, 20070]

Globus Medical Inc	FORGE® FORGE® Oblique		Fully machined corticocancellous spacer (cervical spine fusion) Fully machined cortical spacer designed to provide a natural option for transforaminal lumbar fusion	n/a	FDA 510(k) cleared K153203, 2015 Dec
LifeLink Tissue Bank	Cortical Cancellous Spacer		Fully machined cortical-cancellous spacer (from femur and tibia) for cervical spine		AATB FDA Florida, California, and New York Holds a permit to provide tissue in Maryland
Mountain States Medical ➔ Merged into Zimmer	OsteoStim®		Fully machined cortical spacer (from femur and tibia) for cervical spine		Processed at an AATB-accredited facility
Medtronic Spinal and Biologics	Allograft structural Cornerstone SR Cornerstone™ ASR Cornerstone-Reserve™		Fully machined cortical block (from femur or tibia) with capital D shape Fully machined cortical lateral wall with a cancellous center with capital D shape Fully machined cortical ring with cancellous plug	ClinicalTrials.gov Identifier: NCT01491399, no results posted	AATB standards, FDA regulations, and applicable Public Health Service Guidelines for donor screening
	Cornerstone™ tricortical Cornerstone™ bicortical Cornerstone™ unicortical Cornerstone™ dense cancellous block		Freeze-dried cortical/cancellous (iliac crest) Freeze-dried cortical/cancellous (iliac crest) Freeze-dried anterior cortical wall with cancellous center Freeze-dried dense cancellous with capital D shape		AATB standards, FDA regulations, and applicable Public Health Service Guidelines for donor screening
	Cornerstone™ selective/cortical wedge		Freeze-dried cortical ring		AATB standards, FDA regulations, and applicable Public Health Service Guidelines for donor screening
Orthofix®	AlloQuent-s, Monolithic Cortical Structural allograft		Structural allograft (cervical fusion, lumbar fusion) Different sizes and shapes (ALIF, PLIF, TLIF)	NCT00637312, has results posted – cervical disc: Trial was stopped. Approval not being pursued for device (clinicaltrial.gov)	unk

(continued)

Table 3 (continued)

Company	Allograft spinal graft products	Formulation product composition	Clinical evidence ClinicalTrials.gov ongoing study	Regulatory clearance/approvals US by FDA registered tissue bank establishments 21CFR1270, CFR 1271 AATB; US; Pharmacopoeia USP standard 71
RTI Surgical®	Elemax® Cortical Spacer Allograft Elemax® Cortical Spacer Allograft Elemax® PLIF Allograft	Precision-machined cortical spacer for anterior cervical discectomy and fusion procedures Fully machined cortical lateral wall with a cancellous center with capital D shape for anterior cervical discectomy and fusion procedures Fully machined cortical spacer designed to provide a natural option for PLIF	n/a	AATB Accreditation Certificate – (Florida) FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps) Florida, USA Tutogen Medical, GmbH (Germany) International Organization of Standards (ISO) Tutogen Medical, GmbH (Germany) CMDCAS – RTI Surgical (Florida) CE Certificates Pioneer Surgical Technology (Michigan) International Facility Registrations Health Canada CTO Registration State Tissue Banking Licenses California, Florida, Maryland, New York, Oregon, Illinois, Delaware
	AlloWedge® Bicortical Allograft Bone	Options for approaching opening wedge osteotomies in the foot and ankle Pre-shaped bicortical allografts	n/a	FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps)
	Cross-Fuse® Advantage Lateral Allograft	All cortical bone implant designed for a lateral approach to provide maximum potential for fusion Produced from femoral or tibial tissue	n/a	FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps)
	Bigfoot® ALIF Allograft	All cortical bone implant designed for use as an intervertebral spacer in anterior lumbar interbody fusion (ALIF) approach	n/a	FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps)

			Freeze-dried: rehydrate for a minimum of 30 s Frozen: thaw for a minimum of 15 min		
	Traditional cortical and/or cancellous strut allobone		Femoral head, hemi femoral shaft, humeral head, ilium tricortical block, ilium tricortical strip, proximal and distal femur, proximal and distal humerus, proximal and distal tibia, unicortical block, whole femur, fibula and humerus, and bicortical block	n/a	FDA Establishment Registration and Listing for Human Cells (FDA-HCT/Ps)
SeaSpine, Carlsbad, CA, USA	Capistrano™ System		Cervical allograft spacer system is precision machined from cortical and cancellous allograft bone	n/a	361-HCT/P US FDA 21 CFR 1271 Restricted to homologous use for the repair, replacement, or reconstruction of bony defects by a qualified healthcare professional (e.g., physician)
Stryker	AlloCraft™ CA, CL, CP, CS		Machined from femoral/tibial allograft ➔ ACDF Freeze dried Chamfered edge	n/a	AATB US FDA regulations for tissue management. US FDA 21 CFR 1271
Xtant, USA	Ilium tricortical blocks, unicortical blocks, fibula segments, and femoral struts		Traditional allografts	n/a	Processed by tissue banks that are members of the American Association of Tissue Banks (AATB)
X-spine Systems, Inc./Xtant, USA	Atrix-C™ Cervical Allograft Spacer		Precision-milled cortical bone w/ teeth like keel surfaces	n/a	Processed by tissue banks that are members of the American Association of Tissue Banks (AATB)
Zimmer Biomet	OsteoStim® Cervical Allograft System OsteoStim® PLIF OsteoStim® ALIF/[a]		Fully machined cortical spacer bone for cervical and lumbar w/ teeth like keel surfaces	n/a	Processed by tissue banks that are members of the American Association of Tissue Banks (AATB)

AATB (American Association of Tissue Banks) Policies (2018)
FDBA Freeze-dried bone allograft
n/a not available on ClinicalTrials.org/no clinical data found or clinical trial registered
[a]Indicates cancellous chips "crunch" available

Table 4 Commercially available DBM-based products

Company	DBM-based product (human)	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271
AlloSource®, Centennial, Co, USA, 1995 Allosource.org	AlloFuse® Gel AlloFuse® Putty (identical to StimuBlast Putty and Gel manufactured for Arthrex)	Injectable gel and putty	DBM, reverse phase medium (RPM) carrier Carrier comprised polyethylene oxide-polypropylene oxide block copolymer dissolved in water exhibiting reverse phase characteristics (i.e., an increase in viscosity as temperature increases)	n/a	510(k) cleared K071849, 2008 Dec
	AlloFuse Plus	Paste, putty	DBM, RPM, cancellous chips	n/a	510(k) cleared K103036, 2011 Jan
	AlloFlex	Strips, blocks, fillers	Cancellous bone allograft, DBM, strip form, no carriers added	n/a	Marketed as human tissue
Amend Surgical, Inc	NanoFUSE® Bioactive Matrix	Putty	DBM + 45S5 bioactive glass: bond void filler	n/a	510(k) cleared K161996 2017 Feb
	NanoFUSE® DBM	Putty 2 cc to 10 cc	45S5 bioactive glass + porcine gelatin + demineralized bone matrix (DBM) 45S5 bioactive glass: osteoconductive scaffold, DBM: osteoinductive potential	Kirk et al. 2013 Xynos et al. 2000a Xynos et al. 2000b	Regulated under CFR 1270, 1271 as a human tissue K110976, 2011 May www.accessdata.fda.gov/cdrh_docs/pdf11/K110976.pdf accessdata.fda.gov/cdrh_docs/pdf16/K161996.pdf 510(k)
ATEC, Carlsbad, CA	AlphaGRAFT®DBM AlphaGRAFT ProFuse DBM	Putty or gel	A reverse phase medium sponge-like DBM, superior handling characteristics, and ready-to-use application (thickens at body temp.)	n/a	unk
Aziyo Biologics	OsteoGro		Cancellous bone and partially demineralized bone		

Bacterin International, Inc. ➔ Changed to Xtant Medical	OsteoSelect DBM	Putty	74% DBM dry weight	n/a	510(k) cleared K091321, 2009 Sept K130498, 2013 May
	OsteoSelect Plus DBM	Putty	74% DBM dry weight + demineralized cortical chips (1–4 mm)	n/a	510(k) cleared K150621, 2015 Aug HCT/P (FEI 3005168462)
	OsteoSponge®	The malleable sponge	DBM (100% human demineralized cancellous bone)	Shehadi and Elzein 2017	510(k) cleared HCT/P (FEI 3005168462), 2017 Nov
	OsteoSponge® SC	The malleable sponge	Demineralized cancellous bone intended to treat the pathology of damaged subchondral bone of the articulating joints	Galli et al. 2015	510(k) cleared HCT/P (FEI 3005168462), 2017 Nov
	OsteoWrap®	Flexible handling characteristics with a scalpel or scissors	100% human demineralized cortical bone	n/a	510(k) cleared HCT/P (FEI 3005168462), 2017 Nov
	3Demin®	Various shapes (fiber, boat shape, strip)	100% human demineralized cortical bone fiber Contain BMPs and other growth factor 3Demin allografts are also available as loose cortical fibers in three volume options	n/a	Compliance with FDA guidelines regarding human cells, tissues, and cellular tissue-based products HCT/P 361 regulated viable allogeneic bone scaffold American Association of Tissue Banks guidelines
Berkeley Advanced Biomaterials, CA, USA	H-GENIN™	Putty matrix sponge powder	100% demineralized bone matrix putty and crush mix	n/a	510(k) cleared (as B-GENIN, R-GENIN) K092046, 2010 Mar
Biomet Osteobiologics ➔ Merged into Zimmer Biomet.	InterGro® DBM	Putty (40% DBM), paste (35% DBM)	DBM, lecithin carrier (resorbable, biocompatible, semi-viscous lipid)	Prospective case series	510(k) cleared K082793, 2009 Apr K031399, 2005 Feb

(continued)

Table 4 (continued)

Company	DBM-based product (human)	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271
Bioventus® Surgical	Exponent™	Putty form	Demineralized bone matrix is composed of human demineralized bone (DBM) mixed with resorbable carrier, carboxymethylcellulose (CMC)	n/a	AATB US FDA 21 CFR 1271. (HCT/P)
	PUREBONE	Sponge shape (available in block or strip format)	100% demineralized cancellous bone (osteoconductive matrix with osteoinductive potential that provides a natural scaffold for cellular ingrowth and revascularization) Sterilized by gamma irradiation	n/a	FDA 510(k) cleared AATB US FDA 21 CFR 1271. (HCT/P)
Bone Bank™ Allografts 2017/ Texas Human Biologics	SteriFuse™ DBM Putty	Flowable, formable putty	100% demineralized bone matrix from human bone	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P))
	SteriFuse™ Crunch	Flowable, formable crunch	SteriFuse™ DBM putty with cortical cancellous bone chips	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P))
DePuy Synthes	DBX®	Putty type	DBM + sodium hyaluronate	ClinicalTrials.gov Identifier: NCT02005081: RCT, results are not reported	510(k) cleared K103795, 2011 Apr

	Synthes® Dento	Powder type Granule type Putty type	Powder type: demineralized cortical powder, mineralized cancellous powder, mineralized cortical powder Granule type: demineralized cortical (80%)/cancellous granules, mineralized cortical (80%)/cancellous granules DBM putty type: 93% DBM	n/a	unk
ETEX (Zimmer Biomet, 2014 October)	CaP Plus	CaP Plus	Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC), and DBM	n/a	510(k) cleared K063050, 2007 Nov K080329, 2008 Apr
	EquivaBone Osteoinductive Bone Graft	Powder and hydration solution	Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC) and DBM		510(k) cleared K090855, 2009 Sep K090310, 2009 Mar
Exactech	Optecure	Injectable paste	DBM (81% by dry weight), hydrogel carrier	Prospective RCT: ClinicalTrials.gov Identifier: NCT00254852	510(k) cleared K121989, 2012 Nov K061668, 2006 Sept K050806, 2006 Feb
	Optecure® + CCC	Injectable paste	Polymer powder, DBM, cortical cancellous chips (1–3 mm)	Comparative study allograft vs Optecure® + CCC: ClinicalTrials.gov Identifier: NCT02127112	510(k) cleared K061668, 2006 Sep K121989, 2012 Nov
	Optefil (OSTEOFIL® DBM Paste, OSTEOFIL® RT DBM Paste)	DBM paste or dry powder – hydrated to become injectable paste	DBM in gelatin carrier	n/a	510(k) cleared K043420, 2005 Feb
	Opteform	Putty or dry powder – hydrated to become paste	Gelatin, DBM, and cortical-cancellous bone chips	n/a	510(k) cleared K043421, 2005 Feb

(continued)

Table 4 (continued)

Company	DBM-based product (human)	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271
Integra OrthoBiologics (IsoTis OrthoBiologics), Inc., Irvine, CA/SeaSpine 2018	Accell Connexus	Injectable putty	DBM (70% by weight), RPM	Retrospective comparative: Schizas et al. 2008	510(k) cleared K060306, 2006 Mar K061880, 2007 Aug
	Accell Evo3™	Injectable putty	DBM (Accell Bone Matrix), RPM	NCT02018445 ("Efficacy and Safety of Integra Accell Evo3™ Demineralized Bone Matrix in Instrumented Lumbar Spine Fusion") NCT01714804 (Integra Accell Evo3 Demineralized Bone Matrix) NCT01430299	510(k) cleared K103742, 2011 Mar
	Accell TBM	Preformed matrix (strip, square, round)	100% DBM (Accell Bone Matrix)	n/a	510(k) cleared K081817, 2008 Sep
	Dynagraft II	Injectable gel, putty	DBM (Accell Bone Matrix), RPM, cancellous bone chips	n/a	510(k) cleared K040419, 2005 Mar
	Orthoblast II	Injectable paste, putty	DBM (Accell Bone Matrix), RPM, cancellous bone chips from same donor	n/a	510(k) cleared K050642, 2005 Dec
LifeNet Health	IC Graft Chamber	Freeze dried in injectable delivery chamber, can be mixed with whole blood, PRP, or BMA	DBM, cancellous chips	n/a	Regulated under CFR 1270, 1271 as a human tissue
	Optium DBM Putty	Putty	DBM, glycerol carrier	n/a	510(k) cleared K053098, 2005 Nov
	Optium® DBM Gel	Gel	Particulate DBM & Glycerol	n/a	510(k) cleared K053098, 2005 Nov
	Cellect DBM®	Provided in a specialized cartridge	DBM fibers + cancellous chips	Case reports: Lee and Goodman 2009	510(k) cleared Regulated under CFR 1270 and 1271

Medtronic Spinal and Biologics	OSTEOFIL DBM	Injectable paste, moldable strips	DBM (24% by weight) in porcine gelatin	Prospective case series: Epstein and Epstein 2007	510(k) cleared K043420, 2005 Feb
	Progenix TM Plus	Putty with demineralized cortical chips	DBM in type I bovine collagen and sodium alginate	n/a	510(k) cleared K081950, 2008 Jul
	Progenix Putty	Injectable putty	DBM in type 1 bovine collagen and sodium alginate	n/a (human) Blinded observations/ assessment of study in rabbit (Smucker and Fredericks 2012)	510(k) cleared K080462, 2008 May
	Magnifuse™ Family 1) Magnifuse Bone Graft substitute/bone void filler 2) Magnifuse II Bone Graft		DBM mixed with autograft in 1:1 ratio packed into polyglycolic acid (PGA) resorbable mesh bag 1) DBM + surface-demineralized chips 2) Combination of surface demineralized cortical chips and allograft fibers that have been processed removing the mineral component leaving only the organic portion	ClinicalTrials.gov Identifier: NCT02684045: retrospective case series study, results are not posted	510(k) cleared K123691, 2013 Jan K082615, 2008 Oct
MTF/Synthes	DBX	Paste, putty mix, strip	DBM (32% by weight), sodium hyaluronate carrier (mix vary for paste, putty, mix)	n/a	510(k) cleared K040262, 2005 Mar (putty, paste, matrix mix) K040501, 2005 Apr – (putty, paste, matrix mix) K053218, 2006 Dec (putty, paste, matrix mix) K063676, 2007 Mar (putty, paste, matrix mix) K080399, 2008 Oct (paste) K091217, 2009 Oct (putty) K091218, 2009 Sep (putty) K103795, 2011 Apr (putty K103784, 2011 Apr (putty) K042829, 2006 Jan (strip)

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Table 4 (continued)

Company	DBM-based product (human)	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271
Nanotherapeutics, Inc.	Origen™ DBM with Bioactive Glass (NanoFUSE® DBM)	A malleable, putty-like, bone void filler	Human demineralized bone matrix (DBM) and synthetic calcium-phospho-silicate particulate material particles (45S5 bioactive glass), both coated with gelatin derived from porcine skin	n/a	510(k) cleared K120279, 2012 Apr K110976, 2011 May
NuTech Medical, Inc.	Matrix: Osteoconductive Matrix Plus	Putty type	Allograft cancellous and demineralized cortical mixture Freeze-dried for convenient ambient temperature storage	n/a	
	Matrix: FiberOS	Putty type	Demineralized cortical fibers, mineralized cortical powder, and demineralized cortical powder Gamma sterilized for patient safety Freeze-dried for convenient ambient temperature storage		Nutec
Osteotech/ Medtronic	GRAFTON A-Flex	Round flexible sheet	DBM	n/a	510(k) cleared K051188, 2006 Jan
	GRAFTON Crunch	Packable graft	DBM, demineralized cortical cubes	n/a	510(k) cleared K051188, 2006 Jan
	GRAFTON Flex	Flexible sheets, varying sizes	DBM	Retrospective comparative study	510(k) cleared K051195, 2005 Dec
	GRAFTON Gel	Injectable syringe	DBM	RCT, prospective case series	510(k) cleared K051195, 2005 Dec
	GRAFTON Matrix PLF	Troughs	DBM	RCT	510(k) cleared K051195, 2005 Dec

	GRAFTON Matrix Scoliosis Strips	Strips, various sizes	DBM	Retrospective case series	510(k) cleared (Recalled 10/18/2012)
	GRAFTON Orthoblend Large Defect	Packable graft	DBM, crushed cancellous chips	n/a	510(k) cleared
	GRAFTON Orthoblend Small Defect	Packable, moldable graft	DBM, crushed cancellous chips	n/a	510(k) cleared
	GRAFTON PLUS® DBM Paste	Paste	Human bone allograft demineralized bone matrix (DBM) + inert starch-based carrier has been added	n/a	510(k) cleared K043048, Nov 2005 (Osteotech)-traditional K042707, Nov 2005 (Osteotech)
	Grafton Putty 22076647	Packable, moldable graft	DBM (17% by weight), glycerol	Kang et al. 2012	510(k) cleared K051195, 2005 Dec
Pioneer® Surgical Technology and Regeneration Technologies ➔ All companies merged into RTI Surgical®	BioSet TM	Injectable paste, putty, strips, and blocks with cortical cancellous chips	DBM, inert porcine, gelatin carrier	n/a	510(k) cleared K080418, 2008 Apr Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P)) 12.07.2016 (validated by FDA)
	BioAdapt® DBM	Powder form	Dried granular powder form (70% of DBM by weight) from 100% human bone matrix	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for Human Cellular and Tissue-based Products (HCT/P)) 12.07.2016 (validated by FDA)

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Table 4 (continued)

Company	DBM-based product (human)	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271
	BioReady® DBM Putty and Putty with Chips	Putty/putty with bone chip	Putty: 56% DBM by weight Putty with chips: 42% DBM by weight + small or large mineralized cortical cancellous chip ➔ 100% allograft DBM	n/a	Regulated under 21 CFR Part 1271 (h FDA requirements for human cellular and tissue-based products (HCT/P)) 12.07.2016 (validated by FDA)
SeaSpine, Carlsbad, CA	OsteoBallast™ Demineralized Bone Matrix	DBM in resorbable mesh	100% DBM	n/a	FDA 510(k) cleared
	OsteoSurge® 300 Demineralized Bone Matrix	The moldable putty form	DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone	NCT01430299	It is same material to Accell Evo3
	OsteoSurge® 300c Demineralized Bone Matrix	The moldable putty including cancellous chips	DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone + bioresorbable, reverse phase medium carrier.	n/a	It is same material to Accell Evo3c SeaSpine new sponsor, same material
	OsteoSparx® Demineralized Bone Matrix	Gel or putty-like consistency	DBM + reverse phase medium carrier	n/a	It is same material to Accell Evo3 (NCT01430299)
	OsteoSparx® C Demineralized Bone Matrix	Gel or putty-like consistency.	DBM + reverse phase medium carrier + cancellous bone	n/a	It is same material to Accell Evo3c
	Accell Total Bone Matrix®	Pre-formed shape (round or rectangular)	DBM + Accell® bone matrix ➔ 100% DBM	NCT01430299	It is same material to Accell Evo3
	Accell Evo3c™	Putty	DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + cancellous bone + bioresorbable, reverse phase medium carrier	n/a	FDA510(k) cleared K103742, 2011 Mar

	Accell Evo3™	Putty	DBM + Accell® bone matrix (it is an open-structured, dispersed form of DBM) + bioresorbable, reverse phase medium carrier	1. Case study on posterolateral fusion (12/2013 ~ 06/2017, ClinicalTrials.gov Identifier: NCT02018445) 2. Prospective study on posterolateral fusion (12/2017 ~ 01/2018, ClinicalTrials.gov Identifier: NCT01714804) 3. RCT on posterolateral fusion Accell Evo3 Demineralized Bone Matrix (DBM) (93.5% fused) vs. rhBMP-2(100% fused). (ClinicalTrials.gov Identifier: NCT01430299)	FDA 510(k) cleared K103742, 2011 Mar
	Capistrano™	DBM + allobone	DBM (demineralized bone matrix) + machined cortical and cancellous allograft bone	n/a	FDA 510(k) cleared
Smith & Nephew	VIAGRAF	Putty, paste, gel, crunch, and flex	DBM, glycerol	n/a	510(k) cleared K043209 – 2005 Dec
Spinal Elements	Hero DBM	Putty, paste, gel	DBM, RPM	n/a	Regulated under CFR 1270, 1271 as human tissue
	Hero DBM Powder	Powder	DBM	n/a	Regulated under CFR 1270, 1271 as human tissue
Wright Medical technology	ALLOMATRIX®	Various volumes, consistency varies depending on proportion of cancellous chips utilized	DBM (86% by volume) +/− cancellous bone matrix (CBM) in surgical-grade calcium sulfate powder	Retrospective comparative study	510(k) cleared K041663, 2004 Sept
	ALLOMATRIX ®RCS	Formable putty	DBM, synthetic resorbable conductive scaffold (RCS), calcium sulfate, and hydroxypropylmethylcellulose (HPMC)	n/a	510(k) cleared K041663, 2004 Sept

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Table 4 (continued)

Company	DBM-based product (human)	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/ approval FDA 510(k), CFR 1270, CFR 1271
	ALLOMATRIX™ C	Putty	ALLOMATRIX™ + small cancellous chips	n/a	510(k) cleared K040980, 2004 Jul
	ALLOMATRIX™ CUSTOM	Putty	ALLOMATRIX™ + large cancellous chips	n/a	510(k) cleared K040980, 2004 Jul
	ALLOMATRIX™	Injectable	DBM (86% by volume) + OSTEOSET™ (surgical-grade calcium sulfate)	RCT in trauma treatment ClinicalTrials.gov Identifier: NCT00274378	510(k) cleared K020895, 2004 Mar
	ALLOMATRIX® DR	Putty	Calcium sulfate, DBM, and small cancellous chips	n/a	510(k) cleared K040980, 2004 Jul
	PROSTIM™	Procedure kits, various volumes of injectable paste/formable putty	50% calcium sulfate, 10% calcium phosphate, and 40% DBM by weight	n/a	FDA 510(k) cleared K190283, 2019 Feb
Zimmer ➔ It merged into Zimmer Biomet company	IGNITE	Percutaneous graft for fracture mal/nonunion	DBM in surgical-grade calcium sulfate powder to be mixed with bone marrow aspirate	n/a	510(k) cleared K052913, 2005 Nov
	OSTEOSET DBM Pellets	Packable pellets	3.0 mm or 4.8 mm pellets Surgical-grade calcium sulfate, DBM (53% by volume), stearic acid	n/a	510(k) cleared K022828, 2004 Apr K053642, 2006 Jan
	PROSTIM™ Injectable Inductive Graft	Injectable paste/ formable putty	DBM (40% by weight), calcium sulfate (50% by weight), calcium phosphate (10% by weight)	n/a	510(k) cleared K190283, 2019 Feb
	Puros DBM with RPM Gel and Paste	Gel, paste	DBM, RPM, ground cancellous bone (<500 microns)	n/a	Regulated under CFR 1270, 1271 as human tissue
	Puros DBM with RPM Putty and Putty with chips	Putty	DBM, RPM, +/− cortical bone chips (850 microns–4 mm)	n/a	Regulated under CFR 1270, 1271 as human tissue
	Puros DBM Block and Strip	Blocks, strips in varying sizes	DMB (100%)	n/a	Regulated under CFR 1270, 1271 as human tissue

	Bonus® CC Matrix	Putty type	Demineralized cortical bone (DBM) + mineralized cancellous chips All-inclusive bone grafting kit	n/a	FDA registration number: FEI 1000160576 (till 06.30.2020) AATB and HTC/P
	StaGraft™ DBM Putty and Plus		DBM + natural lecithin carrier + resorbable coralline hydroxyapatite/calcium carbonate granules Available as a 40% DBM Putty, or 35% DBM PLUS	n/a	FDA registration number: FEI 1000160576 (till 06.30.2020)
	StaGraft™ Cancellous DBM Sponge and Strips		Cancellous DBM Sponge and Strips are machined from a single piece of cancellous bone Osteoinductive bone, trabecular structure, sponge-like handling	n/a	FDA registration number: FEI 1000160576 (till 06.30.2020)
	FiberStack™ Demineralized Bone Matrix (DBM)		Manufactured entirely from cortical bone, which has been demonstrated to maintain higher osteoinductivity than cancellous bone after demineralization 100% DBM (without carrier)	n/a	FDA registration number: FEI 1000160576 (till 06.30.2020)

510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval. 501(k) documentation for individual products is available via FDA online database (http://www.accessdata.fda.gov)
Code of Federal Regulations (CFR) 1270 (Human tissue intended for transplantation) and 1271 (Human cells, tissues and tissue-based products) are federal regulations relating to the procurement and processing of human-derived tissues
Human Tissues Banks: https://images.magnetmail.net/images/clients/AATB/attach/Bulletin_Links/18_2/AATB_Accreditation_Policies_February_08_2018.pdf (last update 2018 Feb)
TBI/Tissue Banks International National Processing Center (an AATB-accredited tissue bank)
US Human Tissue Bank Lic States: California, Florida, Maryland, and New York

proteins, and inductive growth factors (Gupta et al. 2015). Even after processing, DBM possesses osteoconductivity and osteoinductivity, but as a putty-/paste-like substance, it lacks structural integrity (Gupta et al. 2015). Since DBM base powder is derived from human bone allograft, disease transmission related with implantation is low, yet possible, although still less than structural-type allografts (bacterial infection estimated at 0.7 for non-massive to 11.7% for massive bone) (Zamborsky et al. 2016; Kwong et al. 2005; Lord et al. 1988).

Due to lack of structural integrity and relatively low osteoinduction potential comparing to autograft, DBM mixed with a carrier (DBM-based product, DBMs) is frequently used as a bone graft extender/carrier in interbody fusion. Commonly, DBMs are mixed with morselized autografts and exogenous peptide/differentiation factors along with collagen matrix, bone marrow aspirate, and/or isolated native blood-derived growth factors to stimulate new bone growth. In previous clinical reports on spine surgery, DBMs with autograft, and DBMs with growth factors (bone marrow aspiration), DBMs mixed with peptides (rhBMP-2/ACS) may be substituted for ICBG (Kang et al. 2012; Morris et al. 2018). DBM-based products or DBM powder are rarely used as a stand-alone graft material (Kinney et al. 2010).

There are several limitations to overcome in the clinical use of DBM-based products. The clinical effectiveness of DBM-based products is known to be variable according to manufacturer, form of product, as well as different lot-based batches from the same product form and manufacturer (Bae et al. 2006, 2010). The possible features of DBM-based products that contribute to varied reliability are varying native BMPs, growth/differentiation factors (donor bone), and dosages (Bae et al. 2006, 2010); forms such as putty, gel, flexible sheets, or mixed with cortical chips; compositions of carriers, scaffolds, gels, and other fillers; particle sizes of final bone powder; quality of the donor bone; and manufacturers processing procedures and sterilization method of products (Peterson et al. 2004; Bae et al. 2006, 2010). Amid these limitations, DBM-based products provide a diverse range of DBM-based grafting options that have been commonly employed for specific applications. DBM-based products introduced to the market over the last two decades and currently used are presented in Table 4.

Exogenous Inductive Differentiation Growth Factors and Other Peptides (Table 5)

Bone Morphogenetic Protein

Bone morphogenetic proteins (BMPs) are soluble members of the transforming growth factor-β superfamily that are involved in the differentiation, maturation, and proliferation of mesenchymal stem cells (MSCs) into osteogenic cells (Miyazono et al. 2005). To describe the acting mechanism, BMPs act via serine-threonine kinase receptors found on the surface of target cells and often transduce their signal via the SMAD pathway, leading to nuclear translocation and subsequent expression of target genes involved in osteogenesis (Hoffmann and Gross 2001; Sykaras and Opperman 2003). The reaction mechanism of BMP is mainly osteoinduction and reactively much less osteogenic potential (Campana et al. 2014). The graft material includes rhBMP-2 (exogenous protein) along with absorbable collage sponge (ACS, rhBMP-2 carrier). The carrier (ACS) has BMP binding competence in order to decrease diffusion away from the desired site for bone formation and increase controlled continual delivery of protein at the site. Although numerous carriers such as metals, collagen, ceramic such as tricalcium phosphate (TCP) and HCO, bioactive glass (BG), and polymers have been described (Agrawal and Sinha 2017), the most commercially available scaffold is an absorbable type 1 collagen sponge (ACS) bovine derived (Kannan et al. 2015).

For several decades, over 20 BMPs have been identified and described. Among them, BMP-1, BMP-2 (BMP-2A), BMP-3 (osteogenin, less osteoinductive) BMP-4 (BMP-2B), BMP-5, BMP-6, BMP-7, and osteoinductive factor (OIF) have been shown to induce bone formation

Table 5 Commercially available bone inductive peptides, proteins-based products, recombinant versions

Company	Peptide, growth factor product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/US approval/PMA, FDA 510 (k)
CeraPedics Inc.	P-15L Bone Graft	Bone graft putty	ABM, lecithin carrier (resorbable, biocompatible, semi-viscous lipid) P-15 synthetic peptide, calcium phosphate particles, porcine derived ABM anorganic bone matrix, along with bovine collagen carrier, P-15L	Ongoing clinical trials NCT03438747 (P-15L Bone Graft in an instrumented TLIF)	PMA
	i-FACTOR Bone Graft 'i-FACTOR™ Peptide Enhanced Bone Graft P-15 Putty, or iFACTOR Putty'	Synthetic small peptide (P-15) and peptide bone matrix (PBM) used in an allograft bone ring and with supplemental anterior plate fixation C3–C4 to C6–C7 following single-level discectomy for intractable radiculopathy (arm pain and/or a neurological deficit), with or without neck pain, or myelopathy due to a single-level abnormality localized to the disc space	A composite bone substitute consisting of a synthetic collagen fragment (P-15) bound to calcium phosphate particles As an engineered product, P-15 quantity and viability remain consistent from lot to lot P-15 in anorganic bone mineral (ABM). This unique combination replicates the organic (type I human collagen) and inorganic (calcium phosphate) components of autograft bone	Arnold et al. 2016b, 2018 NCT00310440 (P-15 synthetic osteoconductive bone substitute, ACDF) NCT01618435 (i-FACTOR Bone Graft in non-instrumented Posterolateral Spondylodesis in Elderly with LSS) NCT02895555 (5-10 CC i-FACTOR putty mixed with local harvested autograft, fusion lumbar spinal stenosis)	PMA cleared P140019, 2015 Nov www.accessdata.fda.gov/cdrh_docs/pdf14/p140019a.pdf

(continued)

Table 5 (continued)

Company	Peptide, growth factor product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/US approval/PMA, FDA 510 (k)
Medtronic Sofamor Danek, Inc., USA (Medtronic BioPharma B.V., Netherlands)	INFUSE™ Bone Graft/LT-CAGE™	Recombinant human bone morphogenetic protein and a carrier/scaffold inserted into a hard LT-CAGE™	rhBMP-2 (derived from a recombinant Chinese Hamster Ovary (CHO) cell line) Bovine absorbable collagen I scaffold (ACS) (filler) Ti metal prosthesis (Ti-6Al-4V)	NCT01491386 NCT01491425	FDA approved, regulated under PMA P000058, 2002 Jul www.accessdata.fda.gov/cdrh_docs/pdf/p000058b.pdf
			rhBMP-2/ACS/INTERFIX™	NCT01491451	
	INFUSE® Bone Graft	LT-CAGE® Lumbar Tapered Fusion Device and INFUSE® Bone Graft	rhBMP-2, collagen scaffold (ACS) (filler) Ti metal prosthesis (Ti-6Al-4V)	NCT00635843 Litrico et al. 2018	
	INFUSE® Bone Graft	INFUSE® Bone Graft	INFUSE® Bone Graft consists of two components – recombinant human bone morphogenetic protein-2 (rhBMP-2, known as dibotermin alfa) 1.5 mg/mL of rhBMP-2; 5.0 mg sucrose, NF; 25 mg glycine, USP; 3. 7 mg L-glutamic acid, FCC; 0.1 mg sodium chloride, USP; 0.1 mg polysorbate 80, NF; and 1.0 mL of sterile water. Reconstituted rhBMP-2 solution has a pH of 4.5 and is clear, colorless, and essentially free from plainly visible particulate matter Placed on an absorbable collagen sponge (ACS): bovine type I collagen obtained from the deep flexor (Achilles) tendon	ClinicalTrials.gov listings	FDA approved, regulated under PMA P000053, 2007 Mar www.accessdata.fda.gov/cdrh_docs/pdf5/p050053b.pdf

	INFUSE/ MASTERGRAFT™	AMPLIFY™	Posterolateral Revision Device The INFUSE/ MASTERGRAFTTM Posterolateral Revision Device is indicated for the repair of symptomatic, posterolateral lumbar spine pseudarthrosis. This device is intended to address a small subset of patients for whom autologous bone and/or bone marrow harvest is not feasible or is not expected to promote fusion. These patients are diabetics and smokers. This device is indicated to treat two or more levels of the lumbar spine Orthopedics Adult Oct. 10, 2008	NCT01491542 https://www.accessdata.fda.gov/cdrh_docs/pdf4/h040004c.pdf	INFUSE/ MASTERGRAFTTM This device has been withdrawn at the request of the sponsor effective Mar 2010
	INFUSE® Bone Graft	Polyetheretherketone (PEEK) in oblique lateral interbody fusion (OLIF)	OLIF 51 procedures with Divergence-L Interbody Fusion Device at a single level from L5–S1 OLIF 25 procedures with Pivox Oblique Lateral Spine System at a single level from L2–L5 ALIF procedures with Divergence-L at a single level from L2–S1	NCT01415908, NCT04073563	PMA supplement approval, 2015 Dec

(continued)

Table 5 (continued)

Company	Peptide, growth factor product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study ClinicalTrials.gov identifier	Regulatory clearance/US approval/PMA, FDA 510 (k)
	INFUSE® Bone Graft PEEK ACDF			NCT00485173, 2013 Arnold et al 2016a; Zadegan et al. 2017b IDE# G010188/ NCT00642876 and IDE# G000123/NCT00437190 (www.clinicaltrials.gov) Arnold et al. 2016a	Not cleared.
	InductOs® (Medtronic Spinal and Biologics)	Dibotermin alfa	Dibotermin alfa (recombinant human bone morphogenetic protein-2; rhBMP-2) is a human protein derived from a recombinant Chinese Hamster Ovary (CHO) cell line Bovine collagen I carrier	NCT02280187, InductOs® in Real World Spine Surgery; A Retrospective, French, Multi-centric, Study (InductOR)	Cleared in EU 1/02/226/ 002
Stryker 2004 (Olympus Biotech 2010–2014, then closed facility)	OP-1 Putty	OP-1 Putty	OP-1/rhBMP-7 produced delivered on a purified type I bovine collagen carrier and Carboxymethylcellulose	For revision posterolateral lumbar spinal fusion spinal fusion Vaccaro et al. 2008 PMID: 17588821 Guerado and Fuerstenberg 2011	Center for Devices and Radiological Health (CDRH) of the Food and Drug Administration (FDA) humanitarian device exemption (HDE) (check current 2018, not

					sold in the USA) OP-1 Implant is approved in 28 additional countries, including Australia, Canada, and the European Union OP-1 no longer marketed in the USA (note, 2019)
Stryker 2004 Pfizer (Wyeth is now a wholly owned subsidiary of Pfizer)	Op-1 Putty		OP-1(rhBMP-7) / purified Type I bovine collagen carrier and carboxymethylcellulose	Delawi et al. 2016 OP-1 group (54% versus 74% in the autograft group, $p = 0.03$)	FDA Advisory Committee: ("against expanded approval") Not recommended
		rhBMP-2/CPM rhBMP-2/CPM matrix	Recombinant human bone morphogenetic protein-2 (rhBMP-2)/calcium phosphate matrix (CPM)	NCT00752557 (bone mineral density) Closed fractures NCT00161629 (radius) NCT00384852 (humerus)	Not yet approved
BioAlpha Inc.	InjectBMP	ExcelOS-Inject ExcelOS 14-01	Injectable Ceramics Bone Graft (beta-TCP) containing rhBMP-2	NCT02714829	Not USA, Korea

Includes US FDA-tracked products (excludes products controlled exclusively under other regulatory agencies outside of USA)

(Wozney 1989, 2002). However, only two commercial forms of recombinant human BMPs currently are available for clinical use (Kannan et al. 2015). Recombinant human forms of BMP-2 (Infuse®; Medtronic) and BMP-7 (OP-1; Stryker) have been developed and approved both in the USA and Europe for commercial purposes by employing mammalian cells transfected with the corresponding human BMP sequence (Campana et al. 2014). Extensive research (over 30 years) has been conducted in support of the US-FDA approval process of rhBMP-2 and rhBMP-7; translational problems include scaling up, as super physiologic concentrations of rhBMP-2 are needed to meet MEDs in widely applicable orthopaedic indications in humans (Vallejo et al. 2002).

Internationally, in Korea, several products were developed employing various production processes for BMP-2 and different carriers. Its approved by Korea Food and Drug Administration (KFDA); to date its not approved by US-FDA. For spine fusion, the product carrier is granular HA and is based on *Escherichia coli*-derived rhBMP-2 (E.BMP-2, CGBio, Korea; E. BMP-2/HA, Novosis®, Korea) designed to improve the protein yield over the production process of using mammalian origin cell lines, such as Chinese hamster ovary (CHO) cells that incur low yield and high cost. There are several animal and clinical studies demonstrating the effectiveness and safety of Novosis® (Lee et al. 2012; Kong et al. 2014; Kim et al. 2015). According to the study of Cho et al. (2017), a fusion rate of 100% for E.BMP-2/HA (Novosis®) was comparable with that of 94.1% for AIBG demonstrating clinical efficacy and safety in PLF. E.BMP-2 production of rhBMP-2-based products and clinically used or in investigation are a rhBMP-2/Beta-TCP putty type (NCT01764906, Novosis® Korea), another Beta-TCP product containing rhBMP-2 (ExcelOS-inject, ExcelOS 14-01, NCT02714829, BioAlpha Inc., Korea), and a collagen gel +DBM containing rhBMP-2 (50 ug/cc) (rhBMP-2 produced from CHO cells, RafugenTM BMP-2, Cellumed Co Ltd., Seoul, Korea) employed as graft for interbody spinal fusion (pivotal RCT completed, 2017; submitted KFDA 2018, approved for dental application KFDA 2013).

US Regulatory approval by the FDA was initially granted for rhBMP-2/ACS (Infuse, Medtronic) in single-level anterior lumbar interbody fusion procedures in 2002 (Burkus et al. 2002). rhBMP-2 was then approved for tibia nonunion as an alternative to autograft in 2004 and for oral maxillofacial reconstructions in 2007 (Rengachary 2002). During last decade, rhBMP-2 has been commonly used off-label in posterolateral lumbar fusion surgery (Morris et al. 2018).

RhBMP-7, an osteogenic growth factor related to BMP-2, was first approved by the FDA in 2001 for use as an alternative to autograft for long bone fracture repair. In 2004, approval was expanded to cover PLLF (Morris et al. 2018). RhBMP-7 or OP-1 was approved for limited use under humanitarian device exemption (HDE) (no longer marketed in the USA (https://www.transparencymarketresearch.com/bone-morphogenetic-protein-market.html). In the last decade, several types of rhBMPs were developed and commoditized to medical market. RhBMP-based products were introduced to the market over the last two decades. Currently used products are presented in Table 5.

The osteogenic/osteoinductive potential of rhBMPs was strongly investigated in both preclinical and clinical studies, with a reported performance that is comparable to autogenous cancellous bone, with fusion rates between 80% and 99% (Campana et al. 2014). There are approximately 80 clinical studies on rhBMP-2 testing various surgical indications. According to a Level I comparison study of ICBG vs. rhBMP-2 with collagen sponge and ceramic granule by Dawson et al. (2009), at 24 months the rhBMP-2-/CS-/CM-treated patients had significantly higher solid fusion rates than those in the iliac crest autograft group (95% vs. 70%). Additionally, patients in the rhBMP-2/CS/CM group reported significantly greater improvement in clinical outcomes than did those in the iliac crest autograft group. According to the studies of Vaccaro et al. (2004, 2005), the use of rhBMP-7

(as OP-1 putty from) in conjunction with bovine collagen and carboxymethylcellulose (carrier) showed similar or slightly superior clinical result in spine fusion (posterolateral non-instrumented fusion) compared with autograft from the iliac crest.

However, limitations for general use of BMPs and complete substitution for autograft remain. First, rhBMPs have marked species-specific concentration requirements for osteogenesis, and thus results from preclinical studies are not considered as valuable background information for human application. Second, the dose-dependent efficacy in humans of rhBMPs has been observed in previous studies, and various clinical trials are aimed toward elucidating the optimal dosage of rhBMP-2/ACS (Govender et al. 2002). However, the optimal dosage/concentration for various off-label applications has rarely been reported or suggested in spine surgery. Third, during clinical trials, several major and minor adverse effects like ectopic bone formation in the neural canal, dysphagia when used in cervical fusion applications, prevertebral swelling, seroma/hematoma formation, radiculitis, osteolysis, heterotopic ossification, retrograde ejaculation, increased rates of new malignancy, and implant subsidence due to end-plate osteolysis are reported (Shields et al. 2006; James et al. 2016). Because of these limitations, numerous ongoing areas of investigation target alterations in dosage for optimal minimal dosage, scaffold to maintain concentration, and the implementation of supplemental proteins or growth factors to regulate the nonspecific action of rhBMP-2 (Agrawal and Sinha 2017; Burke and Dhall 2017; Poorman et al. 2017). Outside the USA, alternative-type protein products are in development (BoneAlbumin™, plasma protein) used to enhance bone allograft (Gmbh, OrthoSera, Austria).

Peptide-Based Materials

Although naturally derived extracellular matrix (ECM) has demonstrated some degree of success in selected studies, it is challenging to modify, characterize, and control the presentation of natural ECM biomaterials (Shekaran and Garcia 2011). The limitations of ECM molecules have spurred the use of ECM-derived peptides or recombinant fragments that incorporate the minimal functional sequence of their parent protein to convey bioactivity to implant materials.

Cerapedics

P-15 is a synthetic 15-amino acid peptide derived from the (766)GTPGPQGIAGQRGVV(780) sequence found in the α1(I) chain of type I collagen. Several preclinical studies have demonstrated that P-15 enhances cell adhesion, osteoblastic gene expression, and mineralization when implanted on anorganic bone matrix (ABM) in vitro and accelerates early bone formation in porcine and rat cranial defects (Shekaran and Garcia 2011). In a head-to-head comparison of DGEA peptide and P-15-coated hydroxyapatite discs implanted into rat tibiae, both peptides improved new bone formation, but P-15 failed to enhance bone implant contact. A recent study in the larger bovine model, ABM/P-15 (ABM an allograft in this application), failed at 4.5 months after uninstrumented posterior lumbar spine surgery; 68% fusion in allograft implanted sheep vs. 0% fusion as determined by bridging between transverse processes was found in ABM/P-15 implanted sheep (Axelsen 2019).

For human applications of a xenograft carrier (a sinterized cancellous bovine bone matrix), the implemented carrier has been employed. P-15 peptide-coated ABM has been used in human periodontal osseous defects resulting in better clinical outcomes than open flap debridement alone and has also been used in a pilot clinical study for long-bone defects (Shekaran and Garcia 2011). In a prospective, randomized, single-blinded trial of single-level ACDF using P-15/CBM in an allograft spacer versus local autograft in an allograft spacer, 89.0% vs. 85.8% fusion rates were reported, respectively, at 1-year follow-up with equivalent clinical outcomes and complications (Hsu et al. 2017).

B2A

B2A is a bioactive synthetic multi-domain peptide that augments osteogenic differentiation via increasing endogenous cellular BMP-2 by pre-osteoblast receptor modulation at spine fusion

site (Lin et al. 2012). The empirical formula of B2A is C241H418N66O65S2 containing 42 amino acids and 3 lysine analogue residues of 6-aminohexanoic (Glazebrook and Young 2016). This peptide has osteoinductive potential; it is used with a scaffold. The osteoconductive scaffold is a ceramic granule from which B2A elutes in vivo. Two commercialized products PREFIX® (Ferring Pharmaceuticals, Saint-Prex, Switzerland) and AMPLEX® (Ferring Pharmaceuticals, Saint-Prex, Switzerland) are based on this converged technology. After grafting of B2A with ceramic granules, complete absorption of B2A occurs within approximately 6–8 weeks (Glazebrook and Young 2016).

There is great interest in the benefits of conjugation technology for modulating release kinetics in grafting materials. However, there are limited preclinical and clinical studies on the safety and effectiveness of B2A/ceramics. B2A/ceramic granule was tested in two animal studies (rabbit and sheep). B2A/ceramic significantly improved the fusion rate in PLLF and PLIF over simple autograft bone graft (Smucker et al. 2008; Cunningham et al. 2009). In a clinical study, higher fusion rates were observed in B2A-coated ceramic granule (formulated as PREFIX®)-grafted patients than in ICBG-grafted patients after an interbody fusion procedure (Sardar et al. 2015). Studies are limited; Clinicaltrials.gov indicates two registered multicenter studies with "unknown" status. Validating the safety and efficacy of this bone graft material necessitates high-quality clinical studies and/or multicenter studies enrolling large number of patients. To date, there is only one published pilot study (Sardar et al. 2015, Canada) with a small/insufficient sample size.

Synthetic Materials and Drafts (Table 6)

Synthetic graft materials are typically employed during fusion surgery as bone graft extenders and sometimes substitutes. Traditionally, these materials provide an osteoconductive scaffold with ideally no reactive inflammatory immunogenic response from host tissues. The known advantageous properties of synthetic materials like ceramics include osteoconductive, biodegradable, no risk of infection, no donor site morbidity, unlimited supply, relatively easy sterilization, easiness of molding sized and shape, and lack of immunogenicity and toxicity (Gupta et al. 2015; Kannan et al. 2015). More recently, the emerging novel synthetics involve new technological advances in material science and/or incorporate a menagerie of cross-product materials in order to address the molecular biologic demands for bone induction, consolidation or healing, and fusion mass incorporation. Design innovation may lead to a true potent autograft substitute.

For making an ideal bone graft extender or graft substitute, several characteristics should be considered. The development of products used for bone regeneration has followed the basic criteria of providing a biocompatible three-dimensional scaffold with controlled architecture capable of stimulating or supporting bone growth in the natural in vivo environment (O'Brien 2011). The ability of the material to be used in conjunction with other cellular and signal-based therapies (peptides, growth factors) is a key strategy in maximizing the efficacy and likely success of fusion. The primary characteristics of bone graft substitutes are shown in Table 6.

Calcium Phosphate Materials

Calcium phosphates are a common base for synthetic graft materials. This is primarily because 70– 90% of inorganic material in the body is a type of calcium phosphate. Calcium phosphate materials have been cleared in the USA for use as "bone void fillers" (FDA MQV, MBP) that can be used for spine fusion and orthopedic applications. The common types of calcium phosphate materials are beta tricalcium phosphate $Ca_3(PO_4)_2$ (TCP) and hydroxyapatite $Ca_{10}(PO_4)_6(OH)_2$ (HA).

TCP was one of the earliest synthesized forms of calcium phosphate materials that was used as an osteoconductive bone void filler. TCP in the form of granules or blocks is available as a three-dimensional structure with interconnected pores from 1 to 1,000 microns. However, TCP and all

Table 6 Commercially available synthetic bone void fillers, extenders, and substitutes products

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
Amend Surgical, Inc., FL, USA	0.5 cc NanoFUSE® (posterolateral fusion)	Putty-like, malleable	Amend Surgical, Inc., NanoFUSE® comprised synthetic calcium-phospho-silicate particulate material particles (45S5 bioactive glass) coated with gelatin derived from porcine skin. (there is a DBM version of this material)	n/a	510(k) cleared 21 CFR 888.3045 K161996, 2017 Feb
	45S5 bioactive glass (1–10 cc)	Particulate material	45 wt% SiO2, 24.5 wt% CaO, 24.5 wt% Na_2O, and 6.0 wt% P_2O_5 Synthetic binder		510(k) cleared K110368, 2017 Jan
Aspine USA, Oakland, CA	Osteo-G Bone Void Filler System	Pellets/paste	Bioabsorbable, calcium sulfate dihydrate (prefabricated or kit to form into various shape implants), radiopaque	n/a	FDA 510(k) cleared K031319, 2003 Jul
APATECH LTD, United Kingdom ➔ Merged into Baxter Healthcare	**ACTIFUSE** synthetic bone graft		Phase-pure silicon-substituted calcium phosphate Osteoconductive bone graft substitutes, comprising a single-phase calcium phosphate scaffold, either granules or granules delivered in a matrix of resorbable polymer	NCT01833962, no results posted	510(k) cleared K090850 {K040082, K071206, K080736, K082073, K081979, K082575}
	ACTIFUSE Shape	Flexible shape	Distinctive moldability and versatility allowing the unique contours of each defect to be addressed Silicon-substituted calcium phosphate	NCT02005081 Anterior cervical corpectomy (ACC), no results posted	FDA 510(k) cleared K082575, 2008 Nov

(continued)

Table 6 (continued)

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
	ACTIFUSE ABX		A sculptable synthetic bone graft substitute Silicon-substituted calcium phosphate	ClinicalTrials.gov Identifier: NCT01852747 (fusion rate for multilevel fusion in spine) ClinicalTrials.gov Identifier: NCT01013389 (RCT, interbody fusion, comparative study with infuse) ClinicalTrials.gov Identifier: NCT01018771 (RCT, PLF fusion, comparative study with infuse)	FDA 510(k) cleared K082575, 2008 Nov
	ACTIFUSE Microgranules	Granules	Synthetic bone graft substitute designed for smaller defects Silicon-substituted calcium phosphate	n/a	FDA 510(k) cleared K082575, 2008 Nov
	ACTIFUSE Granules	Granules	Synthetic bone graft substitute, designed for larger defects Silicon-substituted calcium phosphate	n/a	FDA 510(k) cleared K082575, 2008 Nov
	ACTIFUSE MIS System	Injectable type	A ready-to-use applicator and cartridge designed for controlled delivery during minimally invasive procedures It contains ACTIFUSE ABX	NCT02845141, revision ACL	FDA 510(k) cleared K082575, 2008 Nov
	ACTIFUSE E-Z-Prep Syringe	Putty Matrix	A preloaded syringe containing ACTIFUSE Microgranules	n/a	FDA 510(k) cleared K082575, 2008 Nov
	Inductigraft		MAUDE adverse event report Active bone graft substitute 45S5 bioactive glass (M-45 granules,	NCT01452022, Inductigraft in posterolateral fusion	Not registered in the USA

			MS-45 microspheres) and bovine type I collagen (hydration with saline or blood). For use in posterolateral fusion		
Berkeley Advanced Biomaterials, Berkeley, CA, USA, 1996	Cem-Ostetic®, Bi-Ostetic™, GenerOs™	Granule, block Injectable putty	Bone void fillers are based on nanocrystalline hydroxyapatite (HAP) and tricalcium phosphate (TCP)	Bi-Ostetic Bioactive Glass Foam	FDA 510(k) cleared K170917, 2017 Oct ISO 13485 certified and CGMP
Biomatlante, France	MBC PTM	Various shapes and sizes	Microporous and macroporous biphasic calcium phosphate ceramic consisting of 60% hydroxyapatite (HA) and 40% beta-Tricalcium Phosphate (β-TCP)	NCT00206791	K043005, 2015 May
BioAlpha Inc., Korea	Novomax	Intervertebral spacer	Bioactive glass-ceramic spacer	NCT03532945	unk
	Bongros®-HA		Hydroxyapatite ($Ca_{10}(PO_4)_6(OH)_2$) highly pure with trabecular structure, 3-dimensional interconnected pores		K090793, 2009 May
Biomet Osteobiologies ➔Merge into Zimmer-Biomet	Calcigen™-S	Paste granules	Calcium sulfate dihydrate, isothermic	n/a	FDA 510(k) cleared K013790, 2002 Jun
	BonePlast®	Powder	Calcium sulfate with or without HA/CC	n/a	FDA 510(k) cleared K070864, 2007 Jun
	BonePlast®Quick Set	Quick setting paste	Calcium sulfate (mixed setting solution, QS) (limited to be used in posterolateral fusion)	n/a	FDA 510(k) cleared K070864, 2007 Jun
Biomimetic Therapeutics, Inc., Franklin, TN	Augment Bone Graft		β-Tricalcium phosphate-containing matrices + recombinant human platelet-derived growth factor-BB	Solchaga 2012 (ovine) rhPDGF-BB solution (0.3 mg/mL) was mixed with the β-TCP (1:1, v:v), allowed to incubate at room temperature for 10–15 min and then transferred to a 3 mL syringe with the end removed	

(continued)

Table 6 (continued)

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
	Augment Injectable		β-Tricalcium phosphate-containing matrices + recombinant human platelet-derived growth factor-BB	Solchaga 2012 (ovine) rhPDGF-BB solution (0.3 mg/mL) was mixed with the β-TCP/collagen (3:1, v:w), allowed to incubate at room temperature for 5–15 min and then transferred to a 3 mL syringe with the end removed. The syringe was used to dispense 0.4 mL of Augment Injectable to the interior of the PEEK spacer	
Bioventus® Surgical	Signafuse™	Putty type	Microporous and macroporous biphasic calcium phosphate + bioactive glass Multidirectional interconnected porosity structure similar to that of human cancellous bone (20–30% microporous (pore size <10 μm) and 50–55% macroporous)	n/a in clinical study Comparative study in rabbit (Fredericks et al. 2016)	FDA 510(k) cleared K132071, 2014 Jan (permitted as Biostructures, LLC)
	INTERFACE	Powder type	45S5 bioactive glass Particle size of 200–420 microns is designed for a faster speed of bone fill	n/a	FDA 510(k) cleared K112857, 2011 Dec (permitted as Biostructures, LLC)
	OsteoMatrix™	Strip type	60% hydroxyapatite (HA) + 40% beta-tricalcium phosphate (β-TCP) + type 1 collagen A synthetic two-phase calcium phosphate embedded in a cross-linked collagen carrier	n/a	FDA 510(k) cleared K051774, 2006 Jan (as a product name of MBCP™)

	Osteo Plus™	Granules in delivery syringe	Biphasic calcium phosphate (BCP): 60% hydroxyapatite (HA) + 40% beta-tricalcium phosphate (β-TCP) Synthetic two-phase calcium phosphate granules with interconnected macro and 3D micropores	n/a	FDA 510(k) cleared K051774 (01.20.2006) (as a product name of MBCP™)
Bone Bank Allografts, Texas, USA	Confirm™ Bioactive: Confirm™ Gel: Confirm™ Crunch	Gel and crunch type	Gel type Composition: Bioglass + hyaluronic acid + glycerol Sterile-packed in a syringe Available in three sizes: 2, 5, and 10 cc Uniform Bioglass particle sizes Crunch type Composition: Bioglass + hyaluronic acid + glycerol Sterile-packed in a syringe Available in three sizes: 2, 5, and 10 cc Mixture of Bioglass particle sizes	n/a	FDA 510(k) cleared K133678, 2014 Aug
BonAlive Biomaterials, Biolinja 12, 20750 Turku, Finland	BonAlive®	Granule and putty type Various sizes	S53P4 bioactive glass (53% SiO2, 23% Na2 O, 20% CaO, 4% P2 O)	Long bone defect treatment, Aurégan and Bégué 2015 Osteomyelitis treatment, Malat et al. 2018	BonAlive® products are not sold in the USA. (05.22.2018)
BONESUPPORT AB, Scheelevägen 19, SE-223 70, Lund, Sweden	CERAMENT® BONE VOID FILLER	Injectable type	Combination of two natural materials – hydroxyapatite and calcium sulfate – with a radiopacity enhancing agent 40% hydroxyapatite +60% calcium sulfate + iohexol (as a radio-opacity enhancer)	Ongoing RCT NCT01828905 (active status) BONESUPPORT AB: NCT02820363 Other Study ID Numbers: CLIN001 – FORTIFY US Food and Drug Administration (FDA) ongoing Investigational Device Exemption (IDE) study of its product	FDA 510(k) cleared K073316, 2008 Jun

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Table 6 (continued)

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
CAM Bioceramics BV/CAM implants BV (University of Leiden)/ 1993 Osteotech Inc.	Camceram TCP	Granules (1–4 mm) or block	Beta-tricalcium phosphate with 90% porous (Available specialty compound form; β –TCP, Milled β-TCP, α –TCP Cement Powder)	n/a	FDA 510(k) cleared K050357, 2005 Apr
DePuy Synthes, West Chester, Pennsylvania	HEALOS® Bone Graft Substitute	Putty type	Type 1 collagen + HA scaffold	Yousef MAA, 2017 (MSCs) Villa et al. 2015 Kunakornsawat et al. 2013 Ploumis et al. 2010 Carter et al. 2009 Birch and D'Souza 2009 (Implant Removal) Magit et al. 2006 (w/rhBMP2) Neen et al. 2006 Kraiwattanapong et al. 2005 Jahng et al. 2004 Furstenberg et al. 2010	HEALOS® Bone Graft Substitute (K012751, 2001 Nov and K043308, 2005 Feb)
	HEALOS Fx Injectable Bone Graft Replacement	Injectable type	Type I bovine collagen + hydroxyapatite HEALOS Fx is approximately 20–30% mineral by weight	*Same material of HEALOS® Bone Graft Substitute*	HEALOS® Fx Bone Graft Substitute (K062495) Mixing Device K081758, 2008 Sep
	Conduit	Putty type	Pure β-tricalcium phosphate (β-TCP) + a non-animal-derived sodium hyaluronate	ClinicalTrials.gov Identifier: NCT02056834 (tibia plateau fracture) (observatory case series study) ClinicalTrials.gov Identifier: NCT01615328 (cervical spine fusion)	510(k) cleared K041350, 2004 Jul

	Synthes chronOS™ chronOS™ inject	Granules, blocks, wedges, and cylinders	β-Tricalcium phosphate (β-TCP)	NCT02803177 (vs. cells) NCT02056834 (chronOS Inject, fractures) NCT00943384 (strip +BMA+ local bone) (posterolateral fusion) NCT00841152 (b-TCP vs. bioactive glass) filling defects (tumor)	FDA 510(k) cleared K0430453, 2005 Jan
	CONDUIT® TCP	Granules type	100% β-TCP TCP Granules obtained after high-temperature ceramicization of tribasic calcium phosphate. Interconnected pores 70% of volume (1 and 600 μm)	n/a (MAUD report)	FDA 510(k) cleared K014053, 2002 Mar
ETEX (Zimmer Biomet 2014 October)	CaP Plus	CaP Plus	Synthetic calcium phosphate, an inert carrier, carboxymethyl cellulose (CMC), and DBM	n/a	510(k) cleared K063050, 2007 Nov K080329, 2008 Apr
Globus Medical, Inc.	MicroFuse® Putty and MicroFuse® ST MIS		Resorbable calcium salt bone void filler	Is a bone graft extender	K102392, 2010 Dec MicroFuse® Bone Void Filler (K071187, K082442)
	MicroFuse™ Bone Void Filler MicroFuse™ granules MicroFuse™ blocks	Granules, sheets, and pre-formed blocks	Porous bone graft scaffold composed of bonded poly(lactide-co-glycolide) or poly(lactic acid) microspheres with and without barium sulfate and calcium sulfate form of granules, sheets, and pre-formed blocks. MicroFuse™ implants are available in short-term (ST), mid-term (MT), or long-term (LT) compositions	n/a	K083232, 2008 Dec
Isto Biologics, USA	InQu®	Past Mix, Matrix Granules	Synthetic PLGA (poly(lactide-co-glycolide)) with HyA (hyaluronic acid)	NCT01746212 Bone graft extender	K063359, 2007 Apr
Inion Oy, Lääkärinkatu 2, FIN-33520 Tampere, Finland	Bioactive glass (S53P4)	Variable shape: cylinders, blocks, and morsels	Different size degradable bioactive glass (S53P4)	NCT01304121, no results posted	K070998, 2007 Oct

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Table 6 (continued)

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
Medtronic Spinal and Biologics	MASTERGRAFT®	Granule form Putty type (combined with a type I collagen) Strip type	Biphasic, resorbable ceramics composed of hydroxyapatite (HA) and β-TCP	ClinicalTrials.gov Identifier: NCT01491542 (PLF as Pilot study) ClinicalTrials.gov Identifier: NCT00549913 (PLF, clinical study to evaluate the feasibility, safety, and tolerability of 3 different doses of immunoselected, culture-expanded, nucleated, allogeneic MPCs (NeoFuse))	FDA 510(k) cleared, K081784, 2008 Sep: putty form FDA 510(k) cleared, K082166, 2008 Sep: strip form
Molecular Matrix	Osteo-P bone graft substitute		Osteo-P is a non-mineralized, synthetic bone void filler made of a hyper-crosslinked carbohydrate polymer. It is highly porous, biocompatible, and biodegradable	n/a	510(k) cleared K170165, 2017 Dec
NovaBone Jacksonville, FL, USA ➔ Osteogenics Biomedical	NovaBone Putty – Bioactive Synthetic Bone Graft	Soft malleable putty	Bimodal particle distribution of calcium-phospho-silicate (CPS, Bioglass) + polyethylene glycol (PEG) as additive + glycerin as binder Volume of active ingredient is 70%	n/a	510(k) cleared K082672, 2008 Dec CE approval
	NovaBone-AR	Packable graft	Synthetic calcium-phospho-silicate (Bioglass) particulate, fused into a bulk porous form having a multidirectional interconnected porosity	n/a	510(k) cleared K041613

	NovaBone IRM™	Flexible sheets, varying sizes	IRM (irrigation resistant matrix) Bioactive calcium-phospho-silicate particulate and a synthetic, absorbable binder	Retrospective comparative study	510(k) cleared KO4 16 13, 2005 Dec November 19, 2016 (21 CFR 888.3045)
	NovaBone Bioactive Strip	Strip type	Purified fibrillar collagen and resorbable bioactive synthetic granules (Bioglass)	n/a	K141207, 2014 May
	NovaBone MacroFORM	Moldable type	Open porous structure to facilitate the absorption of bone marrow aspirate Purified collagen and resorbable bioactive synthetic granules (Bioglass)	n/a	510(k) cleared K0140946, 2014 Aug
	NovaBone porous	Powder	Synthetic calcium-phospho-silicate (Bioglass)	n/a	510(k) cleared K090731, 2009 Apr
ORTHOReBIRTH Co., Ltd.	ReBOSSIS	Cottony type: glass wool-like physical form	A synthetic, resorbable bone void filler 40% beta-tricalcium phosphate (β-TCP), 30% siloxane-containing vaterite (a form of calcium carbonate, CaCO3), and 30% poly(L-lactide-co-glycolide) The electrospinning process used in manufacturing ReBOSSIS results in a cotton like form, which had a merit like easier-to-handle, good elasticity and resilient capability	n/a	K142090 ReBOSSIS ORTHOReBIRTH CO., LTD. 2014 Oct K172573/K170620 ReBOSSIS85, 2017 Dec Primary Predicate K140375 scaffold is type I bovine collagen scaffold
Orthovita Inc. ➔ Merged into Stryker	Vitoss	Various types (original, foam pack, foam strip, Morsel, and block)	Highly porous beta-tricalcium phosphate (>90% porous) + type I bovine collagen (may be combined with saline, autogenous blood, and/or bone marrow)	ClinicalTrials.gov Identifier: NCT00147823: RCT (comparative study)	510(k) cleared STRIP and PACK – K081439, 2008 Nov K032288 – Vitoss Scaffold Foam Bone Graft Material
	Vitoss BA (Bioactive Bone Graft Substitute)	Various types (original, foam pack, foam strip)	Highly porous β-TCP + bioactive glass	n/a	510(k) cleared K083033, 2008 Nov
	Vitoss® Bone Graft Substitute-Bioactive Foam Strip	Strip type	Highly porous β-TCP + bioactive glass	n/a	510(k) cleared K072184, 2007 Sept

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Table 6 (continued)

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
	Vitoss BBTrauma	Putty type (foam pack)	Highly porous β-TCP + bioactive glass A broader range of bioactive glass particle size distribution and has a unique porosity, structure, and chemistry to help drive 3D regeneration of bone	n/a	510(k) cleared
	Vitoss BA2X (Bioactive Bone Graft Substitute)	Putty type (foam pack)	Highly porous β-TCP + bioactive glass Increased levels of bioactive glass compared to Vitoss BA and has a unique porosity, structure, and chemistry to help drive 3D regeneration of bone	n/a	510(k) cleared K103173, 2011 Feb; K16321, (2017 Mar (BA Injectable)
	HydroSet HydroSet XT	Injectable type	Tetracalcium phosphate that is formulated to convert to hydroxyapatite, the principal mineral component of bone HydroSet XT is simple and easy form of HydroSet	n/a	510(k) cleared K161447, 2016 Oct
Pioneer Surgical Technology, MI USA ➔ Merged into RTI Surgical	Pioneer FortrOss Bone Void Filler	Putty type	Porous calcium phosphate material mixed with a porcine gelatin carrier	n/a	510(k) cleared K091031, 2009 Nov
	Pioneer E-Matrix Bone Void Filler	Granular gelatin-based	Porous calcium phosphate material mixed with a porcine gelatin carrier	n/a	510(k) cleared K083449, 2009 Jun
Progentix Orthobiology BV, The Netherlands	CuriOS™		Micro-structured calcium phosphate resorbable bone void filler for the repair of bony		K090641, 2009 Oct

			defects. The product comprises a beta-tricalcium phosphate and hydroxyapatite		
Progentix Orthobiology BV, The Netherlands/ NuVasive	AttraX Putty	AttraX Putty cylinders, strips, and blocks	AttraX Putty is a synthetic ceramic granule premixed with a polymeric binder that provides cohesion between the granules Beta-tricalcium phosphate (β-TCP > 90%) and hydroxyapatite (HA <10%) The granule size range: 500–1000 μm The premixed binder is alkylene oxide copolymer (AOC)	NCT02250248, XLIF, Brazil RCT NCT01982045, Netherlands Sponsors: UMC Utrecht NuVasive	K151584, 2015 Jun
Prosidyan Inc., USA	FIBERGRAFT® BG	Morsels	FIBERGRAFT® BG Morsels is an ultraporous synthetic bone graft substitute made entirely from crystalline 45S5 bioactive glass	(Fortier et al. 2017)	Class II (Special Controls) K151154, K141956, K132805, 2017 May (posterolateral fusion)
	FIBERGRAFT® BG Putty Bone Graft Substitute	Putty	FIBERGRAFT™ 45S5 bioactive glass (M-45 granules, MS-45 microspheres) and bovine type I collagen (hydration with saline or blood). For use in posterolateral fusion		K143533, K170306, K180080, 2018 Mar The technological characteristics of the FIBERGRAFT™ BG Putty are similar to FIBERGRAFT™ BG Morsels Bone Graft Substitute
Regeneration Technologies, Inc., FL, USA ➔ Merges with Tutogen to form RTI Biologics® (2008) ➔ Change to RTI Surgical	nanOss® Loaded Advanced Bone Graft Substitute	Prefilled mixing syringe	Nano-structured hydroxyapatite (HA) has extremely high surface area	NCT02586116, ongoing Cervical Spine Belgium Ahn and Webster 2009	K081558 – NanOss Bone Void Filler, 2008 Aug
	nanOss® 3D Advanced Bone Graft Substitute	Strip type	Nano-structured hydroxyapatite granules suspended in a porous gelatin-based foam matrix	ClinicalTrials.gov Identifier: NCT01829997: case series study (active status)	510(k) cleared K132050, 2013 Jun
	nanOss® Advanced Bone Graft Substitute	Putty type	Nano-structured hydroxyapatite granules and an open structured engineered collagen carrier	ClinicalTrials.gov Identifier: NCT01968993: A Prospective, Nonrandomized Study (PLF)	510(k) cleared K141600, 2014 Oct
Science for Biomaterials, France	BIOSORB RESORBABLE BONE VOID FILLER	Variable shape	Resorbable calcium salt bone void filler 9 shapes: stick, granule, cube, block (6 shapes)	n/a	K130953, 2013 Jul K(021963 and K(071155)

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Table 6 (continued)

Company	Synthetic product	Formulation	Product composition	Peer-reviewed clinical evidence ClinicalTrials.gov/ongoing study	Regulatory clearance/approval FDA 510(k), CFR 1270, CFR 1271 MQV, filler, bone void, calcium compound common name – bone grafting material classification name – bone grafting material, synthetic
SeaSpine, Carlsbad, CA	Accell Connexus®			NCT01873586 1: Schizas et al. 2008	
SeaSpine, Carlsbad, CA	OsteoStrux® Putty		Moldable, osteoconductive scaffold composed of purified collagen and β-TCP 20% type I bovine collagen and 80% highly purified β-TCP The matrix was developed to resemble the composition and pore structure of natural human bone	NCT01873586: Case series study; results are not posted.	K073316 2008 Jun
	OsteoStrux® Strip		Strip is a compression-resistant, osteoconductive scaffold composed of purified collagen and β-TCP	NCT01873586	K073316 2008 Jun
Synergy Biomedical, LLC	BioSphere® Putty	Putty type	80% bioactive glass spheres; 20% phospholipid carrier	n/a	K122868, 2013 Apr
	BioSphere MIS Putty (BioSphere MIS)	Prefilled type	Medical-grade 45S5 bioactive glass particles + carrier (same composition of BioSphere® Putty)	n/a	K173301, 2018 Jan
THERICS, LLC	TheriGraft™ TCP Putty Bone Void Filler	Putty type	Synthetic f3-tricalcium phosphate granules (0.1–0.4 mm diameter) in a poloxamer based carrier Approximately 0.1–0.4 mm granules	n/a	510(k) cleared K053228, 2006 Jan

Vivoxid Ltd.: Turku, Finland	Bioactive Glass (S53P4) as granules (BonAlive™)	Granules Plates	By weight, SiO_2 53%, Na_2O 23%, CaO 20%, and P_2O_5 4% (synthetic, osteoconductive, and bacterial growth-inhibiting material)	***NCT00935870*** Sponsor Turku, Finland NCT00841152 Bonalive (Vivoxid Ltd., Turku, Finland)	K071937 2007 Oct
Wright Medical Technology	OSTEOSET®	Pellet type ➔ Moldable in operation room	Engineered calcium sulfate hemihydrate	n/a	K053642, 2006 Jan
	PRO-DENSE™	Injectable type (4, 10, 15, 20 cc)	75% calcium sulfate and 25% tricalcium phosphate	n/a	K113871, 2013 Mar
Zimmer Biomet/ BONESUPPORT AB, Sweden	CERAMENT™	Injectable type	Biphasic ceramic bone substitute: 60% synthetic calcium sulfate (CaS) (calcium sulfate hemihydrate and sintered hydroxyapatite) + 40% hydroxyapatite (HA) pellet + radio-contrast agent iohexol (180 mg/ml)	NCT01828905 ongoing trial	K073316, 2008 Jun
	Pro Osteon® 200R	Powder type	Hydroxyapatite and calcium carbonate diameter of 190–230 microns Calcium carbonate matrix covered by a very thin outer layer of calcium phosphate, approximately 2–10 microns in thickness. The calcium phosphate is located on the outer surface of the porosity throughout the entire structure of the implant	Walsh et al. 2003: A resorbable porous ceramic composite bone graft substitute in a rabbit metaphyseal defect model. Journal of Orthopaedic Research, 2003	510(k) cleared K000515, 2000 Sep
Zimmer Biomet Spine, Inc. (Interpore Cross International, Irvine, CA)	Pro Osteon® 500R (Chapman and Madison 1993)	Powder type	Thin, 2–10 micron layer of hydroxyapatite over a calcium carbonate core Provides a natural scaffold for new bone growth when placed in contact with viable bone	NCT00858598 Thalgott et al. 2001 Harris et al. 1995	510(k) cleared K031336, 2002 Jul

Materials in this class are most always used with BMA, whole blood, serum, and physiological saline and/or also mixed with autograft
BMA, bone marrow aspirate. BMA is typically added at the time of surgery to these synthetic materials for grafting into the spinal fusion surgical bed/site
Whole blood or serum (patient's own) may be used
https://510k.directory/clearances/MQV/1. Accessed April–June 2018

calcium phosphate materials are brittle, as they do not possess the tensile properties of bone. Therefore, TCPs and calcium phosphates have been used in areas of relatively low tensile stress or non-load-bearing applications. Thus, the calcium phosphate-based materials are not recommended alone for use in load-bearing applications (Park et al. 2013). It is important to recognize that most osteoconductive products have been approved for use only in posterolateral spine fusion applications and not in interbody fusion applications. Since TCP has only osteoconductive effects, these TCP-type products may be used in conjunction with biologic osteoinductive or osteogenic supplements of autograft, BMPs, growth factors, mesenchymal stem cell (MSC) derivatives, etc. (see combined products, Table 7) (Gupta et al. 2015; Duarte et al. 2017).

The most widely recognized TCP product is Vitoss® Bone Graft Substitute (Stryker, Allendale, NJ). This material was first commercialized in 2004, and its application in different formats has established it as the preferred TCP material. Another TCP-based material that has been reported is the Augment® Bone Graft from Wright medical. Augment® Bone Graft combines recombinant human platelet-derived growth factor B homodimer (rhPDGF-BB) with a bio-resorbable synthetic bone matrix (β-TCP). This product has been developed for use in bone repair. It is reported that the use of this product eliminates the need for using autograft, proposed as a "substitute." However, Augment® Bone Graft is only indicated for use as an alternative to autograft in the ankle or hindfoot (Augment® bone graft – FDA. https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100006d.pdf). There are several TCP-based products combined with different carriers to provide improved handling characteristics (see combined products, Table 7).

HA is another calcium phosphate material of significance, since x-ray diffraction and chemical studies have demonstrated that the primary mineral phase in bone is HA. HA is a biomaterial for medical devices and is available in the form of nanocrystalline powders, porous granules, and dense blocks. It can be manufactured from natural coral, bovine cortical bone, or synthesized by chemical reactions. HA is stronger (less brit tle) than TCP providing high compression strength but is still somewhat brittle. Due to its brittle quality, HA use is limited in load-bearing applications (Zdeblick et al. 1994; Park et al. 2013). Unlike autograft, allograft, and TCP, the absorption rate of HA is very slow (with incomplete absorption/resorption), and HA remains at the site of implantation for years (Zadegan et al. 2017a). In most circumstances, this prolonged resorption may not be advantageous. Grafting materials are ideally completely resorbed and replaced by new bone eventually. If the material does not resorb, it can act as an obstacle or inhibit new bone formation. Historically, coralline HA has been used effectively as a bone graft extender in patients as an adjunct to autologous bone for PLLF (Morris et al. 2018). The critical amount of graft volume per area of functional level (spine) has not been reported. Yoo et al. suggest that an amount of at least 12 mL of bone graft is needed to achieve a satisfactory bone fusion in minimal invasive TLIF surgery regardless of mixture ratio of HA with autograft bone (Yoo et al. 2015). There are several HA-based products combined with different carriers to provide improved handling characteristics (Tables 6 and 7).

According to study of Nickoli MS et al., ceramic-based bone grafts (TCP) with an osteoinductive stimulus represent a promising bone graft extender in lumbar spine fusion (Nickoli and Hsu 2014). In a meta-analysis review of 1,332 patients in 30 studies, from 1980 to 2013, ceramics used in combination with local autograft resulted in significantly higher fusion rates compared with all other adjuncts and bone marrow aspirate and platelet concentrates (Nickoli and Hsu 2014). Previous clinical studies on HA-based bone graft such as HA when used alone, or in combination with BAG (bioactive glass), BMA (bone marrow aspirate), or rhBMP-2 have been shown to improve function to the and reduce preoperative pain same extent as ICBG, yet have been associated with suboptimal radiographic fusion rates in lumbar spine (Singh et al. 2006; Acharya et al. 2008; Ploumis et al. 2010).

Table 7 Commercially available combination grafting products, naturally occurring peptides, growth differentiating factors, cellularized grafts, cellular bone matrices (CBMs)

Company	Combination product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Advanced Biologics, Carlsbad, CA., 2009 (marketed OsteoAMP in the USA since 2009)	OsteoAMP	Granules or sponge	OsteoAMP, an allogeneic growth factor implant, exploits the angiogenic, mitogenic, and osteoinductive growth factors that are within marrow cells	Field et al. 2014 Cervical Spine-Fusion	Bioventus manages orders and sales of HCT/Ps (not a distributor, FDA)
Bioventus' Surgical, Durham, NC, USA (original developer)			Growth factor-rich naturally occurring growth factors including BMP-2, BMP-7, aFGF, and TGF-β1 bone graft substitute: intended for homologous use repair, replacement, or reconstruction of musculoskeletal defects	ClinicalTrials.gov Identifier: NCT02225444 Lumbar Spine-PLF Roh et al. 2013	Regulated under CFR 1270, 1271 as a human tissue, registration held by Tissue Bank Permit: Millstone Medical Outsourcing, LLC, Olive Branch, MS (Bone, Demineralized Bone Matrix, Ligament, Musculoskeletal Tissues, Tendon.) Maryland, New York State Tissue Bank Permit: Advanced Biologics, LLC (Bone Demineralized Bone Matrix)
AlloSource®, Centennial, Co, USA, 1995 Allosource.org	AlloStem Cellular Bone Autograft	Strips, blocks, cubes, morselized	Partially demineralized allograft bone combined with adipose-derived mesenchymal stem cells (MSC)	n/a	Regulated under CFR 1270, 1271 as a human tissue

(continued)

Table 7 (continued)

Company	Combination product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Aziyo Biologics, Inc. MD, Ga, CA	OsteoGro™	Cancellous Bone	Partially demineralized cortical bone	NCT03425682	Regulated under CFR 1270, 1271 as a human tissue
	VBone	Structural allografts Package Bone matrix	Preserve natural components of the matrix Viable bone matrix		
BBS-Bioactive Bone Substitutes Oyj (Finland)	ARTEBONE®		Tricalcium phosphate (TCP) + natural cocktail of bone proteins (growth factors)	ClinicalTrials.gov Identifier: NCT02480868: case series study for ankle fusion	FDA 510(k) ~2020
Bioventus® Surgical	OsteoAMP	Granule, putty, and sponge form	Cervical and lumbar spine fusion procedures Allograft with growth factors (such as BMP-2, BMP-7, TGF-β1, aFGF, VEGF, and ANG1, within bone marrow cells)	Active but no results posted: Posterolateral Lumbar Fusions (PLF) With OsteoAMP® (ClinicalTrials.gov Identifier: NCT02225444) Comparative study with rhBMP-2 with OsteoAMP (Roh et al. 2013)	AATB US FDA 21 CFR 1271 (HCT/P)
BONESUPPORT AB, Scheelevägen 19 SE-223 70, Lund, Sweden	CERAMENT® G	Injectable type	Injectable antibiotic-eluting bone graft substitute that provides local sustained bactericidal effect and scaffold for fusion CERAMENT (40% hydroxyapatite +60% calcium sulfate) + 17.5 mg gentamicin/mL paste	ClinicalTrials.gov Identifier: NCT02820363: Clinical Trial (RCT) for open tibial fracture (recruiting status) ClinicalTrials.gov Identifier: NCT02128256: Case series study (unknown status)	Combination product, HCT/P GS1, HIBCC, ICCBBA FDA-PMA approval underway (communication from BoneSupport 2020 Feb

	CERAMENT® V	Injectable type	Injectable antibiotic-eluting bone graft substitute that provides local sustained bactericidal effect and scaffold for fusion CERAMENT (40% hydroxyapatite +60% calcium sulfate) + iohexol (as a radio-opacity enhancer) + 66 mg vancomycin/mL paste	US-NCT03389646 trial of Cerament TM V, G for hip or knee prosthesis infection	CE Mark approval FDA-PMA approval underway (communication from BoneSupport 2020 Feb
DePuy Synthes	ViviGen Cellular Bone Matrix Vertigraft®	Cryo Cortical Cortical cancellous bone matrix and demineralized bone	ViviGen® Cellular Bone Matrix comprised cryopreserved viable cortical cancellous bone matrix and demineralized bone. ViviGen Cellular Bone Matrix is a human cells, tissues, and cellular and tissue-based product (HCT/P). ViviGen Cellular Bone Matrix is processed from donated human tissue, resulting from the generous gift of an individual or his/her family	NCT02814825 HCT/P (Divi and Mikhael 2017)	(HCT/P) as defined by the US Food and Drug Administration in 21 CFR 1271.3(d). 21CFR 1271
	CONFORM CUBE®	Cube shape	Demineralized cancellous bone, organic matrix (osteoinductive, promotes cellular ingrowth and vascularization) General bone void filler and use with lumens of allograft spinal spacers	n/a	(HCT/P) as defined by the US Food and Drug Administration in 21 CFR 1271.3(d). 21CFR 1271
	CONFORM SHEET®	Sheet shape	Demineralized cancellous bone, organic matrix (osteoinductive, promotes cellular ingrowth and vascularization) For PLF (posterolateral gutters of the spine)	n/a	(HCT/P) as defined by the US Food and Drug Administration in 21 CFR 1271.3(d). 21CFR 1271

(continued)

Table 7 (continued)

Company	Combination product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
Mesoblast Ltd., Australia	NeoFuse(TM)	Cells + Granules	Allogenic mesenchymal precursor cells (MPCs) combined w/ MasterGraft in PEEK cage	NCT00549913 (Lumbar PLF)	FDA 510(k) cleared, K153615 2016 Jun (HA Enhanced PLIF/TLIF)
Angioblast Systems Inc., USA	NeoFuse(TM)	Cells + Granules	Allogenic mesenchymal precursor cells (MPCs) combined w/ MasterGraft in anterior cervical discectomy and fusion (ACDF) Anterior cervical plate fixation	NCT01106417 (Cervical fusion)	FDA 510(k) cleared, K170318 2017 Jun
MTF Orthofix	Trinity Evolution TM	Moldable allograft fibers, varying sizes	Allogenic DBM, osteoprogenitor cells (OPC), MSC (minimum of 500,000 cells/cc; 100,000 of which are MSC and/or OPC)	NCT00951938 (Anterior cervical) Peppers et al. 2017 Vanichkachorn et al. 2016	Regulated under CFR 1270, 1271 as a human tissue
	Trinity Elite	Moldable allograft fibers, varying sizes	DBM, osteoprogenitor cells, MSC (minimum of 500,000 cells/cc; 100,000 of which are MSC and/or OPC) Trinity Elite and/or local bone	NCT02969616 (PLF, TLIF,ALIF, XLIF, etc., lumbar fusion) NCT00965380	Regulated under CRF 1270, 1271 as a human tissue

			with supplemental pedicle screw fixation allogeneic cancellous bone matrix containing viable osteoprogenitor cells, mesenchymal stem cells, and a demineralized cortical bone (DCB)		
NuVasive	Osteocel	Moldable bone matrix	DBM, OPC, MSC (<50,000 cells/cc, >70% viability)	Retrospective case series	Regulated under CFR 1270, 1271 as a human tissue
	Osteocel Plus	Moldable bone matrix	DBM, OPC, MSC (<50,000 cells/cc, >70% viability)	McAnany et al. 2016, Retrospective comparative study; NCT00948532 (Osteocel® Plus in extreme lateral interbody fusion (XLIF®): Kerr et al. 2011; Tohmeh et al. 2012 Extreme lateral interbody fusion (XLIF) Ammerman et al. 2013 Eastlack et al. 2014: (Osteocel Plus in a polyetheretherketone cage and anterior plating at 1 or 2 consecutive levels) Prospective case series Retrospective case series, clinical trial: ClinicalTrials.gov Identifier: Evaluation of Radiographic and Patient Outcomes Hollawell 2012	Regulated under CFR 1270, 1271 as a human tissue
Organogenesis 2017 Mar/NuTech Medical, Inc.	NuCel®	Putty type	Cryopreserved, bioactive amniotic suspension allograft Cellular, growth factor, and	ClinicalTrials.gov Identifier: NCT02023372: A Prospective, Efficacy Study (RCT) for PLF	unk

(continued)

Table 7 (continued)

Company	Combination product	Formulation	Product composition	Peer-reviewed clinical evidence/ongoing study	Regulatory clearance/approval FDA 510(k), FDA 361, 21 CFR Part 1271 CFR 1270, CFR 1271 21 CFR 3.2(e) HCT/P 361, Human allografts (No Clinical Studies) Biologic Drugs and Devices 351 (Clinical Trials)
			extracellular matrix components	NCT02070484: NuCel vs. DBM	
Osteotech's ➔ Merged into Medtronic	Plexur M(TM)	Moldable type (putty like)	Human allograft bone tissue + resorbable polymer Processed human bone particles that are mixed with resorbable/ biodegradable non-tissue components	MAUDE Adverse Event Report	FDA 510(k) cleared K073405 2008 Mar
RTI Surgical Inc. Allendale, NJ, USA	map3® Cellular Allogeneic Bone Graft	Putty type Strip type	Cortical cancellous bone chip (or strip shape bone) + DBM + cryogenically preserved, viable multipotent adult progenitor (MAPC®)-class cells	ClinicalTrials.gov Identifier: NCT02161016: case series study in foot and ankle. Results posted ClinicalTrials.gov Identifier: NCT02628210: A Prospective, Multi-Center, Non-Randomized Study for lumbar interbody fusion (active status)	Unk status (Regulated under 361 PHS Act 42 U.S.C. 264 and reg. 21CFR Part 1271.1O(s)(4)(ii) (b) + FDA Act {21 U.S. C. 321 (g)++)

Stryker	BIO (Hollawell 2012)	Putty type (1, 2.5, 5, 10 cc)	Allograft bone (cortical and cancellous) + periosteum A viable bone matrix containing endogenous bone forming cells (including mesenchymal stem cells, osteoprogenitor cells, and osteoblasts) as well as osteoinductive and angiogenic growth factors	ClinicalTrials.gov Identifier: NCT03077204: Clinical case series study (cervical spine), recruiting status	AATB US FDA regulations for tissue management. US FDA 21 CFR 1271
Vericel Corporation		Bone repair cells	Bone repair cells (BRCs) with allogeneic, demineralized bone matrix	NCT00797550 (posterolateral spinal fusion) terminated no results NCT00424567 repair pseudarthrosis atrophic nonunion	Biologics License Application (BLA) w/ post-marketing commitments (~2017 June), status unknown
Xtant	OsteoVive™	Putty type	A cell population that includes marrow-isolated adult multilineage-inducible (MIAMI) cells Blend of microparticulate cortical, cancellous, and demineralized cortical allograft bone (particle size range of 100–300 microns)	n/a	FDA 510(k) cleared Compliance with FDA guidelines regarding human cells, tissues, and cellular tissue-based products HCT/P 361 regulated viable allogeneic bone scaffold American Association of Tissue Banks guidelines

510(K) is a premarket submission made to FDA to demonstrate that the device to be marketed is at least as safe and effective, that is, substantially equivalent, to a legally marketed device that is not subject to premarket approval. 501(k) documentation for individual products is available via FDA online database (http://www.accessdata.fda.gov)
Code of Federal Regulations (CFR) 1270 (Human tissue intended for transplantation) and 1271 (Human cells, tissues, and tissue-based products) are federal regulations relating to the procurement and processing of human-derived tissues
Claims: grafting with component to provide the required osteoconduction, osteogenesis, and osteoinduction necessary for successful bone grafting
GS1: it is an international, not-for-profit association that creates and implements standards to bring efficiency and visibility to supply chains across industries
HIBCC Health Industry Business Communications Council
ICCBBA International Council for Commonality in Blood Banking Automation
PEEK, a polyetheretherketone material used for cage devices employed as instrumentation in anterior interbody spinal fusion procedures

Silicate-Substituted Calcium Phosphate

Silicate-substituted calcium phosphate (Si-CaP) constitutes a newer generation of ceramics produced by adding silicate which has been found to play role in bone metabolism to previously developed calcium phosphate ceramics (Gao et al. 2001). This combination provides superior biocompatibility and osteoconductivity. In addition combining Si-CaP with a graft provides negative surface charge that results in enhanced osteoblast activity and neovascularization of the bone which lead to more ideal spine fusion as a substitute of ICBG (Campion et al. 2011; Alimi et al. 2017).

Silicated hydroxyapatite has been prepared by the addition of a small amount of silicon (0.4% to 0.8% by wt.) into the structure of HA. The role of silicate-based materials in improving tissue implant interactions has been reported (Zhou et al. 2017). Silica-substituted HA, such as Actifuse™ from Baxter, is available in the form of granules, pastes, and blocks. The performance of these products has been investigated in preclinical models and clinical study. According to study of Jenis and Banco (2010), a silica-substituted hydroxyapatite (Actifuse™) with BMA has been shown to be effective as a graft substitute as ICBG with significant pain improvement in PLLF. According to study of Licina P et al. (Licina et al. 2015), silicate-substituted calcium phosphate (Actifuse™) and rhBMP-2 with ceramic granule were comparable in view of achieving PLLF.

Clinical data are limited for various types of lumbar surgery and the numbers of enrolled patients in trials. For confirming the efficacy and safety of Si-CaP and/or silicated hydroxyapatite as a bone-grafting substitute, further investigations using greater numbers of subjects will be necessary. And the radio-opaque nature of Si-CaP allows for intra- and post-operative localization, but this radio-dense characteristic immediately after surgery resembling bone and the long residence time exceeding a year has decreased the accurate assessment of the process of bone formation.

Bioactive Glass (Table 8)

Bioactive glass (BAG) is a class of glass-based graft substitute or extender products having a compositional range that allows the formation of nanocrystalline hydroxyapatite (ncHA) as a surface layer when exposed to an aqueous phosphate-containing solution, such as simulated body fluid. The ncHA layer that forms within an aqueous phosphate-containing solution plays a significant role in forming a strong bond with natural bone.

BAG has an established history of bone bonding that occurs as a result of a rapid sequence of reactions on its surface when implanted into living tissues (Hench and Jones 2015). There are two mechanisms of bioactivity for bioactive glass products. Bone bonding is attributed to the (1) formation of an HA layer, which interacts with collagen fibrils of damaged bone to form a bond (Hench and Jones 2015), while the action of the (2) dissolution products from the bioactive glass is reported to simulate osteogenesis (Hench and Polak 2002). When hydrated, a layer of silica gel forms on the surface of the bioactive glass. The adhesion of amorphous calcium, phosphate, and carbonate ions to the silica surface leads to an eventual crystallization of a bone-like HA as early as 24 hours. Bone-forming cells migrate and colonize the surface of the bioactive glass and promote the production of a new bone-like matrix (Beckham et al. 1971). Gao et al. (2001) observed increased expressed detectable mRNA levels of BMP-2 from Saos-2 osteoblastic cells when cultured on two types of BAG (BAG containing 6% Na_2O, 12% K_2O, 20% CaO, 4% P_2O_5, 5% MgO and *53% SiO_2* and biocompatible glass (BCG) containing 6% Na_2O, 12% K_2O, 15% CaO, 4% P_2O_5, 5% MgO and *58% SiO_2* (wt.%)) than on control inert glass (Gao et al. 2001).

The mechanism for the formation of the ncHA layer is now quite well understood and well characterized, but the biological interactions at the ncHA–host bone interface are still under intense investigation in view of potential employment with stem cells (Tsigkou et al. 2014).

In addition, the high pH and the subsequent osmotic effect caused by dissolution of the bioactive glass have been suggested as an antibacterial material quality (Stoor et al. 1998; Allan et al. 2001). Recently, Sanchez-Salcedo et al. (2017) introduce the design and synthesis of a new

Table 8 Composition and properties of bioactive glasses and glass-ceramics used clinically for ontological, musculoskeletal, and dental grafting applications (Baino et al. 2018; Hench and Jones 2015)

Product	Composition wt %									
	Na_2O	CaO	CaF_2	MgO	P_2O_5	SIO_2	B_2O_3	K_2O	CuO	ZnO
45S5 Bioglass Otology: MEP® a, Douek-MED™, Ceravital® a, Bioglass-EPI® a Dental graft: EMRI® a, Biogran®, PerioGlas®, NovaMin® Orthopedics: NovaBone®, GlassBone™, FIBERGRAFT®, BioSphere® Putty	24.5	24.5	0	0	6	45	0	0	0	0
S53P4 Dental graft: AdminDent1 Orthopedics: BonAlive®	23.0	20.0	0	0	4	53	0	0	0	0
A-W glass-ceramic Dental graft: Cerabone®	0	44.7	0.5	4.6	16.2	34	0	0	0	0
Strontium substituted bioactive glasses: StronBone®	4	17.8	0	7.5	4.5	44.5	0	0	0	0
13-93	6	20	0	5	4	53	0	0	0	0
Bioactive glass by the sol-gel process TheraGlass® a	0	30	0	0	0	70	0	0	0	0
Boron bioactive	6	20	0	5	4	0	51.6	12	0.4	1

[a]This product is not commercially available due to side effects, structural problems, lack of clinical effect, etc.

nano-structured zwitterionic mesoporous bioactive glasses (MBGs) with incorporation with amino acid for antibio-fouling capability that inhibits bacterial adhesion (formation of biofilm) wherefrom they report successful results in vitro.

BAG has been used for a variety of clinical applications since it was first created in 1969 (Hench and Jones 2015). There are many types of BAG (Table 6) and glass-based products used (Hench and Jones 2015) in periodontal repair and orthopaedic applications (Table 8).

The originally developed composition was bioactive glass 45S5 (Food and Drug Administration (FDA) approved in 1993 (Jones 2015). 45S5 bioactive glass consists of 45 wt.% SiO_2, 24.5 wt.% CaO, 24.5 wt.% Na_2O, and 6.0 wt.% P_2O_5 which demonstrated effective biological properties. NovaBone®, a product based on this 45S5 technology, has been approved as a bone graft substitute in 1999 (Jones 2013; Hench and Jones 2015). The NovaBone® material is considered an early generation of bioactive glass. This is due to the lack of inherent porosity of the NovaBone® granules or granules in which porosity has been manufactured by the fusion of smaller granules. NovaBone® was compared to autograft in posterior spinal fusion procedures for treatment of adolescent idiopathic scoliosis in 88 patients (Ilharreborde et al. 2008). NovaBone® showed improved clinical results in terms of reduced infection, donor site complication, and fewer mechanical failures in a 4-year follow-up. However, its clinical use for spine fusion applications has not been reported widely.

A commercially available bioactive glass product is BonAlive® (BonAlive Biomaterials, Turku, Finland), which was programmed in Finland based on S53P4 bioactive glass. BonAlive® received European approval for orthopedic use as a bone graft substitute in 2006 (Jones 2015). The S53P4 bioactive glass contains 53 wt.% SiO2, 23 wt.% Na_2O, 20 wt.% CaO, and 4 wt.% P_2O_5. According to Frantzen et al. (2011) a prospective long-term study (11 years) of Frantzen et al., the fusion rate of all fusion sites for BAG-S53P4 with autograft as a bone substitute was 88% at the L4/L5 level and 88% at the L5/S1

level compared to 100% for autograft in degenerative spondylolisthesis patients. Similar results were seen after surgical treatment of a spondylitis patient (Lindfors et al. 2010). BonAlive® was also compared to autograft in the same patients in PLF procedures for treatment of spine burst fractures. At the 10-year follow-up, 5 out of 10 implants had full fusion compared to all 10 autografts (Rantakokko et al. 2012).

Fibergraft® BG Morsels (Prosidyan Inc., USA) is a 100% BAG material (no additives) specifically FDA cleared for orthopedic and spine grafting applications. Traditional bioactive glass does not allow for ease of handling and has slow resorption due to low porosity. Fibergraft® BG Morsels is the first osteostimulative (or bioactive) material engineered to take advantage of the unique properties of bioactive glass. The morsels are engineered with overlapping and interlocking bioactive glass fibers with pores dispersed throughout. The material structure and ultra-porous, nano-, micro-, and macro-porosity provides direct connectivity for cell in-growth and material resorption, enabling new bone formation.

A 95% radiographic success rate was reported in a retrospective study of Fibergraft® BG Morsels use when mixed with local autograft and bone marrow aspirate in 63 patients at 1 year after 1-, 2-, and 3-level posterolateral fusions (Barcohana et al. 2017). Additionally, a high rate of 88.5% (46/52 levels with complete fusion) together with a 5.8% (3/52, levels partial fusion) in anterior cervical fusion was demonstrated after use of Fibergraft® BG Morsels mixed with BMA, bone dust, and or local bone in 27 patients (51 levels of fusion) at approximately 6 months after anterior cervical discectomy and fusion study (Fortier et al. 2017).

Fibergraft® BG Morsels (Prosidyan Inc., USA) is also provided in a putty form as Fibergraft® BG Putty and in a Matrix form as Fibergraft® BG Matrix. All Fibergraft® products are specifically FDA cleared for orthopedic and spine grafting applications. The BG Putty can be used for Minimally Invasive Surgery (MIS) applications, while the BG Matrix can be combined with bone marrow aspirate and used as a compression-resistant strip that can be molded to the shape of the defect.

Clinical and in vivo studies on commercially available bioactive glass particulates show that BAG can perform better than other bio-ceramic particles and have performed similarly to autograft in multiple in vivo studies (Walsh et al. 2017; Bedi 2017).

Unmet Challenges for Engineered Bioactive Glass Matrices

The major scientific and technical challenges exist with previously developed bioactive glass. Glass based materials lack osteogenesis, are difficult in clinical handling, not load bearing due to brittleness, and have slow resorption due to low porosity (Hench and Jones 2015; Jones 2015). To overcome these limitations and use BAG as effective substitute for autograft, several experiments were attempted to combat these limitations.

First, to enhance osteogenesis, tissue regeneration through gene activation by controlled release of inorganic ions from BAG is required. However, the role of the dissolution products from implanted BAG on bone marrow-derived mesenchymal stem cells (MSC) is not yet controllable. In some studies dissolution products induced osteogenic differentiation into osteoblast-like cells, and in others, it did not (Reilly et al. 2007; Karpov et al. 2008; Brauer et al. 2010). To control this problem, the fundamental mechanisms involved in ionic stimulation in the stem cell nucleus and the exact mechanism of "how the bioactive glass particles/dissolution products" should be explained (Hench and Jones 2015).

Second, particles and putties containing a variety of BAG particulates are in widespread clinical use, but large interconnected macroporous scaffolds for regeneration of large bone defects were not developed. To overcome and address this, the bottom-up sol–gel process, where gelation of nanoparticles in a sol (polycondensation) forms a glass network by avoiding sintering of crystalized Bioglass 45S5, was initially developed (Li et al. 1991). After, a room temperature gelation process was employed, allowing pores interconnection with a compression strength equivalent to porous bone (Jones et al. 2006). Melt-derived glass scaffolds were introduced to make macroporous scaffolds (Wu et al. 2011). According to a review by

Hench and Jones (2015), none of described techniques are being further developed for use by medical device companies even though sol–gel and melt-derived scaffolds still exist.

Third, tissue-engineered constructs for replacement of large bone defects have been investigated for many years but are still not available as routine clinical products. To achieve this, a stable vasculature is necessary during initial grafting. Tsigkou et al. (2010) demonstrated that it is possible in mice models (Tsigkou et al. 2010). More research is needed to test the possible enhancement of angiogenesis optimal activity duration in humans (Azevedo et al. 2015).

Fourth, load-bearing devices that can be used in orthopedics over the long term, which also regenerate living bone, are still not available clinically. Therefore, the 3D printing technology was adapted to bioactive glass scaffolds to generate interconnected pores similar in diameter to the porous foam scaffolds but with higher compressive strengths (Fu et al. 2011; Kolan et al. 2011). However, BAG scaffolds are still brittle and therefore not suitable for all grafting applications, such as sites that are under cyclic loads.

Mixed Use Graft Materials with Antibacterial Effects (Table 7)

Infection Prevention and Treatment of Previous Surgical Site Infection

For improvement of bone graft materials including substitutes, dual-functional graft materials have been designed. Among several possible additional options, prevention or treatment of surgical site infection with/without bone destruction is needed for clinical application (Turner et al. 2005; Anderson et al. 2014). Risk factors associated with surgical conditions (relatively wide soft tissue dissection, muscular damage, long operation time, and limited control of bleeding during operation) and patient characteristics and health status (old age, comorbidities like diabetes mellitus, renal failure and vasculopathy, and smoking, etc.) in spine fusion operations.

For prevention or control of the post-operative infection, systemic and localized bactericide are necessary. However systemic delivery of antibiotics to infected site or vulnerable to infection is limited by abnormal blood supply in operated site, drug toxicity to organs, antimicrobial-resistant form of bacteria, etc. (Shiels et al. 2017). Due to mentioned causes, newly designed graft materials have been developed for local bactericidal carrier, which may increase the safety and satisfaction after treatment (Lentino 2003; Radcliff et al. 2015).

A variety of materials including calcium-based substitutes, synthetic polymers, DBM, and protein-based materials have been proposed as alternative delivery vehicles with bone fusion function (McLaren 2004; Nelson 2004). Because the most common pathogen responsible for spinal infections after surgery is the gram-positive bacteria *Staphylococcus aureus*, the antibiotic candidates for biomaterials for infection-targeted delivery (or prevention) may be limited to vancomycin, aminoglycoside series like tobramycin, gentamicin, amikacin, and quinolone series like ciprofloxacin (Turner et al. 2005; Logoluso et al. 2016; Shiels et al. 2017; Boles et al. 2018; Wells et al. 2018).

Several animal studies have shown that calcium sulfate pellets are substantially resorbed and replaced with new bone formation by 6 weeks and a similar rate of pellet resorption has been reported clinically (Turner et al. 2001; McKee et al. 2002). According to study by Shiels SM.et al., vancomycin continued to be released from the DBM over the course of 6 days while maintaining sufficient eluate concentrations to maintain a zone of inhibition similar or larger than a vancomycin control in spine fusion in rabbit (Shiels et al. 2017).

There are several obstacles to overcome in order to use this newly designed bone graft material in clinical spine fusion. First, the ideal shape, desired materials of bone graft, and release concentrations are not established. McLaren et al. questioned the effect of laboratory sampling methods on characterizing the elution of tobramycin from calcium sulfate and the reliability of in vitro elution data in predicting the in vivo release of antibiotics (McLaren et al. 2002). Second, local site effects by eluted antibiotics are of

concern. Since neither the optimal level of antibiotic nor the duration of its release has been established, the effect of high local levels of antibiotics on the ability of grafted material to enhance bone healing is largely unknown. In a rabbit study, the use of vancomycin-loaded DBM showed a decrease in the fusion rate compared to DBM when used in a sterile wound (Shiels et al. 2017). Furthermore, an in vitro study suggests that vancomycin has toxic effects on hMSCs, a cell population particularly important for bone formation (Chu et al. 2017). Finally, clinical studies on the use of antibiotic-impregnated graft materials for spine fusion in humans are few. Pilot studies focused on the use of antibiotic-impregnated graft material in total joint arthroplasty and osteomyelitis (Logoluso et al. 2016) (Table 7).

Conclusion

A wide variety of bone graft materials are used in spinal surgery applications. Increasingly, over the past decade, diverse materials and composites are being developed as grafting options for use in spinal surgery. Consideration of the ideal properties of a grafting material and the material's mechanism of action, structural and handling characteristics, FDA classification and related approval or registration, and available clinical and preclinical data will optimize appropriate grafting choice for a certain surgical application for spinal fusion. Moreover, bone grafts do not fuse immediately; instead, they provide a foundation or scaffold for the patient's body to grow new bone in anatomical sites wherein bone did not previously exist such as in a spinal fusion site.

The development of products used for bone regeneration has followed the basic criteria of providing a biocompatible three-dimensional scaffold with controlled architecture capable of stimulating or supporting bone growth in the natural in vivo environment. The ability of the material to be used in conjunction with other cellular and signal (growth factors)-based therapies is a key strategy in maximizing the efficacy and likely success of fusion. However, while many bone graft substitutes perform well as bone graft extenders, only autogenous bone grafts are osteogenic and BMPs are osteoinductive.

Variations in anatomical location, surgical application (meticulous surgical preparation including adequate decortication), instrumentation type, and the patient's risk factors (metabolic and nutritional status, vitamin D, diabetes, smoking, drug and alcohol abuse) are critically important factors to consider in choosing an ideal grafting agent or bone graft to achieve a successful biologic bone union.

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Mechanobiology of the Intervertebral Disc and Treatments Working in Conjunction with the Human Anatomy

12

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Contents

Abstract

Degenerative conditions of the spine benefit from a methodical approach for the management of patients with chronic low back pain when offered surgery. Surgical solutions should consider the severity of the disease along with the approach in order to provide the patient with the best potential long-term outcomes. Posterior dynamic stabilization is considered to be an alternative therapy to rigid spinal fusion and is intended to produce equal stability within the affected vertebral space, while promoting additional mobility. Through its use in treating conditions such as spondylolisthesis, disc degeneration, and disc herniation, posterior dynamic stabilization has emerged as a potential solution to unintended consequences of more conventional therapeutic modalities, like rigid spinal fusion. Complications, such as adjacent disc disease, may be

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mitigated through an approach that permits additional mobility, returning the pathological segments to their intact range of movement and functionality. This chapter will review the history and development of posterior dynamic stabilization devices from their early inception to the current state of the art, as well as analyze the current pros and cons (garnered through both biomechanical and clinical testing) of each. Specifically, it will focus on the following device categories: interspinous spacers, pedicle screw and rod-based devices, and total facet replacement systems. Finally, there will be a discussion regarding the shortcomings of current metrics used to test such devices, along with an analysis on the cooperation between industry leaders and surgeons in designing said devices.

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Mechanobiology · Posterior dynamic stabilization · Interspinous spacers · Pedicle rods and screws · Total facet arthroplasty · Fusion · Rigid · VAS · ODI

Introduction

The motion of the spine can be studied in the most basic form by investigating a single index level or functional spinal unit (FSU). The FSU is a three-joint complex comprised of two vertebral bodies with three articulations, including the intervertebral, disc as well as the two posterior facet joints. The intervertebral disc forms an integral part of the FSU and has a propensity for degeneration with increasing age. Anatomically, the disc consists of highly oriented unidirectional layers arranged concentrically in alternating lamellar structures in conjunction with a gelatinous inner core, referred to as the nucleus pulposus. The nucleus has the ability to absorb transient forces, of which shock loads may have highest magnitudes, and to subsequently distribute loads to the end plates of the vertebrae. The other important articulations within the FSU are the facet joints which are also susceptible to disease. Facets, in the normal condition, play a role in controlling the motion of the FSU. This three-joint complex within each FSU controls the kinematic response to load. The primary modes of loading taken into consideration when evaluating the kinematic response to physiologic loads include axial compression, flexion extension bending, lateral bending, and axial torsion.

As degeneration occurs the disc may become fibrotic, compromising its ability to dissipate and distribute loads. Consequently, non-physiologic loads are then distributed to the vertebral end plates and the annulus of the disc which may lead to morphologic end plate changes and annular fissuring. With the onset of the degenerative cascade, both the intervertebral disc along with facets becomes compromised. The degeneration within the FSU may lead to the inability to withstand even

physiological loads and eventually, depending on the severity, instability may develop. Both clinically and biomechanically, instability can be defined by the inability of the FSU to control physiological displacement. With instability, the neurological structures are prone to impingement and injury. Instability of the intervertebral disc changes the kinematic loading profile of the spine with increased load transfer through the facet joints and ligamentum flavum. With time, these structures all undergo hypertrophy with narrowing of the central neural canal as well as the lateral recesses and neural foramina.

Mechanobiology

The intervertebral disc is comprised of at least two distinct cellular populations. Within the nucleus pulposus resides a chondrocyte like cellular population, while the cells of the annulus and cartilaginous endplate are primarily fibroblast like with an elongated shape. In a healthy state these cells work to continuously remodel the ECM, maintaining a balance of catabolic and anabolic remodeling. The cellular populations which reside in the soft tissue structures of the intervertebral disc (IVD) respond to applied mechanical stimuli, a phenomenon known as mechanotransduction (Johnson and Roberts 2003). The loads transmitted to the FSU are applied from various vector orientations, with axial compressive forces being converted to a hydrostatic pressure by the nucleus pulposus and then shear stress on the collagen fibers within the annulus (Vergroesen et al. 2015).

The local tissue environment is a key factor in the outcome when treating spinal pathologies. In a diseased state the accumulation of inflammatory cytokines, such as IL-6, IL-1β, and TNF-α, disrupt the balance between anabolic and catabolic remodeling leading to increased matrix degradation. Cytokine accumulation within the IVD may be the product of native cellular activity or the result of immune cells infiltrating the region and disrupting the microenvironment. Recent research has identified the presence of immune cells within degenerated or injured disc tissue. In the case of disc herniation, both neutrophils and macrophage have been identified in pathological tissues removed during microdiscectomy procedures. These cells are biologically active, producing inflammatory factors such as TNF-α. Even if the pathologic disc tissue is removed, pain may persist due to the continued presence of inflammation. Furthermore, inflammation of the disc may accelerate the degenerative process. For example, the presence of TNF-α has been associated with loss in disc height due to matrix destruction (Kang et al. 2015; Wang et al. 2017). Early intervention may be crucial in halting the degenerative cascade, with evidence suggesting the local tissue environment of the disc can be modulated with conservative therapies such as steroid injection or physical therapy (Fig. 1).

Additionally, the classical surgical treatments of degenerative disc disease also alter the kinematic response of an FSU. This abnormal motion may be caused by decompressive-type destabilizing procedures or by increasing the range of motion of the level adjacent to a fusion, also referred to as a "neo hinge." Finite element analysis of the von Misses stresses at the level above a fused level may also exhibit abnormal increases in the loads, and over time, hyper mobility may become evident. The von Misses stresses applied to that segment are altered both in distribution as well as in magnitude (Castellvi et al. 2007). Thus, the need for additional treatments which aim to restore the appropriate kinematic signature has led to serious consideration for the exploration of motion preservation technology as an alternative to fusion in the treatment of lumbar DDD. The goal of these motion preservation systems is to restore the mechanics of the intervertebral disc, thus disrupting the positive feedback loop which results in continued degeneration.

Degenerative Matrix and Utility

With the introduction of motion preservation technology, the matrix shown in Table 1 is proposed as a means to discretize the severity of the pathology by providing three distinct categories: mild, moderate and severe. Similarly, the targeted FSU for treatment can be further broken down into three distinct

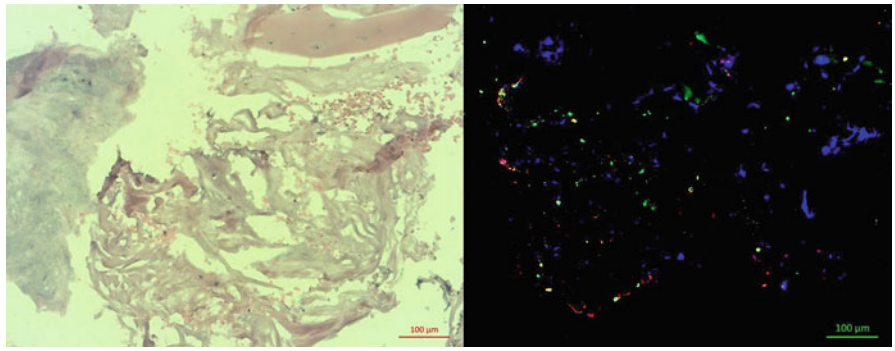

Fig. 1 Inflammatory response of a moderately degenerated human intervertebral disc. (**a**) Tissue sections were stained with hematoyxlin and eosin. Hematoxylin stains cell nuclei blue, while eosin stains extracellular matrix and cytoplasm pink (**b**) Immunofluorescence microscopy techniques were used to identify specific cellular markers of infiltrating immune cells for the same section. Red coloration depicts macrophages identified by the presence of surface marker CD68. Green coloration depicts neutrophils and granulocytes identified by the presence of the surface maker CD66b. Nuclear staining shown is shown in blue

Table 1 Matrix of degenerative condition versus the region of the spine within an FSU

		Region		
		Anterior	Middle	Posterior
Severity	**Mild**	Nucleus replacement Nucleus augmentation Biologics	Annuloplasty	Ligament replacement Interspinous spacers
	Moderate	Nucleus replacement Nucleus augmentation Biologics Total disc replacement	Porsterior pedicle-based systems Facet replacement	Interspinous Interlaminar
	Severe	Fusion	Fusion	Fusion

regions: the anterior, middle and posterior columns. The resulting intersections of these two variables (level of degeneration and region within FSU) provide potential treatment solutions with appropriate implant class descriptions at the junctions shown. This matrix is intended to methodically classify the severity of the pathology, origin or source of pain, and identify a potential implant or procedural solution in a systematic fashion. As technology increases, ideally the design and application of these technologies may be more precise and further refinement of technology classification may result.

Posterior Region

Degenerative conditions that affect the posterior regions may compromise anatomical structures including the facets joints and osteoligamentous tissue. Pathologically, these conditions may occur in combination with a degenerated anterior column. The potential consequences of facet degeneration are clinically well recognized and contribute to conditions such as stenosis. Other consequences include ligamentum flavum infolding into the spinal canal, osteophyte production with subsequent neuroforaminal stenosis, generation of inflammatory proteins with subsequent pain, reduced range of motion from hypertrophic facets and degenerative spondylolisthesis. The posterior degeneration of the lumbar spine is part of the overall degenerative cascade, but interventions through a posterior approach can stabilize or reverse this degenerative cascade, potentially obviating the need for intervention of the middle or posterior columns. The

classification in terms of degeneration has also been aided by the prevalence of imaging modalities and other diagnostic tools, such as diffusion weighted imaging.

A posterior approach provides bone anchoring locations and access to the anterior column via the pedicles. Also, the anatomical layout allows for bone and bone graft substitutes to be placed in the lateral gutters, and between spinous and along transverse processes from the same posterior approach. The posterior column, in combination with the anterior column, absorbs stresses and loads placed onto the spinal column. The articulating cartilaginous surfaces of the two facets within the FSU provide guided motion as a kinematic response to load. Furthermore, facets articulate in combination with the third joint, the intervertebral disc in order to offload, to some degree, a portion of the high loads from the anterior column.

The bony structures of the posterior region, including the lamina and pedicles, present excellent bone anchoring for fixation hardware. The cortical strength and designs that have taken advantage of cortical implants have been well documented. Ease of access is a main benefit of posterior approached. Implants intended to facilitate arthrodesis or preserve motion can be anchored in the posterior column with relatively simple access procedures. In particular, the cortical bone that comprises the pedicle provides a competent bone implant interface for the attachment of fusion constructs and motion preservation devices alike. Both implant designs require osteointegration at the bone implant interface for immediate and long-term stability.

Posterior approaches to the spine are well understood and described, provide direct and extensive access to locations with good bone anchoring and a portal to the vertebral bodies, and allow the surgeon to perform extensive corrective procedures indirectly to the anterior column. Despite the strength of cortical bone fixation in the posterior column, pedicle-based fixation devices often require a strong bone-implant interface access the anterior column via the middle region through a posterior approach. The large surface area of the vertebral endplates allow for the development of a wide variety of mechanical and potentially biological corrective forces to be applied so as to improve FSU mechanics. Direct replacement or removal of degenerative encroaching tissue or material may reduce pain and inflammation, promoting further healing of the diseased FSU while allowing easy access to the lateral gutters and other important structures.

Common Device Categories

Within the PDS space, three major technological approaches have emerged: (1) Interspinous Spacer Devices, (2) Pedicle Screw/Rod-based devices and (3) Total Facet Replacement. Each category has its own counter and normal indication for use in patients. This chapter summarizes all the major modern modalities of treatment for each and will present a detailed list of differing technologies, their claims, and an analysis of them. Notably, this is not all encompassing, as this industry is bristling with new improvements and technologies, some of which are not made public and are in various stages of preliminary research and development (Khoueir et al. 2007).

Interspinous Spacer Devices

Interspinous Spacer Devices are widely recognized as a means to address lumbar spinal stenosis via decompression. In fact, they have a reputation as devices with few significant negative effects. The general premise of this technology involves the placement of a device between the vertebral spinous processes to stabilize the structure and inhibit the compression of the spinal cord. The four major kinds of interspinous devices that are used heavily in the market are as follows: Wallis, XSTOP, DIAM, and Coflex. Each has been assessed in patients and an analysis of their efficacy is as follows.

Wallis implants are comprised of a Polyetheretherketone (PEEK) block, a common material used in both orthopedic and neurosurgical

implants. This implant classifies as a floating system, and it adheres to the spinous process via two Dacron ribbons which warp around them (the spinous processes), creating a tight fit (Sobottke et al. 2009). It has been consistently demonstrated that the Wallis implant can prevent further disc degeneration and pain in patients with spinal stenosis. Floman et al. showed this in their 2007 study where they analyzed whether the Wallis interspinous implant may reduce the number of recurrent lumbar disc herniation in patients with primary disc excision (Floman et al. 2007). The research concluded that while the device did not impact the rate of recurrent herniation, there was a marked decrease in the Visual Analog Scale (VAS) of pain, in both the back and the legs. A study conducted by Senegas et al., performed in 1988, showed a similar point (Senegas et al. 1988). They demonstrated that widening the lumbar vertebral canal served as an effective treatment for patients suffering from spinal stenosis and postoperative spinal stability. The researchers mentioned the method's virtues: it did not need the whole lumbar laminectomy, which usually causes spinal instability. Sobottke et al. further proves the point. After the study analyzed the various interspinous implants, Wallis, X-STOP and DIAM, they found that all devices created significant and long-lasting symptom control (Sobottke et al. 2009). Despite no statistically significant difference in device performance, between the three brands, it should be noted that all produced favorable results in terms of patient satisfaction and treatment of Lumbar Spinal Stenosis (LSS) pain.

In a series of similar technologies within the interspinous Spacer Device market, one example, X-STOP, is an implant crafted out of titanium and coated with a PEEK composite. The spacer is oval in shape and carries two wings on its lateral sides which are intended to prevent lateral migration (Sobottke et al. 2009). Sobottke et al. found that X-STOP displayed a positive ability to combat LSS pain and served as a means to surgically decompress the spine. Puzzilli et al. highlighted this conclusion in their study on the efficacy of X-STOP as a treatment for LSS. This study involved a 3-year patient follow up with 542 patients in total. Of these 542, 422 underwent surgical implantation of X-STOP, while just 120 patients served as the control and were managed conservatively. Results showed a substantial 83.5% of X-STOP treated patients reported positive results in the later follow-up appointments, while 50% of the control group reported these same results. Notably, 38 out of the 120 control cases selected to receive another surgery to decompress the spine, as they found the control (conservative therapy) unsatisfactory. The authors concluded that interspinous process decompression via an interspinous spacer device offered an effective and less invasive alternative to classical microsurgical posterior decompression. This was specifically true in selected patients with spinal stenosis and lumbar degenerative disk diseases (Puzzilli et al. 2014). Furthermore, less than 6% of the patients that did receive the X-STOP intervention had the device removed because of worsening neurological complications.

The Device for Intervertebral Assisted Motion, or (DIAM), is comprised of a sleeve of polyester that surrounds a core of silicon. This device is situated between two adjacent spinous processes. It is bound by three mesh bands which tether it to the spinous process and to the supraspinous ligament for extra support (Sobottke et al. 2009). In a study done by Fabrizi et al., the DIAM device and the Aperius PercLID system were compared in patients, DIAM: 1,315; Aperius PercLID: 260. The patient population was comprised of patients with a spectrum of spinal pathologies including: degenerative disc disease (478), foraminal stenosis (347), disc herniation (283), black disc and facet syndrome (143), and topping-off (64). The study also differentiated between a single level (1,100) and a multilevel (475) intervention and resulted in an overwhelming majority of patients displaying symptom resolution and improvement. They, therefore, declared that both technologies showed clinical benefits, displaying the merits of the system (Fabrizi et al. 2011).

Sharing a similar role to the above devices, Coflex is a titanium-based implant that exists in a characteristically "U" shape. It adheres to the spinous processes by means of wings that are

crimped to the bone. It is believed that the compliant "U" shape of the implant allows for additional load to be transferred through the disc as well (Kettler et al. 2008). Xu et al., in their publication, "Complication in degenerative lumbar disease treated with a dynamic interspinous spacer (Coflex)," resolved that the technology employed in this device was relatively safe, with only 11 patient complications in a sample size of 131. These complications involved three device-related issues (spinal process fracture, Coflex loosening, and fixed wing breakage), two tissue injuries (dura mater tear), and one superficial wound infection. The low complication and reoperation rate of the Coflex technology demonstrates its clinical utility (Xu et al. 2013). The authors of this study mentioned that care should be taken to prevent non-device-related complications emphasizing the importance of surgical proficiency and technique.

Pintauro et al. comprehensively reviewed the different interspinous spacer devices (Pintauro et al. 2017). There, the authors systematically analyzed each of the above technologies and sought to determine if the preliminary generation of implants is preferable to the second generation in terms of outcomes and complications. This review used 37 studies conducted from 2011 to 2016 to gain an up-to-date depiction on the current measures of success. This analysis generated an impressive finding, in that second-generation devices had a significantly lower rate of reoperation as compared to first generation devices (3.7% vs. 11%), which was not influenced by the type of Interspinous process device. This claim argued that older technologies were marginally obsolete, noting that the long-term functionality of first generation is questionable, and that newer devices did not suffer from the same degree of reemergence of symptoms in patients. The authors hypothesized that the differences in outcomes between first and second generation devices was due to two key factors: (1) they do not require additional decompression surgery with their utilization and (2) they are more frequently comprised of PEEK, which may be a more robust and nondegenerative material. The study acknowledged that there was insufficient randomized control trial data to emphatically make the claim that newer generation implants are superior. No statistically significant difference between the symptom relief of patients when their treatment with older versus newer devices was analyzed. The paper also acknowledged the influence of patient selection on the success rate of the surgery, emphasizing the importance of the proposed degeneration matrix and consideration of the stage of degeneration in selecting the appropriate treatment strategy (Pintauro et al. 2017).

In a study conducted by Richter et al., 60 patients were isolated, 30 were treated with decompression surgery for lumbar spinal stenosis and 30 with both decompression surgery and Coflex (a second-generation device). The study found, "... no significant difference between both groups in all parameters, including patient satisfaction and subjective operation decision." (Richter et al. 2009). The implementation of interspinous spacer devices on the whole has shown positive outcomes for patients in a myriad of different ways (pain and re-operation rate); however this study demonstrates that more research into this issue must be conducted to gain better insight into the significance of this treatment modality (implants) compared to spinal decompression surgery.

Pedicle Screw and Rod-Based Devices

One of the more versatile modalities of treatment within the posterior dynamic stabilization device space is that of pedicle screws and rods. These implants differ in terms of materials, design and efficacy in patients. Moreover, this section will be divided into two parts. The first subsection discusses the role of rigid rod-based systems, while the second subsection discusses one of pedicle screw-based systems.

The use of the Isobar TTL (Fig. 2) is considered as a means of mitigating lumbar degenerative disease. This technology is one of the preliminary semirigid rods that was used for dynamic fusion. The physical makeup of this device is a rod comprised of titanium alloy and a dampener which is made out of titanium O-rings that are stacked

Fig. 2 Isobar TTL construct on an anatomical model

upon one another vertically (Gomleksiz et al. 2012). The Isobar TTL device was utilized in a study conducted by Zhang et al., in which 38 cases of lumbar degenerative disease were analyzed in a retrospective study done between June 2007 and May 2011 (Zhang et al. 2012). The cases broke down into the following categories of pathology: 4 cases of grade I spondylolisthesis, 11 cases of lumbar instability and lumbar disc protrusion, 21 cases of lumbar spinal stenosis and lumbar disc protrusion, and 2 cases of postoperative recurrence of lumbar disc protrusion. Of the cases presented in the study, 22 of them displayed adjacent segment disc degeneration. The cases all shared a similar procedure of posterior decompression and the implantation of the Isobar TTL device. The evidence conferred in this study demonstrated near unanimous success in treatment of patients' symptoms. In fact, in the study's 38 cases, 32 were considered "excellent," 3 cases "good," 2 cases "fair," and only 1 case displayed a poor result. The final conclusion showed that the Isobar TTL stabilization system was a more than adequate means of treating lumbar degenerative disease characterized by a lower VAS score.

In a separate study, Gao et al. suggested that using Isobar TTL in a posterior approach provided a fixation system that had shown to "delay degeneration of intervertebral discs" (Gao et al. 2014). They appeared interested in Isobar TTL's unique features that "allowed for mobility of the fixation segments, maintained intervertebral space height, reduced the bearing load in both facet joints and discs and could prevent intervertebral disc degeneration." This study utilized MRI imaging to retrospectively assess 54 patients that had undergone dynamic lumbar fixation using the Isobar TTL. There was a heavy emphasis on both pre- and postoperative imaging to determine how this technology affected spinal health. It was found that after 24 months postoperatively, the associated diffusion coefficient (ADC) values increased significantly. The ADC is an indicator of the health of the nucleus pulposus, the central component of the intervertebral disc. Thus, an increase in the ADC showed an increase in health and hydration (concentration of water) of the disc. It should also be noted that DWI (Diffusion weighted imaging) was used to measure in vivo water molecule diffusion. Thus, this DWI value can demonstrate the structural characteristics of tissue. In effect, the DWI and ADC score are correlated, as a DWI may demonstrate disc health through the ADC value.

Barrey et al. commented on the use of Isobar TTL as a dynamic fusion system without the supposed effects of pseudoarthrosis, bone refraction and mechanical failure that other rigid apparatus suffered from (Barrey et al. 2013). This study is unique because of its long-term patient follow-up, totaling 10.2 years, of 18 patients with degenerative lumbar disc disease. The most important conclusion of this study is that within the 18-patient sample size, there were no adverse

reactions to the treatment, and all patients showed positive signs of a successful treatment. Thus, there were no observed complications or revision surgeries in their sample. Notably this observation did not match those previously reported by other dynamic systems such as Dynesys (27.5% of patients) in a study done by Bothmann et al. (2008). Stoll et al. found that 10% of 73 patients with a Dynesys system displayed complications following the implantation of the device (Stoll et al. 2002). However, it is difficult to compare the efficacy of the two devices (Isobar TTL system vs. the Dynesys system) due to the limited sample size. Therefore, the author indicated that more work needs to be done to assess both systems and measure their respective outcomes.

Cook et al. analyzed the properties of the implant when placed into a cadaveric model. By performing a comprehensive analysis of each FSU's kinematic response to load they found the Isobar TTL rod is uniquely suited as a dynamic fusion system and it provided the same immediate stabilization as that of a rigid fixture, but with a greater potential to handle greater compressive loads, the evidence of which was proven statistically significant. The author, therefore, believed that the Isobar TTL system could mitigate the common problems facing more rigid implantable systems, specifically greater load sharing between the anterior and posterior columns and axial distraction, the latter of which they found could lead to pedicle travel during bending. This data was garnered through the biomechanical analysis of ten human lumbar cadaveric specimens measured upon various indices such as range of motion, anterior column load sharing, facet engagement via vertex distance map (VDM), interpedicular distance excursion, and finite helical screw axis (HSA). Analysis of which showcased the robust mobility of the device and its ability to assist in sharing of loads as previously mentioned (Cook et al. 2015). This evidence may aid in understanding why physicians see clinical benefits in patients, as this potentially sheds light on some of the factors that attribute to the success of an implant under physiological conditions.

Another rod technology to emerge was BalanC, a dynamic rod-based system. The device itself was comprised of two portions marked "dynamic" and "fusion." The dynamic portion of the device contained a complex of PEEK and Silicone, and the more rigid fusion portion was made entirely out of PEEK. Under testing performed by Cheng et al., the device did not display a statistically significant difference in biomechanical performance when compared to titanium and pure PEEK rods (Cheng et al. 2010).

One of the first posterior dynamic stabilization devices to gain wide usage was the Graf Ligamentoplasty system. This technology was notable for its braided polypropylene to connect two titanium pedicle screws (one on the superior and one on the inferior vertebra- on the symptomatic level) to create an apparatus that would provide structural integrity but still maintain a robust mobile characteristic. The intention of the device was to permit load sharing, primarily to the posterior annulus, and to allow micro-tears in the anterior annulus fibrosus to heal (Gomleksiz et al. 2012). Rigby et al. conducted a mid- and long-term follow up study on 51 patients that received the Graf ligament stabilization surgery. There was a very high rate of complication (12 out of the 51 suffered complications), and of those that had complications, four patients required additional follow-up surgeries due to their unresolved condition. A poll conducted during the study showed that 41% of patients indicated that they would choose to not have the operation again. Seven of the patients in the group later went on to have full bony fusion procedures due to unresolved issues. This study's conclusion indicated that the device should be used with caution (Rigby et al. 2001). Hadlow et al. criticized the Graf ligament technology, as they found that this modality of treatment was associated with a worse outcome at 1 year and a significant higher revision rate at 2 years (Hadlow et al. 1998). Sengupta mentions that the Graf ligament has a propensity for producing lateral canal stenosis in patients, particularly in cases where the patient suffers from degeneration of the facet joints or in-folding of the ligamentum flavum, demonstrating early clinical failure (Sengupta 2004). The author further mentions that evidence has elucidated the exact mechanism in which the device

may treat symptoms, as clinical success may be from restriction of movement or from shifting loads to the posterior annulus.

In contrast, Madan et al. showed that the Graf system demonstrated superior results to that of a more conventional rigid fixation and fusion device. The author assessed the outcomes of two groups of 27–28 patients, the first of which was treated with the Graf ligamentoplasty and the second was an anterior lumbar interbody fusion device (ALIF) known as a Hartshill Horseshoe (Madan and Boeree 2003). After a follow-up period of 2.1 years, it was found that the Graf system and ALIF system had successful outcomes in 93% and 77.8%, respectively. The authors attributed this result to the increased lumbar segment mobility and better stabilization results. Likewise, a study performed by Grevitt et al., followed 50 patients postoperatively after Graf stabilization had been performed. A marked decrease was observed in the mean disability score (59% preoperatively compared to 31% postoperatively) and noted that 72% of patients stated the procedure produced good or excellent results (Grevitt et al. 1995). Markwalder and Wenger stated the same, although with the caveat that patient selection was primarily "young patients with painful mechanical disease who are resistant to conservative treatment and yield favorable long-term results" (Markwalder and Wenger 2003). This study demonstrated that while the patient population may be narrow, the device still had potential to combat the demonstrated symptoms. It is evident that more work in this space must be done to gain more knowledge regarding the benefits and potential complications of this technology.

The Dynamic Neutralization System (Dynesys) sought to stabilize the spine without bone grafting (Molinari 2007). The exact specifications of this device apparatus involve a titanium-alloy pedicle screw system connected by an elastic compound. Welch et al. stated that the device showed the ability to mitigate symptoms in patients (back and leg pain) and seemed to avoid any major surgical or device-related complications, some of which are more common in fusion approaches. A group of 101 patients were analyzed using the Oswestry Disability Index (ODI), and postoperative treatment groups displayed a near 30% reduction in disability (55.6% to 26.3%). Additionally, the pain data was conveyed by use of a 12-month follow-up questionnaire in which leg pain and back pain saw substantial reductions in mean values (80.3 to 25.5 and 54 to 29.4, respectively). While they did share a positive outlook on the device's ability to confer strong clinical results, they admitted that more research was needed (Welch et al. 2007). But Schwarzenbach et al. stated "Dynesys technology suggested it had limitations in elderly patients with osteopathic bone or those with severe segmental macro-instability with degenerative olisthesis and advanced disc degeneration," denoting an extra risk of failure. The study highlighted that no complications were found in their analysis and stated that more studies were needed to show that this technology definitively demonstrated a decrease in postsurgical complications (Schwarzenbach et al. 2005) (Fig. 3).

The use of PEEK rods has been a known method of posterior dynamic stabilization for some time. The material properties of such a technology are tremendously advantageous to this type of intervention due to its nonrigid physical nature, its radiolucent quality, and its versatility. Ormond et al., in their retrospective case series, showed that PEEK rods demonstrated similar fusion to Titanium rods. They argued initially that the semirigidity of PEEK rods would provide a reduction in stress-shielding and increased anterior load-sharing properties. This clinical evaluation of the technology showed that these assertions were well founded (Ormond et al. 2016). Additionally, a study in which the PEEK rods were retrieved from 12 patients conducted by Kurtz et al., demonstrated that the rods were comparable to their Titanium counterparts and displayed no cases of PEEK rod or pedicle screw fracture. This study shows that this modality of treatment (PEEK rods) is effective in not producing any major material-specific complications (Kurtz et al. 2013). While the study is limited in its sample size, it seems evident that the semirigid nature of PEEK serves as a comparable material for future device innovation within this space.

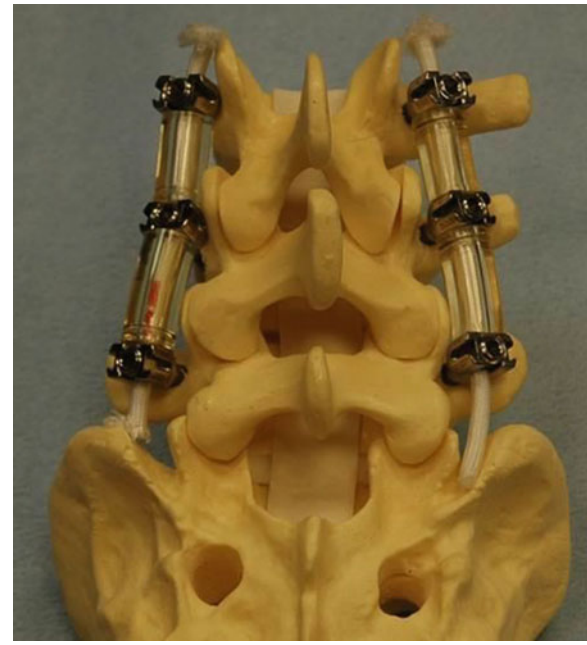

Fig. 3 Dynesys construct on an anatomical model

Notably, however, the same study mentioned that "seven out of eight periprosthetic tissue samples taken from the PEEK rods displayed signs of extensive degeneration, four of which had areas of tissue calcification." Also, PEEK wear shedding and PEEK debris were found in two out of the eight patients and was minimal, producing no significant inflammation.

The Bioflex Spring Rod Pedicle Screw System is comprised of a special Nitinol coil spring made of a small 4 mm diameter wire. The wire is set between the screws for the purpose of generating increased flexibility (Sengupta and Herkowitz 2012). An example of this technology being implemented in patients is shown in a study conducted by Heo et al. The study found that this approach was not significantly beneficial in preventing adjacent level degeneration completely. Based on MRI scans, only 2 of the 13 discs in the implantation segment showed any improvement in their disc degeneration, while 3 of the cranial adjacent discs (out of 25) and 4 of the caudal (out of 25) demonstrated a progression of disc degeneration (Heo et al. 2012). The biomechanics of this system were evaluated by Zhang et al., in which they found that the Bioflex system did not preserve ROM at implantation segments to that of any preoperative values but did preserve functional motion to these same levels (Zhang et al. 2009). This demonstrates that the biomechanical properties are indicative of a stable and effective PDS system; however, more clinical trials are needed to determine if the biomechanical advantages can translate into clinical utility.

Sengupta and Mulholland discussed the Fulcrum Assisted Soft Stabilization (FASS) in their publication assessing whether or not the aforementioned system could be a new means of treatment for degenerative lower back pain. The biomechanical properties of the technology displayed an ability to unload the affected disc and maintain a controlled range of motion. This was achieved by stabilizing the lumbar spine using pedicle screws, ligament, and a fulcrum to permit unloading. The thought process involved the transition of force from the disc to the ligament and fulcrum to achieve this characteristic unloading. Although done in cadaveric models, this study conveyed a new innovation to the PDS field (Sengupta and Mulholland 2005). While little clinical information has been produced as of late, the idea of circumventing any load on the affected disc by means of a mechanical transfer poses an interesting means

of combating the problems that consistently affect PDS systems.

The AccuFlex Rod system was composed of a metal rod with a distinct double helical cut inside of it to permit increased flexibility, primarily in the flexion and extension direction. Because this implant is quite similar to that of conventional metal rod constructs, it may be easily adapted to a surgeon's repertoire of procedures, according to Mandigo et al. (2007). In their study, they compared patients treated with Accuflex rod and with conventional rigid fusion devices. They resolved that the Accuflex technology displayed extremely similar characteristics to rigid fusion devices, demonstrating no significant differences in rate of fusion and highlighting the device's ability to serve as an alternative to other rod-based therapies. Reyes-Sanchez et al. conducted a study with a 2-year follow-up and found that 83% of patients showed a benefit in clinical symptoms after lumbar stabilization with the Accuflex system. They also showcased that the device had a 22% hardware failure rate, which is relatively high compared to other technologies. These competing claims show that the Accuflex system, like others mentioned before, have demonstrated clinical efficacy, in terms of relieving problems associated with lumbar destabilization, but may also show signs of common device complications (Reyes-Sánchez et al. 2010).

Cosmic Posterior Dynamic System is another variant of the pedicle screw and rod system. It employs a 6.25 mm rod which is attached in a non-rigid fashion by pedicle screws with a distinctive hinged screw head, which according to Kim et al., causes load sharing between the anterior vertebral column and the implant. The device is used for conditions such as symptomatic lumbar stenosis, chronically recurring lumbagly in the case of discogenic pain and facet syndrome, recurrent disk herniation, and spondylodesis (Maleci et al. 2011). Moreover, Stoffel et al. analyzed these claims and reviewed 103 patients that were implanted with the Cosmic system and found that 91% of the patients in their study were satisfied with their treatment. Some of the problems displayed in cases involved screw loosening (two patients), disk protrusion in an instrumented segment (three patients), symptomatic degeneration of an adjacent segment (six patients) and osteoporotic fracture of an adjacent vertebra (one patient). Importantly, pain scores were significantly reduced (VAS pre-op 65% +/−1; post op 21% +/−2) and disability scores also decreased showing a marked reduction in ODI by approximately 30% (Stoffel et al. 2010). Safinas, a system similar to the cosmic rod and screw system mentioned above, allows limited motion due to the hinged screw design. Ozer et al. demonstrated that the implementation of this technology resulted in "comparable relief of pain and maintenance of sagittal balance to that of a standard rigid screw-rod fixation" (Ozer et al. 2010). It is evident that the dynamic screw design shows promise in its ability to assist in PDS. There has been wide recognition of the positive outcomes with the use of this technology. While the clinical results are not significantly different than the current rigid fixation techniques, it demonstrates an opportunity for further investigation and research. Additionally, better design clinical studies may highlight the quality-of-life improvements that are currently demonstrated from clinical trials.

An ideological culmination of these technologies presents itself as a dynamic rod and dynamic screw apparatus. This set up entails the utilization of pedicle screws with hinges for increased load sharing and rods that are capable of moving to accommodate for stabilization. Bozkus et al. demonstrated in their biomechanical study that dynamic hinged pedicle screws had a unique ability to increase ROM (flexion extension and lateral bending, and axial rotation). It was noted that this improvement showed a much closer range of motion compared to normal than that of a rigid pedicle screw (30% less than normal ROM, but 160% greater than standard rigid screws) (Bozkus et al. 2010). Kaner et al. reinforces this conclusion. In that study, they assess the use of both dynamic screws and dynamic rods. They observed a significant improvement in the ODI and VAS values of their patients. They also observed "that using dynamic rods with dynamic screws prevented deformity in the rods due to the lower load transfer because of a decrease in the stress shield." This provides an exciting example

of a synergistic effect of current technologies with the potential of providing more mobility for patients (Kaner et al. 2009).

Total Facet Replacement Systems

Total Facet Replacement Systems serve the purpose of fully replacing the facet joints of the spine with a mechanical fixture. This surgery has the potential to be "an alternative treatment to lumbar fusion and instrumentation after laminectomy for spinal stenosis" (Serhan et al. 2011). One of the emerging technologies within this space is known as the Total Facet Arthroplasty System (TFAS). The TFAS is "a sliding ball-in-bowl type joint with a pedicle anchor to treat spinal stenosis," according to Serhan et al. The technology was tested biomechanically using cadaveric spines to assess the loading of this type of implant compared to a more conventional rigid posterior instrumentation system (Sjovold et al. 2012). Sjovold et al. found that TFAS implementation produced near intact anterior column load sharing, which was measured by a disc pressure gauge. It was also found that the rigid system displayed larger implant loads than the TFAS system, potentially demonstrating a successful finding that the TFAS system has loading characteristics preferable to those of more rigid systems. However, the study claimed that more testing was needed to understand the physiological implications of such data (Fig. 4).

The total posterior arthroplasty system (TOPS) is a pedicle screw-based device containing an elastic core. This elastic core serves as a flexible apparatus, permitting additional movement in the treated segment. A study evaluating TOPS was conducted by Anekstein et al., in which they sought to measure the clinical outcomes of patients with the TOPS system implanted to relieve their degenerative spondylolisthesis and spinal stenosis. It was found that there was a substantial decrease in VAS scores (88 to 8.8) in a 7-year follow-up. The results from the long-term follow-up permits the discussion that the device is a solid means of mitigating symptoms associated with Spondylolisthesis and Spinal Stenosis. ODI also dropped dramatically (from 49.1 to 7.8) during the 7-year follow-up (Anekstein et al. 2015).

StabilimaxNZ is built upon the neutral zone hypothesis of back pain, according to Panjabi and Timm (2007). The neutral zone was defined as the region of intervertebral laxity around a neutral position. This assumption is contingent on the relationship between spinal instability, movement, and pain. Thus, they hypothesized that an increase in the neutral zone, due to instability or injury, results in accelerated degeneration of discs and the manifestation of back pain. The device was designed with these biomechanical principles in mind and incorporated a pedicle

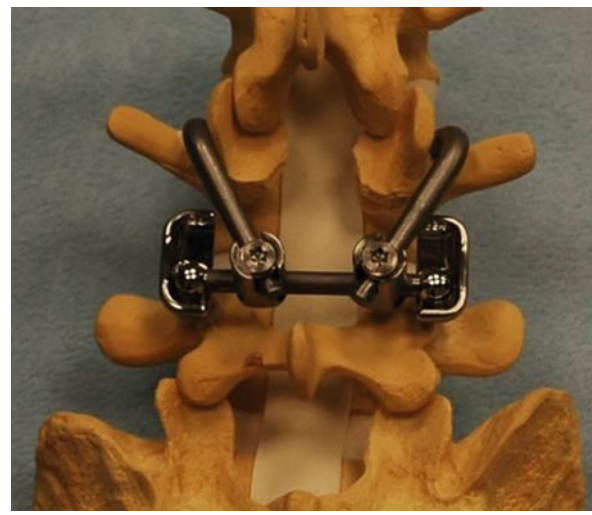

Fig. 4 TFAS construct on an anatomical model

Fig. 5 Stabilimax on an anatomical model

screw-based dynamic stabilization system, dual concentric springs combined with a ball and socket joint at the end. Therefore, according to their hypothesis, the device intends not only to maintain and maximized the range of motion but also add resistance to the passive spinal system to retain a normalized neutral zone, and thus mitigating symptoms. While there has not been any major clinical data published on this device, early biomechanical studies found the device shows promise for single level procedures (Fig. 5).

Posterior stabilization devices that provide immediate postoperative stability and improve chances of arthrodesis in the spinal column have also evolved in parallel with anterior stabilization devices. Cripton et al. investigated the load-sharing properties of lumbar spine segments after being stabilized with a rigid posterior implant (Cripton et al. 2000). Uniaxial strain gauges were used to create six-axis load cells to measure loads and forces through these implants, and pressure transducers measured the IDP. The authors concluded that these implants were not suitable for severe anterior column injuries in the absence of anterior stabilization systems.

These studies showed that PDS devices allow load sharing, but they may not be more efficacious than rigid rod posterior constructs. The rigid systems may also lead to excess load-transfer through the anterior column which can't be handled without anterior plates. Nevertheless, clinical validation through long-term investigations can improve our understanding of these systems.

Spinal Fusion

Posterior Dynamic Stabilization (PDS) and the technology that accompanies it, have remained a vital instrument for surgical implementation. Likewise, there has been tremendous innovation within this space considering the various technologies and approaches to combating common conditions, such as spondylolisthesis, disc degeneration, and other spinal movement disorders. The history of motion preservation requires an examination of the predated rigid body devices. Spinal fusion is a procedure where vertebrae are conjoined thereby creating a greater stabilized structure. While the current gold standard of care remains as rigid spinal fusion, many have argued that the consequences and unintended complications of this system call for a new method of treatment. Thus, the posterior dynamic stabilization (PDS) system emerged as a potential solution. The PDS of vertebrae claimed to yield a beneficial characteristic: it can allow a kinematic signature not found in rigid rod constructs (Gomleksiz et al. 2012; Cheng et al. 2010).

Merits and Downfalls of the PDS System

Understanding the market pressure to adapt to a more dynamic system is contingent upon recognizing the specific pathologies that are resultant of the rigid fusion system. These systems had a

propensity of causing disc degeneration at both the upper and lower margins of the therapeutic window, which often manifested as significant osteoporosis. Rigid systems also had an anterior loading preference, and thus resulted in an imbalance of load sharing between the posterior and anterior elements of the vertebra. PDS was intended to ameliorate these specific concerns and, by virtue, engender a new wave of medical device innovation.

Conclusions

The efficacy of a tool is a function heavily influenced by its effectiveness and ease of use. Technologies that need expansive series of training may dissuade surgeons from adapting such a device. The devices covered within this chapter have showed not only innovation within the posterior dynamic stabilization space, but also a conservation of treatment modality in terms of tools and methods used to treat relevant conditions. A surgeon may have a propensity to retain tools and techniques that have been proven rather than explore new alternative forms of treatment, and so it is evident that the devices mentioned above all display characteristics that are similar to the current state of the art (pedicle screw, rod, drill usage). This observation is reinforced by the findings in the World Health Organization report titled, "Increasing complexity of medical technology and consequences for training and outcome of care," (World Health Organization 2010). In conjunction with its analysis of the use of complicated technology, and the burdens that they may cause, the report emphasizes the importance of training and procedural practice to combat any nondevice-related complications. It is imperative that both surgeons and device innovators work in a synergistic manner to achieve a robust and long-standing educational and co-operational relationship to permit the smooth transition of new technologies into the operating space.

An important observation regarding the value of already existing metrics for rigid fixation technology was found during this review: the merit of applying existing metrics rigid fixation technologies to more motion preserving technologies is debatable. Moreover, there may come a time in which new methods of scoring and characterizing PDS technology compared to rigid instrumentation may be necessary to permit the observation of the novel properties of PDS, which may not be easily elucidated through conventional metrics. An example of this principle is the use of the interpedicular travel characteristic (IPT), which was implemented by Cheng et al. in their biomechanical evaluation of the StabilimaxNZ and ScientX technologies. The author found that most biomechanical testing catered to the specifications and characteristics of rigid systems. Therefore, a new metric was needed to characterize more motion preservation devices. The use of IPT was advantageous because it was a novel property that was more founded in motion preserving technology than its more rigid counterpart. While it remains to be seen if there is a direct correlation between this measurement and positive clinical outcome, it provides an example of researchers recognizing that the novel properties of motion preserving technology may not be best tested through the same procedures as more rigid technology. Moreover, this consideration would need to be a joint effort among both biomechanical and clinical scientists to trace the correlation between these new characteristics and their clinical outcome. It has been shown in the literature throughout this chapter that PDS technology may result in similar, preferable results compared to more conventional rigid implants. Thus, this difference must be studied in more detail if there is generally no statistically significant difference between existing rigid technologies and more dynamic ones with current metrics.

Dedication

Dr. Antonio Castellvi was an early adopter and a pioneer in the field of motion preservation technology. Through his clinical work in motion preservation and design contributions to posterior dynamic stabilization constructs, posterior dynamic stabilization gained special consideration and credibility including the development

of technologies such as the Scient'X Isobar TTL, Archus Total Facet Arthroplasty System (TFAS), while also challenging the status quo in that rigid fixation is preferable to a motion preservation technology. Graduating with honors from the University of Zaragoza Medical School in Spain and training in orthopedic surgery at the University of South Florida with a fellowship in spine at the University of Rochester, Dr. Castellvi's career spanned continents and brought the leading minds in spine surgery together. A surgeon, a prolific researcher, a mentor, and a friend, Dr. Castellvi's curiosity was only second to his compassion for others. He continues to be missed and remembered; this chapter is in his honor.

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Design Rationale for Posterior Dynamic Stabilization Relevant for Spine Surgery

13

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Abstract

Motion sparing posterior dynamic stabilization (PDS) devices have been introduced as an alternative to spinal fusion. A majority of these devices are based on instrumentation and techniques that surgeons are most familiar with, due to their experience with posterior fixation for spinal fusion. The goal of this new generation of devices is to allow controlled motion of the treated spinal segment that closely mimics physiologic spinal kinetics and kinematics, with the most common indication for use being spinal stenosis. The rationale for dynamic stabilization as an alternative to spinal fusion is to restore spinal stability, while avoiding (or delaying) degeneration of adjacent segments. Most commonly used PDS devices are either pedicle screw-based or interspinous process-based. The pedicle screw-based devices are commonly approved for use in spinal fusion, or as an adjunct to fusion, but not as stand-alone devices in the absence of fusion. Despite familiar surgical techniques and extensive preclinical testing, most pedicle screw-based PDS devices are still considered investigational for the treatment of disorders of the spine. One of the main reasons is that it is not yet clear whether PDS truly offer advantages over conventional spinal fusion or decompression alone, in terms of patient reported outcome scores. Other technical factors that pose a challenge for PDS devices are long-term fixation to the spine via pedicle screws or interspinous fixation, and variations in device stiffness, level of stabilization offered, and the range of motion allowed by PDS devices over time. This chapter presents an overview of in vitro testing methodologies used to evaluate PDS devices, followed by a summary of clinical performance of stand-alone dynamic stabilization devices with or without direct decompression.

Keywords

Spine · Dynamic stabilization · Biomechanics · Posterior Stabilization · Design rationale · Metrics · Spine surgery · Interspinous devices

Introduction

Spinal Fusion and Structural Integrity

Spinal surgery may be performed to address biomechanical instability introduced in the spinal column due to trauma (Puttlitz et al. 2000; Benzel 2001c), infection (Weiss et al. 1997), or tumors (Bakar et al. 2016). Besides addressing instability, the most common objective for performing surgery is treating pain by achieving neural decompression, correcting deformity, and addressing aberrant spinal kinematics (Schlenk et al. 2003; Panjabi and Timm 2007).

Surgery disrupts either the passive load sharing elements (ligaments and bone) or active musculature, or both. Hence, the surgical procedure itself can destabilize the spine (Hasegawa et al. 2013; Vadapalli et al. 2006; Benzel 2001b). To address biomechanical instability and to compensate for the destabilization introduced by surgery, fusion devices are considered the "gold standard" for treatment (Serhan et al. 2011). Over 400,000 fusion discharges occur annually in the United States (Rajaee et al. 2012).

An intervertebral fusion device contains bone graft (or substitute) that promotes bone healing and osteogenesis, and this process is enhanced during weight-bearing activities (Egger et al. 1993). However, to avoid excessive loading and motion, particularly during the bone healing process, the spinal segment is immediately immobilized by additional hardware commonly implanted in the posterior region. This allows for early overall mobility for patients, while also

needing less external support (Shono et al. 1998). Over time, as the structural integrity of the bone fusion increases, the integrity of posterior fixation device component can decrease (Benzel 2001a). As shown in Fig. 1, the theoretical net structural integrity (combination of bone fusion and posterior fixation device) stays the same over time. In the absence of adequate bone fusion, late failure of posterior fixation can occur (Bellato et al. 2015; Agarwal et al. 2009).

This highlights an important functional requirement for posterior dynamic stabilization (PDS) devices that will be discussed further in this chapter: a PDS device, which is commonly used "without" a bone graft, needs to maintain its structural integrity over a longer period of time. Hence, fatigue-strength-enhancement is crucial for a PDS device (Bhamare et al. 2013).

Spinal Fusion and Related Complications

When the goal is spinal segment immobilization to address gross instability, whether due to spine deformation-related issues, trauma, or tumors, spinal fusion surgery may be the only viable alternative. However, irreversible bone fusion can have a negative impact when addressing a smaller amount of instability, as in the case of spinal decompression surgery for stenosis. When a spinal segment is irreversibly fused, and overall patient mobility is desirable, the vertebral levels adjacent to the fused segment are subjected to additional loading and stress during activities of daily living (Lee and Langrana 1984). This phenomenon is termed as adjacent segment disease (Fig. 2), or ASD (Saavedra-Pozo et al. 2014; Panjabi and Timm 2007; Lindsey et al. 2015). ASD is defined as the presence of new degenerative changes at adjacent spinal levels, accompanied by radiculopathy, myelopathy, or instability (Saavedra-Pozo et al. 2014). The incidence of ASD is approximately 3% in the cervical spine and approximately 8% in the lumbar spine (Saavedra-Pozo et al. 2014). When considering the occurrence of ASD, it is important to differentiate between radiographic and symptomatic ASD (Virk et al. 2014). Also, given the average age of the population being treated, ASD, at least in part, is also related to the natural history of disc degeneration and not just altered biomechanics due to surgical treatment (Saavedra-Pozo et al. 2014). Hence, determining a cause-and-effect relationship in vivo is challenging.

In accordance with Wolff law, some level of compressive forces borne by the bone fusion mass is necessary for fusion and healing to occur (Kowalski et al. 2001). Excessively rigid posterior spinal fixation devices can also lead to stress shielding of the fusion mass (Saphier et al. 2007; Kanayama et al. 2000). Stress shielding refers to a

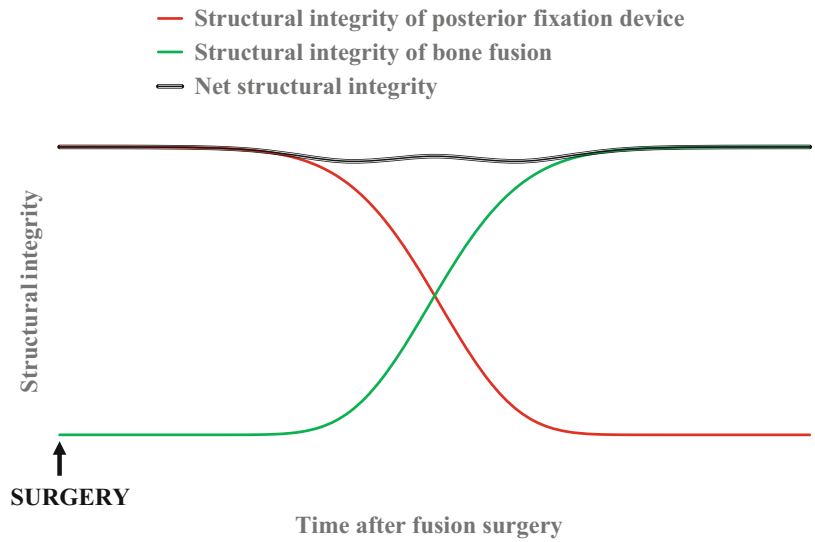

Fig. 1 Structural integrity after fusion surgery. (Source: Created in Microsoft Excel, adapted from "Benzel, E.C., 2001a. Spinal Fusion. In Biomechanics of spine stabilization. American Association of Neurological Surgeons, pp. 121–133")

reduction of load and stress seen by bone fusion mass (< ~70% of the total load), as a disproportionately large amount of the total load may be borne by the posterior fixation device (Fig. 3). This occurrence can further be complicated due to low bone-mineral density and osteoporosis (Bhamare et al. 2013; Park et al. 2013).

Failed bony fusion, or pseudarthrosis, is also an iatrogenic complication, with incidence rates ranging from 5% to 35% in the lumbar spine (Chun et al. 2015). While controversial, it is important to note that according to the United States Food and Drug Administration (FDA) guidelines, greater than 3 mm of translation motion and greater than 5 of angular motion on flexion-extension radiographs should be considered as a failed bony fusion (Gruskay et al. 2014; Chun et al. 2015).

Donor-site morbidity (due to bone grafting for fusion mass) is also a complication reported after spinal fusion (Vaz et al. 2010), which may be addressed by using alternatives such as recombinant human bone morphogenetic proteins (rhBMPs). Prolonged recuperation time also remains a concern (Serhan et al. 2011). Overall, patient satisfaction rate for lumbar spinal fusion averages around 60–70% (Turner et al. 1992; Slosar et al. 2000).

Rationale for Dynamic Stabilization and Device Classification

To address some of the limitations posed by fusion surgery, there has been a growing interest in the field of dynamic spine stabilization (Bhamare

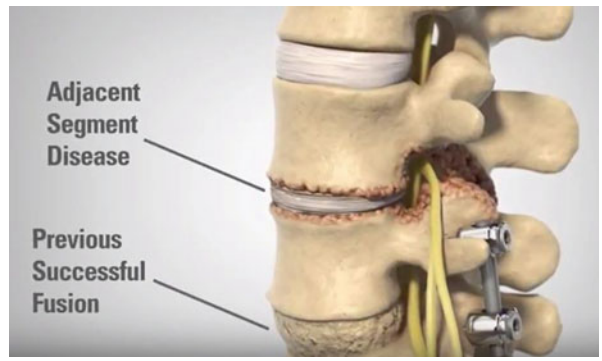

Fig. 2 Adjacent segment disease (ASD) after fusion surgery. (Source: https://www.youtube.com/watch?v=yQwYISvBkzo)

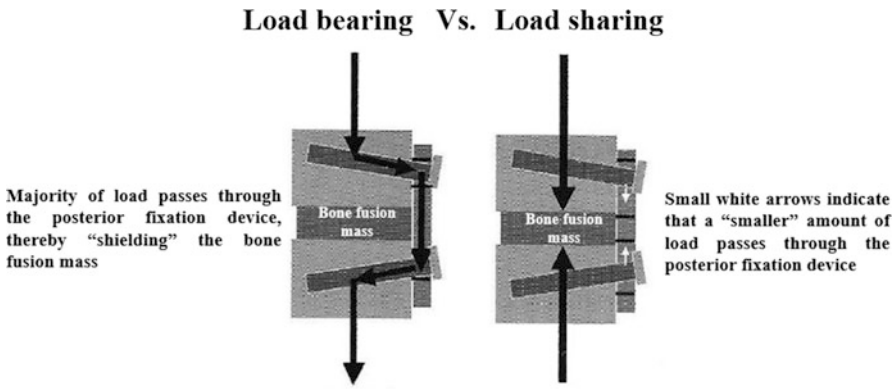

Fig. 3 Load bearing vs. load sharing after fusion surgery. (Source: http://www.bioline.org.br/showimage?ni/photo/ni05146f1.jpg, adapted from "Benzel, E.C., 2005. Spine Surgery: Techniques, Complication Avoidance, and Management")

et al. 2013). These devices may be viable alternatives addressing a range of spinal disorders, including stenosis and discogenic low back pain (Serhan et al. 2011). The rationale for dynamic stabilization is that by preserving functional range of spinal motion, one can alleviate at least some of the complications related to spinal fusion listed above. It should be noted that up to 5° of angular motion may be present on flexion-extension radiographs in the case of a successful fusion (Gruskay et al. 2014; Chun et al. 2015). Hence, if the ROM allowed under a similar radiographic evaluation for a dynamic stabilization device is less than 5°, justifying the use of the device as a truly non-fusion dynamic stabilization device is controversial. To the best of our knowledge, no pedicle screw-based PDS device has been approved by the FDA for use other than an adjunct to spinal fusion (Fig. 4).

While a dynamic stabilization device may not increase the range of motion (ROM) of the segment being treated, the objective is to preserve normal motion as much as possible, while at the same time limiting abnormal motion (Sengupta and Herkowitz 2012). In the case of a PDS device, some loss of ROM (compared to ROM before surgery) may be unavoidable (Sengupta and Herkowitz 2012). Another important consideration for a dynamic stabilization device is to ensure the adequate level of load transfer through the joint. In the case of a PDS device, it has to sustain loads for a longer amount of time, compared to posterior fixation devices used for fusion, since there is no bone fusion mass (Fig. 1). Hence, to avoid fatigue failure and implant loosening, which are often seen in a PDS device (Bhamare et al. 2013), the PDS device should be load-sharing, and not load-bearing (Sengupta and Herkowitz 2012). While there is no fusion mass to share load with (Fig. 3), the PDS device should be able to share load with other load-bearing spinal components. It should be noted that ROM and loading can be interdependent (Grob et al. 2005; Mulholland and Sengupta 2002; Kirkaldy-Willis and Farfan 1982; Doria et al. 2014), and hence, alteration (or restoration) of one may also impact the other.

One way to classify dynamic stabilization devices is by defining whether the device replaces an existing joint or a mobile anatomical region, or whether it augments it. Thus, preservation of motion after surgery can be achieved by either replacing the entire intervertebral disc (disc replacement), just the nucleus (nucleus replacement), or the facet joints (facet replacement). Alternately, preservation of motion after surgery can be achieved by augmenting the posterior spinal elements. The indications for use of each of these devices can be very different. However, from a biomechanical perspective, each device aims to address the instability introduced by surgery by allowing "some" motion at the joint

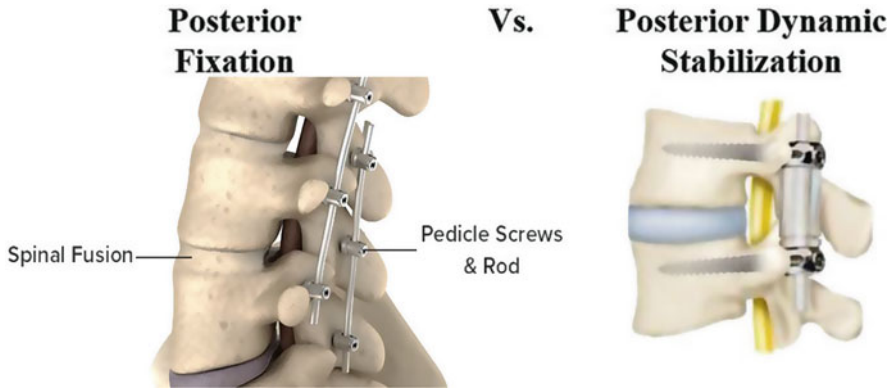

Fig. 4 Posterior fixation vs. Dynesys posterior dynamic stabilization device with flexible components. (Sources: SpinalFusion.jpg and https://www.hindawi.com/journals/aorth/2013/753470.fig.0012.jpg, and "What is Spinal fusion?." *Atlantic Brain and Spine*, www.brainspinesurgery.com/spinal-fusion/)

(vs. fusing the joint) and sharing load within the joint.

This chapter will focus on posterior dynamic stabilization: devices that either allow some motion or control motion at a spinal joint, by augmenting the posterior spinal elements, that is, PDS devices, with a focus pedicle screw and interspinous PDS devices used in the lumbar spine.

Posterior Dynamic Stabilization: Methods for Testing and Performance Evaluation

Pedicle-Based PDS Devices: Preclinical In Vitro Mechanical Testing

Static and dynamic reliability testing of PDS devices is based on standards developed by the American Society for Testing and Materials (ASTM) and/or the International Standardization Organization (ISO). For pedicle screw-based PDS devices, the ASTM F1717 and/or ISO 12189 standards are used for assembly level testing (Fig. 5) (La Barbera et al. 2015), wherein the complete instrumentation system is subjected to bending loads and stresses (Bhamare et al. 2013). These standards describe implant assembly with simulated vertebral body test blocks in either a vertebrectomy model (ASTM F1717) or a model with anterior support (ISO12189 – calibrated springs – Fig. 5) (La Barbera and Villa 2017). While the F1717 standard reflects the worst-case load-bearing scenario, the ISO12189 standard reflects a load-sharing scenario (Fig. 3). In the context of PDS devices, an important distinction between the two standards is the ASTM F1717 may not be directly usable, due to the combination of the allowable degree of freedom in the simulated vertebral body test blocks and the allowable motion of PDS device itself.

Component and Interface Level Static and Dynamic Testing

Component and interface (bone-implant as well as inter-component) testing is also performed both statically and dynamically. In the case of pedicle screw-based PDS devices, component level performance is commonly performed for pedicle screw pullout (ASTM F543) and bending loads (ASTM F1798) as well as for flexible rod component bending strength (ASTM F2193).

For both component and interface level testing, dynamic cyclic testing for pedicle screw-based PDS systems is performed to a runout of 10 million cycles. With 125 significant bends performed annually, 10 million cycles represents 80 years of wear (Vermesan et al. 2014; Schwarzenbach et al. 2005). This testing characterizes the asymptotic endurance level for load/stress, that is, the level below which the implant/ component/material does not fail and can be cycled infinitely.

Preclinical In Vitro Biomechanical Testing and Simulation

PDS devices are commonly evaluated for biomechanical performance characterization using

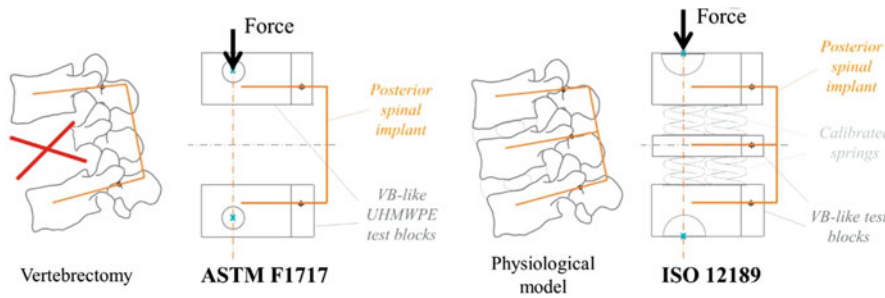

Fig. 5 Testing setups for posterior spinal implants per ASTM F1717 and ISO12189 standards. (Source: https://ars.els-cdn.com/content/image/1-s2.0-S1529943015012024-spinee56502-fig-0001_lrg.jpg)

cadaveric experiments. The primary modes of loading tested in these experiments are shown in Fig. 6 below.

Physiologic loading and range of motion are applied to cadaveric specimens by applying pure moments and a compressive follower load (Patwardhan et al. 1999). Specimens are tested intact, after destabilization surgery, and finally after device implantation under load control or by using a hybrid testing protocol (Goel et al. 2005; Bennett et al. 2015). Testing can also be simulated using finite element (FE) modeling, provided the FE model is validated against experimental results. Figure 7 shows an FE model of the lumbar spine and the corresponding cadaveric experimental setup for testing a dynamic stabilization system.

In addition to characterizing range of motion (ROM), biomechanical testing and simulation also allow for quantification of interpedicular travel (IPT) and displacement (Fig. 8), which is particularly useful for design, development and optimization of dynamic stabilization devices (Cook et al. 2012; Yeager et al. 2015). Limiting interpedicular motion in PDS implants may lead to implant loosening over time (Lima et al. 2017). Using these testing and simulation methods, it has been determined that an axial stiffness of 45 N/mm and bending stiffness of 30 N/mm can reduce spinal ROM by 30% (compared to intact specimen ROM), and this is thought to be an optimal level of motion reduction after surgery (Erbulut et al. 2013; Schmidt et al. 2009). When pedicle screw-based PDS have stiffness characteristics that are greater than optimum, there can be a larger reduction in ROM, thereby rendering their performance almost similar to fusion devices.

Evaluating In Vivo Performance

In addition to ROM measurements from in vivo flexion extension radiographs, IPT measurements can also be characterized in vivo. More recently, translation per degree of rotation (TPDR – Fig. 9) and qualitative stability index (QSI) have been used to characterize instability in vivo (Hipp et al. 2015). A QSI score of 2 indicates a TPDR value 2 standard deviations compared to values observed in healthy controls, and this in turn may indicate instability and poor quality of motion. Similar measurements may also be performed using fluoroscopy (Davis et al. 2015), and these instability measurements can be adapted for evaluating in vivo ROM quality and characterizing in vivo performance of PDS devices. Finally, patient reported outcome measures (PROMs) (Nayak et al. 2015) that quantify quality of life, pain, and disease-specific disability after surgery

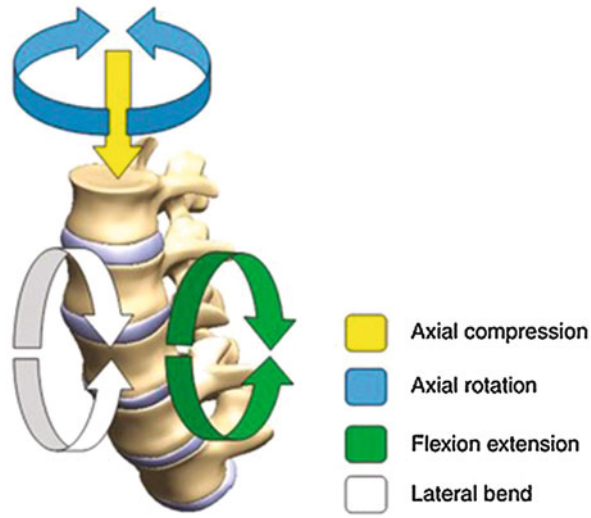

Fig. 6 Primary modes of loading tested in a cadaveric experimental setup. (Source: https://clinicalgate.com/dynamic-stabilization-of-the-lumbar-spine-indications-and-techniques/)

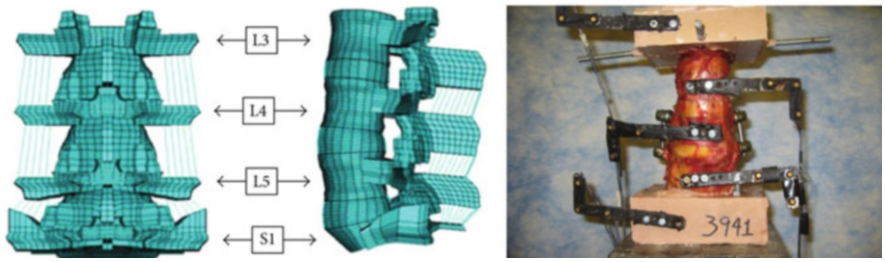

Fig. 7 Finite element modeling of the spine and the corresponding experimental setup. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3626386/)

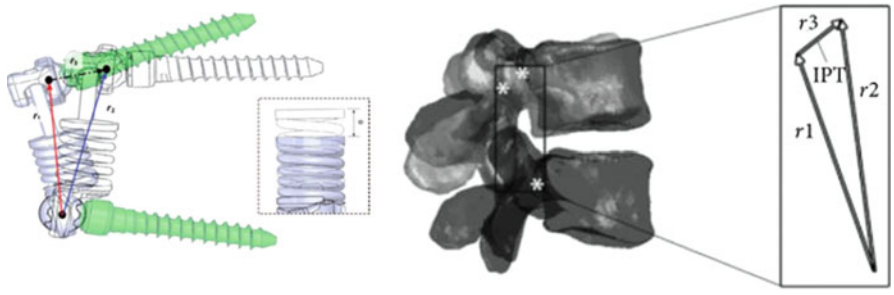

Fig. 8 Interpedicular travel (r3) and displacement measurement for a PDS device during in vitro biomechanical testing. (Sources: http://www.isass.org/pdf/sas10/4-Friday/Abstract_301.pdf and https://www.hindawi.com/journals/aorth/2015/895931/)

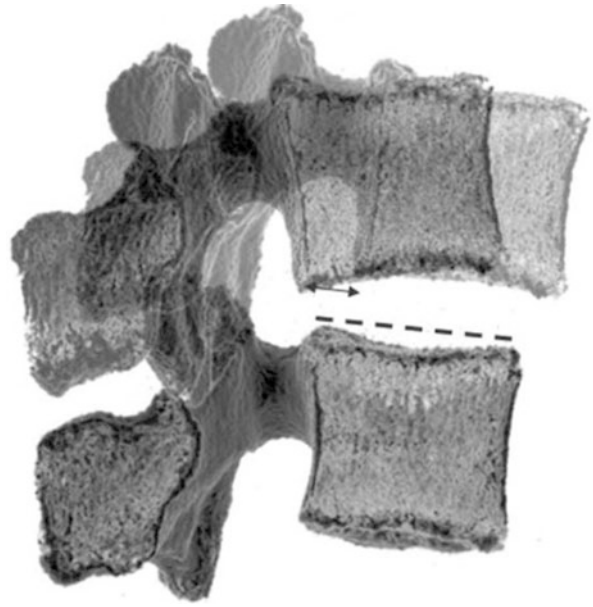

Fig. 9 Measurement of TPDR (translation per degree of rotation) from radiographs. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4528437/)

are critical for evaluating the long-term performance of PDS devices.

Pedicle Screw-Based PDS Devices: In Vivo Performance and Failure Modes

Pedicle screw-based PDS devices are based on instrumentation and techniques that surgeons are most familiar with, due to their experience with posterior fixation for spinal fusion (Barrey et al. 2008). These devices are commonly approved for use in spinal fusion, or as an adjunct to fusion, but not as stand-alone devices in the absence of fusion. Despite familiar surgical techniques and extensive preclinical testing, pedicle screw-based PDS devices are still considered investigational for the treatment of disorders of the spine. One of the main reasons is that it is not yet clear from randomized clinical trials (RCTs) whether pedicle screw-based PDS truly offer advantages over conventional spinal fusion, in terms of health outcomes. Other reasons range from some PDS devices not being truly dynamic (in vivo range of motion is similar to fusion) to device failure and screw loosening (Kaner et al. 2010b; Stoffel et al. 2010; Kocak et al. 2010; Grob et al. 2005; Chen et al. 2011).

Below is a summary of some of the pedicle screw-based PDS devices that have been studied in vivo as stand-alone devices, that is, without fusion and bone graft. A discussion of failure modes, where applicable, is also included.

Accuflex System (Globus Medical Inc.)

The Accuflex system (Fig. 10) consists of a flexible rod anchored by pedicle screws made of titanium alloy. Flexibility in the rod is achieved by helical cuts along the length of the rod. The flexible rod system has undergone extensive in vitro static and dynamic biomechanical testing (Reyes-Sánchez et al. 2010). In a 20-patient study with 2-year follow-up, improvements in all clinical measurements and PROMs were observed (Reyes-Sánchez et al. 2010). However, hardware fatigue failure was also observed in ~22% of the subjects. Failure included rod breakage as well as pedicle screw breakage in the bone. Both these failure mechanisms were caused due a combination of a large bending moment and stress concentration in the failure regions.

BioFlex System (Bio-Spine)

The BioFlex system (Fig. 11) consists of a flexible spring made out of Nitinol (a shape memory alloy) anchored by pedicle screws made out of titanium alloy. In a 12-patient study with 2-year follow-up, reduced ROM was observed at the treated level (compared to ROM before surgery), with minimal

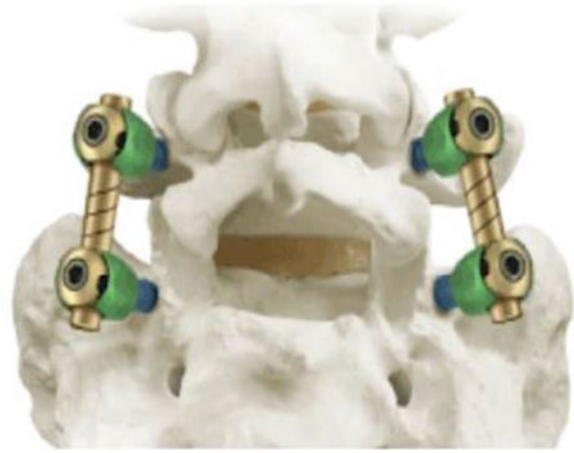

Fig. 10 Accuflex system with a flexible rod. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

Fig. 11 BioFlex system with flexible springs. (Source: https://pubmed.ncbi.nlm.nih.gov/20401848/)

changes at adjacent levels (Zhang et al. 2009). In another study with short-term follow-up (less than 1 year), 28 patients treated solely with the BioFlex (Kim et al. 2007), a similar reduced ROM was observed at the treated level. Limited long-term data is available for this device. It should also be noted that Nitinol is a notch-sensitive material which can reduce fatigue strength (Yoshihara 2013). Notch sensitivity describes the sensitivity of a material to geometric discontinuities and can have a significant negative effect on fatigue strength.

CD Horizon Agile (Medtronic Sofamor Danek)

In the CD Horizon Agile system (Fig. 12), the rod component between the pedicle screws is available in different sizes to offer a less stiff (longer spacer) or a more stiff (shorter spacer) option for dynamic stabilization. The spacer, made out of a thermoplastic polymer (polycarbonate urethane or PCU), encloses a titanium alloy cable. While allowing a greater ROM that most other PDS devices, the implant was noted to break due to shear-related failure of the cable component, particularly in cases of advanced instability (Doria et al. 2014). Shear-related failure occurred due to kinking of the cable component during anterior-posterior translation of the spinal segment (Hoff et al. 2012).

Cosmic Posterior Dynamic System (Ulrich Medical)

The Cosmic posterior dynamic system (Fig. 13) includes a hinged pedicle screw which can reduce stresses at the bone screw interface while allowing segmental motion (Gomleksiz et al. 2012). The pedicle screw (threads) includes a calcium phosphate coating to promote osteointegration. The rod in this system is rigid. In a study with 30 patients and over 3 years of follow-up (Kaner et al. 2010a), significant improvement in PROMs were observed, and no screw breakage was observed. One instance of screw loosening was reported.

Dynesys (Zimmer Biomet)

Dynesys (Fig. 4, right) has the largest amount of clinical follow-up data, compared to other pedicle screw-based PDS. Between the pedicle screws, the system consists of a thermoplastic spacer (PCU) that encloses a cord (made out of polyethylene terephthalate or PET). A comprehensive literature review (Pham et al. 2016) spanning 21 studies and a total of 1166 patients with mean follow-up of almost 3 years has shown that the pedicle screw loosening rate is ~12% (higher than the rate commonly observed after fusion) and ASD rate is ~7%, (slightly lower than the rate commonly observed after fusion). The pedicle screw fracture rate for Dynesys was less than 2%. In another study with 46 patients and mean follow-up of over 4 years (Zhang et al. 2016), significant improvements in PROMs were observed for patients treated with Dynesys,

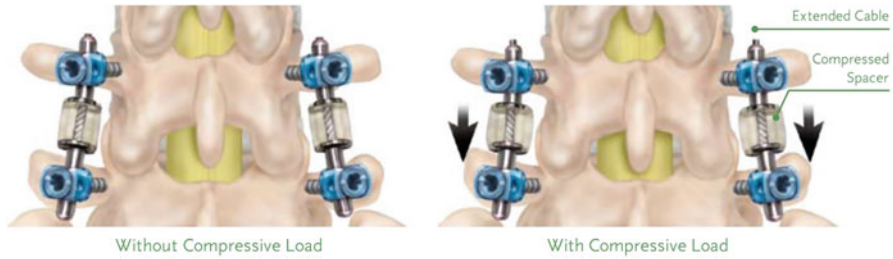

Fig. 12 CD Horizon Agile. (Source https://pubmed.ncbi.nlm.nih.gov/20401848/)

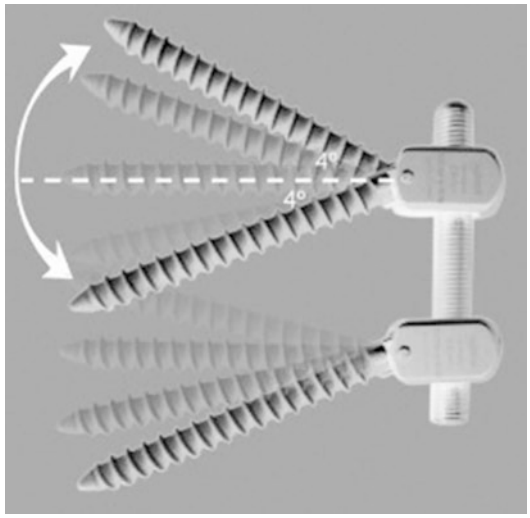

Fig. 13 Cosmic PDS with a hinged pedicle screw. (Source: https://pubmed.ncbi.nlm.nih.gov/20401848/)

as well as for patients treated with fusion. While the mean ROM (flexion-extension radiographs) was lower than 5° for both groups (patients treated with Dynesys or fusion), the Dynesys system did allow slight greater ROM and lower ASD rate, compared to patients treated with fusion.

Graf Ligament (SEM Co.)

The Graf ligament (Fig. 14) represents the earliest attempts in using a flexible PDS. The device includes a braided polyester (polypropylene) tension band between titanium pedicle screws.

The hypothesis for this device was that abnormal rotational motion was responsible for pain generation, and this device was designed to control the same by locking the lumbar facets in an extended position (Doria et al. 2014; Erbulut et al. 2013). The Graf ligament transfers load from the anterior disc to the posterior annulus, increasing disc pressure, which can accelerate disc degeneration (Gomleksiz et al. 2012) and even cause lateral recess stenosis. In a review of 43 patients with a minimum of 8 years follow-up (Choi et al. 2009), angular instability was observed in 28% of the segments, while translational instability was observed in 5% of the segments. Additionally, adjacent segment instability was observed in 42% and 30% of the subjects at the upper and lower segments, respectively. No instrumentation failures were reported. In another study with 31 patients and 7-year follow-up, significant improvements in PROMs have been reported, despite an established degenerative process (Gardner and Pande 2002).

Isobar TTL (Scient'x)

The Isobar TTL system (Fig. 15) is composed of a semirigid titanium alloy rod with a dampener stacked with titanium alloy rings. This rod is inserted between titanium alloy pedicle screws and the system allows some axial and angular motion. In a review of 37 patients with a mean follow-up of 2 years, excellent improvement PROMs have been reported (Li et al. 2013). However, ROM after surgery was significantly lower (compared to ROM before surgery) and new signs

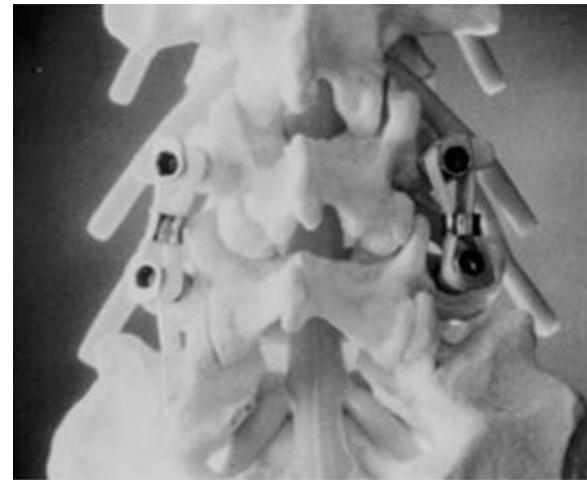

Fig. 14 Graf ligament inserted between pedicle screws. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

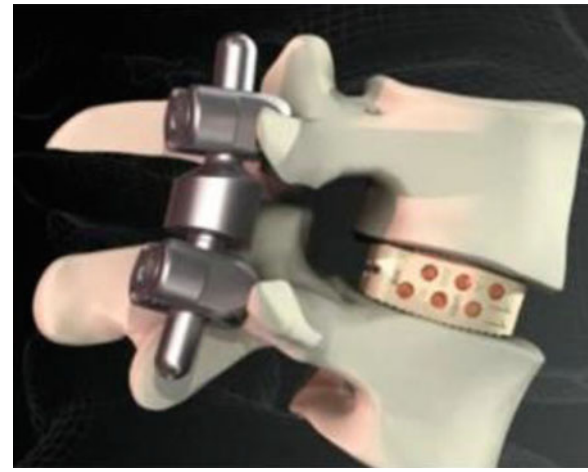

Fig. 15 Isobar semi-rigid rod. (Source https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

of degeneration were observed at adjacent levels in 39% of the patients, with 8% of the patients requiring revision due to ASD.

NFlex (Synthes Spine)

In the NFlex device (Fig. 16), a polyaxial titanium alloy pedicle screw is affixed to a central titanium core which is integrated with a PCU spacer. This design allows for a physiologic change in interpedicular distance (Fig. 8). In a study reporting 2-year clinical outcomes in 65 patients (Coe et al. 2012), 25 patients received non-fusion dynamic stabilization solely with Isobar TTL. Significant improvements in PROMs were observed in these patients, with one instance each of rod fracture and pedicle screw loosening.

Stabilimax NZ (Rachiotek LLC)

The Stabilimax NZ device (Fig. 17) aims to provide maximum support in the neutral zone (NZ – the initial portion of the total range of

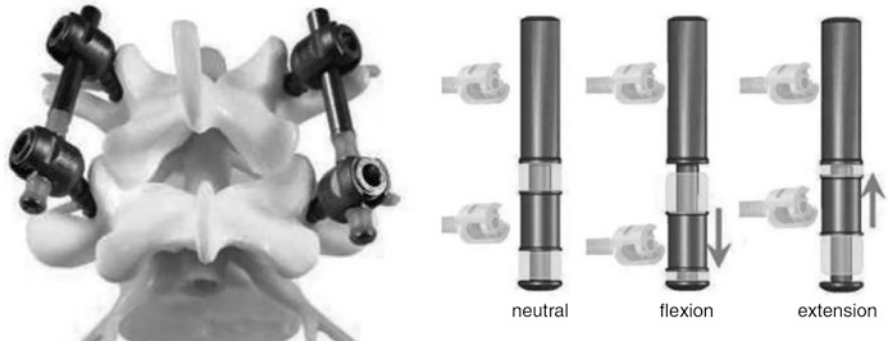

Fig. 16 NFlex device in neutral, flexion and extension positions. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3424174/)

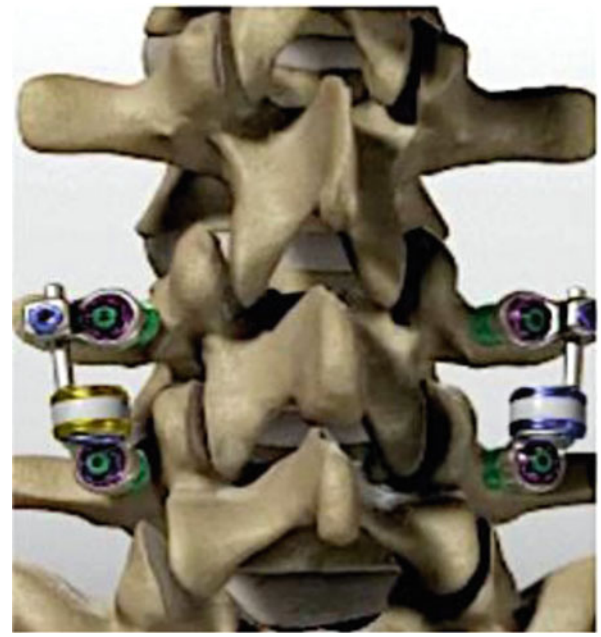

Fig. 17 Stabilimax NZ device dual springs and ball-socket joints. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

motion, where minimal resistance to motion is offered by passive spinal structures) while maintaining maximum possible total range of motion (reduced support in the final portion of total range of motion, where maximal resistance to motion is offered by active and passive spinal structures) (Panjabi and Timm 2007). This is achieved through the use of dual concentric springs that permit physiologic interpedicular travel and the use of ball and socket joints to reduce bending moment at the bone screw interface and permitting axial rotation. In a preliminary report on 60 patients with 2-year follow-up (Neel Anand et al. 2012), significant improvements in PROMs were observed. IPT travel (Fig. 8) was also physiologic. However, pedicle screw breakage was also seen in 10% of the cases. Grit blasted surface of the pedicle screws was found to be the root cause of failure (grit blasting of titanium alloy screws can promote osteointegration, but it can also make the surface notch sensitive, thereby reducing fatigue life). The surface treatment was later changed using laser shock peening (LSP). LSP improves fatigue life by impacting residual stresses (Bhamare et al. 2013).

Percudyn (Interventional Spine)

In the Percudyn device (Fig. 18), a PCU stabilizer is installed onto an anchor. This is a pedicle screw-based device without an interpedicular connection. Biomechanically, the Percudyn device serves to augment the posterior elements of the functional facet by serving as a mechanical stop between the inferior and superior articular facets (Smith et al. 2011). In a study reporting on 96 patients at a 2-year follow-up period (Canero and Carbone 2015), significant improvements were observed in PROMs, with more than 70% of the patients satisfied with the procedure, while 10% of the patients required revision surgery at longer follow-up.

Interspinous Devices: Preclinical In Vitro Mechanical Testing

The motion preserving interspinous devices could be divided into devices that oppose motion in a rigid manner and devices that oppose it in a flexible manner. Rigid, or static, devices consist of relatively noncompressible solid materials like titanium or PEEK; their main function is to ensure a consistent level of posterior distraction during extension. The flexible interspinous devices allow for compression during extension and could be classified as flexible/dynamic devices. They offer a higher level of elasticity that allows their deformation during extension. This is achieved by the material and/or their shape.

Parchi et al. 2014 have characterized the biomechanical effects of interspinous devices by:

1. Modifying/Stabilizing the motion segment and altering the range of motion (ROM)
2. Decompression of the spinal canal and foramina via posterior distraction
3. Reduction of intradiscal pressure and facet load
4. Impact on sagittal alignment and instantaneous axis of rotation (IAR) of the treated segment

Human cadaveric studies to investigate the range of motion, instantaneous access or rotation, or measuring the intradiscal pressures of intact condition and post-decompression and/or interspinous device insertion are commonly used to evaluate the in vitro performance of these devices. Several biomechanical studies on interspinous device are reported in literature (Lindsey et al. 2003, Phillips et al. 2006, Tsai et al. 2006, Lafage et al. 2007). In cadaveric studies, interspinous devices improve the stability of the treated motion segment in flexion-extension but do not stabilize the spine in axial rotation or lateral bending. Zheng et al. (2010) found also that size of the interspinous device affect their performance, smaller interspinous device did not provide the stabilization of larger devices. He found that using a spacer with height equal to the distance of the interspinous process was associated with a slight flexion of the segment and less effects on the dimension of the spinal canal and foramen. An oversized device, on the other hand, could induce a kyphotic position and may increase disc loading. Selecting the appropriate device design, size, and material while taking in consideration the treatment goal, patients' pathology, bone quality, and

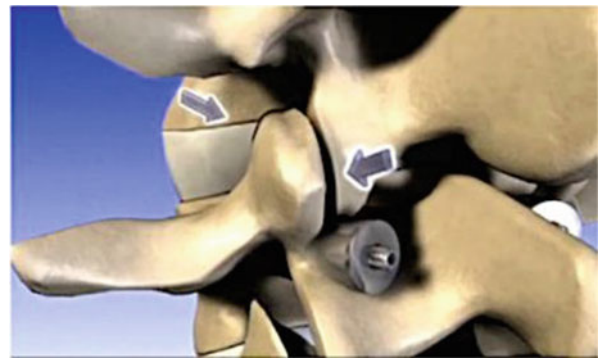

Fig. 18 Percudyn PCU spacer inserted onto the anchor. (Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

symptoms should be carefully considered to achieve the best biomechanical and clinical outcome.

Posterior Dynamic Interspinous Devices: In Vivo Performance and Failure Modes

The interspinous devices were designed as an alternative treatment for neurogenic claudication and pain which is attributed to facet joint disease. The spine is kept in a flexed position by which the interspinous devices increase the total canal and foraminal size, which decompresses the cauda equina, which is responsible for neurogenic claudication. This device allows for neural decompression with minimal tissue resection; thus, the device is less invasive and can be implanted without a laminectomy. It avoids the risk of epidural scaring and cerebrospinal fluid leakage by functioning through indirect decompression. In some cases, interspinous dynamic stabilization is used to prevent the instability that occurs after decompression.

These devices limit extension of the spine, allow for the unloading of the facet joint, and allow for the relief of pain attributed to facet disease as well (Khoueir et al. 2007). The notion of interspinous device to produce segmental posterior distraction was first introduced in the 1960s by Dr. Fred Knowles. He is better known for his hip pin design; however, he reported limited success with the spinal device due to subsidence and displacement. His ideas were latter improved upon, in the form of the Xstop device (Kyphon, Sunnyvale, California). There have been multiple interspinous devices which have been developed, such as the X-stop, DIAM, Wallis system, and the CoFlex system. All these devices work to limit spinal extension. The interspinous spacers may be helpful when more conservative (nonoperative) care does not improve symptoms. All of these devices allow the spine to be held in a position of slight flexion, in order to decompress the spinal cord or nerve roots. The spine, however, may still rotate axially or bend laterally when the device is in place.

The Wallis System (Zimmer)

The Wallis system was the first interspinous device introduced in Europe around 1986 and was developed by Sénégas (Fig. 19). The design originated with a titanium block inserted between adjacent processes, which is then held in place with a flat Dacron cord or ribbon wrapped around the spinous process above and below the block. This first-generation device provided positive results and so the second generation of Wallis implants was developed. The main change was seen in the material used for the interspinous block, which was changed to PEEK, which is a

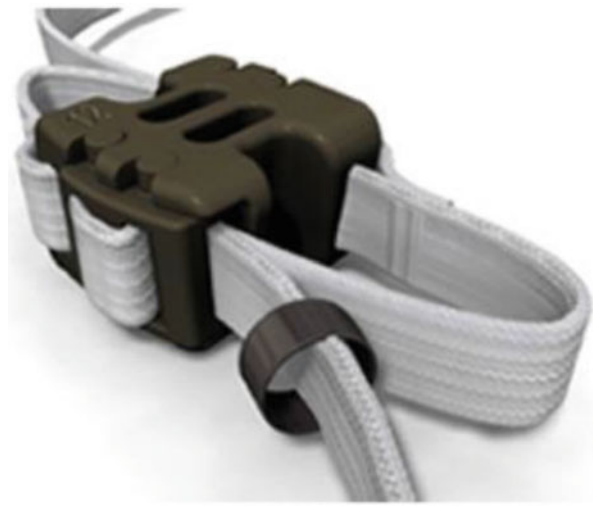

Fig. 19 Wallis® posterior dynamic stabilization system (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

plastic like polymer that has more flexibility than titanium. The design and material allow for the minimization of the need for bone resection. In a controlled study which was done between 1998 and 1993, more than 300 patients were treated for degenerative lesions, in which positive results were found. Trials of the first-generation implant provided evidence that the interspinous system of nonrigid stabilization is effective against lower back pain caused by degenerative instability (Anderson et al. 2006). More recently Song et al. (2019)) provided information on 33 patients treated for degenerative lumbar spine diseases with the Wallis system. ROM of surgical segments was significantly lower than those before operation ($P < 0.05$), while ROM of the upper and lower adjacent segments and disc height did not change significantly ($P > 0.05$).

X-STOP (Medtronic)

The X-stop is made of titanium and PEEK components, with side wings encapsulating the lateral sides of the spinous processes to reduce the risk of implant migration (Fig. 20). FDA approval was obtained in 2005 after a 2-year clinical study. The device is approved for use in patients aged 50 years or older with lower-extremity neurogenic pain from lumbar spinal stenosis and can be implanted under local anesthesia. In the pilot study, inclusion criteria were mild or moderate symptoms that were relieved by flexion and the ability to walk at least 50 ft. Exclusion criteria were a fixed motor deficit or prior treatment with X-stop (Anderson et al. 2006).

DIAM (Medtronic)

The Device for Intervertebral Assisted Motion (DIAM) is made of a silicon H-shaped spacer encased within a Polyethylene terephthalate (Polyester) jacket that is secured (after removal of the interspinous ligament) with two associated tethers, around the supra-adjacent and sub-adjacent spinous processes (Fig. 21). In the past, DIAM has been successful in long-term treatment of lower back pain caused by degenerative disc disease. The first clinical case was performed in 1997 in France, and 25,000 patients have been treated outside the United States since then. In 2010 study, Buric et al. found that over two-thirds of patients achieved and maintained significant, clinically apparent differences in both VAS scores and Roland-Morris Disability Questionnaire (RMDQ) scores over a 48-month period (Buric and Pulidori 2011). FDA

Fig. 20 X-Stop device interspinous spacer Medtronic (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

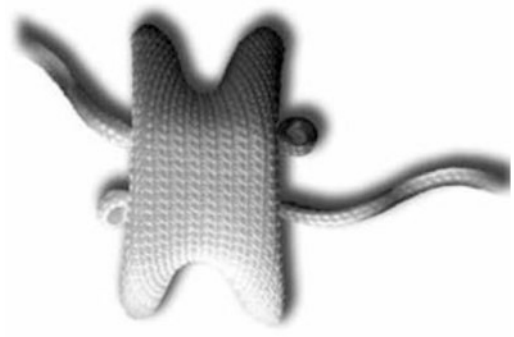

Fig. 21 Device for intervertebral assisted motion (DIAM) (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

randomized clinical trials to evaluate the effectiveness of DIAM versus decompression versus posterolateral fusion were completed in December 2010. However, in 2016 the FDA's Orthopedic and Rehabilitation Devices Panel of the Medical Devices Advisory Committee recommended against approval for the DIAM spinal stabilization system.

Recent study by Krappel et al. (2017) reported on a multicenter prospective randomized clinical study of 146 patients with a single level disc herniation (L2 to L5): 75 investigational (herniectomy and DIAM) and 71 control (herniectomy alone) treated and followed up for 24 months. Leg pain, back pain, and the level of disability were not significantly different between groups; however, the number of patients reaching the minimum clinically important difference (MCID) improvement for back pain was significantly higher in the investigational group at 6 through 24 months.

Coflex Interlaminar Stabilization Device (RTI Surgical)

The CoFlex is based on the interspinous-U design from Fixano (Péronnas, France) that was clinically used from 1995 onward (Fig. 22). It is made in its classic form as a titanium U-shaped metal design that is maintained between spinous processes with side wings, so as to control movement while allowing motion, being marketed as a non-fusion

Fig. 22 Coflex® interlaminar stabilization (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

device. In 2012 the FDA approved the Coflex device after an IDE study.

Schmidt et al. (2018) performed a prospective, randomized, multicenter study with 2-year follow-up to compare the performance of decompression with and without Coflex interlaminar stabilization. This study reports a multicenter, randomized controlled trial in which decompression with interlaminar stabilization (D + ILS) was compared with decompression alone decompression alone (DA) for treatment of moderate to severe lumbar spinal stenosis. 230 patients (1:1 ratio) randomized to either DA or D + ILS (Coflex) were treated at seven sites in Germany. There was no significant difference in the individual patient-reported outcomes (e.g., ODI, VAS, ZCQ) between the treatments. However, microsurgical D + ILS increases walking distance, decreases compensatory pain management, and maintains radiographic foraminal height, extending the durability and sustainability of a decompression procedure. To date, Coflex has been implanted in more than 163,000 patients in over 60 countries worldwide.

In recent years multiple companies have offered various devices, such as NuVasive with ExtendSure; Biomech's (Taipei, Taiwan) Promise and Rocker designs, made of PEEK and mobile core and articulated design, respectively; Cousin Biotech (Wervicq-Sud, France) with Biolig silicon encapsulated in woven synthetics; Alphatec (Carlsbad, California) with the HeliFix screwtype PEEK space design; Vertiflex (San Clemente, California) with the Superion implant whose deployable wings aim at less invasive insertion (FDA cleared after completing PMA clinical studies in 2016); Orthofix (Bussolengo, Italy) with InSWing; Pioneer with BacJac; Maxx Spine (Bad Schwalbach, Germany) with I-MAXX; Sintea Plustek (Assago, Italy) with Viking; Globus Medical with Flexus; and Privelop (Neunkirchen-Seelscheid, Germany) (Serhan et al. 2011) (Fig. 23).

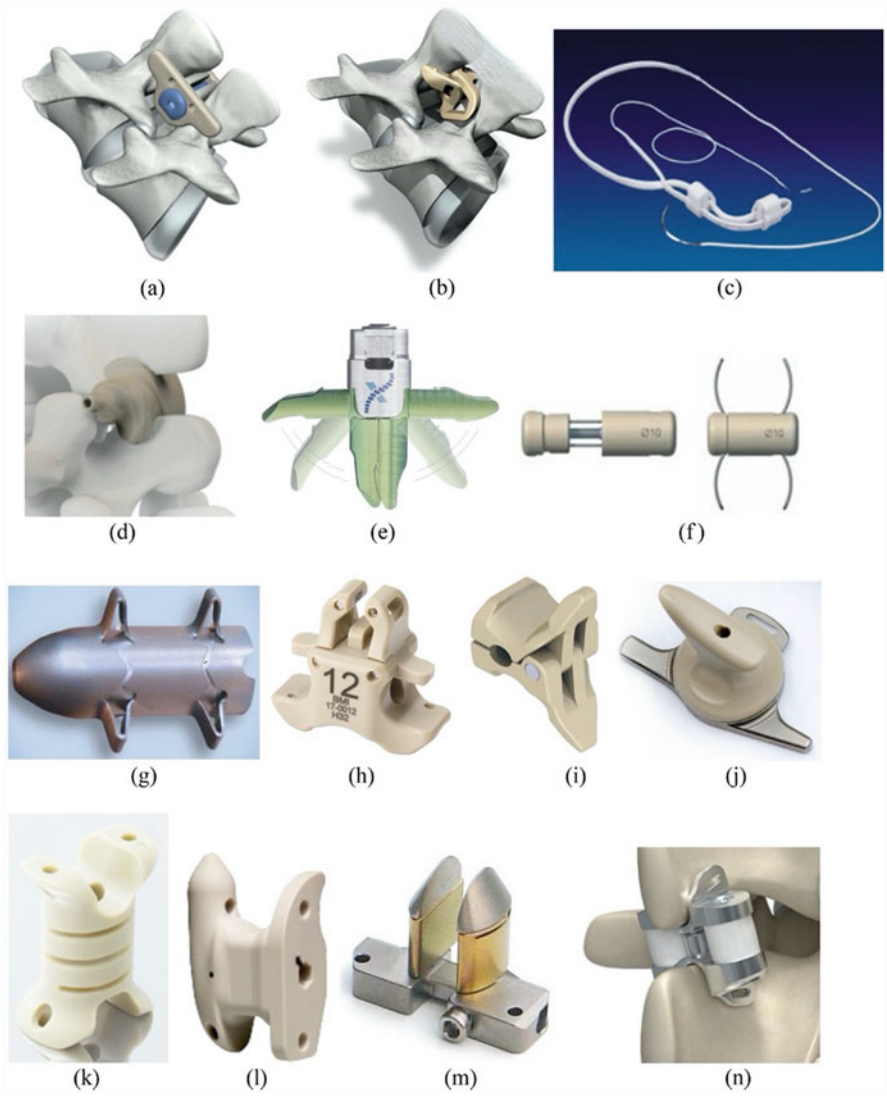

Fig. 23 Other interspinous spacer alternatives: (a) Promise; (b) Rocker; (c) Biolig; (d) HeliFix; (e) Superion; (f) InSpace; (g) Aperius; (h) InSWing; (i) BacJac; (j) I-MAXX; (k) Viking; (l) Flexus; (m) Spinos; and (n) Wellex (Eden Spine) source (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4365627/)

Discussion

Traditional fusion continues to be the gold standard for treating degenerative spinal disorders. Dynamic spinal stabilization is based on the concept of restricting movement of spinal segments rather than preventing the movement, that is, it restricts movements in the directions that may cause pain or instability, but permits motion in other directions. Dynamic spinal stabilization can achieve spinal stability and prevent diseases of adjacent segments without requiring fusion. Clinical indications for the use of PDS devices are still very broad and lack sufficient evidence. Scientific reviews have indicated that use of PDS pedicle-based systems as an adjunct to fusion may be acceptable. In fact, a majority of the devices described above as well as other devices (Transition: Globus Medical, and CD Horizon Legacy PEEK rod: Medtronic Sofamor Danek, to name a few) are successfully used as an adjunct to fusion across one or multiple spinal levels. However, fatigue failure is a concern when pedicle screw-based PDS systems are used as stand-alone stabilization devices. Failures have been reported at both the implant component interfaces as well as the bone implant interface. In terms of patient reported scores, PDS systems have produced clinical outcomes comparable to that of fusion, and the incidence of ASD is lower when compared to fusion, at least during short-term follow-up. RCTs with long-term follow-up are required to confirm whether the incidence of symptomatic ASD (and not just radiographic ASD) continues to stay lower when compared to fusion, as well as to prove the safety and efficacy of PDS devices. In summary, improvements in in vitro testing modalities, fatigue behavior, long-term follow-up, and a clear definition of clinical indications for using PDS as stand-alone stabilization devices are required to verify the benefits of this technology.

Similar to pedicle-based dynamic stabilization, interspinous devices are indicated to treat skeletally mature patients suffering from pain, numbness, and/or cramping in the legs (neurogenic intermittent claudication) secondary to a diagnosis of moderate degenerative lumbar spinal stenosis, with or without grade 1 spondylolisthesis, confirmed by x-ray, MRI, and/or CT evidence of thickened ligamentum flavum, narrowed lateral recess, and/or central canal or foraminal narrowing. Interspinous devices are also indicated for patients with impaired physical function who experience relief in flexion from symptoms of leg/buttock/groin pain, numbness, and/or cramping, with or without back pain, and who have undergone at least 6 months of nonoperative treatment. Interspinous devices may be implanted at one or two adjacent lumbar levels in patients in whom treatment is indicated at no more than two levels, from L1 to L5 (Khoueir et al. 2007; Senegas 2002).

Interspinous dynamic stabilization has theoretical advantages over conventional fusion, as it maintains stability by restricting mobility, whereas fusion simply prevents motion. Relatively good clinical results have been reported in the literature. However, despite the increasing use of this technology, few long-term review studies have been conducted to assess its safety and efficacy. Interspinous dynamic stabilization produced slightly better clinical outcomes than conservative treatments for spinal stenosis. The complication rate of interspinous dynamic stabilization has been reported to be 0–32.3% in 3- to 41-month follow-up studies. The complication rate of combined interspinous dynamic stabilization and decompression treatment (32.3%) was greater than that of decompression alone (6.5%), but no complication that significantly affected treatment results was found (Anderson et al. 2006; Zucherman et al. 2005). The typical complications of interspinous devices include spinous process fracture, especially with stiff design; novel radiculopathy, especially with devices with limited motion-constraining ability; and returning or increased pain around the implant area. Implant dislodgement is also a potential complication, particularly in those designs with limited fixation means. Compared to stiff and rigid interspinous designs, dynamic designs such as the Wallis or Coflex have relatively lower device complications.

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Lessons Learned from Positive Biomechanics and Poor Clinical Outcomes

14

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Abstract

Biomechanical testings are essential to the research process. However, understanding the assumptions, inevitable part of engineering solution as it translates to clinical outcomes is paramount to the iterative process in implant design. Therefore, it is critical to consider that beneficial biomechanical data may not actually yield good clinical outcomes.

Keywords

Spine biomechanics · Clinical outcome · Spinal fusion · Dynamic Stabilization · Adjacent segment degeneration

Design excellence tools have been widely used for many years, historically mainly in the automotive industry, and more recently in the medical device industry. A plethora of tools are available; however, only their appropriate selection and deployment during the various stages of the new medical device development can optimize the overall process.

In every lab-based biomechanical study (i.e., finite element (FE) analyses, in vitro, in vivo, etc.), there is a "limitations" section stating the assumptions that the reader should keep in mind for proper interpretation of the findings. Such assumptions for real-life scenarios are inevitable and are the part of engineering solutions. Similarly, long- and short-term clinical outcomes of a study will highlight the discrepancies between actual biomechanical data and surgical outcomes, for example. Thus, beneficial biomechanical data may not actually yield good clinical outcomes. The design and development of a medical device is an iterative process, and decreasing the number of iterations can be helpful. This chapter addresses these issues for the devices specifically used to provide stability to the spine with the ultimate goal of improving patient satisfaction.

Preclinical tests are necessary for evaluating the safety and efficacy of new techniques and devices including: biocompatibility, structural integrity, and biomechanical performance before clinical trials. Biomechanical testing for a spinal device involves multiple steps, including bench-top testing as per ASTM and ISO standards, cadaver studies, etc. Safety can be evaluated with biocompatibility and mechanical tests, and efficacy can be investigated with finite element analysis (FEA), in vitro, and animal tests. Although finite element modeling (FEM) (Fig. 1a) technique has limitations, nowadays, this technique is part of the first step in biomechanical investigations due to its many advantages (Agarwal et al. 2017). The advantages include relatively shorter completion time, ability to analyze complex engineering problems, and undertaking parametric studies, to name a few. Additionally, many engineering parameters important for the design and development of a medical device, such as reaction force, stress, strain, and load transmission, are among the various components that can be obtained. It is not practical to understand the roles of these parameters using any other testing protocol. FEM's ability to analyze failures and to modify the parameters accordingly with minimal effort and time makes FEM a strong engineering tool in the biomedical device industry.

In mechanical testing, a spinal implant must stay functional during both static and dynamic tests (predicting lifetime) to determine the worst-case scenarios for failure. Commonly, test protocols are developed as per the international standards, i.e., ISO and ASTM (Fig. 1b). In vitro cadaver or animal studies assess the performance of a device in response to clinically relevant loads or displacements. These studies allow for the measurement of stiffness or flexibility of the construct (Fig. 1c). In flexibility protocols, range of motion in three main planes in response to the applied loads can be compared to the intact spine. The data can be further processed to determine

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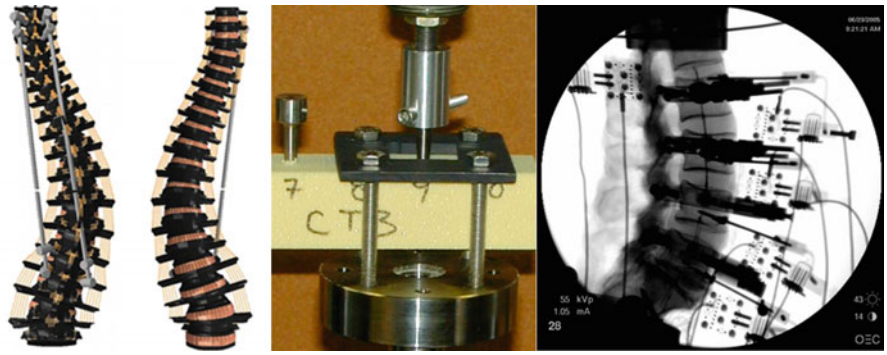

Fig. 1 (**a**) Intact and instrumented scoliotic FEM (Agarwal et al. 2017), (**b**) Mechanical setup for pull-out testing of a pedicle screw, and (**c**) Radiograph of a cadaveric lumbar spine testing setup. Showing follower preload path to simulate muscle action in an in vitro protocol. The LED markers attached to the vertebral bodies allow determination of the construct kinematics (Goel et al. 2006)

instantaneous center of rotation, neutral zone, disc height, disc bulge, spinal alignment, creep, and viscoelastic behavior of the system, etc. Also, transducers can be placed at relevant locations on the constructs to investigate other parameters such as intradiscal pressure and elongation (Goel et al. 2006).

Positive data from such studies can allow for the manufacturing of devices that are better targeted for clinical applications in patients. Nonetheless, there are also inherent limitations as the cadaveric specimens do not represent the variabilities in patient populations and differences in age, gender, and pathologies encountered in real life. Therefore, the final safety and efficacy of a new technique or system can only be revealed following clinical trials – an iterative process as stated above.

Spinal fusion technique may be the best example to start with to raise the issue of "positive biomechanics and poor clinical outcomes." For instance, although more than 90% of the fusion treatments deliver the expected biomechanical fusion outcome immediately after the surgery, reported successful clinical outcomes have only been reported up to 70%.

Spinal Fusion

Adjacent segment degeneration: Spinal fusion is widely accepted for the treatment of discogenic pain, segmental spinal instability or spondylolisthesis, and spinal deformity. It is well-known that spinal fusion provides stability to the index segment/s and can relieve back pain after the surgery. Targeted area/s within the spinal functional unit for bony fusion are the spinous processes, the transverse processes, the laminae, the facet joints, and the intervertebral disc spaces (Evans 1985). Lumbar fusion shows positive biomechanical research outcomes in terms of immediate segmental stability and does not represent the fusion that matures over time. Furthermore, it is almost impossible to predict devices functionality in the body, as the device interacts with spinal boney tissues during daily activities that could lead to device loosening, subsidence, and/or migration.

Spinal fusion treatment adjusts the motion and load transmission at the index levels. This segmental adjustment causes higher motion and stress distribution on the adjacent segments, which can lead to subsequent degeneration called adjacent segment degeneration (ASD). Clinical reports of ASD following spinal fusion in patients were sparse in the 1950s (Unander-Scharin 1950; Anderson 1956). It became evident once long-term clinical outcomes were analyzed. We now know that spinal fusion techniques can be one of the contributing factors to ASD. The prevalence of radiographic ASD postoperatively after spinal fusion is high. Potential risk factors associated with adjacent segment disease after spinal fusions include injuries to the facet joint of the adjacent

segment, fusion length, sagittal alignment, pre-existing degenerated disc disease at the adjacent levels, lumbar stenosis, age, osteoporosis, female gender, and postmenopausal state (Park et al. 2004; Moreau et al. 2016). Due to many risk factors not predicted by earlier biomechanical studies, the importance of future research with expended objectives is paramount (Eck et al. 2002; Chin et al. 2016; Voronov et al. 2016; Lafage et al. 2017; Natarajan and Andersson 2017).

Spinal instability can cause back pain. In the case of instability, spinal fusion has been advocated as the gold standard treatment to relieve associated back pain. Spinal instability can be described as abnormal motion at the joint and/or load transmission. For example, changes in the mechanical properties of the intervertebral disc (due to degeneration, replacement with artificial discs, and interbody augmentation) can alter the normal load transmission. Studies suggest that the altered load transmission pattern causes the pain, rather than changes in load magnitude. Obviously, fusion techniques will lead to altered load transmission at the index and adjacent segments. Over time, at the adjacent levels, the increased force and hypermobility may lead not only to disc degeneration, but also to hypertrophic degenerative arthritis of the facet joints, spinal stenosis, degenerative spondylolisthesis, or herniated nucleus pulposes (Brodsky 1976; Lee 1988; Wimmer et al. 1997; Etebar and Cahill 1999; Kumar et al. 2001). Biomechanical studies, at least in the past, were not able to address all of these variables.

Many studies have reported the effects of fusion techniques and related incidence of ASD as fusion can lead to additional surgeries (Whitecloud et al. 1994; Schlegel et al. 1996; Phillips et al. 2000; Chen et al. 2001a, b). Lee's biomechanical study published in 1984 (Lee and Langrana 1984) reported the altered kinematics and biomechanics of three different fusion procedures (posterior, bilateral, and anterior) at the index and adjacent segments. The study demonstrated the desirable stability effects of all the fusion techniques, but increased stress on the adjacent segments specifically at the facet joints was observed. The same authors published a clinical study reporting 18 patients who developed adjacent segment symptoms after the first 5 years of fusion treatment (Lee 1988).

The study of Evans (1985) indicated lists of essential biomechanical criteria of a good fusion device. For example, the intensity of force or stress on the graft should not be so great as to damage the fusion device. Optimal grafts should bear loads without graft migration immediately following surgery, and it should resist shear force to prevent sliding on the host bone. The study also showed the potential restoration of normal anatomic functionality of the treated segment. This raises the following question: If the segment is fused and the segmental motion eliminated, how can the force be transferred comparable to a normal intact spinal segment? Brodke et al. (1997) investigated initial stiffness of posterior lumbar interbody fusions with rigid posterior instrumentation. The additional posterior instrumentation along with interbody graft led to increased stiffness and prevented graft reposition. Eck et al. (2002) performed a cadaver study to investigate biomechanical effect of cervical spinal fusion on adjacent level intradiscal pressure. They found that the intradiscal pressure increased by up to 73.2% and 45.3% at superior and inferior adjacent level, respectively. These results suggest a biomechanical cause of disc degeneration at the adjacent levels. Other studies have reported that up to 40% of postfusion low back pain involves the sacroiliac joint (SIJ) (Katz et al. 2003; Maigne and Planchon 2005). FE studies have predicted that posterior lumbar spinal fusion causes increases in motion and stress across the SIJ (Fig. 2) (Ivanov et al. 2009).

One of the risk factors for adjacent segment degeneration is postoperative lumbar sagittal misalignment caused by rigid fixation, as well as the number of treated level (Umehara et al. 2000). At the end, postoperative lumbar sagittal malalignment and loss of motion at the fused level change the structural response to external loads. Therefore, one can expect accelerated degenerative changes at the levels adjacent to the fusion site secondary to hypo-lordosis in the instrumented segment. Additionally,

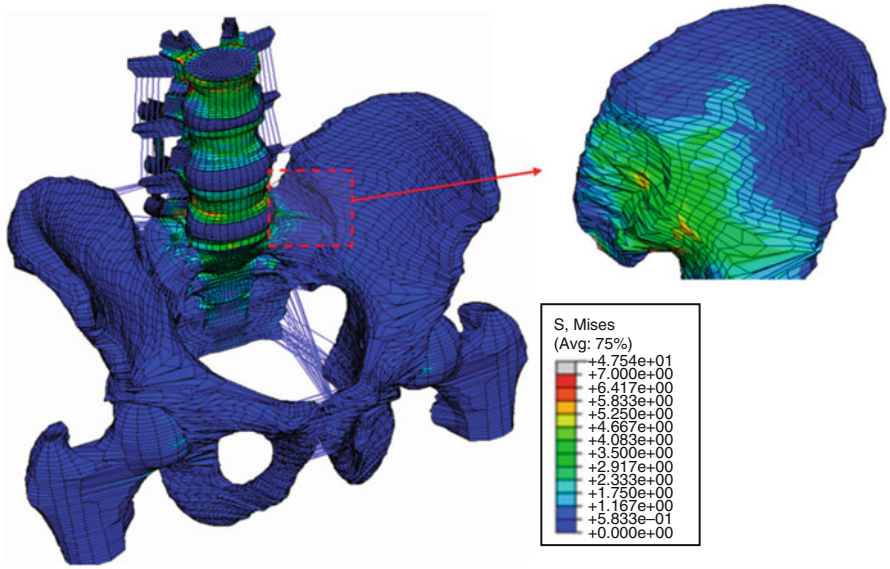

Fig. 2 Finite element model (FEM) of the lumbar spine and pelvis. Stress distribution at the sacroiliac area after simulation is shown. Sacroiliac joint reaction was observed using the model with L4-S1 fusion under 25 Nm bending moment and 400 N compressive follower load (Ivanov et al. 2009)

the load across the posterior transpediclular devices increases due to hyperlordosis. Similarly, Akamaru et al. (2003) reported a very large increase in flexion/extension motion at proximal and distal adjacent levels with hypo-lordotic alignment, compared to the intact spine.

Reports have demonstrated good result with posterior lumbar fusion with pedicle screw fixation. In spite of the procedure at achieving successful spinal fusion, long-term follow-up studies have revealed postoperative segmental instability, spinal stenosis, intervertebral disc herniation, retrospondylolisthesis, and fracture at the adjacent segments (Brunet and Wiley 1984; Whitecloud et al. 1994; Kerr et al. 2015). More recently, significant correlation between thoracic kyphosis, lumbar lordosis, pelvic tilt (PT) and pelvic incidence (PI) parameters, and the occurrence of ASD after lumbar fusion has been reported (Rothenfluh et al. 2015; Nakashima et al. 2015; Yamasaki et al. 2017; Matsumoto et al. 2017). Patients having a pelvic incidence-lumbar lordosis mismatch (greater than +/− 10°) exhibit a ten times higher risk for undergoing revision surgery compared to nonmismatched patients (Rothenfluh et al. 2015). The risk of ASD incidence was 5.1 times greater in subjects with preoperative PT greater than 22.5° (Yamasaki et al. 2017). Matsumoto et al., through finite element model simulations of various parameters, found that the preoperative global sagittal imbalance (SVA >50 mm and higher PT), lower pre- and postoperative LL, and a PI-LL mismatch were significantly associated with ASD (Matsumoto et al. 2017; Shah et al. 2019). This study has revealed the biomechanical relationship between ASD (proximal and distal junctions) and different spinal and pelvic parameters following lumbar arthrodesis. A validated FE model from T1 to femur without rib cage was used. The sagittal vertical axis (SVA), lumbar lordosis (LL), thoracic kyphosis (TK), pelvic incidence (PI), pelvic tilt (PT), and sacral slope (SS) were modified to develop three different sagittally balanced models, simulating different compensate-mechanisms. As shown in Fig. 3, these are (a) Normal (Balanced: SVA = 0 mm, LL = 50°, TK = 25°, PI = 45°, PT = 10°, and SS = 35°); (b) Flat back (Balanced with

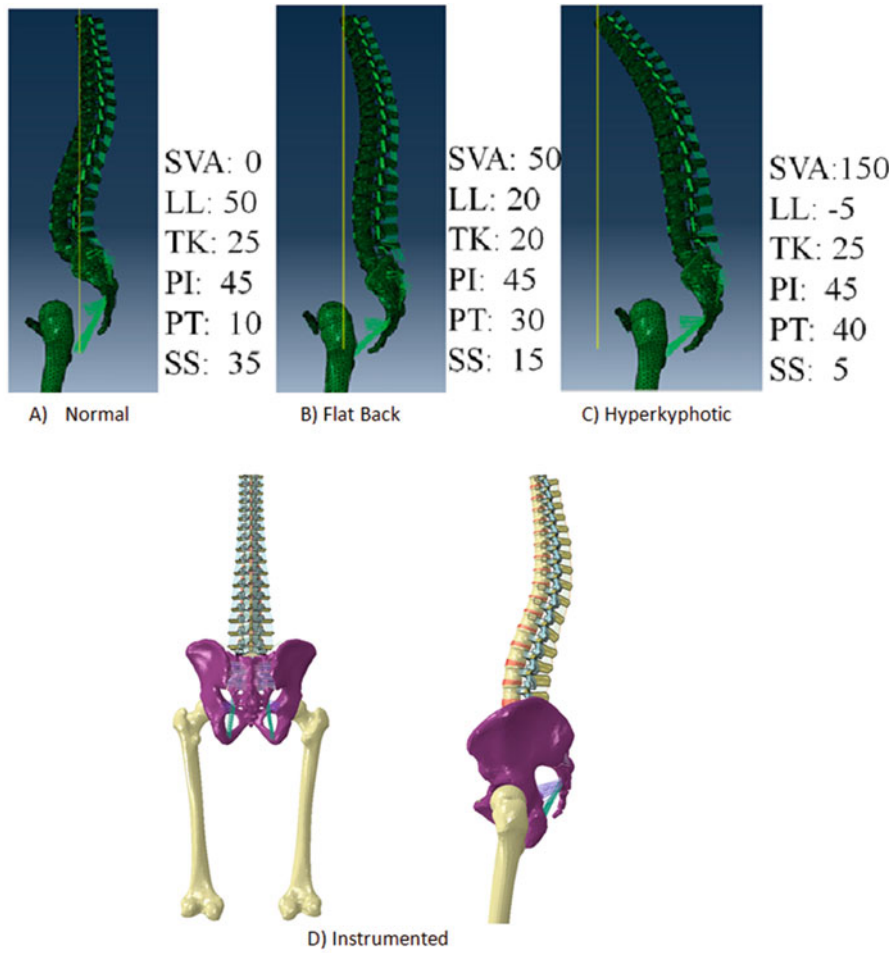

Fig. 3 Three different finite element models (FEM) used for the investigations. Yellow line indicates the C7 Plum line. (**a**) Normal spine, (**b**) flat back, (**c**) hyperkyphotic, and (**d**) posterior and sagittal view of instrumented models from L2-L5. *SVA* sagittal vertical axis, *LL* lumbar lordosis, *TK* thoracic kyphosis, *PI* pelvic incidence, *PT* pelvic tilt, and *SS* sacral slope (Matsumoto et al. 2019)

compensatory mechanism: SVA = 50 mm, LL = 20°, TK = 20°, PI = 45°, PT = 30°, and SS = 15°); and (c) Hyperkyphotic (Imbalance: SVA = 150 mm, LL = -5°, TK = 25°, PI = 45°, PT = 40°, and SS = 5°). A posterior rigid pedicle screw fixation system was simulated across L2-L5 (Fig. 3). The model was fixed at the distal femurs, and 2 Nm moments were applied at T1 to simulate flexion (FLEX), extension (EXT), right bending (RB), left bending (LB), right rotation (RR), and left rotation (LR) in intact and instrumented models. The von Mises stress on the proximal vertebra (L1) and distal vertebra (S1) as an indicator of proximal junctional kyphosis (PJK) and distal junctional kyphosis (DJK) was calculated and compared.

The maximum von Mises stress at the proximal vertebra increased by up to 143% (average of all motions: 74.9%) in the flat back model, and 18% (6.0%) in kyphotic model, compared to the normal balanced model (Fig. 4a). The maximum von Mises stress at the distal vertebra increased by up to 196% (average of all motions: 49.5%) in the flat back model, and 527% (141.8%) in kyphotic model, compared to normal (Fig. 4b). In the instrumented flat back, the maximum von Mises

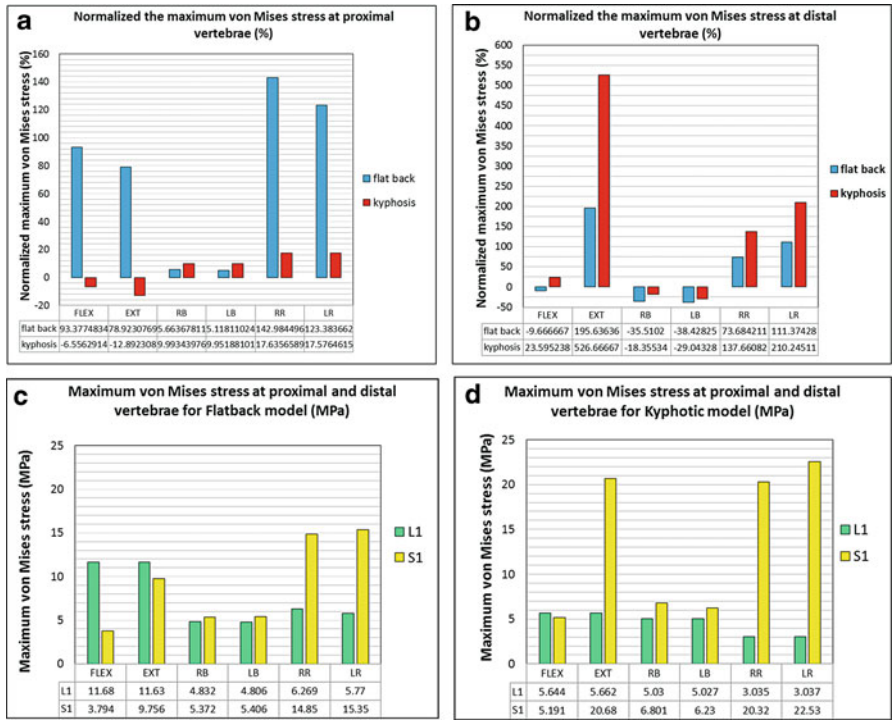

Fig. 4 (**a**) The normalized maximum von Mises stress at the proximal vertebrae (%), (**b**) the normalized maximum von Mises stress at the distal vertebrae (%), (**c**) the maximum von Mises stress at the proximal and distal vertebrae for the instrumented flat back model (%), and (**d**) the maximum von Mises stress at the proximal and distal vertebrae for the instrumented kyphotic model (%) (Matsumoto et al. 2018)

stresses at the proximal vertebra and distal vertebra were up to 11.7 MPa (average of all motions: 7.5 MPa), and 15.4 MPa (9.1 MPa) (Fig. 4c). In an instrumented kyphotic model, the maximum von Mises stresses at the proximal vertebra and distal vertebra were up to 5.6 MPa (average of all motions: 4.6 MPa) and up to 22.5 MPa, respectively (Fig. 4d) (Matsumoto et al. 2019).

The results show that the von Mises stress on adjacent vertebra increased by up to 196% in the flat back model, and 527% in the kyphotic model, compared to the normal model. The data suggests that when considering L2-5 fixation in flat back and kyphotic models, care should be taken to restore the normal lumbar alignment. Our data tends to suggest that the kyphotic model may contribute to higher incidences of DJK than PJK. Surgeons may consider using dynamic stabilization devices in the distal region for kyphotic patients (Matsumoto et al. 2018; Shah et al. 2019).

Subsequent to poor clinical outcomes, biomechanical studies have emerged to address ASD. Agarwal et al. (2016) conducted an in vitro study using 12 L2-S1 specimens instrumented with either titanium rods or PEEK (polyetheretherketone) rods and compared the effects of these materials on the kinematics of the adjacent level. They found that lower rigidity (PEEK rods) did not make a significant difference in terms of superior adjacent level motion in flexion and extension, compared to titanium. However, other biomechanical studies have shown that dynamic posterior stabilization constructs provide posterior band stiffness closer to the normal spine and protect adjacent levels, from excessive motion compare to more rigid constructs (Erbulut et al. 2014). The finite element models provide a good platform to study the biomechanical effects of new implant designs and surgical techniques. For example, the comparison

of TLIF versus PLIF using a validated L4-L5 model showed that the TLIF cages showed the higher stresses compared to ALIF and PLIF on the endplate stresses. In this FE model, the footprints of the cages were modified showing that the increase in footprint showed to lower the stresses compared to smaller footprints. Another modification of simulating different material properties of the cages showed that PEEK cages produced lower stresses compared to the titanium cages (Sudershan 2017). The change in parameters led to the simulation of parametric analyses which was difficult and expensive for in vitro studies. Thus, FEA is a very useful tool in studying in-depth biomechanics.

Dynamic Stabilization

Center of rotation (COR) of artificial disc designs: Initially, biomechanical studies of total disc replacement (TDR) devices reported that adjacent segment degeneration can be eliminated or reduced by implanting a dynamic device, instead of after anterior cervical discectomy and fusion (ACDF) (DiAngelo et al. 2003; Dmitriev et al. 2005). Therefore, TDR for the cervical spine instead of ACDF is potentially favorable by decreasing the incidence of adjacent segment degeneration. A recent study (Laxer et al. 2017) investigated the potential bias in the reports of outcomes from patients with TDR, because many of the studies' investigators reported financial conflicts of interest related to industry support, stock ownership, or consulting income from the TDR device company. They did not identify such bias. Therefore, the biomechanical data correlated with the clinical outcomes, regarding adjacent segment degeneration.

However, the relevance of the sliding articulation feature of a cervical artificial disc has emerged as studies have revealed the relationship between segmental sagittal translation and COR of the segment. The COR is a function of rotation and translation within the cervical spinal functional unit (Bogduk and Mercer 2000). Protraction is defined as flexion of the lower cervical spine and extension of the upper cervical spine, and the opposite is true for retraction (Ordway et al. 1999). Amevo et al. showed that 77% of patients with neck pain displayed abnormal instantaneous COR (Amevo et al. 1991). Similarly, Hanten et al. reported that patients with neck pain have little to no cervical sagittal plane translation mobility compared to healthy subjects (Hanten et al. 2000).

Consequently, the COR of an artificial disc affects the biomechanics of the spine. Fundamentally, the facet joints of the cervical spine play a major role in controlling the segmental axes of rotation (Penning 1988). Mo et al. (2015) postulated that facet joint stress was eliminated when an artificial disc had a sliding articulation feature to allow translation in the sagittal plane. This is supported by an early study of Nowitzke et al. (1994) that showed the relationship between cervical zygapophyseal joints geometry and the patterns of movement of the cervical vertebrae in the sagittal plane. The study further exhibits the location of the instantaneous center of location of the segment as a function of the facet joints. Similarly, a biomechanical study showed that an artificial disc with a fixed center of location may increase facet loading at the index segment (Faizan et al. 2012).

Our recent FE study investigated an elastomer total disc replacement (Fig. 5c) in the lumbar spine. The objective was to compare the biomechanical effects of the TDR in the lumbar spine as compared to natural spinal kinematics. An experimentally validated FE model of a ligamentous L1-S1 lumbar spinal model was used (Fig. 5a). To simulate the surgical procedure for disc replacement, the CAD model for the elastomer TDR was imported into the FEA software, and inserted into the L4-L5 segment following removal of the anterior annulus fibrosus, ALL ligament, and entire nucleus pulposus. A pure moment of 10 Nm combined with an applied follower load of 400 N was used to simulate the model in flexion-extension, lateral bending, and axial rotation. Range of motion, intradiscal

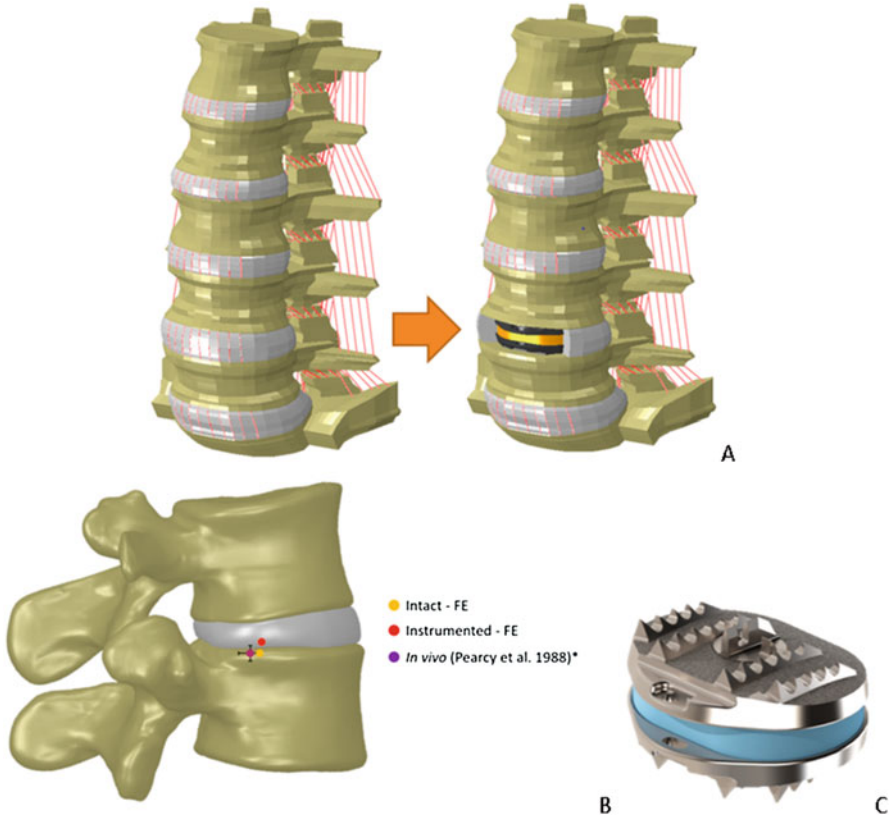

Fig. 5 (**a**) FE models of the intact and instrumented spine, (**b**) location of extension-to-flexion range of motion for the intact and instrumented spine, at index level, compared to in vitro data, and (**c**) total disc replacement device with titanium alloy endplates and CarboSil 20 80A silicone rubber flexible component

pressure, and facet loads across the segments were calculated. COR for full extension to full flexion was also calculated for the intact and instrumented models (Fig. 5b).

Figure 6 shows the kinematic data for index and superior adjacent levels. Range of motion of the instrumented model was 88% and 80% of the intact model in extension and flexion, respectively. COR was in good agreement with in vitro study reported by Pearcy and Bogduk (1988). Following instrumentation, the motion at the superior adjacent level was increased slightly in flexion (8%) and extension (20%). When comparing the intact model and the in vitro study, there was up to a 12% increase in intradiscal pressure at the superior adjacent segment after instrumentation. The loads at the facet increased by 1% in flexion and decreased by 5% in extension, compared to the intact model.

Our study showed that the elastomer lumbar TDR device not only preserved the range of motion, but also maintained the loading condition at the facet joints. In addition, the device may minimize the risk of adjacent segment disc and facet degeneration.

Further, poor clinical outcomes such as heterotopic ossification, wear debris, or metal hypersensitivity, of total disc replacements have yet to be biomechanically addressed (Sengupta 2015).

Posterior dynamic stabilization systems: Dynesys (Zimmer Spine, Minneapolis MN) is the most widely implanted posterior stabilization system (PDS) in the world. In addition, numerous

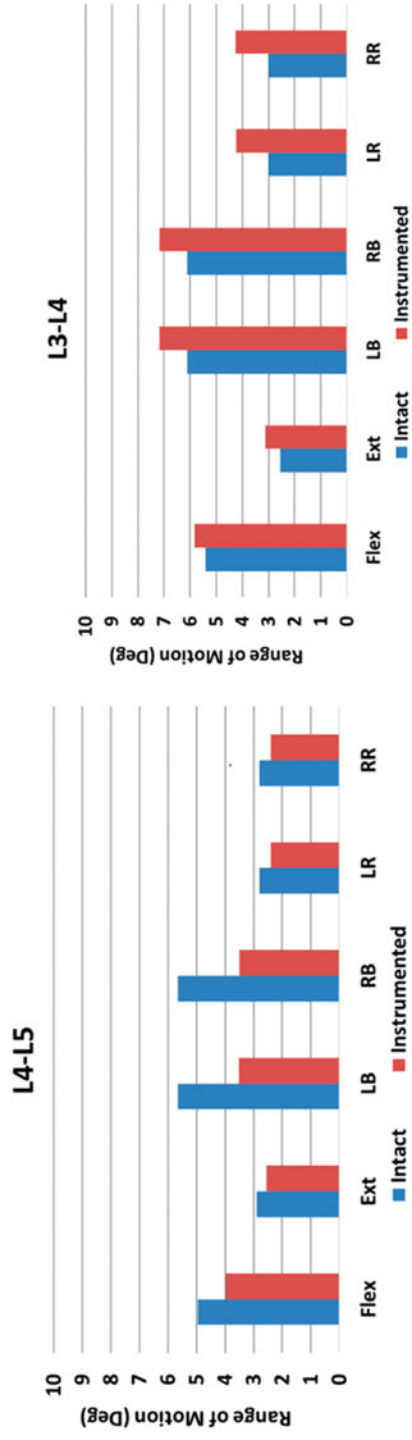

Fig. 6 Range of motion for intact and instrumented spines at index level and superior adjacent levels under anatomical loading

clinical and biomechanical articles have been published about the system since 1999. Dynesys is a second generation PDS system and was introduced in 1994. The first set of results was presented by the inventor Gill Dubois (Freudiger et al. 1999). In this study, Dynesys was tested on four cadaveric lumbar spines, three cases at L4-L5 and one case at L3-L4 level under bending, compressive, and shear loads. The loads were different for flexion and extension, average of 18.4 Nm flexion moment with 2296 N compressive and 458 N anterior shear load, and average of 12.5 Nm extension moments, with 667 N compressive and 74 N shear loads. The study reported motion reduction in flexion and extension at the index segment with Dynesys, which was described as an efficient supporting structure. The first clinical experience of the device was also published by the inventor in 2002 (Stoll et al. 2002). The study investigated the safety and efficacy of Dynesys for lumbar instability conditions. A consecutive series of 73 patients underwent Dynesys implantation and were evaluated pre- and postoperatively. The follow-up time range was between 11.2 and 79.1 months. No screw breakage was observed and loosening was suspected in only seven screws, based on radiological appearances, and only one of the patients had to be reoperated on due to screw loosening. Clinically, the authors claimed that Dynesys is a safe and efficient device to treat degenerative lumbar disease compared to spinal fusion techniques. They hypothesized that Dynesys could address the incidence of adjacent segment degeneration long-term. However, Sengupta and Herkowitz (2012) analyzed their data, and it was discovered that 60.2% of the patients had spinal stenosis, and questioned the etiology of the good clinical outcome reports. Was the success primarily due to the Dynesys instrumentation or the decompression? Successful clinical reports decreased more than half of the Dynesys cases without accompanying decompression (Grob et al. 2005; Würgler-Hauri et al. 2008).

Additionally, studies have revealed that Dynesys acts like a rigid system and does not address the adjacent-segment degeneration problem (Schmoelz et al. 2003; Schnake et al. 2006). Schnake et al. (2006) reported the clinical outcomes of 26 patients with spondylolisthesis, treated with decompression and dynamic stabilization with Dynesys. Twenty-nine percent of patients had indications of adjacent segment degeneration with regard to osteochondritis and arthritis of the facet joints. Similarly, Kumar et al. (2008) reported that 22% of 32 patients treated with Dynesys developed adjacent segment degeneration. A cadaver study (Schmoelz et al. 2003) reported similar range of motion in flexion and limited range of motion in extension with Dynesys compared to intact case. Clinical outcomes agreed with the cadaver study that the system limits extension motion. Motion limitation in extension may also be the reason for the poor clinical outcomes in terms of screw loosening or breakages, which is a relatively common complication with Dynesys (Stoll et al. 2002; Grob et al. 2005; Ko et al. 2010; Pham et al. 2016). Ultimately, Dynesys can only be used at the adjunct level of the fusion as approved by the FDA in the United States, and stand-alone use of Dynesys without fusion is considered an off-label use.

Similarly, most of the posterior dynamic stabilization systems (PDSS) have been reported as a possible alternative technique to spinal fusion, as a way to reduce the incidence of ASD. For example, Graft system was designed and proposed in 1991 for degenerative spinal diseases. This stabilization technique was aimed to prevent the abnormal flexion and restore segmental lordosis. Initial clinical results of the system were promising. Grevitt et al. (1995) reported on 50 consecutive patients who underwent Graft stabilization for intractable symptomatic degenerative disc disease. After a follow-up period of 24 months, the clinical results were good or excellent in 36 patients, and fair in 5 patients. Only one patient was reported as worse, and the system was suggested as a reasonable alternative to fusion. Other reports have demonstrated similar positive clinical results on the Graft system (Markwalder and Wenger 2003). However, one report demonstrated superior clinical outcomes for posterolateral fusion as compared to the Graft system (Hadlow et al.

1998). Additionally, there was a higher rate of revision surgery in Graft patients as compared to fusion patients, 18% and 29% at 1 and 2 years postoperatively, respectively. Late failure of the system was discussed by Mulholland and Sengupta (2002), and failure was related to transferring the load to the posterior annulus.

There are many advantages of using dynamic stabilization systems over fusion systems. It is designed to provide desirable environments for spinal movement and can limit abnormal motion, along with restoring load transmission patterns. However, careful consideration of the design must take place since a dynamic system must provide stability for its life time, unlike rigid fusion systems. Rigid spinal fusion systems need to provide stability only until the segment has fused. Dynamic systems have to withstand constant loading, which usually leads to fatigue failure or screw loosening (Schnake et al. 2006; Ko et al. 2010; Wu et al. 2011). Due to this reason, most of the dynamic stabilization devices, particularly pedicle screw-based systems, are designed to be stiffer to bear constant loading (Erbulut et al. 2014). However, if an implant is too stiff, instead of load-shearing it becomes load-bearing, which causes implant failure or screw loosening (Welch et al. 2007; Wu et al. 2011). Rohlmann et al. suggested that implant stiffness greater than 1000 N/mm may not be considered as dynamic because the mechanical effect would be similar to a fusion system (Rohlmann et al. 2007). Schmidt et al. (2009) determined the desirable stiffness parameter ranges for posterior dynamic stabilization systems. They found that only axial stiffness of 45 N/mm and bending stiffness of 30 N/mm are enough to reduce the segmental flexibility by 30%. Wilke et al. suggested that a dynamic device should allow 70% of the intact motion to achieve the desirable segmental stabilization.

For example, interspinous process (ISP) devices are considered to be dynamic stabilization systems and known to be useful for spinal pathologies such as spinal stenosis or facet arthritis. However, lack of design considerations of the device has been seen after the clinical and biomechanical tests. Clinical cases of ISP device failure have been reported. Not only has the gradual erosion at the spinous process due to consistent dynamic interaction at bone-device interface been observed (Miller et al. 2010), but also spinous process fracture due to stress concentration (Bowers et al. 2010; Kim et al. 2012). In our FE study, the biomechanical effects of an implanted interspinous process (ISP) device on load shearing at the index and adjacent segments were evaluated by using a hybrid protocol (Erbulut et al. 2015). Our stress results at the spinous process were in agreement with the literature that the maximum von Miss stress increased with implanted models up to 53 MPa. In addition, although the facet loads were decreased at the implanted level, FE model predicted that it was increased up to 60% at both the superior and inferior adjacent levels with extension (Table 1). Similarly, ISP devices decreased intradiscal pressure (IDP) at the index level, but not at the adjacent segments (Table 2).

Biomechanical data is essential in research process. Understanding the limitations of biomechanical data as it translates to clinical outcomes is paramount to the iterative process in implant design. Knowing that beneficial biomechanical data may not actually yield good clinical outcomes is important. Biomechanical data can also be utilized to analyze poor clinical outcomes to understand the reason for failure. Optimizing this process may help to address the poor clinical outcome by engaging biomechanical work again.

Although, the finite element models provide a good platform to study the biomechanical effects of a new implant designs and surgical techniques, care must be taken to consider the limitations. Some of the assumptions and simplifications include the homogeneity of tissue materials, lack of accurate muscle representations, linear material behavior, and loading and boundary conditions. For example, the various components of spine models are still to be considered as homogeneous and isotropic for stress distribution analysis in most published studies. Most of these assumptions are clearly inevitable, but a researcher should be knowledgeable to avoid misleading results from a FE simulation.

Table 1 Calculated facet loads of intact and instrumented models at index and adjacent levels (*Rt* Right, *Lt* Left)

	Flexion			Extension			Lateral Bending			Axial Rotation		
Condition	L2–3	L3–4	L4–5	L2–3	L3–4	L4–5	L2–3	L3–4	L4–5	L2–3	L3–4	L4–5
Intact												
Rt	45.63	76.68	25.89	127.13	147.36	120.37	29.40	54.67	76.17	0	0	0
Lt	54.40	77.44	19.46	151.72	156.99	194.33	37.51	59.35	21.93	172.11	175.72	214.00
Implanted												
Rt	45.65	76.68	25.89	184.02	0.06	192.95	29.84	66.32	73.95	0	0	0
Lt	54.40	77.44	19.46	230.38	11.06	299.92	37.53	46.12	23.55	172.16	150.12	215.17

Values expressed in N (Newton)

Table 2 Calculated intradiscal pressures of intact and instrumented models at index and adjacent levels

	Flexion			Extension			Lateral Bending			Axial Rotation		
Condition	L2–3	L3–4	L4–5	L2–3	L3–4	L4–5	L2–3	L3–4	L4–5	L2–3	L3–4	L4–5
Intact	1.44	1.34	1.46	0.87	0.98	0.90	2.04	1.80	2.11	1.34	1.33	1.22
Implanted	1.44	1.34	1.46	1.21	0.47	0.96	2.04	1.7	2.11	1.34	1.33	1.22

Values expressed in MPa (Megapascal)

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Lessons Learned from Positive Biomechanics and Positive Clinical Outcomes

15

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Abstract

This chapter seeks to explore how biomechanical studies positively influence clinical procedures by reviewing the literature relevant to three of the largest modalities in spinal surgery: anterior cervical plating, pedicle screws and rods, and interbody fusion devices. The area of focus within anterior cervical plating includes the introduction of plating systems to increase stability and the recent shift towards more dynamic systems. Furthermore, the differences between various pedicle screw and rod constructs as well as lumbar interbody fusion device configurations and approaches will be examined in detail to demonstrate the correlation between biomechanical results and clinical outcomes. The lessons garnered throughout this review will demonstrate how biomechanics can be best utilized to evaluate the efficacy of new devices, provide possible explanations to device complications, and refine design interactions to improve care and compare various device designs. Therefore, researchers and surgeons should be able to distill the important elements of using biomechanical and clinical data synergistically to prove both device and procedural success.

Keywords

Pullout strength · Bone implant interface · Cervical plating · Interbody fusion · Stability · Pedicle screw · VAS score · ODI score · Screw trajectory

Introduction

This chapter presents an introduction to the relationship between biomechanical and clinical testing of spine implant technologies, with the intended goal of highlighting specific areas of interest in which biomechanical studies have had a positive influence on clinical results rather than providing a comprehensive review of the literature within the field. It is important for both device innovators and physicians to understand the role of biomechanics testing to evaluate not only the physical characteristics of the devices, but predict their real-world performance under physiologic conditions. Thus, the integration of the breakthroughs garnered through this research aids in creating optimized designs and procedural tactics. In fact, the standard procedure for introducing a new technology to the market place involves a series of checkpoints in which the device is tested in a multitude of mediums: biomaterials, biomechanics, surgical safety, and both short- and long-term surgical benefits and complications. Ideally, biomechanical testing paves the way for further clinical research if the conclusions distilled from such work demonstrate an effective solution to a clinical problem that has yet to be solved.

This chapter will highlight this pipeline through its discussion of both entities of development: biomechanical and clinical efficacy. Furthermore, the successful integration of these research areas is paramount in creating an effective and useful device. Biomechanical success criteria include metrics like range of motion (ROM) and neutral zone (NZ) measured in response to axial compression (AC), flexion-extension (FE), lateral bending (LB), or axial torsion (AT) loading conditions. All of these testing conditions are intended to produce physiological loads by placing the device in a cadaveric model simulating real-world conditions. Clinically relevant metrics include visual analogue scale (VAS) scores, Oswestry disability index ODI scores,

fusion rates, non-union rates, pseudoarthrosis rates, infection rates, and device complication rates. The chapter will utilize three major categories of devices to denote how biomechanical testing has proven an effective means of predicting clinical success, and the respective lessons learned from such discoveries.

Anterior Cervical Plating

Cervical plating, a fixation system that is primarily utilized for spine segment stabilization, has indications for usage in pathologies such as spondylosis due to its hypothesized ability to enhance the rate of arthrodesis, Fig. 1. Moftakhar et al., in their paper providing a comprehensive overview of the anterior cervical plating technology, mention that plating has been shown to aid with earlier patient mobilization, a reduction in the need for postoperative collars, increased in graft loading, a reduction in graft dislodgement, and an increase in the ability to treat spinal deformities (Moftakhar and Trost 2004).

A bounty of technologies exist within the anterior cervical plate (ACP) space, as surgeons and device manufacturers aim to prevent and mitigate common complications associated with anterior cervical discectomy fusion (ACDF), primarily non-unions and pseudoarthrosis. While the first ACDF was performed in the mid-twentieth century by Bailey and Badgley, the market is still full of different ACP technologies, which necessitate further investigation of this surgical approach (Moftakhar and Trost 2004). ACP systems can be categorized based on their design characteristics, including plate-screw interaction and system rigidity, Fig. 2. This portion of the chapter will first highlight the topics of plating versus non-plating and rigid versus dynamic plating systems. It will include a discussion on the various biomechanical studies performed on ACP systems to evaluate their robustness and practicality, with respect to classic biomechanical models and metrics. The chapter will then focus on the clinical outcomes and the efficacy of these devices. Lastly, there will be an integration of these conclusions garnered from each of the aforementioned sections in order to provide the reader with a concise means of

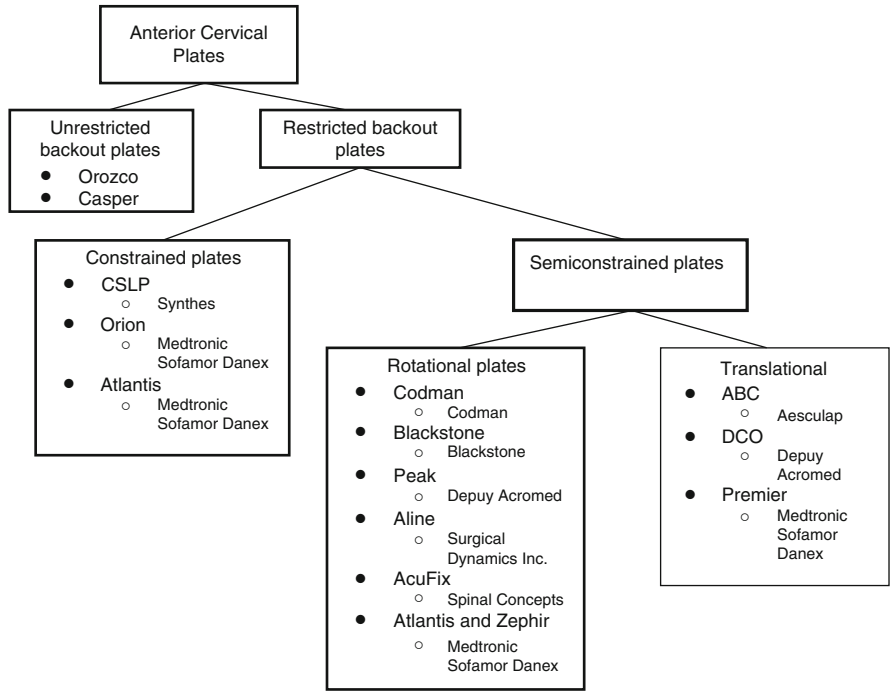

Fig. 1 Categories of Anterior Cervical Plates (Moftakhar and Trost 2004)

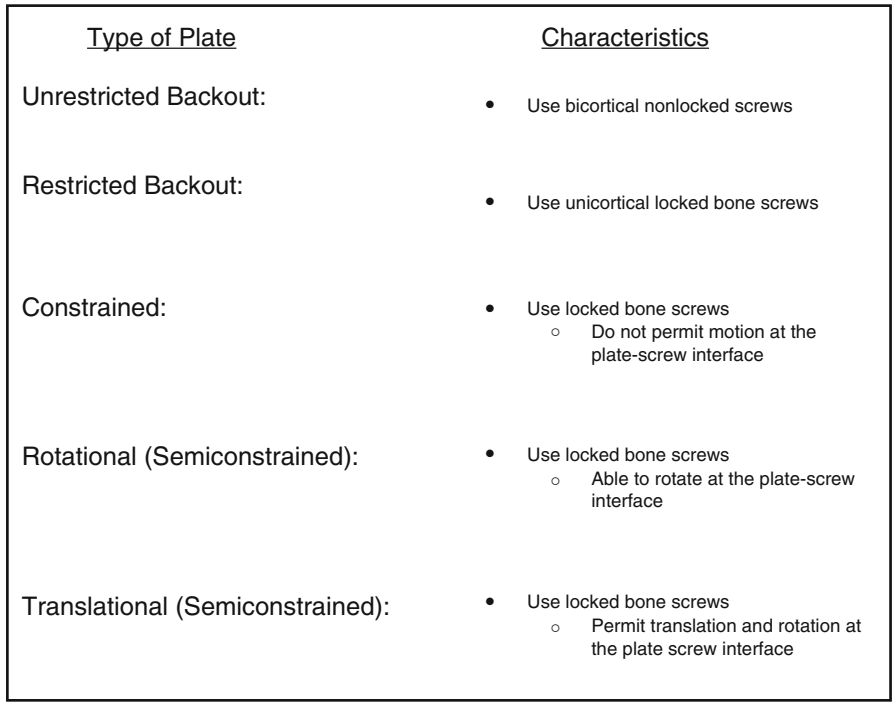

Fig. 2 Characteristics of Plate Designs (Moftakhar and Trost 2004)

reconciling whether the biomechanical models reflect the efficacy of this technology.

Plating vs. Non-Plating

Biomechanics

Ideally, a biomechanically successful ACP system would be able to significantly reduce the motion of a destabilized spinal segment in order to reduce pain associated with cervical trauma or degeneration, thus producing a stable spine segment (Rubin and Lanyon 1984). Hakalo et al. (2008) investigated the benefits associated with cervical plating in an in vivo biomechanical study that compared the stability and subsidence of different instrumentation systems in a porcine model.

Using a C3-C4 porcine model, ACDF procedures were performed in order to compare stabilization with either a cage alone or with a cage and plate. The specimens were instrumented and then dissected in order to evaluate the stability of the instrumented levels' devices using the MTS 858 Mini Bionix testing machine. A 2.5 Nm moment was applied to the cervical segments in flexion-extension and LB at a speed of 40 cm/min and the displacement of C3 with respect to C4 was measured. In order to keep the results relative, the stability of the vertebrae after discectomy and instrumentation was calculated and normalized to the intact condition. Then, a subsidence test was performed in the specimens that received instrumentation; in which, each segment underwent 21,000 cycles of axial loading ranging from 20 to 200 N at a frequency of 2.5 Hz (subsidence was measured by subtracting displacements before and after the cyclical test while the specimen was subjected to a 200 N preload).

The cage and plate systems resulted in significantly increased segmental stability when compared to the cage alone cohort. Stability is often the metric used to demonstrate the ability of a spinal segment ability to withstand anatomical loading. It may also permit proper load distribution at the cage-bone interface, impacting the rate of arthrodesis and fusion time (Rubin and Lanyon 1984). Subsidence was also shown to be largest in the cage-alone group and was reduced

by 50% in the cage and plate group. It is a relatively common phenomenon in spinal instrumentation caused by the difference between the mechanical properties of bone and implant materials, as well as the patterns of trabecular structure within vertebrae. Thus, the cage and the graft-bone bed interface may lead to subsidence, potentially manifesting in poor clinical results (Gercek et al. 2003). Biomechanical studies may be limited in their clinical relevance; however, the increase in stability and decrease in subsidence demonstrated with the implementation of cervical plates and interbody cages may indicate improved clinical outcomes when compared to ACDF procedures using interbody cages alone.

Clinical Efficacy

The clinical efficacy of single-level ACDF was assessed in the study conducted by Wang et al. They intended to determine whether or not cervical plating contributed to preferable clinical outcomes and reduced rates of pseudoarthrosis, which were measured by factors such as patient reported outcome success (based on Odom's criteria), graft collapse, and kyphotic deformity angle increase. Utilizing a patient population of 80 (36 with fusions without plating and 44 with it) and implementing a follow-up period of 6 years, they were able to demonstrate the benefits cervical plating. While they determined that the resultant rates of pseudoarthrosis between the plated and non-plated patients were not statistically significant, it was shown that cervical plating was safe and not associated with a significant increase in complication rates. This is a noteworthy conclusion because while the study may not have been sufficiently powered to detect a statistically significant difference, the authors conclude that the cervical plating method was as effective as the current standard practice. Additionally, the use of anterior cervical plates showed a marked decrease in the kyphotic deformity angle when compared to the non-plated population (1.2 degrees to 1.9 degrees respectfully). Moreover, rates of pseudoarthrosis were lower in the plated group than those in the non-plated group (4.5–8.3%, respectively). Although this finding was also not statistically significant, it is a promising conclusion regarding the efficacy of this technology and may have paved the way for future inquiry into the cervical plating (Wang and McDonough 1999). The finding that single-level anterior cervical plating is inconsequential and does not substantially aid in fusion rates was reinforced by the research published by Connolly et al. Similar to the study performed by Wang and McDonough (1999), researchers assessed the efficacy of using plating for the treatment of spondylosis using a total of 43 patients, 25 of which were treated with anterior cervical discectomy, autograft fusion, and plate fixation, while 18 were treated in the same manner without plating. The study found that plating did not significantly affect the fusion rate for single-level interventions (Connolly and Esses 1996). However, Connolly did foreshadow to the potential for using plating technology for reducing multilevel fusion complications.

Compared to single-level cervical fusion, three-level fusions are known to carry a higher risk of non-union and pseudoarthrosis. Wang et al. also conducted a study highlighting the benefits of using anterior cervical plates as a method of stabilization. By tracking 59 patients over a 7-year period, with a 3.2-year follow-up, they were able to compare the success of anterior plates on multilevel cervical discectomy to the success of standalone cages. The researchers found that 14 of the 59 patients monitored developed the pseudoarthrosis. However, a breakdown of this ratio engendered an interesting conclusion, of the 40 total patients in the plating group 7 (18%) had some degree of pseudoarthrosis compared to 7 out of 19 (37%) of the patients in the non-plate group. While this result was not statistically significant, the anterior cervical plate provided increased stability and higher rates of fusion when compared to a more conventional treatment. The authors noted that, while the incorporation of anterior cervical plates produced favorable results when compared to the standard treatment, it still had a fairly high percentage of failure of fusion. This conclusion provides justification for further study into the efficacy of cervical plating in order to distinguish how best to stabilize and support fusion within the spine (Wang and McDonough

2001). Through these two respective studies, ACP primarily demonstrated clinical efficacy in multilevel discectomy.

The dichotomy between the effect of cervical plating between single and multilevel discectomies is further demonstrated through the study conducted by Kaiser et al. Through a retrospective review of 540 patients who underwent either one- or two-level ACDF procedures, 251 with and 289 without plating, the researchers concluded that plating marginally increased the rate of fusion in the single level but resulted in a substantial increase in the rate of fusion in the case of two-level ACDF procedures. The fusion rates of plating versus non-plating two-level ACDF procedures were 91% and 72%, respectively, and the fusion rates of plating versus non-plating for one-level ACDF were much closer, 96% and 90%, respectively. These results along with the conclusions from the aforementioned studies provide substantial evidence that cervical plating has benefits in multilevel ACDF procedures (Kaiser and Haid 2002).

Integration

As demonstrated by the biomechanical test conducted by Hakalo et al., cervical plating showed promise for clinical use because of additional increase in stability to degenerated specimens and its theoretical ability to reduce subsidence of the implant. This conclusion is reinforced by the clinical data which also shows that plating can be advantageous, more so in multilevel cases than in single level ones. Plating contributes to reduced pseudoarthrosis, although not statistically significant, and comparable amounts of complications to that of the standard treatment. Therefore, it is evident that the biomechanical testing rightfully and accurately forecasted the technology's clinical success. It should be noted that the ability to utilize knowledge, such as the evidence that plating permits a more stable environment in a porcine model, is paramount to refining clinical practice and availability of different modalities of therapy. Thus, the anterior cervical plating model is a positive result for the use of both biomechanical and clinical testing in synchrony.

Dynamic vs. Fixed

Biomechanical Efficacy

While the use of plates is supported throughout the literature, their design has seen some fluctuation in recent years with evidence suggesting that the use of rigid fixation may reduce mechanical loading of the graft. A lack of mechanical stimulation may cause a negative effect on new bone formation as well as bone remodeling (Churches et al. 1979). This idea is supported by Wolff's Law, in that stress shielding and reduced load sharing lead to a decrease in bone (Frost 1994). Dynamic cervical plate systems have been developed to provide less rigid fixation, thus allowing for graft loading to accelerate the time to union.

Brodke et al. investigated the benefits associated with the use of dynamic cervical plates by performing an in vitro biomechanical study using a simulated cervical corpectomy model to compare the load-sharing properties of four cervical plate systems (Brodke and Gollogly 2001). The study consisted of two static plate systems – Synthes CSLP (Synthes Spine, Paoli, PA) and Sofamor-Danek Orion (Medtronic Sofamor Danek, Memphis, TN), and two dynamic systems – Depuy Acromed DOC (Depuy Acromed, Raynham, MA) and Aesculap ABC (Aesculap, Tuttlingen, Germany). Six specimens of each of the four plate types were mounted on ultra-high-molecular-weight polyethylene blocks intended to simulate vertebral bodies. Load-sharing between the graft and plate was measured under two conditions (30-mm and a 27-mm graft) while subjected to a linearly increased AC load. The 27-mm graft condition was intended to simulate a 10% loss in graft height or subsidence. Load transmission through the graft was measured at the inferior graft-endplate interface using a thin film force transducer. Measurements of load sharing were expressed as a percentage of the load applied to the vertebral segment.

Under the 30-mm graft condition, all four instrumentation systems transmitted more than 60% of the axial load through the graft, indicating that both locked and dynamic cervical plates effectively shared loads under parameters where subsidence or collapse did not occur. However,

under the 10% graft loss condition, only the dynamic plates shared significant portions of the load to the graft, with values of 88% for ABC and 96% for DOC. The locked cervical plates prevented graft from sharing any portion of the axial load until a minimum of 90 N was applied, even at the maximum load of 120 N, only reported 11% and 17% of the applied load was transferred through the graft for the Orion and CSLP, respectively.

This preliminary biomechanical study demonstrated the benefits associated with dynamic cervical plate systems when compared to traditional static systems. Physiological strain levels with an appropriate distribution can produce an osteogenic stimulus that is capable of increasing bone mass (Rubin and Lanyon 1984). Therefore, load-sharing is desirable in a cervical plate system because the transfer of load through the graft would lead to increased rate of bone formation and increased fusion rate. Static systems were able to effectively share loads under the 30-mm graft condition; however, their performance in the simulated loss condition (27 mm) indicated that there could be a significant reduction in their performance, should graft collapse or subsidence occur. On the contrary, the dynamic plate systems demonstrated their ability to share load through the graft over a range of conditions and could lead to consistently improved patient outcomes.

ACP has also been shown to have a significant effect on the loading characteristics of the posterior cervical spine. Petterson et al. performed a study in which the instantaneous axis of rotation (IAR), anterior column load sharing, and posterior element strain of cadaveric specimens were compared between rigid and dynamic plating systems (Peterson et al. 2018a, b). This study found that rigid plates cause a shift in the IAR of the spinal segment from the posterior third to the anterior periphery of the disc space. As a result of this anterior shift, the distance between the posterior elements and center of rotation is larger, therefore increasing the forces acting on the posterior elements. They also showed that the magnitude of the anterior IAR shift is directly correlated to the stiffness of the plating system used. Thus, a dynamic plate with lower material stiffness could minimize the anterior shift in IAR and reduce posterior element strain, which is a significant finding given that mechanical loading of the posterior elements has been identified as a possible contributor to low back pain (Cohen and Raja 2007).

Clinical Efficacy

Building upon the conclusion derived the biomechanical literature, Saphier et al. conducted a prospective study to determine if dynamic plates yielded any additional clinical benefit compared to static plates. The study focused on two Medtronic ACP systems, the ORION ACP system (rigid plating) and the PREMIER ACP system (dynamic plating) (Saphier and Arginteanu 2007). Twenty-five of the 50 patients underwent one- or two-level ACDF procedures with the rigid system and the other 25 with the dynamic system between 1998 and 2002. The procedure's success was determined radiographically by measuring vertical translation and in terms of patient reported outcomes using a 6-month follow-up questionnaire focused on pain, disability, and overall satisfaction.

Seventeen of the patients in the ORION group underwent one-level fusion and the remaining eight underwent two-level fusion. In the PREMIER cohort, 18 patients received one-level fusion and the other seven had two-level fusion performed. Patients treated with the dynamic system reported significantly lower pain scores and increased functionality on average when compared to the patients with rigid plates. While the difference between the rigid and dynamic groups was not statistically significant the overall satisfaction of patients in the dynamic plating group was on average higher.

Other clinical studies designed to compare static and dynamic plating systems have come to similar conclusions. In a 2013 meta-analysis of clinical studies comparing dynamic and static plating systems Li et al. found static plating systems to have higher complications rates and slower fusion rates compared to dynamic systems. This literature review included 315 patients across five studies, including 172 patients implanted with dynamic cervical plated and 143 patients

with fixed plates. Complications were reported in two of the five studies and were only in the static plate group. These complications included plate break, screw dislocation, and screw back-out. Also included in the meta-analysis was a blinded study evaluating the success of 66 patients divided evenly between dynamic and screw plating systems (Li et al. 2013). Based on VAS, neck disability index, and radiologic evaluation it was determined that plating systems produce improved clinical outcomes in multilevel fusions, but are not significantly improved with respect to single-level fusions (Nunley et al. 2013).

Integration

Cervical plating has been shown to serve as an effective means of providing stability, specifically in multilevel pathology. This conclusion was garnered via both biomechanical and clinical testing, thus demonstrating the benefit of utilizing both research approaches. Through well-planned biomechanical studies researchers may determine how both healthy and pathological spine segments function. Furthermore, from this understanding the spine research community can better evaluate the effect of instrumentation and other therapeutic modalities on these specimens. The increased number of levels in a diseased spinal segment coincides with an increase in instability, pain, and degeneration. Moreover, as the number of diseased levels increases, the effectiveness of traditional plating therapies decreases, while that of the dynamic systems is maintained. This conclusion may not have been reached without an understanding of the biomechanics of both single and multilevel spinal segments. The development of cervical plating systems from rigid to dynamic constructs should serve as an example of how biomechanics can guide developing technologies.

Pedicle Screws and Rods

Pedicle screw fixation is intended to provide spinal stabilization for the treatment of traumatic injuries, deformity, and degenerative diseases. Roy-Camille introduced early pedicle screw instrumentation to the US healthcare market in 1979 as rigid systems with thick rods or plates designed to provide maximum stability. However, due to a series of complications, the Food and Drug Administration (FDA) was forced to prohibit manufacturers from promoting the use of screws in the spine in 1993 and required patients be warned regarding the pedicle screws' experimental nature (Mulholland 1994). Both clinical and biomechanical studies have since been performed to evaluate various aspects of pedicle screw and rod systems and prove their efficacy in fixating the spine. As a result, their design has been refined as evidenced by their 95% success rate with respect to facilitating fusion (Choi and Park 2013). Pedicle screw development relied on both biomechanical and clinical success; thus, it is important to analyze how this development progressed.

Unilateral v. Bilateral Rod Constructs

Pedicle screws and rods are widely popular for single- and multilevel spinal fusions and have been used in various lumbar disorders. Several posterior fixation techniques are currently available to assist spinal fusion, with bilateral fixation being considered as the "gold standard" (Liu et al. 2016). Unilateral fixation has been introduced as an alternative to bilateral fixation because it is a less invasive procedure which still provides necessary stability. However, unilateral versus bilateral fixation has been widely debated as each method has both positive and negative indications. Thus, there may not be a clearly superior system. Traditionally, most surgeons would perform a bilateral screw fixation, but recently it was discovered that internal fixation of this type can result in a decrease in bone mineral content caused by excessive rigidity. A brief overview of the biomechanical and clinical comparison of the two constructs will be presented in an effort to determine how a mechanical evaluation of the construct may guide clinical practice.

Biomechanics

Godzik et al. conducted a biomechanical study assessing the stability of unilateral (UPS) versus bilateral (BPS) pedicle screw fixation with and without interbody support, using lateral lumbar interbody fusion approach (Godzik et al. 2018). The researchers determined that when an interbody cage was used, there was a negligible difference in terms of the stability generated between a unilateral versus a bilateral pedicle screw approach. They were able to come to this conclusion by using 13 cadaveric specimens divided into two groups. Specimens in group 1 were tested in three stages: intact, UPS alone, and BPS. Group two specimens were tested in four stages: intact, interbody alone, interbody cage with UPS, and interbody cage with BPS. Conventional biomechanical metrics were used for the assessment of segmental stability: FE, LB, and AT. ROM was calculated for each stage of testing. Results showed the bilateral construct appeared to have an increase in immediate stability, but the difference in stability between unilateral and bilateral screw constructs was statistically insignificant when an interbody cage was included in the construct. This conclusion may indicate that in a clinical setting, when both an interbody cage and pedicle screw fixation are implemented, the clinical outcomes between patients instrumented with unilateral and bilateral pedicle screw fixation would be comparable.

A similar conclusion was drawn from a study conducted by Liu et al., in which the researchers also compared three different posterior fixation techniques for two-level lumbar spine disorders in cadaveric specimens (Liu et al. 2016). The three instrumentation systems included UPS, UPS with contralateral translaminar facet screw (UPSFS), and BPS. Polyaxial pedicle screws (6 mm diameter, 45 mm length) were used in the study. Eight intact cadaveric lumbar spines (four from L1-L5, four from L1-S1) were tested by applying pure moments of ± 8 Nm followed by testing left facetectomized L3-L4 and L4-L5 segments (to simulate unstable conditions). ROM and NZ of L3-L5 were recorded, and the results of the study showed that all fixation types could significantly reduce the ROM of L3-L5 in all loading conditions when compared to the intact state, with the exception of AT. Only BPS significantly reduced the AT ROM in comparison to intact condition. With respect to NZ, there was significant reduction in all the three conditions under flexion extension when compared to intact stage of testing; however, no significant difference was found in LB and AT. Overall, BPS offered the highest stability, with UPSFS being the least invasive with good fixation strength – which could possibly be used to replace BPS. These results further support the above assertion that unilateral and bilateral fixation techniques are not statistically significantly different, while bilateral fixation has the highest stabilization effect.

Clinical Efficacy

According to studies conducted by Ding et al., unilateral and bilateral pedicle screw fixation systems produce similar clinical results (Ding and Chen 2014). Unilateral and bilateral screw systems were compared in a meta-analysis conducted by Ding et al., which included information from over 400 patients across five studies. The results revealed that there was no significant difference between the fusion rates of unilateral and bilateral pedicle screw fixation; however, UPS patients benefited from improved perioperative results (significantly shorter operative time and significantly less blood loss for unilateral pedicle screw fixation). The conclusions of this study suggest there is little difference in the clinical outcomes of unilateral and bilateral pedicle screw fixation. While bilateral screw fixation may produce marginally improved fusion rates, unilateral screw fixation presents shorter operative time and less blood loss.

Moreover, a comprehensive overview on the outcome differentials between unilateral and bilateral rod constructs was performed by Molinari et al. to address the controversy between the two constructs in terms of efficacy and safety. Through a series of analysis on studies ranging from the topics such as complications, non-union rates, infection ODI and VAS scores, cage migration, and screw failure, it was deemed that there were no statistically significant differences between the

two treatment modalities. The authors did encourage further investigation into this conclusion because most reports only involve single-level lumbar unilateral instrumentation (Molinari et al. 2015). A study conducted by Cheriyan et al. mirrored this conclusion by emphasizing that there was no statistically significant difference in terms of fusion rates and complications regarding unilateral or bilateral instrumentation (Cheriyan et al. 2015). Although the study did indicate that there was an increased likelihood of cage migration in the unilateral construct, the results were statistically insignificant and thus would require additional follow-up research to make a definitive conclusion. Thus, it is apparent that the unilateral instrumentation approach is a functional alternative to a bilateral approach, and may be indicated or contraindicated depending on the circumstance of the procedure.

Integration

Clinical success of spinal instrumentation is not solely dependent on fusion rates, and perioperative measures are also an important consideration. As the success of pedicle screw and rod systems surpasses 95% surgeons and device manufacturers must begin to investigate means to improve other success metrics, such as blood loss and operation time. Replacing BPS with UPS would allow for significant reductions in both blood loss and operation time. Biomechanical evaluation of unilateral and bilateral constructs indicated that both systems were able to provide the necessary stability to facilitate fusion. Clinical evaluation of both systems validates this biomechanical conclusion. This is a noteworthy correlation as it indicates that biomechanical comparison of two systems with respect to segmental stability is a successful method of predicting clinical results. While the unilateral construct requires more research and scrutiny, results indicate that it may serve as a promising alternative to the bilateral approach.

Trajectory

Achieving solid implant fixation when using pedicle screws is a problem which may be intensified in patients with osteoporosis and other disorders that lead to the diminution of bone density. Innovations aimed at addressing this issue have been seen in recent years with the hopes that better implant fixation will lead to improved patient outcomes. Cortical bone trajectory (CBT) is an alternative approach to traditional pedicle screw placement intended to increase screw-bone purchase in the lumbar spine by placing the screws in environments with higher bone mineral density than the traditional approach (Matsukawa et al. 2017). Common pedicle screw complications include screw loosening – which has been estimated to range from 1% to 15% in non-osteoporotic patients and exceed 60% in osteoporotic bones (El Saman et al. 2013). A more reliable avenue is necessary due to the complications of traditional transpedicular screw trajectory and surgical approach. The CBT trajectory differs from the transpedicular approach by maximizing cortical bone contact via a caudocephalad and mediolateral trajectory, leading to a reduction in soft tissue dissection, blood loss, and postoperative complications.

Biomechanics

Santoni et al. performed a human cadaveric biomechanical study to evaluate the efficacy of the CBT approach compared to the traditional pedicle screw placement approach (Santoni et al. 2009). Five fresh human lumbar spines were utilized from L1-L5 and the vertebral bodies were stripped of all muscular and ligamentous tissue, and then they were implanted with a set of pedicle screws. Each specimen received a pedicle screw using the traditional approach on one side and the CBT approach on the other. The vertebral body was then coupled to a six degree of freedom load cell, via a custom designed fixture and a screw pullout test was performed. Screws were withdrawn uni-axially at a rate of 10 mm/min until a sharp drop in the force profile was observed or there was observation of bone failure, and contralateral pedicle screws were then evaluated in the same fashion and yield force for each screw was calculated.

The study showed that the mean resistance against pullout for the new CBT was 30% greater than the traditional approach, 367 N and 287 N, respectively. This is a significant finding given

that CBT screws were smaller in both length and diameter compared to traditional ones. Other biomechanical studies have demonstrated improved performance associated with the use of CBT as well. A study conducted by Wray et al. suggests this improvement in pullout strength is due to an alignment of screws with denser bone, regardless of DXA or qCT evaluation of bone quality (Wray et al. 2015). While screw pullout tests should not be the deciding factor in care pathways, the improvement in performance and decrease in size seen with the use of CBT pedicle screws could indicate that they may be preferable to the traditional screw and approach.

Clinical Efficacy

Two clinical studies conducted by Takenaka et al. and Kasukawa et al. found a significant reduction in blood loss using the CBT technique versus the traditional transpedicular screw placements during PLIF and TLIF procedures, respectively (Takenaka et al. 2017; Kasukawa et al. 2015).

Kasukawa's study evaluated clinical and radiological results of TLIF performed with CBT pedicle screw insertion versus traditional screw placement. Twenty-six patients were separated into three groups: minimally invasive pedicle screw insertion (M-TLIF), percutaneous pedicle screw insertion (P-TLIF), or pedicle screw insertion following the CBT (CBT-TLIF). Blood loss was significantly less with patients in the CBT-TLIF cohort compared to M-TLIF and P-TLIF groups. Operation time, postoperative bone union, lordotic angle maintenance, and screw placement accuracy were similar between the three groups. Takenaka et al. compared the effectiveness of PLIF using CBT and transpedicular screw techniques and found no significant difference between groups in operative time or fusion rates (Takenaka et al. 2017). However, the CBT group experienced a significant reduction in blood loss, postoperative creatine kinase levels, and pain scoring when compared to the traditional pedicle screw approach. CBT provided additional benefits of reduced perioperative pain and earlier return to normal activity levels. An additional study conducted by Mizuno et al. found that the CBT proved to be less invasive and equally effective as the traditional approach (Mizuno et al. 2014). The authors concluded that midline lumbar fusion procedures should follow the CBT when treating single-level degenerative pathologies in combination with midline insertion of an interbody graft. The CBT technique has been shown to be a viable alternative to the transpedicular approach in the treatment of spinal instability, degenerative disease, trauma, and spinal deformities because of its improved screw pull-out strength and reduction in intra and postoperative complications.

Integration

CBT development demonstrated how biomechanical analysis can be used to improve clinical outcomes. Osteoporotic patients have traditionally been a challenge for surgeons and device manufacturers due to their reduced trabecular structures. Augmenting purchase using techniques such as vertebroplasty has proven difficult, making the optimization of inherent bony purchase essential for improvement of pedicle screw–based treatments. The pattern of more dense trabecular bone structures in the most cephalad region of the pedicle and vertebral body has allowed surgeons and manufacturers to best adapt their approach to screw placement and design. As a result, the CBT is able to provide sufficient fixation to facilitate fusion while also significantly reducing blood loss, decreasing perioperative pain, and allowing patients to recover faster.

Interbody Devices

According to a historical review conducted by de Kunder et al., anterior lumbar interbody fusion (ALIF) was first introduced in 1933 by Burns and Capener and paved the way for future innovation in the treatment of degenerative disc disease, spondylolisthesis, and other spine destabilizing conditions (Kunder et al. 2018). By 1944, Briggs and Milligan began utilizing the now conventional procedure known as posterior lumbar interbody fusion (PILF) to treat disc herniations that impinged on spinal nerves and aid in spine stabilization. Through the years, spinal fusion using an interbody device has become the

"gold standard" in the treatment for spinal destabilization pathology. Moreover, because of its wide use, spinal fusion procedures have evolved to include new approaches and mechanisms with which devices are able to stabilize the respective treatment levels.

Examples of innovations within this treatment modality include the incorporation of expandable cages to increase the tension within the spinal column and provide increased structural integrity, additional screws or blades to provide increased fixation into the vertebral bone, use of different materials such as PEEK and Titanium composites to permit preferable bone growth and stability of fusion, incorporation of biomaterial surface coatings to increase osteoconduction, and the addition of large bone graft windows to increase the rate of bone growth and osteoblastic differentiation. Initial adjustments to interbody cage design lead to substantial improvements in clinical success (fusion and patient reported measures have both shown to increase over time with the integration of new technologies). However, with the wide range of recently introduced innovative device designs, fusion and clinical success rates have been relatively consistent, thus creating the need for analysis on the current state of the art and a better understanding of what other metrics could be amended to provide clinical improvements.

Device Design

Biomechanics

Current ALIF cages vary widely in their designs, which may suggest differences in initial stability and long-term performance. Tstantrizos et al. investigated the biomechanical stability of five stand-alone ALIF constructs by utilizing an in vitro cadaveric model (Tstantrizos et al. 2000). The five cages of interest included the paired BAK cage (a threaded design), the Anterior Lumbar I/F cage (an oval fenestrated carbon implant with saw teeth), the Titanium Interbody Spacer or TIS (a round titanium implant with long serrated teeth), the SynCage (an oval titanium implant with short serrated teeth), and the ScrewCage (a rectangular titanium body with saw teeth housing a conical threading component). Forty-two lumbar spines L1-S1 were tested in the intact condition and then again after the insertion of an ALIF cage into the L3-L4 disc space. Each spinal segment was mounted on a custom six degrees of freedom testing machine and an electromagnetic tracking system was used to measure relative segmental motion via rigid sensors attached to the vertebral bodies. The loading protocol consisted of AR, FE, and LB conditions. NZ and ROM were extrapolated from the load-displacement curves of each loading condition. Pull-out force was also determined using a strain-gauge force transducer. With regard to anterior column stability, the five stand-alone cages were shown to be effective in reducing ROM but increased in NZ under all loading conditions. ROM represents an absolute measure of the total joint compliance under an applied moment. NZ represents an absolute measure of joint laxity and can be understood as the region of physiologic motion where the osteoligamentous structure of a functional spine unit does not provide resistance to motion (Panjabi 1992). The increase in NZ demonstrated in these devices could be from the absence of muscle contraction seen in a cadaveric model. Clinically, an increase in NZ may depict segmental instability.

Due to their shared ability to reduce ROM, a wide variety of cage designs are utilized in interbody fusion procedures today; a majority of which are capable of achieving arthrodesis. Significant differences were demonstrated between the devices above, with regard to specific directional loading and pullout force. However, each device managed to show that it could provide substantial stabilization to an FSU after implementation. Such results suggest that alternative metrics need to be created in order for biomechanical analysis of interbody devices to provide more valuable information. Specific attention should be focused on subsidence and migration associated with the interbody devices in addition to the traditional biomechanical measures of ROM and NZ. While biomechanics are effective in demonstrating that a device has the ability to provide stability to an unstable FSU, new metrics of quantifying clinical success associated with various cage designs need to be generated in order to

further differentiate between the variety of interbody cages designs.

Clinical Efficacy

A series of recent clinical studies evaluating new interbody cage designs did not demonstrate significantly different outcomes compared to more traditional designs. This is evidenced by a study conducted by Sasso et al. which compared the clinical efficacy of a cylindrical threaded titanium cage (INTER FIX device) to a femoral ring allograft (control group) in patients with degenerative disc disease undergoing an ALIF surgery (Sasso et al. 2004). Patients who received the INTER FIX device had a reduction of ODI scores from 51.1 (preoperative) to 33.7 (postoperative), whereas the control group also had reduced ODI scores from 52.7 (preoperative) to 38.4 (postoperative) demonstrating no statistical difference between the mean scores of the two groups. In a separate clinical study, researchers compared the clinical outcomes of the Stablilis Stand Alone Cage (SAC) to the Bagby and Kuslich (BAK) device in an ALIF procedure for patients with degenerative disc disease (Lavelle et al. 2014). They found that there was no significant difference between the SAC and BAK devices in terms of mean operative time or blood loss or ODI scores. The ODI scores for patients in the BAK and SAC groups improved significantly (53.6 to 38.6 and 50.5 to 35.8, respectively).

Integration

Despite design differences, various interbody fusion devices possess similar biomechanical and clinical outcomes. The shared ability to reduce the ROM in cadaveric spine models and the reduction in ODI confer the impression that additional design features may not significantly affect device performance characteristics. This evidence reinforces the conclusion that interbody fusion implant biomechanical models correlate with their clinical results. Moreover, this information permits surgeons and device manufacturers an opportunity to develop new means of assessing performance because the current metrics do not generate significantly different results based on attempted design changes. This is not to say that these devices are performing exactly the same, rather it is more accurate to deduce that scale of these differences is not being recognized by standard measures.

Interbody Fusion Approaches

Spine interbody fusion is an effective treatment option for the stabilization of painful motion segments to relieve nerve compression, restore lordosis, and correct deformities (Mobbs et al. 2015). Depending on the direction of approach, there are several surgical techniques utilized during lumbar interbody fusion: posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), minimally invasive transforaminal lumbar interbody fusion (MI-TLIF), oblique lumbar interbody fusion/anterior to psoas (OLIF/ATP), lateral lumbar interbody fusion (LLIF), extreme lateral interbody fusion (XLIF), and anterior lumbar interbody fusion (ALIF). Each technique has its own pros and cons; thus, comparative biomechanical analysis coupled with clinical studies could provide valuable insight in choosing the right treatment strategy. In order to understand the differentiation in clinical outcome of the various surgical approaches, it is important to recognize the indications and contraindications for each. Once the nuances of each surgical approach are appreciated, one may then apply scrutiny regarding the patient data resultant in their comparison.

PLIF is suitable for patients with segmental instability, disc herniation, spinal stenosis, and pseudoarthrosis. Advantages include increased visualization of nerve roots, adequate interbody height restoration, and the potential for 360-degree fusion through a single incision. However, disadvantages entail iatrogenic injury due to prolonged muscle retraction, retraction of nerve roots causing chronic radiculopathy, and difficulty restoring lordosis.

TLIF was developed to address the limitations of PLIF like the length of neural retraction, dural tears, and nerve root injury. TLIF involves direct access to the intervertebral foraminal space, which is advantageous due to its decreased muscle retraction time and bypassing the nerve roots,

dura, and ligamentum flavum. This technique also permits a minimally invasive approach while preserving ligamentous structures allowing for increased biomechanical stability. A disadvantage of the TLIF approach, much like the PLIF, is the risk of paraspinal iatrogenic injury due to retraction.

ALIF has become the predominant surgical procedure in patients with discogenic low back pain especially in the areas of L4-L5 and L5-S1. This approach permits adequate access to the entire ventral surface of the disc and completed surgical dissection and allows for proper lateral exposure to the vertebral bodies permitting dynamic disc space clearance and endplate preparation. The reduction in posterior paraspinal muscle retraction decreases postoperative pain and impairment. One of the major limitations of this approach is the risk of vascular injury to the superior mesenteric artery which may cause thrombosis.

LLIF involves accessing the pathological disc space by a lateral retroperitoneal transpsoas entrance and is more suitable for disc spaces from T12-L1 to L4-L5, but is contraindicated below L5-S1 due to the iliac crest obstructing access and potential damage to the lumbar plexus. There is also risk of psoas muscle injury, bowel perforation, and vascular injury; however, it remains an option for sagittal and coronal deformities, especially lumbar scoliosis with laterolisthesis.

Lastly, OLIF, a minimally invasive approach, allows access through a small corridor between the peritoneum and the psoas muscle. Like the LLIF, the OLIF does not require laminectomy, facetectomy, posterior surgery, or stripping of paraspinal musculature. Neuromonitoring is not needed in the OLIF approach, as compared to the LLIF, because of the lack of psoas muscle dissection; therefore, it is most suitable for levels L1-S1. Comparable to LLIF, OLIF is also reasonable approach for sagittal and coronal deformities, especially in lumbar degeneration. Advantages include aggressive deformity correction, high fusion rates with complete disc space clearance, decreased psoas muscle and lumbar plexus injury, but the potential risks for sympathetic dysfunction and vascular injury are still apparent (Mobbs et al. 2015).

Biomechanics

Mica et al. evaluated the biomechanical stability of an expandable interbody cage (Luna 360) deployed in situ using a TLIF approach and compared it to a traditional lumbar interbody cage using an ALIF approach (control) (Mica et al. 2017). Twelve cadaveric spine specimens (L1-L5) were tested in the intact condition and after implantation of both the control and test device in the L2-L3 and L3-L4 index levels of each specimen. Additionally, the effect of supplemental pedicle screw-rod stabilization was assessed. Moments were applied to the segments under three loading conditions: FE, LB, and AR and segmental motions were recorded using an optoelectronic motion measurement system in order to calculate ROM. It was determined that the expandable TLIF cage and ALIF control device significantly reduced FE, LB, and AR motion with and without compressive preload when compared to the intact condition. Under all loading conditions (FE under 400 N preload, LB, and AR), the postoperative motions of the two constructs did not differ statistically. Adding bilateral pedicle screws resulted in further reduction of ROM for all the test modes compared to intact condition, with no statistical significance between the test and control device. The two approaches were found to be equivalent biomechanically demonstrating the consistency of performance among the different approaches and technologies within this modality of treatment.

Niemeyer et al. performed a similar study using titanium cages deployed as either TLIF or ALIF with and without posterior pedicle fixation and showed that the different cage design and approach resulted in only minor differences in segmental stability when combined with posterior pedicle screw fixation (Niemeyer et al. 2006). However, with pedicle screw fixation, the ALIF cage provided more stability than the TLIF cage in flexion-extension and axial rotation, but the absolute biomechanical differences were minor. While

it is noteworthy that there was an observable difference in the ROM of the ALIF and TLIF groups with posterior pedicle screw fixation, the size of such a difference may be clinically negligible.

Ames et al. compared PLIF to TLIF at one and two levels with and without posterior fixation (Ames et al. 2005). Fourteen cadaveric specimens were subjected to either PLIF or TLIF at L2-L3 (single-level) and L3-L4 (two-level). ProSpace Interbody allograft was inserted into disc spaces in both cases. Pure moments (max. 4 Nm) were applied to the specimens. No significant differences were found in ROM between the approaches. Results also showed that posterior fixation with a pedicle-screw-rod construct was beneficial and could be used to achieve stability after fusion across one or two levels using either technique. These biomechanical studies conclude that the various interbody fusion approaches do not differ significantly, suggesting that perioperative parameters should be assessed to decide the safest treatment as per a patient's needs. However, more research may be required to understand the stabilizing effect of augmentation techniques in conjunction with the fusion approaches to clearly understand their effects on spine stability.

Clinical Efficacy

A number of publications have sought to reconcile whether or not various interbody fusion approaches posed significant advantages over one another in terms of clinical outcome. Zhang et al. compared PILF to TLIF outcomes in a meta-analysis containing seven comparative studies. They determined that while the respective approaches possessed different complication profiles, they had no statistically significant difference between important metrics such as clinical satisfaction or radiographic fusion (Zhang et al. 2014). Likewise, Phan et al. compared fusion characteristics between ALIF and TLIF and found a distinctly similar outcome (Phan et al. 2015). They noted that the complication profiles may vary, but that this might be a result of the different techniques and directions of approach. The fusion rates were 88.6% and 91.9%, respectively, demonstrating the similarity between the end results of the fusion surgery despite the noticeably different surgical approach.

Moreover, Watkins et al. compared three approaches against one another: ALIF, LLIF, and TLIF. Utilizing a patient population of 220 (309 operative levels) and radiographic analysis to measure variables such as lordosis restoration, disc height, and spondylolisthesis reduction, they determined that all groups showed a reduction in spondylolisthesis (Watkins et al. 2014). There was some degree of differentiation in regards to the lordosis improvement (ALIF, 4.5 degrees; ranked superiorly to TLIF, 0.8 degrees; and LLIF, 2.2 degrees) and disc height (ALIF, 2.2 mm; LLIF, 2.0 mm; and ranked superiorly to TLIF, 0.5). However, even when one approach appears to be superior the benefits are marginal when compared to the other techniques, demonstrating that the different surgical approaches could in some ways still be ubiquitous to one another. These studies show that while different approaches may have some degree of variability in their outcomes, their fusion results are generally similar and lead to reasonably comparable results.

Integration

Both biomechanical and clinical data suggest that despite the change in approach direction, stabilization and fusion (two common measures of implant success) are comparable amongst all. Thus, as argued in the aforementioned section, it would behoove both industry and surgeons alike to create additional means of distinction between the different device approaches in order to better understand how they affect the body under physiological loads.

Perioperative Factors

As the modalities of interbody fusion have reached a performance plateau, factors outside of pure fusion and stabilization are of increasing importance in the comparison of different methods. Perioperative measures such as infection rates, blood loss, device complications,

surgical complications, and invasiveness are noteworthy metrics.

Tormenti et al., in their retrospective analysis of 531 patients, found that open-TLIF was a successful means of achieving arthrodesis in the lumbar spine (Tormenti et al. 2012). However, the researchers noted that there was a propensity for complications (durotomy and infection) in revision or multilevel fusion cases. Wong et al. compared intraoperative and perioperative complications between minimally invasive and conventional open-TLIF using a retrospective analysis of 513 patients (Wong et al. 2015). They were able to conclude that the minimally invasive approach was as successful or better than the open approach as mentioned by Tormenti et al. This argument is further echoed by Sulaiman et al., in which they concluded that minimally invasive TLIF actually performed superiorly to an open-TLIF approach in the metrics of average length of surgical time, estimated blood loss, ODI score, VAS rating, and direct cost of treatment (Sulaiman and Singh 2014). Due to the similar fusion results in both surgeries, surgeons should be concerned with perioperative measure as much or more so than classical metrics of success, like fusion and non-union. Furthermore, they may progress from questioning the fundamental specifications of device design to bettering the procedural variables. Choy et al. analyzed the perioperative results and complications in 1474 patients who had undergone ALIF and found the overall rate of surgical and medical complication was 14.5%. It was noted that complications were often associated with longer operation times (Choy et al. 2017). The anterior approach exposes more of the body (especially blood vessels and organs) increasing the risk of vascular damage.

These studies show how different approaches may correspond to different intra and postoperative complications. As devices grow more complex and achieve marginally fewer positive outcome differentials, perioperative measures will still be a means of increasing positive outcomes at a faster rate. Surgeons can still affect a large difference that may manifest itself in fewer complications and more successful procedures via the analysis and attention to these perioperative measures.

Conclusion

It has been demonstrated throughout this chapter that both biomechanical and clinical testing have proven beneficial in driving industry leaders and surgeons to adopt successful devices and practices. While the methods of such discoveries are far from perfect, and could benefit from additional inquiry and research, the correlation of both testing modalities serves as a vehicle for advancing the state of the art within the spinal surgery space. It is imperative that future research continues to challenge the therapeutic status quo and promotes the use of innovative designs and methods of intervention to further the quality standards of the industry. Biomechanical testing has been shown to pave the way for preliminary discoveries that may have robust clinical ramifications. It also serves to determine when new technologies do not lead to their intended outcome before they are moved into clinical models. Thus, the synergistic relationship among these two testing modalities should be enhanced to ensure the future prosperity of spinal surgery.

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16 The Sacroiliac Joint: A Review of Anatomy, Biomechanics, Diagnosis, and Treatment Including Clinical and Biomechanical Studies (In Vitro and In Silico)

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Abstract

Sacroiliac joint (SIJ) is one of the most overlooked sources of LBP. The joint is responsible for the pain in 15–30% of people suffering from LBP. Fixation is increasingly recognized as a common surgical intervention for the treatment of chronic pain originating from sacroiliac joint (SIJ). Many studies have investigated the clinical outcomes and biomechanics of various SIJ surgical procedures. However, there is currently no agreement on the surgical indications for SIJ fusion or the best and most successful surgical technique for sacroiliac joint fixation and SIJ pain treatment.

Biomechanics of normal, and injured SIJs and biomechanical differences due to sex are well documented. Various studies have investigated the clinical outcomes of different surgical techniques and devices intended for treatment of the SIJ pain, and they have shown that these techniques are effective indeed. Several questions related to clinical and biomechanical effects of surgical parameters such as number, design/shape and positioning of implants, and unilateral versus bilateral placement remain unanswered. Biomechanical studies using in vitro and in silico techniques are crucial in addressing such unanswered questions. These are synthesized in the review.

Keywords

Sacroiliac joint · Fusion · Biomechanics · Surgery · Anatomy · Diagnosis · Treatment · Clinical · In vitro · In silico

Background

Low back pain (LBP) is the most common reason for primary care visits after common cold, with approximately 90% of adults being impacted by this condition at some point in their lives (Weksler et al. 2007; Frymoyer 1988). Apart from hindering the quality of life of those affected by LBP, if left untreated or improperly diagnosed, LBP may also profoundly impact affected patients' work productivity and therefore economic success. LBP accounts for annual cost up to 60 billion dollars due to decreased productivity and income as well as medical expenses (Koenig et al. 2016; Rudolf 2012; Murray 2011).

The majority of LBP cases originate from the lumbar spine. One of the most overlooked sources of LBP is the sacroiliac joint (SIJ) due to its complex nature and the fact that the pain emanating from this region can mimic other hip and spine conditions (Weksler et al. 2007; Smith 1999). However, recent studies have reported a higher prevalence of the SIJ as a source for LBP, with some reports estimated that the SIJ is the actual source of pain in 15–30% of cases of LBP (Sachs and Capobianco 2012; Lingutla et al. 2016; Schwarzer et al. 1995). Increased physicians' awareness of the prevalence of the SIJ as a source of LBP has given rise to an increased clinical suspicion of SIJ dysfunction as a pain generator and planning treatment accordingly.

Lumbar spine fusion, particularly L5–S1 segment, directly impacts the biomechanics of the SIJ by increasing both the motion and stress across the articular surface of the joint (Ivanov et al. 2009). As a significant source of LBP, focus on the SIJ is presently quite high. Current nonsurgical treatment and pain management strategies include physical therapy, SI joint injections, and radiofrequency (RF) ablation. When patients continue to present chronic LBP characteristic with the SIJ, surgical procedures become a final resort.

Anatomy

The SIJ, the largest axial joint in the body, is the articulation of the spine with the pelvis that allows for the transfer of loads to the pelvis and lower extremities (Dietrichs 1991; Cohen 2005). The

SIJ lies between the sacrum and the ilium, spanning about 1–2 mm in width and held together by fibrous capsule (Fig. 1). The sacral side of the joint is covered with hyaline cartilage thicker than iliac cartilage, which appears more fibrocartilaginous (Foley and Buschbacher 2007).

Ligaments

Several ligaments support and limit the movement and mobility of the SIJ. These ligaments include the interosseous sacroiliac ligament, the posterior and anterior ligaments, and sacrotuberous, sacrospinous, and iliolumbar ligaments. The interosseous ligament, also known as the axial ligament, connects the sacrum and ilium at S1 and S2 levels. The posterior sacroiliac ligament is quite strong and consists of multiple bundles which pass from the lateral crest of the sacrum to the posterior superior iliac spine and the posterior end of the iliac crest. The anterior sacroiliac ligament is a thin ligament that is weaker than the posterior ligament and runs over the joint obliquely from sacrum to ilium. The sacrotuberous ligament is located at the inferior-posterior part of the pelvis and runs from the sacrum to the ischial tuberosity. The sacrospinous ligament's attachment is behind of the sacrotuberous ligament, and it connects the outer edge of the sacrum and coccyx to the Ischia of the ilium. The iliolumbar originates from the tip of the fifth lumbar vertebral body to the iliac crest (Fig. 2) (Ombregt 2013). The long dorsal sacroiliac ligament can stretch in periods of reduced lumbar lordosis, such as during pregnancy, which will be discussed further. Table 1 summarizes sacroiliac joint ligaments' locations and their functions.

Muscles

While no muscles are designed to act on the SIJ to produce active movements, the joint is still surrounded by some of the largest and most powerful muscles of the body. These muscles include the erector spinae, psoas, quadratus lumborum, piriformis, abdominal obliques, gluteal, and hamstrings. While they do not act directly on the SIJ, the muscles that cross the joint act on the hip or the lumbar spine (Miller et al. 1987; Solonen 1957; Albee 1909). Movements of the SIJ are indirectly produced by gravity and muscles acting on the trunk and lower limbs rather than active movements of the sacrum (Ombregt 2013). Table 2 summarizes sacroiliac joint muscles' actions and their effect on SIJ.

Function and Biomechanics

The flat shape of SIJ along with its ligaments helps it to transfer large bending moments and compression loads. However, it is weak against shear loads; it is counteracted by compression of SIJ which is generated by a self-bracing mechanism. The self-bracing mechanism consists of a loading mode of pelvis and forces produced by muscles and ligaments which are normal to the joint surface. The loading mode of the pelvis due to gravity and the free body diagram of the self-bracing mechanism which involves normal and tangential forces of the joint surface, hip joint force, and muscle or ligament force are shown in Fig. 3a, b, respectively. The friction coefficient of SIJ surfaces without grooves and ridges was measured as 0.4. This resistance can be increased by grooves and ridges and wedge angle β to prevent sliding of SIJ surfaces due to shear (Snijders et al. 1993). It was shown that M. transversus abdominis and the pelvic floor muscles are playing a major rule in SIJ stability by enlarging the SIJ compression load to resist shear loads (Pel et al. 2008).

Pool-Goudzwaard et al. (2003) conducted a study on 12 human cadavers to assess the effect of the iliolumbar ligament (IL) on SIJ stability. Four cases were tested: (1) Intact IL, (2) random dissection of IL, (3) further dissection of IL, and (4) cut IL. The moment-rotation relationships were assessed by applying various moments to SIJ and measuring the rotation in the sagittal plane. The sacrum and iliac bones were fixed, and the moment was applied by a traction device to generate a tension in the string. Eight light-reflecting markers were utilized to calculate the rotation. Dissection of the ventral side of the iliolumbar ligament is causing less SIJ stability

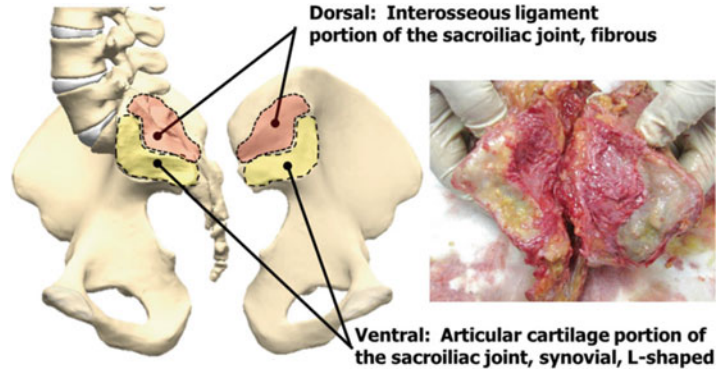


Fig. 1 Articular surfaces of the sacroiliac joint (Dall et al. 2015)

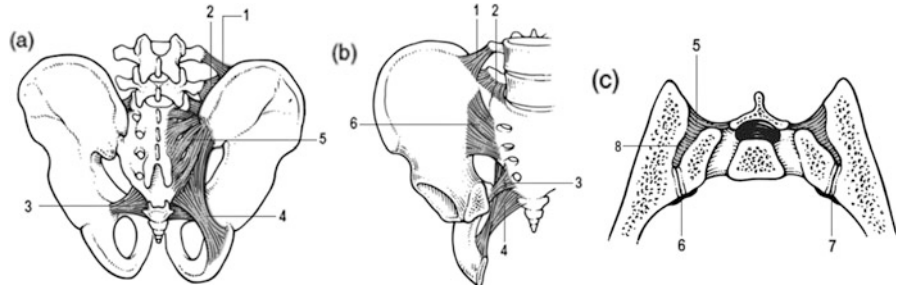


Fig. 2 (**a**) Posterior view; (**b**) anterior view; and (**c**) sacroiliac joint cut in transverse plane. (1, 2) Superior and inferior iliolumbar ligaments; (3) sacrospinous ligament; (4) sacrotuberous ligament; (5) posterior sacroiliac ligaments; (6) anterior sacroiliac ligaments; (7) sacroiliac joint; (8) interosseous ligament (Ombregt 2013)

Table 1 Sacroiliac joint ligaments' locations and their functions (Dall et al. 2015)

Ligament	Location	Primary restraint
Dorsal ligaments	PSIS to sacral tubercles	Sacral extension
Long ligament		
Short ligament		
Sacrotuberous	PSIS and sacrum to ischial tuberosity	Sacral flexion
Sacrospinous	Apex of sacrum to ischial spine	Sacral flexion
Ventral ligament	Crosses ventral and caudal aspect of SIJ	Sacral flexion
		Axial rotation
Interosseous	Between sacrum and ilium dorsal to SIJ	Sacral flexion
		Axial rotation
Iliolumbar *Ventral band* *Dorsal band* *Sacroiliac part*	Transverse process of L5 to iliac tuberosity and crest	Lateral side bending *Ventral band* Forward flexion *Dorsal band*

in the sagittal plane. Dorsal side and sacroiliac part of the IL does not have a significant role in providing SIJ stability (Pool-Goudzwaard et al. 2003). It is also stabilizing the lumbar vertebra on the sacrum (Yamamoto et al. 1990).

The posterior sacroiliac ligaments are contributed most to the SIJ mobility, while the anterior sacroiliac ligament has little influence (Vrahas et al. 1995). The motion of ilium respect to sacrum is called nutation which is anterior sacral tilt and counternutation which is posterior sacral tilt. Resisting the nutation and counternutation of the joint is done by the sacrotuberous ligament (STL), the sacrospinous ligament (SSL), and the long

Table 2 Sacroiliac joint muscles' actions and their effect on SIJ (Dall et al. 2015)

Muscle	Primary action	Effect on SIJ
Erector spinae *Iliocostalis lumborum* *Longissimus thoracis*	Bilateral: back extension Unilateral: side bending	Hydraulic amplifier effect
Multifidus	Back extension, side bending, and rotation	Imparts sacral flexion, force closure of SIJ with deep abdominals
Gluteus maximus	Hip extension, hip lateral rotation	Stabilizes SIJ
Piriformis	Hip lateral rotation	May alter SIJ motion via direct attachment to ventral aspect of sacrum
Biceps femoris	Hip extension, knee flexion	Long head: Imparts sacral extension via attachment to sacrotuberous ligament
Deep abdominals *Transversus abdominis*	Compression of abdominal cavity	Force closure of SIJ
Iliacus	Hip flexion (open chain) and tilts pelvis/sacrum ventrally (closed chain)	Synchronous tilting of the pelvis/sacrum ventrally (closed chain)
Pelvic floor	Support pelvic viscera	Imparts sacral extension

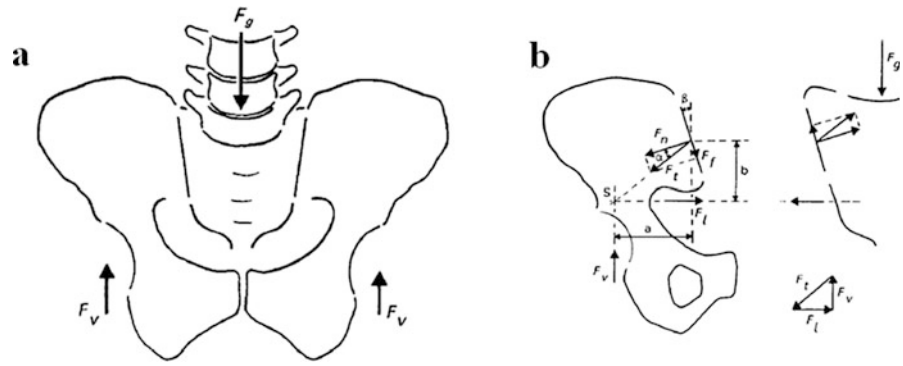


Fig. 3 (**a**) Pelvis free-body diagram due to gravity. Trunk weight (F_g) and hip joint forces (F_v). (**b**) Free-body diagram of self-bracing effect of the sacroiliac joint. SIJ reaction force: normal and tangential (F_n and F_f), ligament or muscle force (F_l), and hip joint force (F_v) (Snijders et al. 1993)

dorsal ligament (LDL), respectively (Vleeming et al. 1992a; Sashin 1930). During pregnancy by increased laxity of SIJ ligaments, the pain is mostly experienced in LDL due to its counteraction to the counternutation (Eichenseer et al. 2011). Pain in this region is also common in men due to its location which is superficial and will put asymmetric stress on the SIJ. Flattening of lumbar lordosis brings about a decrease in SIJ nutation (Vleeming et al. 2012).

A cadaveric study was done by Wang et al. (Wang and Dumas 1998) to calculate the SIJ motion and influence of anterior and posterior ligaments on the SIJ stability. Four female cadaver specimens were tested by applying five different eccentric compressive loads (combination of compression, bending moment, and forward shear due to inclination angle) to the sacrum. The main motions of the sacrum were lateral rotation and nutation rotation which were less than 1.2°. The lateral rotation is restricted by transverse portions of anterior and posterior ligaments. Also, the nutation rotation is prevented by the top portion of anterior and lower portion of

posterior ligaments (i.e., Shear resisting couple), and dissection of these two ligaments has a significant influence on the joint stability. It was shown that interosseous ligaments are the strongest ligaments which provide less motion in the joint's translation.

Dujardin et al. (2002) assessed the SIJ micromotion under compression load applied to the ischial tuberosity. By sectioning SSL and STL, SIJ stability will decrease. Buyruk et al. (1995) using Doppler imaging of vibrations showed that left and right SIJ stiffnesses are different in various conditions, which means there is asymmetry in the SIJ stiffness resulting in low back pain and pelvic pain. Rothkotter et al. (Rothkotter and Berner 1988) indicated that the SIJ ligamentous structure failed at 3368 N under transverse loading with displacement range from 5.5 to 6.6 mm. They found that under dorsocranial loading, the self-bracing mechanism of the SIJ between the sacrum and ilium is working better than other loading directions.

Range of Motion

The sacrum can move with respect to the ilium in six degrees of freedom which is shown in Fig. 4. The intersection of the middle osteoligamentous column and the lumbosacral intervertebral disc is defined as the lumbosacral pivot point. Placing constructs posterior to this pivot point extending to the anterior of the point would provide rotational stability (McCord et al. 1992).

While the primary function of the SIJ is to absorb and transmit forces from the spine to the pelvis, it is also responsible for facilitating parturition and limiting x-axis rotation (Dietrichs 1991; Cohen 2005). The SIJ is unique in that it is rather stable, and motion of the joint is quite minimal (Foley and Buschbacher 2007). The exact range of motion (ROM) of the SIJ has been debated and studied extensively, with varying results. There are different methods to measure the SIJ motion such as roentgen stereophotogrammetric, radiostereometric, ultrasound, and Doppler (Vlaanderen et al. 2005; Jacob and Kissling 1995; Sturesson et al. 1989, 2000a); they indicated that the SIJ rotation and translation in different planes do not exceed 2–3° and 2 mm, respectively (Foley and Buschbacher 2007; Zheng et al. 1997). The joint's ROM is greatest in flexion-extension with a value of approximately 3°. Axial rotation of the SIJ is about 1.5°, and lateral bending provides the least ROM with approximately 0.8° (Miller et al. 1987). As the characteristics of the SIJ change with aging, these values can increase or decrease depending on the circumstance.

Many studies have been conducted concerning the biomechanics of the SIJ, and the results can be summarized quite simply: the SIJ rotates about all three axes, and these incredibly small movements are very difficult to measure (Walker 1992; White and Panjabi 1990). In an attempt to understand the load-displacement behavior of single and paired SI joints, a study involving eight elderly cadavers was conducted by Miller et al. (1987). In this

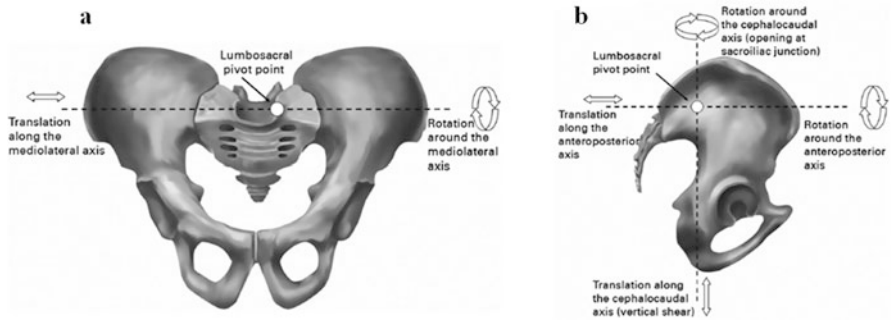


Fig. 4 Pelvis six degrees of movement and lumbosacral pivot point: (**a**) coronal plane, (**b**) sagittal plane (Berber et al. 2011)

study, rotations about all three axes were measured for one and both iliac fixed, with static test loads applied in superior, lateral, anterior, and posterior directions. According to their results, movements in all planes with one leg fixed ranged from 2 to 7.8 times greater than those measured with both legs fixed.

Another series of cadaveric studies by Vleeming et al. (1992a, b) was conducted to investigate the biomechanics of the SIJ, reporting that the ROM for flexion and extension rarely exceeded 2°, with an upper limit of 4° during sagittal rotation. To compare male and female SIJ ROM, a cadaver study by Brunner et al. (1991) found that the maximum ROM for men and women was 1.2° and 2.8°, respectively. Another study by Sturesson et al. (1989) involved measuring SIJ movements in 25 patients diagnosed with SIJ pain. According to their results, all movements were incredibly small, with translations never exceeding 1.6 mm and an upper rotational limit of 3°. This study also found that no differences in ROM existed between symptomatic and asymptomatic SI joints, which led the authors to conclude that three-dimensional motion analysis is not a useful tool for identifying painful SI joints in most patients (Sturesson et al. 1989). Jacob et al. (Jacob and Kissling 1995) reported mobility of SIJ of 15 healthy people using a three-dimensional stereophotogrammetric method. The average total rotation and translation were 1.7 and 0.7 mm, respectively.

Sexual Dimorphism

Sexual dimorphism exists in the pelvis with the male pelvis being larger, a distinction that decreases in the later years of childhood. While the sacral base articular facet for the fifth lumbar vertebra occupies more than a third of the width of the sacral base, it occupies less than a third in females. Compared to the male sacrum, the female sacrum is wider, more uneven, less curved, and more backward tilted. Males tend to have a relatively long and narrow pelvis, with a longer and more conical pelvic cavity than those of females (Figs. 5 and 6). In the second decade of life, women develop a groove in the iliac bone, the paraglenoidal sulcus, which usually does not occur for men. Such gender-related differences in the development of the SIJ can lead to a higher rate of SIJ misalignment in young women (Vleeming et al. 2012).

According to a study by Ebraheim and Biyani (2003), the SIJ surface area is relatively greater in adult males than females, which consequentially allows males to withstand greater biomechanical loading. While the average auricular surface area for females has been reported to range from 10.7 to 14.2 cm^2 (Miller et al. 1987; Ebraheim and Biyani 2003) with an upper limit of 18 cm^2 (Sashin 1930), this ligamentous area for males is approximately 22.3 cm^2 (Miller et al. 1987). Another reason that males can withstand greater biomechanical loading can be attributed to the fact that males possess significantly higher lumbar isometric strength, almost twice as strong as those of females, thus requiring more significant load transfers through the SI joints (Graves et al. 1990; Masi 1992).

Another significant influence on the development of particular SIJ form is the center of gravity, which has been reported to exist in different positions for males and females. Compared to men, who have a more ventral center of gravity, the center of gravity in females commonly passes in front of or through the SIJ (Tischauer et al. 1973; Bellamy et al. 1983). This difference implies that men would have a greater lever arm than women, accounting for the higher loads on the joints and stronger SI joints in males (Vleeming et al. 2012). This characteristic also may explain why males have more restricted mobility, as the average movement for men is approximately 40% less than that of women (Vleeming et al. 2012; Sturesson et al. 2000a, b).

The increased mobility of the SIJ in women can be attributed to individual anatomical correlations. Two features that allow for higher mobility in women are the less pronounced curvature of the SIJ surfaces and a greater pubic angle compared to those of males (Vleeming et al. 2012). While males typically have an average pubic angle of 50–82°, females have an average pubic angle of 90° (Bertino 2000). A possible reason for these

Structural Aspects	Female	Male
General structure	Light and thin	Heavy and thick
Pelvic brim (inlet)	Wide and more oval	Narrow and heart-shaped
Pubic arch	Greater than 90 angle	Less than 90 angle

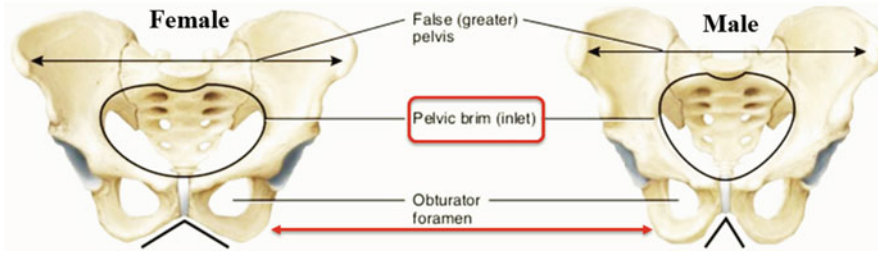


Fig. 5 Comparison of the female and male pelvic brim (inlet) (Tortora and Derrickson 2010)

Structural Aspect	Female	Male
Pelvic Outlet	Wider	Narrower

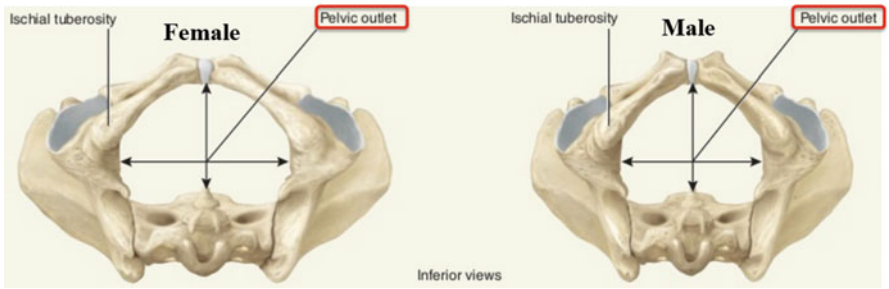


Fig. 6 Comparison of the female and male pelvic outlet (Tortora and Derrickson 2010)

differences can be attributed to the facilitation of parturition in females, which involves the influence of hormones such as relaxin (Dietrichs 1991; Cohen 2005; Ross 2000). Under the effect of relaxin, relative symphysiolysis appears to occur, and both of these factors loosen the SIJ fibrous apparatus, thus increasing mobility (Vleeming et al. 2012). While these unique aspects of the SIJ provide females with the necessary ability to give birth, they also may predispose females to a greater risk of experiencing pelvic pain (Brooke 1924; Hisaw 1925; Chamberlain 1930; Borell and Fernstrom 1957). One factor that plays a major role in determining the severity of this predisposition involves the laxity of the female SI joints during pregnancy. According to a study by Damen et al. (2001), females who experience asymmetric laxity of the SI joints during pregnancy are three times more likely to develop moderate to severe pelvic girdle pain (PGP) than females who experience symmetric laxity. As the particular form of the SIJ differs immensely between males and females, it becomes rather clear that women are more likely to develop PGP and are therefore at greater risk of experiencing LBP. Figures 5 and 6 and Table 3 show the anatomical and biomechanical differences between male and female pelvis.

Table 3 A biomechanical comparison of the female and male SIJ

Biomechanical aspects	Female	Male
SIJ motions	More rotational	More translational
SIJ surface area	Lesser	Greater
Interosseous sacroiliac ligament	Larger	Smaller
Anterior sacroiliac ligaments	Smaller	Larger
Posterior sacroiliac ligaments	Smaller	Larger

Causes of SIJ Pain

The mechanism of SIJ injury has been viewed as a combination of axial loading and abrupt rotation (Dreyfuss et al. 1995). From an anatomical perspective, pathologic changes specific to different SI joint structures can result in SIJ pain. These changes include, but are not limited to, capsular and ligamentous tension, hypomobility or hypermobility, extraneous compression or shearing forces, microfractures or macrofractures, soft tissue injury, and inflammation (Cohen 2005). Also, numerous other factors can predispose a person to a gradual development of SIJ pain.

As the primary function of the SIJ is to transfer loads between the spine and lower extremities effectively, simple daily activities such as walking and lifting objects can also cause stress and wear on the joint over time. However, dysfunction and pain of the joint often are not solely due to these activities. Many other causes of SIJ pain exist and impact the joint in combination with daily load bearing and aging. Some of the most common sources of SIJ pain include injuries sustained from falling directly on the buttocks, and collisions during sports and car accidents. Abnormal loading due to lumbar spinal fusions, limb length discrepancy, or prior medical procedures may also play a role in SIJ pain and dysfunction.

As mentioned, many studies have reported that prior lumbar fusion can directly increase angular motion and stress across the patient's SIJ, and the magnitude of both of these parameters is strongly correlated to the specific lumbar levels fused as well as the number of segments fused (Ivanov et al. 2009). When surgical arthrodesis causes degeneration of an adjacent segment, such as the SIJ, this profound adverse effect is known as adjacent segment disease (ASD) (Ivanov et al. 2009; Park et al. 2004; Ha et al. 2008; Hilibrand and Robbins 2004).

Other causes of SIJ pain and dysfunction have also been studied extensively – one of which involves limb length discrepancy (LLD). While it has commonly been accepted that LLD is related to LBP, the exact mechanism of this relation is unknown. However, several authors have reported the correlation between LLD and LBP to be strongly related to SIJ dysfunction (Cohen 2005; Schuit et al. 1989; Winter and Pinto 1986; Golightly et al. 2007). Due to the length discrepancy, the mechanical alignment of the SI joints becomes increasingly imbalanced, resulting in an increased load distribution across both SI joints (Cohen 2005; Winter and Pinto 1986; Golightly et al. 2007).

Apart from injuries, prior lumbar fusion, and LLD, several other factors can also cause the gradual development of SIJ pain. Additional sources of increased stress and pain across the SI joints include joint infection, spondyloarthropathies such as ankylosing spondylitis, inflammatory bowel disease (Cohen 2005), gait abnormalities (Herzog and Conway 1994), scoliosis (Schoenberger and Hellmich 1964), and excessive exercise (Marymount et al. 1986). Regardless of the cause, the association of pain with SIJ dysfunction is rather consistent.

Symptoms of SIJ dysfunction include pain in the lower back that sometimes radiates to the back of the thigh, and knee. Patients with LBP often experience pain when sitting, leaning forward, and with an increase in intra-abdominal pressure (DonTigny 1985). While these pain characteristics are associated with SIJ dysfunction, they also are consistent with other hip and spine conditions, making accurate diagnosis and confirmation of the SIJ as the pain source a rather difficult task. Table 4 summarizes the causes of intra-articular and extra-articular SIJ pain.

During pregnancy, many hormonal and biomechanical changes are occurring which contribute to ligaments laxity. One of the leading

Table 4 Causes of intra-articular and extra-articular SIJ pain (Holmes et al. 2015)

Intra-articular pain	Extra-articular pain
• Arthritis • Spondyloarthropathy • Malignancies • Trauma • Infection	• Ligamentous injury • Bone fractures • Malignancies • Myofascial pain • Enthesopathy • Trauma • Pregnancy

musculoskeletal changes is increasing the mass of uterus and breast which causes anterior displacement of the center of gravity. This effect heightens joint loads (e.g., increased hip-joint anterior torque by eight times) and is aggravated by the laxity of other ligaments and other joints which may contribute to pain and risk of injury (Fitzgerald and Segal 2015).

Diagnosis of SIJ Dysfunction

Symptoms of SIJ dysfunction include pain in the lower back, buttock, back of the thigh, and knee. Patients with LBP often experience pain when sitting, leaning forward, and with an increase in intra-abdominal pressure (DonTigny 1985). While these pain characteristics are associated with SIJ dysfunction, they also are consistent with other hip or spine conditions, making accurate diagnosis and confirmation of the SIJ as the pain source a rather difficult task.

Due to the complexity of diagnosing the SIJ as the pain source, numerous physical examination tests have been utilized, many of which incorporate distraction of the sacroiliac joints. Two of the most commonly performed tests are the Gaenslen's test and Patrick's test, also known as the FABER test (Cohen 2005). Other provocation tests for assessing SIJ pain include distraction/compression tests, the thigh thrust test, and the sacral thrust test (Table 5) (Laslett et al. 2005). It is commonly accepted that if three or more of these tests are deemed positive, then they can be considered reliable for diagnosing the SIJ as the source of pain (Laslett 2006). Despite the various physical diagnostic tests available, many clinical studies have shown rather inconsistent findings in the success of identifying the pain source to be SIJ dysfunction (Schwarzer et al. 1995; Cohen 2005). For this reason, other techniques have been suggested in conjunction with physical diagnostic tests to improve reliability.

Two techniques that are implemented in addition to physical examinations include radiological studies and diagnostic blocks, or intra-articular injections. Radiological imaging tests, however, have proven to be rather insufficient, yielding reports of low sensitivities and poor correlations with diagnostic injections and symptoms (Cohen 2005). However, an exception is the high specificity of MRI in the setting of the seronegative spondyloarthropathies (90–100%) (Battafarano et al. 1993; Docherty et al. 1992; Murphey et al. 1991). Diagnostic blocks, on the other hand, are often considered to be one of the most reliable methods for diagnosing SIJ pain. These blocks, which are typically fluoroscopically guided, are used to determine if the patient experiences a significant reduction in pain while the anesthetic is active (Foley and Buschbacher 2007). A controversial aspect of diagnostic blocks is that no actual "gold standard" exists for this technique, though it is commonly accepted that a successful injection helps the diagnosis of SIJ dysfunction (Cohen 2005; Foley and Buschbacher 2007; Broadhurst and Bond 1998). After determining that the sacroiliac joint is the pain generator in patients with LBP, there are several treatment strategies for relieving SIJ pain.

Nonsurgical Management

The first step in the treatment of SIJ dysfunction involves nonsurgical management (NSM). Nonsurgical treatment options include physical therapy, steroid injections, radiofrequency (RF) ablation, and prolotherapy. For patients with leg length discrepancy (LLD), only utilizing shoe inserts can help eliminate LLD, consequentially equalizing and decreasing the load distribution across the joints over time (Cohen 2005; Kiapour et al. 2012). This conservative management strategy, however, is not a valid treatment option for

Table 5 A comparison of provocation tests

Provocation test	Patient position	Technique description
Gaenslen's test	Supine	With a symptomatic leg resting on the edge of a table and the nonsymptomatic hip and knee flexed, a force is applied to the symptomatic leg while a counterforce is simultaneously applied to the flexed leg, producing pelvic torque (Kokmeyer et al. 2002; Dreyfuss et al. 1996)
Distraction test	Supine	A vertical, posteriorly directed force is applied to both anterior superior iliac spines (ASIS) (Sashin 1930; Cook and Hegedus 2013; Laslett 2008; Laslett et al. 2003)
Compression test	On side	Pressure is applied to the upper part of the iliac crest, producing forward pressure on the sacrum (Magee 2008)
Thigh thrust test	Supine	The hip is flexed to 90° to stretch posterior structures. With one hand fixated below the sacrum, the other applies downward axial pressure along the femur, which is used as a lever to push the ilium posteriorly (Vercellini 2011; Broadhurst and Bond 1998; Laslett 1997; Laslett and Williams 1998)
Sacral thrust test	Prone	With one hand placed directly on the sacrum and the other hand reinforcing it, an anteriorly directed pressure is applied over the sacrum (Vercellini 2011; Broadhurst and Bond 1998)

patients with causes of SIJ pain irrelevant to LLD. For such patients, other measures must be taken.

For patients with SIJ pain not related to LLD, physical therapy and chiropractic manipulation are typically advocated for NSM strategies. Several studies of physical therapy and chiropractic manipulation programs have reported promising long-term results, achieving reductions in pain and disability, as well as enhanced mobility (Sasso et al. 2001; Cibulka and Delitta 1993; Osterbauer et al. 1993); however, there is currently a lack of prospectively controlled studies to back up these treatment strategies (Cohen 2005). Other stabilization plans have also been introduced, such as pelvic belts. These belts have shown to decrease sagittal rotation and consequentially enhance pelvic stability, especially in pregnant women (Vleeming et al. 1992c; Damen et al. 2002). In addition to therapeutic measures, intra-articular injections have also been advocated for SIJ pain relief.

Studies regarding the effectiveness of corticosteroid injections have been conducted to quantify the magnitude of pain reduction in patients with varying reported results. A controlled study by Maugars et al. (1996) reported that after a 6-month follow-up, the subjects experienced a mean pain reduction of 33%. While this is one of the lowest pain reduction rates that have been reported, it should be noted that the sample size was rather small with ten subjects. In contrast, another study conducted by Bollow et al. (1996) consisted of a mean follow-up duration of 10 months and reported a statistically significant pain reduction in 92.5% of the subjects. With a larger sample size of 66 subjects, such a high-pain reduction rate in the majority of subjects indicates that there is effectiveness in administering intra-articular corticosteroid injections for many patients despite the different reported results. For those who do not find significant reductions in pain from intra-articular injections, alternative treatment measures must be considered.

Radiofrequency (RF) denervation procedures are utilized as another treatment strategy with a goal of providing intermediate-term pain relief. Several studies have proven that lateral branch RF denervation strategies may improve the pain, disability, and quality of life for patients suffering from chronic SIJ pain (Cohen et al. 2008; Patel et al. 2012). However, similar to intra-articular injections, the reported success rates of RF denervation vary immensely. A retrospective study conducted by Ferrante et al. (2001) involved the targeting of the intra-articular nerves via a bipolar leapfrog RF technique, and a success rate of 36.4% was reported at follow-up of 6 months. In contrast, a prospective, observational study conducted by Burnham and Yasui (2007) focusing on the targeting of the L5–S3 nerves via the same RF procedure reported a success rate of 89% after 12 months. With such inconsistent reported

success rates, perhaps larger studies are required to confirm the effectiveness of RF denervation. Nevertheless, the disparity of success reports raises greater clinical suspicion regarding the reliability of such procedures.

Open SIJ Fusion

When NSM strategies fail to reduce the pain and discomfort of patients with suspected SIJ dysfunction, surgical measures become an option, beginning with open arthrodesis, or fusion of the SIJ. A study of open fusion of the SIJ was conducted by Smith-Petersen and Rogers to determine the success of arthrodesis. According to their results, in approximately 96% of cases, the patients were able to return to their previous work, though it should also be noted that the average time required to go back to regular activities was approximately four and a half months (Smith-Peterson and Rogers 1926).

While the success of open arthrodesis of the SIJ has been reported in numerous studies (Smith-Peterson and Rogers 1926; Wheeler 1912; Harris 1933; Ledonio et al. 2014a; Alaranta et al. 1990), several aspects of this procedure have also been deemed worthy of improvement. Smith et al. conducted a multicenter comparison between open and minimally invasive SIJ fusion procedures using triangular titanium implants to compare the clinical outcomes. According to their results, open surgical fusion required longer operative time, greater blood loss, and longer hospital stays. Apart from having less advantageous operative measures, open arthrodesis of the SIJ also showed less superior SIJ pain rating changes over the duration of 12 and 24 months (Smith et al. 2013). According to their study, the mean change in VAS pain score at 24 months was approximately −2.0 and −5.6 for open surgical fusion and minimally invasive fusion, respectively, demonstrating the advantage of minimally invasive surgery in regard to pain-recovery ratings. Results of the study also further confirm the superiority of minimally invasive approaches compared to open surgical fusion, as minimally invasive techniques are accompanied by less tissue damage, blood loss, and duration of hospitalization (Ledonio et al. 2014a; Smith et al. 2013).

Minimally Invasive SIJ Fusion

To date, numerous studies have been conducted to investigate the effectiveness of minimally invasive SIJ fusion techniques. Among the various studies, several of the parameters measured included pain scores, disability indices, quality of life, patient satisfaction, and economical outcomes.

One of the most commonly used outcome instruments for assessing variations in pain is the visual analog scale (VAS) (Damen et al. 2002). The VAS is obtained by marking on the patient a 100-mm line along which the patient indicates the intensity of the pain they are experiencing (Wise and Dall 2008). The scoring of the VAS typically ranges from 0 to 100, though it can also be expressed between 0 and 10. Due to its high degree of reliability, validity, and responsiveness, the VAS is a widely utilized instrument for gauging pre- to posttreatment outcomes (Gatchel 2006; Alaranta et al. 1990; Million et al. 1982).

Another commonly used measure of pain and disability is the Oswestry Low Back Pain Disability Index (ODI), which is a self-rating questionnaire that measures a patient's degree of functional impairment. Advantageous aspects that make the ODI a popular outcome instrument include the ease of administration and the short amount of time needed to complete and evaluate. Another commonly used questionnaire that measures health-related quality of life is the Medical Outcomes Short Form-36 Health-Status Survey (SF-36), which is comprised of eight separate scales, along with a standardized mental component scale (MCS) and physical component scale (PCS) (Gatchel 2006). While the SF-36 consists of 36 questions, a shorter, yet still valid version known as the SF-12 has been adapted to have only 12 questions (Ware et al. 2002). The short form surveys allow for assessment of a patient's quality of life from the health care recipient's point of view (Gatchel 2006).

In conclusion, there is a wide range of treatment options for sacroiliitis, and most do improve with conservative, nonsurgical interventions. For those with refractory SI joint-mediated pain, minimally invasive SI Joint fusion has been found to be a safe and effective alternative.

Clinical Studies

Wise et al. (Wise and Dall 2008) performed percutaneous posterior minimally invasive SIJ fusion for 13 consecutive patients to assess the outcome of this technique within 24–35 months follow-up. It was shown that the total fusion rate was 89% and there was a significant improvement in pain scores. After Wise, a new percutaneous lateral SIJ arthrodesis technique using a hollow modular anchorage screw was introduced by Al-Khayer et al. (2008). No one had combined MIS method and bone grafting for SIJ fusion before Al-khayar. Nine patients underwent surgery with 2 years follow-up, and it was shown that the VAS score fell from 8.1 Preoperation to 4.6 postoperation. This new technique provided a safe and successful fusion for SIJ pains. Hollow modular anchorage screw was also utilized by Khurana et al. (2009) for 15 patients during 9–39 months follow-up. They observed good results regarding pain score improvement and concluded that this method is a suitable surgery process for SIJ fusion. Mason et al. (2013) did a study using this fixation system for 55 patients within 12–84 months follow-up. This fusion resulted in reduced VAS score from 8.1 to 4.5 and reduced pain.

As one key focus of the medical field is the improvement of surgical procedures and the discovery of novel treatment approaches, various studies have been performed to further confirm the important trend toward less invasive arthrodesis procedures.

Among the different techniques for minimally invasive SIJ fusion, perhaps the most popular fusion system involves triangular titanium implants with a porous titanium plasma spray coating. The shape, coating, and interference fit of these implants allow for initial stabilization or mechanical fixation, and then effective stabilization of the joint is eventually achieved from long-term biological fixation (Rudolf 2012; Smith et al. 2013; Lindsey et al. 2014). They have various unique features which make them different from traditional cages and screws. Due to their design, an interference fit was provided to allow them the proper fixation. Their triangular profile reduces implant rotation significantly, and their porous surface minimizes the implant micromotion and enhances bone ingrowth resulting in better fusion. Biomechanical studies showed that an 8 mm cannulated screw is three times weaker in shear and bending than a triangular implant (Fig. 7). In this fusion system, no grafts are placed in the sacroiliac joint, therefore all fusions are obtained by their porous coating (Wang et al. 2014).

During a minimally invasive SIJ fusion, the patient is administered general anesthesia and is placed in the prone position to use intraoperative fluoroscopy (Rudolf 2012; Sachs and Capobianco 2012; Smith et al. 2013). A 3 cm lateral incision is then made in the buttock region, and the gluteal fascia is penetrated and dissected to reach the outer table of the ilium. A Steinmann pin is then passed through the ilium across the SI joint to the middle of the sacrum and lateral to the neural foramen (Cher et al. 2013). A soft tissue protector is inserted over the pin, and a drill is utilized to create a pathway and decorticate the bone. Upon removal of the drill, a triangular broach is malleated across the joint to prepare the triangular channel for the first implant. Finally, using a pin guidance system, the implants can be placed, which is followed by irrigation of the incision and closure of the tissue layers (Rudolf 2012; Sachs and Capobianco 2012, 2013; Smith et al. 2013; Cher et al. 2013).

A prospective study by Duhon et al. (Cher et al. 2013) was conducted to determine the safety and effectiveness of MIS fusion with a follow-up duration of 6 months. In this study, the safety cohort consisted of 94 subjects while the effectiveness cohort consisted of 32 subjects, 26 of which were available for postoperative follow-up at 6 months. According to the results, mean SI joint pain at baseline was about 76, while the 6-month follow-up pain score was approximately

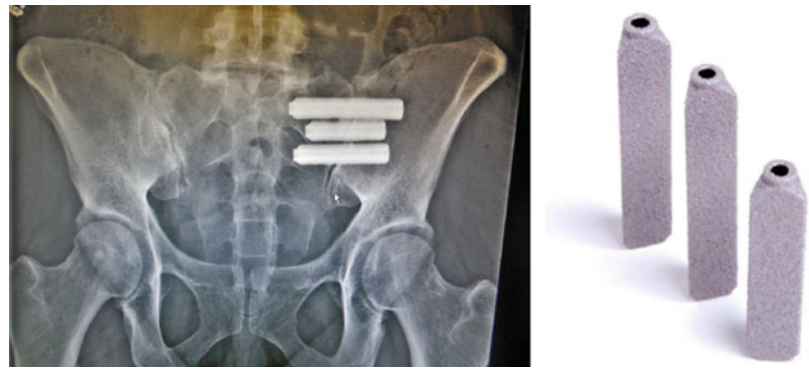


Fig. 7 Triangular titanium implant with porous-coating – lateral approach (Wang et al. 2014)

29.3, indicating an improvement of about 49 points. Furthermore, the mean ODI at baseline was about 55.3 and decreased to approximately 38.9 points, showing an improvement of about 15.8 points. To determine the 6-month outcome of quality of life, this study incorporated Short Form-36 (SF-36) PCS and MCS questionnaires. The results from this study revealed that the SF-36 PCS and SF-36 MCS improved by about 6.7 and 5.8 points, respectively. Finally, patient satisfaction was assessed and recorded to be approximately 85%, a rather high rate of satisfaction.

A similar study was conducted by Cummings and Capobianco (2013), except with a longer follow-up duration of 1 year involving 18 subjects. Similarly, the parameters measured were pain score, disability index for back functionality, quality of life via Short Form-12 questionnaires, and patient satisfaction. Upon a 12-month follow-up, the results of this study revealed an improvement in VAS pain score of about 6.6 points, ODI improvement of −37.5 points, and SF-12 PCS and SF-12 MCS improvements of 11.19 and 20.37 points, respectively. Similar to the study by Duhon et al. (Cher et al. 2013), patient satisfaction was again rather high with a value of 95% satisfaction and 89% of patients claiming that they would undergo the same surgery again.

A study by Sachs and Capobianco (2012) was performed to investigate the successful outcomes for minimally invasive arthrodesis after a 1-year follow-up duration for the first 11 consecutive patients who underwent MIS SIJ fusion using triangular porous plasma coated titanium implants by a single surgeon. At baseline, the mean pain score was approximately 7.9, which decreased to about 2.3 after 12 months. This improvement in mean pain score of about 6.2 points from baseline was considered clinically and statistically significant, and patient satisfaction was immensely high with 100% of subjects claiming that they would again undergo the same surgery.

Sachs and Capobianco (2013) also conducted a retrospective 1-year outcome analysis of MIS–SIJ fusion in 40 patients. The parameters measured in this study primarily involved pain score changes and patient satisfaction; postoperative complications were also taken into consideration. The pain scores in this study were measured on a numerical rating scale (NRS) from 0 to 10, with 10 indicating the highest amount of pain. At baseline, the mean pain score was approximately 8.7, while at follow-up of 12 months, the average pain score decreased to about 0.9, indicating an improvement of approximately 7.8 points. According to the results, patient satisfaction was highest in this study with a value of 100% of the subjects declaring that they would undergo the same surgery again.

It is shown that lumbosacral fusion is contributed to 75% of SIJ degeneration (Ha et al. 2008). Schroeder et al. (2013) performed a clinical study on six patients who had SIJ fusion besides long fusions ending in sacrum with the 10.25 months average follow-up. SIJ fixation improved the results of all scores like Leg VAS score, Back VAS score, SRS 22, and also ODI score from 22.2 to 10.5. They indicated that the SIJ fixation in patients with long fusions results in back pain reduction. The SIJ fusion was achieved by using

titanium triangular implants within the follow-up which led to minimized rotation and micromotion due to osteogenic interference fit used in this study and not having implant loosening and breakage. Long fusions to the sacrum are providing increased motion and force at the SIJ resulting in an increase in SIJ pain (Rudolf 2012; Ha et al. 2008). Unoki et al. (2015) reported a retrospective study to determine the effect of multiple segment fusion on the incidence of SIJ pain for 262 patients. It was indicated that multiple segment fusion (at least 3) could enhance the incidence of SIJ pain. Another clinical study conducted by Shin et al. (2013) indicated that greater pelvic tilt and insufficient restored lumbar lordosis by far play a role in generating SIJ pain after PLIF surgery.

While the effectiveness and safety of minimally invasive fusion of the SIJ have been reported to be significant over the duration of 6 and 12 months, studies of longer follow-up durations have been conducted to confirm the long-term success of these implants. A study by Duhon et al. (2016) was carried out to determine the long-term results over a 2-year follow-up duration from a prospective multicenter clinical trial. Similar to the 6-month study by Duhon et al. (Cher et al. 2013), this analysis also measured parameters of SIJ pain rating, ODI, Short Form-36 PCS and MCS, and patient satisfaction. According to their results, SIJ pain decreased from a baseline value of 79.8–26.0 after 2 years, and the ODI decreased from 55.2 at baseline to 30.9 at 2 years. Furthermore, SF-36 PCS and MCS improved by approximately 8.9 and 10.1 points, respectively, and 88.5% of subjects reported decreased pain at follow-up of 2 years (Duhon et al. 2016). A similar 2-year retrospective follow-up study of 45 subjects was conducted by Rudolf (2012), which reported a mean pain score improvement of approximately 5.9 points and an 82% patient satisfaction rate.

To further investigate and confirm the previous findings of the effectiveness and safety of minimally invasive fusion procedures, Rudolf and Capobianco (2014) conducted a 5-year clinical and radiographic outcome study of 17 patients treated with MIS–SIJ fusion for degenerative sacroiliitis and sacroiliac joint disruptions. The parameters measured in this study include pain on a visual analog scale (VAS) from 0 to 10, mean ODI score, and patient satisfaction. The results of this study revealed an improvement in VAS pain score from 8.3 at baseline to 2.4 after 5 years, with a patient satisfaction rate of 82% after 1 year. While a preoperative mean ODI score was not reported, the reported mean ODI score at the 5-year follow-up was approximately 21.5.

Regardless of the duration of follow-up time and the parameters measured, the numerous studies of the outcomes of MIS SI joint fusion reveal that fusion of the SIJ via minimally invasive approaches with triangular titanium implants can be considered a safe and efficient option for treatment of SIJ pain (Rudolf 2012; Sachs and Capobianco 2012, 2013; Wang et al. 2014; Cher et al. 2013; Cummings and Capobianco 2013; Duhon et al. 2016; Rudolf and Capobianco 2014). A comparison of the studies performed and the outcomes of MIS SIJ fusion is shown in Table 6.

While pain scores, disability indices, and quality of life questionnaires have served as important measures for determining the long-term effects of SI joint-fusion procedures, other studies have been conducted to investigate the success of such operations from a unique perspective involving work productivity and economic concerns.

One study conducted by Saavoss et al. (Koenig et al. 2016) analyzed the productivity benefits for patients with chronic SIJ dysfunction to compare worker function and economic outcomes between nonsurgical management and MIS SIJ fusion. The importance of this study was to determine the impact of arthrodesis on worker productivity, a relationship which has not been previously examined. According to their results, patients who underwent MIS–SIJ fusion were expected to have an increase in the probability of working for 16% compared to patients who received nonsurgical management, and the expected difference in earnings among the groups was deemed to be not statistically significant with a value of approximately $3128. When the metrics of working probability and expected change in earnings were combined, the annual increase in worker productivity between patients receiving MIS SIJ

Table 6 SIJ fusion with triangular implants outcome reports

Study	Patients included	Prior lumbar fusion	Follow-up duration	Pain score improvement	Patient satisfaction
Sachs and Capobianco (2012)	11 (10F/1M)	18%	12 months	70%	100%
Rudolf (2012)	50 (34F/16M)	44%	12 months	56%	82%
Rudolf (2013)	18 (12F/6M)	No prior fusion	24 months	80%	89%
	15 (11F/4M)	Prior lumbar fusion	24 months	73%	92%
	7 (3F/4M)	Prior lumbar pathology treated conservatively	24 months	63%	63%
Schroeder et al. (2013)	6 (6F/0M)	100%	10.25 months (4–15)	61%	100%
Gaetani et al. (2013)	12 (12F/0M)	8.3%	10 months (8–18)	4	100%
Cummings and Capobianco (2013)	18 (12F/6M)	61%	12 months	74%	95%
Sachs and Capobianco (2013)	40 (30F/10M)	30%	12 months	90%	100%
Duhon et al. (2013)	32 (21F/11M)	69%	6 months	67%	85%
Smith et al. (2013)	114 (82F/32M)	47.4%	24 months	79%	82%
Kim et al. (2013)	31 (24F/7M)	48%	12 months	N/A	87%
Ledonio et al. (2014a)	17 (11F/6M)	82%	12 months	78%	94%
Ledonio et al. (2014b)	22 (17F/5M)	64%	15 months (12–26)	54% (17%)	73%
Smith et al. (2013)	144 (102F/42M)	62%	12 months	68%	80%
Rudolf and Capobianco (2014)	17 (13F/4M)	47%	60 months	71%	82%
Vanaclocha-Vanaclocha et al. (2014)	24 (15F/9M)	8%	23 months (1–4.5 years)	43%	89%
Whang et al. (2015)	102 (75F/27M)	38%	6 months	63%	79%
Duhon et al. (2015)	172 (120F/52M)	44.2%	24 months	67%	78%
Polly et al. (2015)	102 (75F/27M)	38%	24 months	83%	73%
Sturesson et al. (2016)	52 (38F/14M)	N/A	6 months	55%	55%

fusion and those receiving nonsurgical management was estimated to be approximately $6924.

SI-LOK is another MI SIJ fixation system which locates three hydroxyapatite-coated screws across the sacroiliac joints laterally (Fig. 8). There are optional bone graft slots inside the screw which can be used to enhance fusion. Also, the optional lag screw thread allows applying

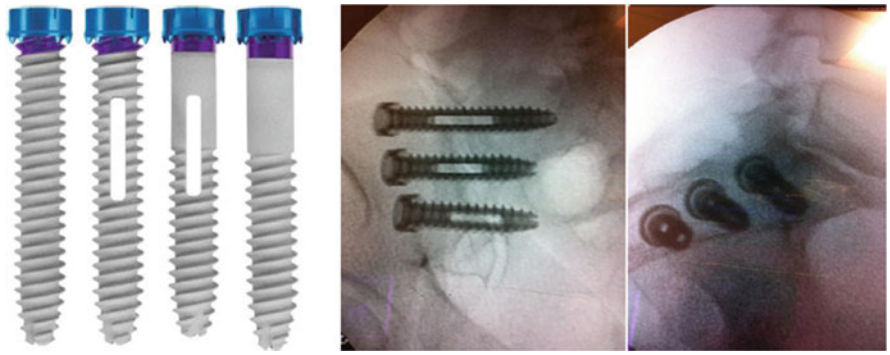


Fig. 8 SI-LOK sacroiliac joint fixation system – lateral approach (Wang et al. 2014)

compression force during placement (Wang et al. 2014). There is no biomechanical study on this screw yet, however, prospective 1-year outcomes of 32 patients were reported. VAS back pain improved from 55.8 ± 26.7 to 28.5 ± 21.6 ($P < 0.01$) *and ODI improved from* 55.6 ± 16.1 to 34.6 ± 19.4 at 1 year (Rappoport et al. 2017).

SImmetry is another cannulated titanium screw type SIJ fixation system which usually is used with two screws (one is antirotation screw) laterally across the SIJ (Fig. 9). There is no bone graft slot in this system, and the bone graft is placed across the articular part of the joint (Wang et al. 2014). This surgery technique is defined comprehensively in (Beaubien et al. 2015). One-year outcomes of 18 patients were reported as follows: VAS reduced from 81.7 (15.2) to 44.1 (22.9), and radiographic arthrodesis was identified on CT scan in 15 of 17 patients (88%) (Kube and Muir 2016).

SIFix is one of the posterior MI SIJ fixation systems and uses two-threaded cancellous bone to stabilize the joint. This method can be done bilaterally with a single midline incision (Fig. 10).

Beck et al. (2015) conducted posterior fusion surgery utilizing RI-ALTO implants for 20 patients during 17–45 months follow-up. The fusion rate and satisfaction ratings were 97% and 76%, respectively. It was shown that this method is safe and effective in SIJ fusion and reduces surgical morbidity due to posterior approach (Fig. 11).

From significantly successful reports of surgical outcomes, patient satisfaction, recovery rate, and implant survivorship, minimally invasive procedures have now become the predominant focus for treating patients with chronic SIJ pain.

In conclusion, the results of clinical studies showed that the minimally invasive approaches, compared to open surgical fusion, as minimally invasive techniques are accompanied by less tissue damage, blood loss, and duration of hospitalization. Furthermore, there are various techniques and different types of SIJ fusion implants for minimally invasive approaches. Since some clinical questions could not be answered through clinical studies, in vitro and in silico studies have been used to address these questions.

In Vitro and In Silico Studies

Soriano-Baron et al. (2015) conducted a cadaver study to investigate the effect of placement of sacroiliac joint fusion implants which were triangular implants. Nine human cadaveric specimens from L4-pelvis were used to perform the range of motion testing for one leg stance under three conditions: intact, cut pubic symphysis to allow the right and left SI joints to move freely, and treated. The treated condition was performed using two different approaches for SIJ fusion implant placement which were posterior and transarticular techniques. In the posterior procedure, the three implants were placed inline in the inlet view, and parallel in the outlet and lateral views. In the transarticular approach, the superior and inferior implants were placed similar to

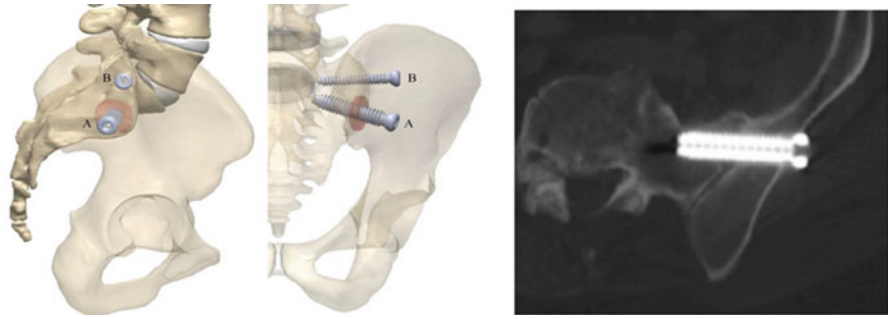
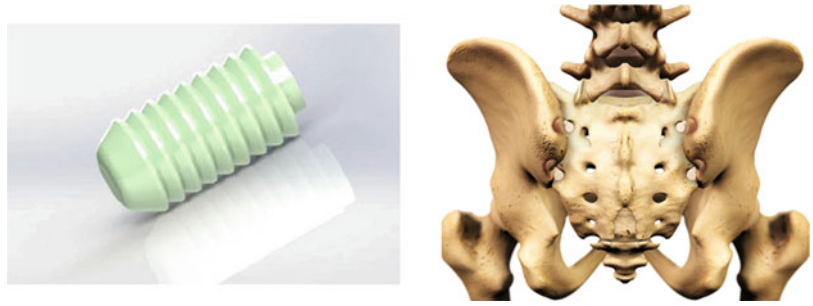


Fig. 9 SImmetry sacroiliac joint fusion system – lateral approach (Wang et al. 2014)

Fig. 10 SIFix sacroiliac joint fixation system – posterior approach (Mason et al. 2013)



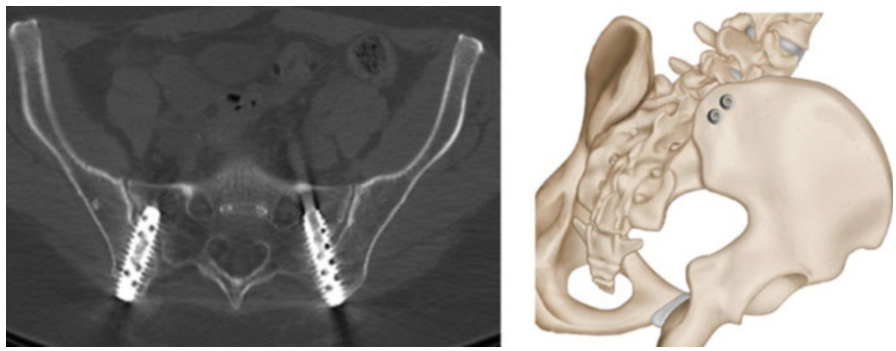


Fig. 11 RI-ALTO sacroiliac joint fusion system – posterior approach (Beck et al. 2015)

the posterior technique, and the middle implant was positioned toward the anterior third of the sacrum across the cartilaginous portion of the SI joint. The 7.5 Nm pure moment was applied to simulate the flexion, extension, lateral bendings, and axial rotations under one-leg stance condition. They showed that placement of three implants in both approaches significantly reduced the ROM in all motions. Interestingly, there was no significant difference between these two techniques regarding motion reduction (Soriano-Baron et al. 2015).

Hammer et al. (2013) using finite element analysis showed that SIJ cartilage and ligaments are playing a significant role in pelvic stability. By increasing in SIJ cartilage and ISL, IL, ASL, and PSL stiffness would decrease the pelvic motion with highest strains at ISL, and pubic ligaments have the least effect on the pelvic motion. These ligaments are contributed to transferring loads horizontally at the acetabulum and ilium. In contrast, increasing stiffness of SS and ST has opposite effect and causes an increase in the pelvic motion, and both are doing vertical load transfer

followed by sacrum translation. Moreover, in standing position, the ligaments strain is higher than in sitting position.

Eichenseer et al. (2011) also evaluated the correlation between ligaments stiffness and SIJ stress and motion. They showed that decreasing ligaments stiffness results in an increase in stress and motion at SIJ. Moreover, ISL has the highest strains under different spine motions which confirmed the finding of Hammer's study.

Mao et al. (2014) investigated the effect of lumbar lordosis alteration on sacrum angular displacement after lumbosacral fusion. Decreasing and increasing lumbar lordosis result in increased sacrum angular motion. In addition, fusion at L4–S1 level is providing higher sacrum angular displacement compared to L3–L5 level. Therefore, it can be the reason why SIJ degeneration incidence is higher in fusions at S1 rather than L5.

Lindsey et al. (2015) assessed the range of motion of SIJ and the adjacent lumbar spinal motion segments after SIJ fusion using triangular implants via finite element analysis. They evaluated the ROM of their model which was L3-Pelvis under 10 Nm moment to simulate flexion, extension, lateral bendings, and axial rotation. They showed that SIJ fusion using three triangular implants provided a significant reduction in SIJ motion in all six motions. Moreover, SIJ motion reduction by fusion resulted in least increase in adjacent lumbar segment motion.

Bruna-Rosso et al. (2016) used finite element method to analyze SIJ biomechanics under RIALTO fusion implant which is a new sacroiliac fusion device. Thousand newton compression load was applied to the pelvis to simulate the experimental test. They evaluated the effect of number of implants (one and two implants) and their placement at SIJ. Proximal insertion of the implant which was farther from the SIJ center of rotation was more efficient than distal insertion of the implant. Proximal insertion of one implant even had better performance than using two implants in terms of motion reduction. There is no significant difference in providing stability between two trajectories of placement which were medial and oblique for using one-implant instrumentation, although medial placement provided higher stability compared to oblique in two-implant instrumentation. Overall, the more parallel and farther the implant was inserted from the SIJ center of rotation, the more stability is provided.

Lindsey et al. (2018) performed another finite element study on SIJ fusion with triangular implants to assess the biomechanical effects of length, orientation, and number of implants under all six spine motions. The variables were one, two, and three implants; superior implant lengths of 55 and 75 mm; midline implant length of 45 mm; and inferior implant length of 45 mm for inline orientation and 50 mm for transarticular orientation. They showed that the transarticular orientation provided better fixation compared to inline orientation due to crossing more the cartilaginous portion of SIJ, although Soriano-Barron revealed that there was no significant difference between these two approaches. Using longer superior implant led to more reduced SIJ motion under different spine motions. In addition, placing two implants close together is less stable than two implants far from each other. Overall, placing implants in the thicker cortical bone areas and a more dense bone region is providing more stability.

A finite element analysis was conducted by Kiapour et al. (2012) to quantify the changes in load distribution through the SIJ as a result of LLD. In this study, the peak stresses and contact loads across the SIJ were measured for leg-length discrepancies of 1, 2, and 3 cm. The results showed that the peak loads and stresses of both legs were always higher than that of the intact model, with a greater magnitude consistently occurring on the longer leg side. Furthermore, as the length discrepancies increased from 1 to 3 cm, the stresses increased accordingly.

Zhang et al. (2014) studied the biomechanical stability of four different SI screw fixations under two types of SI dislocation using finite element method. They placed implants at SIJ in four different configurations: Single screw in S1, single screw in S2, two screws in S1, and one screw in

S1 and another one in S2. Then biomechanical analysis of implanted pelvis was done under inferior translation, flexion, and lateral bending. In type B dislocation, except LPS and SPS ligaments, all ligaments are damaged, and in type C, all ligaments are damaged. The weakest placement configuration was the single screw in S2 in both injury types due to placement farther from S1 end plate which confirmed the study of Bruna-Rosso. Two screws at S1 and S2 were the strongest placement compared to placing two screws closely in S1 in both dislocation types which is in contrast to the finding by Bruna-Rosso.

Ivanov et al. (2009) evaluated sacrum angular motion and stress across SIJ after lumbar fusion. Fusion was performed at different levels of L4–L5, L5–S1, and L4–S1. They showed that lumbar fusion would result in an increase in SIJ motion and stress across SIJ. L4–S1 level fusion provided the greatest SIJ motion and stress across SIJ compared to fusions at other levels.

Another study conducted by Lindsey et al. (2014) investigated the outcomes of minimally invasive SIJ fusion from an in vitro biomechanical approach, comparing the initial and cycled properties. Because the goal of fusion is a reduction in joint motion, the effectiveness of the implants was measured by joint-motion properties in flexion-extension, lateral bending, and axial rotation. The results of this study revealed a significant decrease in flexion-extension range of motion (ROM), and an insignificantly altered lateral bending and axial rotation in the treated specimen compared to the intact condition. Although deemed statistically insignificant, lateral bending and axial rotation were decreased in the majority of subjects, indicating that the implants effectively reduced joint motion in most of the specimens.

A recent study performed by Lindsey et al. (2017) evaluated and compared the biomechanical impact of unilateral and bilateral triangular implant placement across the SI joint. They found that the unilateral and bilateral SIJ fusion lead significant motion reduction across SIJ.

Lee et al. (2017) investigated the biomechanics of intact and treated pelvis via FE and experimental analysis. The spine-pelvis-femur FE model included ligaments and muscles as truss elements. It was demonstrated that posterior iliosacral screw fixation provided higher stability and lower risk of implant failure compared to sacral bar fixation and a locking compression plate fixation.

Joukar et al. (2017) studied the biomechanical differences between male and female SIJs using finite element analysis. They found out that female SIJ had higher mobility, stresses, loads, and pelvis ligament strains compared to the male SIJ which led to higher stress across the joint, especially on the sacrum under identical loading conditions. This could be a possible reason for higher incidence of SIJ pain and pelvic-stress fracture in females.

Joukar et al. (Joukar 2017) investigated the effect of unilateral and bilateral SIJ fusion and different placements of fully threaded screw and half threaded screw during standing upright (similar to RI-ALTO and SI-LOK implant systems), respectively, on the SIJ male and female models' range of motion and stresses. The fully-threaded and half-threaded screws were located posterior and lateral into the SI joint, respectively. Unilateral stabilization significantly reduced the fused SIJ range of motion along with reduction in contralateral (nonfused) SIJ motion during standing upright. Moreover, regardless of sex, lateral and posterior placements of the implants had similar performance on the SIJ stability. Both male and female models showed high reduction in stress and range of motion after treatment compared to the intact model, however, female model showed more stress and motion reductions after SIJ fusion due to higher stress and range of motion values in prior fusion compared to the male model. SIJ implants are more effective in females in terms of stability but may be more prone to higher rate of loosening/failure compared to males. The motion reduction at the SI joint after unilateral and bilateral fusions resulted in minimal changes at the adjacent lumbar levels for both male and female models. Although, the implant shape effects were minimal, the implant placements played a major role in stresses on the bone and implant. In both unilateral and bilateral fusions, SIJ stabilization was primarily due to the inferior and superior implants.

Joukar et al. (2019) developed a validated finite element (FE) model of lumbo-pelvic segment to investigate the biomechanical effects of fixation of the sacroiliac joint using triangular implants on the hip joint. Their model included the most critical anatomical features including connective tissue and articular cartilage across the hip joint. They performed an analysis with femurs fixed in double-leg-stance configuration and application of a 400 N compressive follower preload applied across the lumbo-sacral segment followed by a 10 Nm bending moment applied to the topmost level of the spine segment. Intact model was modified to include SIJ fixation and unilateral and bilateral joint instrumentations. The analyses demonstrated a decrease in range of motion of the SI joint in the instrumented model, compared to the intact. The bilateral fixation resulted in a greater reduction in motion compared to unilateral fixation. The contact stresses and load sharing did not significantly change in contralateral SI joint, following unilateral fixation.

The average hip contact stress and contact area changed less than 5% and 10% respectively in instrumented models relative to intact in most of anatomical motions. The data suggested a low risk of developing adjacent segment disease across the hip joint due to minimal changes in contact area and load sharing at the hip joint following instrumentation with the triangular implant compared to the intact. The changes in the lumbar spine segment were minimal as well.

In conclusion, in vitro studies were performed to address different unanswered questions in clinical studies such as implant failure, range of motion, and bone failure. Since in vitro studies were unable to record some biomechanical data like stresses across bones and implants, and ligament strains, in silico studies were used to overcome these limits of experimental tests.

Summary

SIJ is a complex joint sitting in between the sacrum and iliac bone on either side. The joint plays a vital role in transmitting upper body loads to lower extremities via the hip joints. The wedging of the sacrum in between pelvic bones, irregular and rough surface of the joint itself, and tight banding due to ligaments and pelvic floor muscles (levator ani and coccygeus muscles) make the SIJ extremely stable. SIJ pain can be due to, but are not limited to, capsular and ligamentous tension, hypo- or hypermobility, extraneous compression or shearing forces, and a host of other factors. Other sources of pain are the surgical arthrodesis at one level causing degeneration of an adjacent segment, leg length discrepancy, and spondylo-arthropathies. There are anatomical differences between male and female pelvis, including SIJ characteristics. In females, ligaments become lax during pregnancy. These factors may make females more prone to low back pain. To restore quality of life and alleviate LBP due to SIJs, conservative and surgical treatments are available.

The first step in the treatment of SIJ dysfunction involves a thorough diagnostic workup followed by nonsurgical management. When nonsurgical management strategies fail, surgical management (open or minimal fusion) is considered. Several studies have investigated the clinical outcomes of surgical techniques for the sacroiliac joint. The studies have shown that minimally invasive techniques involve less tissue damage, blood loss, and duration of hospitalization, thus leading to superior clinical outcomes.

Despite the satisfactory data on clinical outcomes of SIJ fixation surgery, the data on biomechanics of SIJ in general and fixation techniques in particular are sparse. The existing literature suggests that at least two fixation devices spaced apart in their locations on either side of the pivot point of SIJ facilitate "solid" fixation/stabilization across the joint. Both unilateral and bilateral SIJ fusions reduce motion. However, if bilateral SIJ fusion is considered, it is essential to ensure that implant design and SIJ morphology permit such a procedure.

Both males and females showed high performance after SIJ fusion treatment, however, females showed more stress and motion reductions after SIJ fusion. Regardless of sex, lateral and posterior placements of the implants had similar performance on the SIJ stability. SIJ implants

are more effective in females in terms of stability but may be more prone to higher rate of loosening/failure compared to males. The optimum number of implants and implant placement location is two or three implants (depending on the bone quality and implant type) across S1 and S2 levels of the sacrum. Having more parallel and farther from SIJ-pivot-point implant placement results in higher stability of the joint. Using longer superior implant placed in S1 level (proximally) closer to the sacral midline leads to higher reduction in SIJ motion. It is better to place the implant in thicker cortical bone areas and a more dense bone region leading to better stability. Most importantly, SIJ fusion has no effect on the adjacent segments on either sides, spine or hip.

Finally, regarding the shapes of the implants, currently, there are two popular designs on the market: circular sections such as SImmetry, SI-LOK, and RI-ALTO; and triangular design such as iFuse. Further biomechanical studies and long-term clinical follow-ups are required to delineate the optimum design (e.g., implant shape) since the existing literature on biomechanics of circular SIJ devices (SImmetry and SI-LOK implant systems) is limited.

In conclusion, despite the existing literature, there are several unanswered questions related to the effect of surgical parameters on the clinical outcome of the SIJ fixation procedures. For example, the effects of different implant shapes on the biomechanical and long-term clinical outcomes of the sacroiliac joint are not fully understood. It is particularly crucial to understand the relationship between bone quality/density and effectiveness of the surgical technique from a biomechanics perspective and the long-term clinical outcomes. Such questions can be answered by looking at parameters such as load-sharing at the bone-implant interface, distribution of the load across the implant, failure mechanism of the bone/implant, and bone remodeling. The clinical studies, due to their inherent limitations, are unable to address such issues. Such knowledge will be crucial for improvement of existing techniques or development of more efficient instrumentation that would yield superior clinical outcomes for SIJ fixation.

Conclusion

The sacroiliac joint (SIJ) is one of the most overlooked sources of LBP. The joint is responsible for the pain in 15–30% of people suffering from LBP. Various studies have investigated the clinical outcomes of different surgical settings intended for treatment of the pain, and they have shown that these techniques are effective indeed. Several questions related to clinical and biomechanical effects of surgical parameters such as number and positioning of implants, unilateral versus bilateral placement, etc., remain unanswered. Biomechanical studies using in vitro and in silico techniques are crucial in addressing such unanswered questions. These were synthesized in the review.

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Part III

Considerations and Guidelines for New Technologies

Cyclical Loading to Evaluate the Bone Implant Interface

17

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Abstract

The goal of in vitro cyclical loading studies in spine biomechanics is to provide empirical data related to the long-term efficacy of spinal implants. Ultimately, these studies are used to determine if an implant has the ability to provide biomechanical stability over extended periods of time until arthrodesis achieves. In these studies, the bone implant interface should be gradually stressed according to physiological loading patterns to determine the rate at which the interfacial strength between the bone and implant degrades. When designed properly, these studies may able be used to determine the ultimate failure load of the bone implant interface. While study design is always an important aspect in benchtop research, the repetitive nature of in vitro cyclical loading studies exacerbates the effects of study design and emphasizes the importance of rigorous planning based on a strong understanding of the boundary conditions. This chapter is therefore focused on the most important aspects of study design surrounding in vitro spine biomechanics including specimen preparation, loading rate, loading magnitude, loading modality, outcome measures, and failure criteria and how they influence the results of these studies.

Keywords

Cyclical loading · Bone implant interface · Biomechanics · Pure Moment · Fatigue · Stair step loading · Functional spinal unit

Introduction

Knowledge about the spine has been fortified by insight gained through biomechanics research. New technologies and treatment modalities are often a result of in vitro biomechanical studies using human cadaveric spine segments. Comparative biomechanics studies are utilized in

the engineering design process to determine if an instrumentation system or stand-alone device meets design requirements – a conclusion often measured by the ability of the system to provide mechanical stabilization. Moreover, biomechanical studies provide a critical tool for researchers and clinicians to increase basic understanding of the spine and to facilitate evidence-based clinical decision-making.

Biomechanics studies have largely been conducted according to the pure moment protocols pioneered by Panjabi's conceptual framework in 1988 (Panjabi 1988). Adherence to this basic framework across biomechanics literature has served to prevent confusion due to unique and individualized testing protocols, allowing for broader comparisons. As illustrated in Fig. 1 below, pure moment application creates a consistent force throughout the construct without introducing shear forces. A moment is defined as a force that causes rotation of a rigid body about a specific point or axis, while a pure moment is defined as a pair of parallel forces, applied in equal measure but opposite direction to create rotation while mitigating translation. Shear forces, forces acting in parallel to the cross-sectional plane of the construct, cannot be accurately measured and are therefore detrimental to reproducibility. Biomechanics studies conducted according to Panjabi's framework are often referred to as flexibility, stability, or static tests and provide measures of initial stability through metrics such as range of motion (ROM), neutral zone, and construct stiffness.

While Panjabi's work delineated an integral scheme, which has been invaluable to our understanding of the spine and various treatment modalities thereof, we acknowledge limitations of these studies. Standard in vitro biomechanics studies provide information relative to the immediate postoperative time period, and while initial stability measures are important, instrumentation intended to provide stabilization necessary to facilitate fusion must exist for extended periods until solid arthrodesis has formed. Additionally, standard flexibility tests cannot identify common potential risk and failure patterns. As modern spine testers advance, so does our ability to test these constructs using advanced cyclical loading protocols.

The goal of this chapter will be to review testing protocols and provide specific guidance on considerations for in vitro biomechanical studies focused on cyclical loading. As the prevalence and complexity of these cyclical studies continues to advance, it is imperative that the research

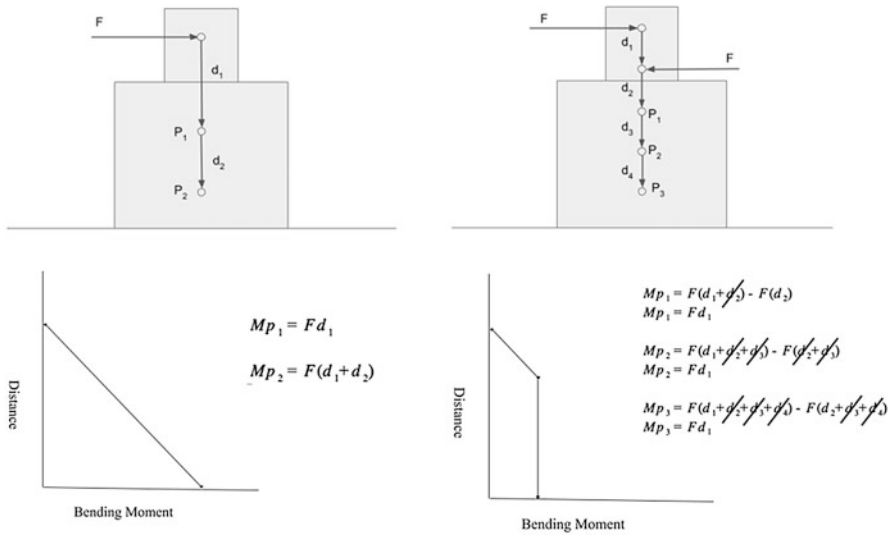

Fig. 1 Illustration of a pure moment and the resulting bending moment

community follow common boundary conditions and testing methodologies to more effectively compare results between research studies and prevent the misinterpretation due to testing variability. As such, we will review standardized cyclical testing protocols, considerations for in vitro cyclical testing protocols, and highlight results of current notable in vitro fatigue studies in the literature.

Fatigue Testing Review

Fatigue Testing Terminology

Long-term performance of implanted systems is of utmost importance given the longitudinal nature of their use in the spine and the severe consequences of construct failure. Proper evaluation and understanding of the literature surrounding cyclical fatigue tests is contingent upon understanding some of the basic testing terminology.

Stress is the force per unit area of a given construct. Compressive stresses are conventionally represented as positive forces while tensile stresses are negative. The amount of deformation (δ) caused by an applied stress can be expressed as a fraction of construct length (L) to calculate strain ($\varepsilon = \delta/L$). Plots of stress versus strain are used to calculate the Young's modulus – determined using the linear portion of a stress–strain curve and may be interpreted as a measure of construct stiffness. Stress–strain curves can also be used to determine the ultimate failure strength of a construct, representing the maximum sustained stress that can be applied before failure. However, repetitive loading can cause materials to fail at loads significantly lower than their ultimate failure strength. This is known as fatigue failure. Unfortunately, it is not possible to generate a proper stress–strain curve to determine the interfacial fatigue strength of spinal constructs due to the limitations of working with cadaveric tissue. However, that does not mean that fatigue factors, such as creep, do not play a role in the failure resulting from in vitro and in vivo repetitive loading of spinal constructs.

In materials science, a material's fatigue strength represents the maximum stress which can be sustained for more than 10^7 loading cycles without failure. Fatigue failure is driven by the accumulation of microcracks which occur below the ultimate strength of a material and is influenced by material properties including strength and toughness and environmental factors like creep and corrosion. A material's strength refers to its resistance to plastic flow while toughness refers to its ability to resist crack propagation. Creep is the slow deformation of a material in response to consistent loading.

Standardized Cyclical Loading Protocols

Standardized testing protocols for cyclical loading of spinal constructs, governed by ASTM 1717, were developed to evaluate the strength of these systems in response to repetitive loading conditions (ASTM 2014). The goal of these test protocols is not to predict clinical performance but to provide a controlled environment in which past, present, and future implant systems may be evaluated comparatively. Notably, the tests intended to evaluate the strength of the instrumentation itself and not the stability provided to a lumbar spine segment.

Cadaveric tissue is supplemented with ultra-high-molecular-weight polyethylene (UHMWPE) blocks, which are machined and instrumented to create a vertebrectomy model. Precise dimensional control ensures that the appropriate forces are transmitted through the testing construct as they are eccentrically loaded. Replacing cadaveric tissue with polymer blocks eliminates variability attributable to differences in bone density and geometric anatomy of the system. This test setup produces an ideal scenario in terms of the bone implant interface (BII) and worst-case scenario for the construct, as all of the applied load must be transferred from the superior to inferior levels through the test system.

To conduct these tests, a compressive bending moment is generated via a sinusoidal cyclic

compressive load, which is applied in load control to the superior block at a rate of up to 5 Hz. Prior to cyclic fatigue testing, the magnitude of the compressive force applied is determined by the static bending strength of the construct. Testing is conducted until either failure occurs or the system reaches predefined runoff criteria of 5,000,000 cycles, a benchmark intended to represent approximately 2 years of loading at an average of 7,000 loading cycles per day.

In Vitro Cyclical Loading

While the information related to construct failure gained from experiments conducted according to ASTM 1717 are valuable, they are not well suited to predict clinical failure. In a clinical scenario, instrumentation failure is most often attributable to a failure of the BII, either by aseptic loosening or abrupt fracture. A testing paradigm, which addresses questions related to the physiologic performance of spinal constructs outside of the postoperative period, is therefore necessary to evaluate the long-term strength of the BII. This interfacial strength is often measured indirectly through measures of construct stability or determination of failure conditions. The goal of these tests is to provide information as to how failure occurs, when this failure may occur, the failure modality, and any patient characteristics which may increase the risk of failure.

Common forms of fatigue failure include implant migration, subsidence, and aseptic screw loosening – the latter of which is characterized by an initial phase of micromotion followed by a slower continuous phase of migration (Xie et al. 2019). Cyclical loading studies are therefore designed to force the failure of instrumentation systems with respect to criteria based on these aforementioned patterns. Typical outcome measures in cyclical in vitro biomechanics studies include range of motion (ROM) as an indicator of aseptic loosening, axial displacement as an indicator of subsidence, and construct stiffness as an indicator of interfacial stiffness. Active measurement of these parameters during cyclic loading is not always possible; therefore, cyclical loading is often conducted in series with nondestructive static biomechanics experiments to assess stability at various time points.

In Vitro Cyclical Loading Methodology

There is no standardized in vitro fatigue protocol to evaluate spinal implants. Rather, experiments are designed and conducted to answer specific research questions because the destructive nature of these tests limits their scope. While testing constructs and experimental conditions may change between experiments, the underlying goal remains the same: to gradually stress the BII through the application of physiological loads to demonstrate longitudinal efficacy. The methods of each publication should be critically reviewed to understand the boundary conditions and the study conclusions. Tests for pedicle screws, pedicle screw constructs, and interbody devices are often different, and testing protocols and setups are often tailored to a specific construct. In this section, we will review the important parameters in the cyclical loading of cadaveric tissue and how they may vary based on the test construct. Constructs were categorized as follows: (1) pedicle screws (individual screw cyclical loading), (2) pedicle screw constructs (pedicle screw and rod constructs), and (3) interbody devices.

Universal Methods

Regardless of the test article, there are certain aspects of cyclical loading studies which should remain relatively standard: specimen preparation, hydration, measurement time points, and measurement frequency.

Specimen Preparation

As with standard static biomechanics tests, specimens are often mounted in a test fixture with a resin-based potting compound, wherein all soft tissue is removed from the bony elements.

Failure to properly remove soft tissues will result in increased micromotion between the specimen and potting compound, eventually leading to construct failure. Due to the destructive nature of cyclical loading, construct failure often leads to specimen disqualification, deficits in statistical power, and costly repetition of testing procedures.

Specimen Selection and Handling

The results of in vitro cyclical loading studies are highly dependent on the characteristics of the specimens used for testing due to large variations in tissue quality between donors, thereby necessitating that tissue used for these protocols is representative of the intended population. Measurement techniques like DEXA and calibrated CT scans should be used to quantify bone density and morphological characteristics when possible (McCubbrey et al. 1995; Weiser et al. 2017a). In doing so, statistical tests can be used to ensure that the outcomes of the given paper were not influenced by factors such as bone mineral density or pedicle diameter.

A single cyclical loading experiment may take up to 14 h to complete depending on the loading frequency and failure criteria and as such active measures must be taken to maintain the hydration and physiologic performance of the tissue. This may include using a saline spray to hydrate the specimen periodically (at least every 20 min) or wrapping the specimen in saline soaked gauze, which is periodically replenished. Alternatively, testing may be performed in a controlled environment with 100% humidity to prevent dehydration over the course of testing procedures.

Proper techniques should also be followed for the storage and handling of cadaveric tissue including freezing of specimens at −20 °C and wrapping them in saline-soaked gauze while not in use. It is also recommended to avoid any freeze thaw cycles after potting procedures have been performed to prevent weakening of the specimen and test fixture interface. Specimens are generally thawed overnight at 4 °C before testing. Testing at room temperature is the de facto standard, and testing before a specimen is allowed to reach room temperature could result in artificially high interfacial strength or measured stability due to the increased stiffness of soft tissues. Specimens may be warmed by leaving them at room temperature for at least 2 h or with the use of a warm saline bath.

Recording Frequency

In order to capture the extent of induced motion, measurements must be done at sufficient rates which vary from 10 to 200 Hz throughout the literature. While a higher sampling frequency leads to more accurate data collection, it also translates to larger file sizes requiring more computational power for analysis. Generally speaking, higher sampling rates should be used with higher loading frequencies, and the sampling rate should be maximized within the technical constraints of the researcher.

Loading Rate

Loading rate refers to the speed with which loads are applied to a spinal construct. This metric is usually expressed in Hertz (Hz), which indicates the number of loading cycles applied during each second of testing. ASTM 1717 dictates that 5 Hz is the absolute maximum loading rate for spinal constructs; however, these tests were conducted with polyethylene blocks allowing for a more aggressive loading rate. When designing studies with cadaveric tissue, the loading rate should be reduced in order to provide a more physiologic test scenario and prevent unwarranted damage to the specimen.

Given the viscoelastic nature of bony tissues, loading at a rate which exceeds the rate of physiologic loading may artificially increase the interfacial stiffness or cause the formation of microcracks which lead to reduced fatigue capacity. On the other hand, slower loading rates may lead to increased displacement and lead to issues with the rate of specimen degradation exceeding the rate of fatigue damage of the BII (Xie et al. 2019). The majority of in vitro

biomechanics studies report loading rates between 0.5 and 2 Hz.

Outcome Measures

The metrics used to evaluate the efficacy of spinal instrumentation vary based on the type of construct being tested. Some are evaluated during cyclical fatigue loading, while most outcomes are based on static in vitro biomechanics tests performed before and after cyclic loading. Both active and periodic assessments are intended to show how the strength of the BII changes in response to repetitive loads. In vitro cyclical loading protocols are often designed as comparative studies in which a new technology or treatment strategy is compared to the current clinical standard. In this case, nondestructive measurement techniques are used to assess the stability of a construct before and after cyclical loading. These repeatable measurements allow for each specimen to serve as its own control. Therefore, by normalizing data collected after cyclical loading to a baseline measurement, the damage caused at the BII can be accurately evaluated. Destructive tests (i.e., screw pullout tests) are also used; however, studies designed to include destructive outcomes require the use of multiple cohorts thereby increasing biologic variability and cost.

Pedicle Screws

The fatigue strength of pedicle screw fixation is often assessed by comparing the number of cycles to failure and peak pullout-strength after cyclic loading. The number of cycles required to induce fatigue failure assesses the fatigue strength of the BII of the screw. Pedicle screw failure may be determined by a displacement criterion, relative screw motion, bony fracture, or other study-specific means. Failure based on displacement criteria generally refers to the amount of screw head displacement measured in response to an applied load. Screw head displacement may be measured directly by attaching a tracking body to the screw or indirectly by monitoring displacement of the loading frame. Relative screw motion is assessed using optoelectronic measurement systems with a tracking body attached to both the pedicle screw and tissue sample, allowing for calculation of relative motion between the bone and pedicle screw. Comparison of the axial pullout strength after cyclical loading and fatigue failure to that of a control group without cyclical loading determines the damage at the BII.

Other more advanced means of evaluating the strength of the bone screw interfaced have been described but have yet to gain popularity in the literature. Lai et al. describe the determination of a microfracture event in which a sharp increase in displacement is observed during cyclical loading, helping to identify the method of fatigue failure (Lai et al. 2018). Advanced imaging techniques like micro computed tomography (micro-CT) allow for precise and accurate identification of screw breach, quantification of trabecular damage or pedicle fractures.

Pedicle Screw Constructs

Unlike the evaluation of individual screws, pedicle screw constructs are evaluated using spinal segments or functional spinal units. Therefore, the strength of the BII is measured indirectly through measures of construct stability like range of motion, which should be periodically evaluated in each specimen to evaluate the efficacy at various time points (Cheng et al. 2011; Agarwal et al. 2016; Wilke et al. 2006, 2016; Duff et al. 2018). At minimum, the stability of each specimen should be evaluated at intact, baseline, and post-cyclical loading conditions. Inclusion of additional stability measurements throughout cyclical loading allows for the determination of further outcome measures such as number of cycles to failure and failure load (Wilke et al. 2016). Measurements of stability should be conducted in a nondestructive fashion to ensure that damage is not accumulated outside of the cyclical loading schemes. At the very least, flexibility measurements should be conducted

according to the loading magnitudes published in the literature, with loads applied to the cervical spine topping out at ±2.5 Nm and loads applied to the lumbar spine topping out at ±10 Nm. Some research groups have opted to reduce the loading magnitude used to measure stability in cyclical loading protocols to further reduce the risk of introducing additional damage to the BII, which is especially important if multiple stability measurements are performed throughout the study.

Interbody Devices

The evaluation of interbody device performance in response to cyclical loading is similar to the process described for pedicle screw constructs; metrics of construct stability are measured at various time points to determine fatigue performance (Freeman et al. 2016; Palepu et al. 2017). Other common interbody failure methods like implant subsidence (evaluated radiographically by periodic measurements of disc height performed in series with cyclical loading or with the use of motion tracking bodies attached to the vertebral body) and migration (movement of the interbody device with respect to the cadaveric specimen quantified by fixing a motion tracking system directly to the interbody device) should also be considered (Freeman et al. 2016; Pekmezci et al. 2016; Alkalay et al. 2018). Subsidence may also be evaluated by measurement of the interfacial stiffness at the BII, as described by Alkalay et al. This stiffness may be extracted from the hysteresis plot generated during compressive loading of interbody constructs (Alkalay et al. 2018).

Stand-alone interbody devices often rely on spikes, fins, or anchoring blades to achieve fixation. The damage caused to bony structures, specifically the vertebral endplate and trabeculae, by these means of fixation are not well understood. Therefore, advanced imaging techniques such as micro computed tomography (micro-CT) may be used to identify the presence of endplate fractures or to quantify the damage by measuring the volume of bone displaced (Palepu et al. 2018).

Loading Modality

Loading modality refers to the method in which a specimen is loaded. This is done in isolation of a particular mode of loading such as screw toggling, axial compression, or flexion-extension bending thereby mitigating the application of shear forces and controlling to match physiologic loads. Ideally, cyclical loads should be applied based on the typical failure patterns observed clinically.

The loading modality is also highly dependent on the type of testing machine used, with standard uniaxial MTS machines limiting researchers to the application of uniaxial compressive forces. These machines are therefore combined with test fixtures to produce bending moments through eccentric loading patterns as seen in Fig. 2. When a column or spinal construct is loaded asymmetrically (with respect to the central axis), a bending moment is produced through the column, the magnitude of which is driven by the moment arm formula. The magnitude of the moment is calculated as the product of the applied force by the distance to the center axis. Offset loads are often applied through a hinge joint, connecting the test article to the MTS machine via a rigid connection that serves as the lever. While these MTS machines can be used in conjunction with lever arms to offset forces and generate bending moments, readers should be aware of the uneven load distribution these constructs create. Per Panjabi's conceptual framework, the application of eccentric bending moments creates an uneven bending moment through the column, or in this case spinal construct, which peaks towards the middle of the construct.

More advanced spine testers allow for the application of pure moment loads in a dynamic fashion, allowing for active control of all six degrees of freedom. Use of a dynamic spine tester for cyclical loading of spinal constructs allows for the application of pure moment loads in a given loading pattern, while all other modes of loading are allowed to move freely. In doing so, researchers can apply flexion-extension, lateral bending, and axial rotation moments and evaluate how fatigue affects the performance of instrumentation with respect to each individual

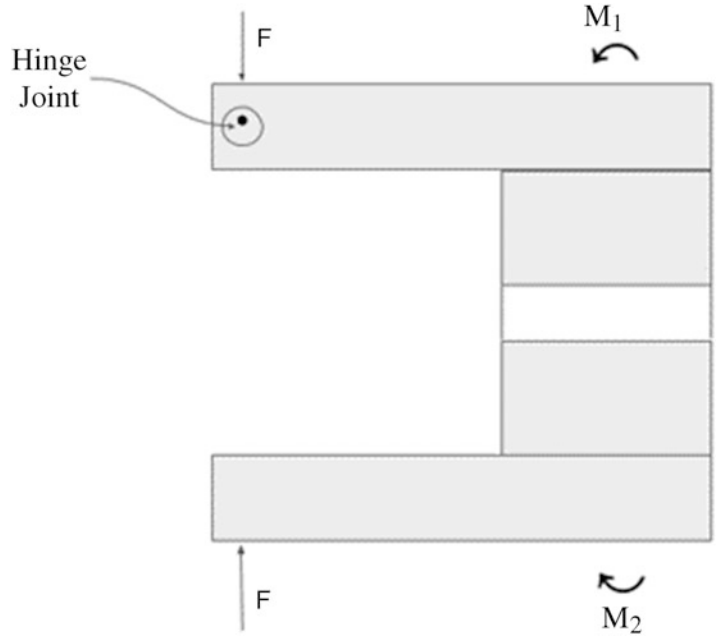

Fig. 2 Illustration of an FSU mounted to facilitate eccentric moment loading

loading modality. While separate cohorts must be used to test the effects of each aforementioned loading modality, these machines do not require a change in testing setup to change the type of fatigue loading being evaluated.

Pedicle Screws

Pedicle screws are loaded perpendicular to the long axis of the screw (in the cranio-caudal direction), accomplished directly by applying a compressive force to the screw head or indirectly by applying the force through a connecting rod (Weiser et al. 2017a; Lai et al. 2018; Akpolat et al. 2016; Baluch et al. 2014; Bostelmann et al. 2017; Kueny et al. 2014; Lindtner et al. 2018; Qian et al. 2018). Screw loading with a compressive force perpendicular to the screw's long axis is intended to reproduce the toggle failure commonly observed during aseptic screw loosening. Trends in recent literature demonstrate the application of compressive forces through a connecting rod as this provides a more physiological loading modality. By attaching the pedicle screw to an MTS machine via a standard rod in combination with the use of a lever arm, a bending moment is created about the head of the screw, approximating flexion-extension and compressive loading (Lindtner et al. 2018). To accomplish this, both the superior and inferior vertebral bodies are rigidly fixed. Use of an x-y slide or bearing table allows for translation in the transverse plane and may help reduce the effects of shear forces during cyclic loading. Failure to reduce shear forces, which act as axial pullout forces in cranio-caudal loading, may lead to early fatigue failure (Akpolat et al. 2016).

Pedicle Screw Constructs

Cyclical loading of pedicle screw constructs is intended to produce physiologic loading patterns that are often subjected to combined compressive and flexion bending moments. Bending moments are applied eccentrically using custom test fixtures where the magnitude of the applied moment is given by the magnitude of the compressive force multiplied by the distance from the central axis of the specimen to the axis of loading (Agarwal et al. 2016; Duff et al. 2018; Shimamoto et al. 2001). Typically, the center of the vertebral body or test fixture is used to approximate the central axis of

the specimen (Shimamoto et al. 2001). The central axis of the loading machine or test fixture represents the loading axis. All specimens should be prepared and mounted in a reproducible fashion as geometric variations may have an effect on the study results.

These experiments are performed with the cranial aspect of the test construct fixed to the test machine and the caudal aspect attached to an x-y slide or similar fixture. Alternatively, the specimen may be mounted in a spine tester with the ability to apply pure moments in a cyclical manner as described by Cheng et al. (2011). Programmable spine testers allow for active control (with respect to one individual mode of loading), while all other motors are passively controlled to allow for coupled motion and thereby reduce the effects of shear loading. This is commonly referred to as load control because the motors are set to maintain zero force in any given direction, functioning like an x-y slide allowing motion in the transverse plane.

While most studies focus on compressive forces and flexion-extension bending, it is important that other loading modalities such as lateral bending and axial rotation are considered. Wilke et al. demonstrated a technique in which specimens were cyclically loaded with eccentrically applied compressive forces while the specimen was rotated 360°, producing a cycle of flexion, left lateral bending, right lateral bending, and extension bending moments. This more complex loading scheme allows for the application of compression, shear, and bonding forces in a reproducible fashion (Wilke et al. 2006, 2016). As a result, the applied forces are more physiological and may improve the quality of the data. Other research groups have suggested breaking protocols into blocks of flexion-extension, lateral bending, and axial rotation loading patterns; however, these techniques have yet to be applied to pedicle screw constructs.

Interbody Devices

Cyclical loading protocols conducted to evaluate interbody devices most often include the application of flexion-extension bending moments as flexion-extension is considered the main mode of loading in the lumbar spine. Unlike tests designed to evaluate pedicle screws and pedicle screw constructs, interbody constructs are most often subject to pure moment loads, with or without the use of a follower load. Inclusion of a follower load is intended to provide a more physiologic loading schema, with compressive forces transmitted throughout the spine via a system of pulleys attached to each index level. Compressive preloads may also be employed as a simplified alternative to the use of a follower load.

Although most studies focus on flexion-extension loading, lateral bending and axial torsion loading modalities should also be evaluated if possible. Cheng et al. advocate for independent cohorts for the evaluation of flexion-extension, lateral bending, and axial rotation fatigue performance of interbody devices. Other authors have applied multiple loading schemes to each specimen, alternating between flexion-extension and lateral bending paradigms until failure has occurred (Freeman et al. 2016). Each of these strategies has their own merit; separation into multiple cohorts allows for the researcher to determine if the construct is vulnerable to failure with respect to a given loading modality, while combined loading techniques may provide a more physiologic result. When evaluating the effect of compressive loading on interbody performance, the anatomical differences between cadaveric specimens should be considered in order to reduce the effects of coupled moments. Alkalay et al. describe the application of compressive forces through each specimen's instantaneous center of rotation (ICR) to mitigate these effects (Alkalay et al. 2018).

Magnitude of Loading

The magnitude of loading should be adjusted to achieve physiological loading if possible, reflecting values of the forces acting on the spine during daily activities, i.e., walking (Rohlmann et al. 1997). Stair-step loading protocols (initial

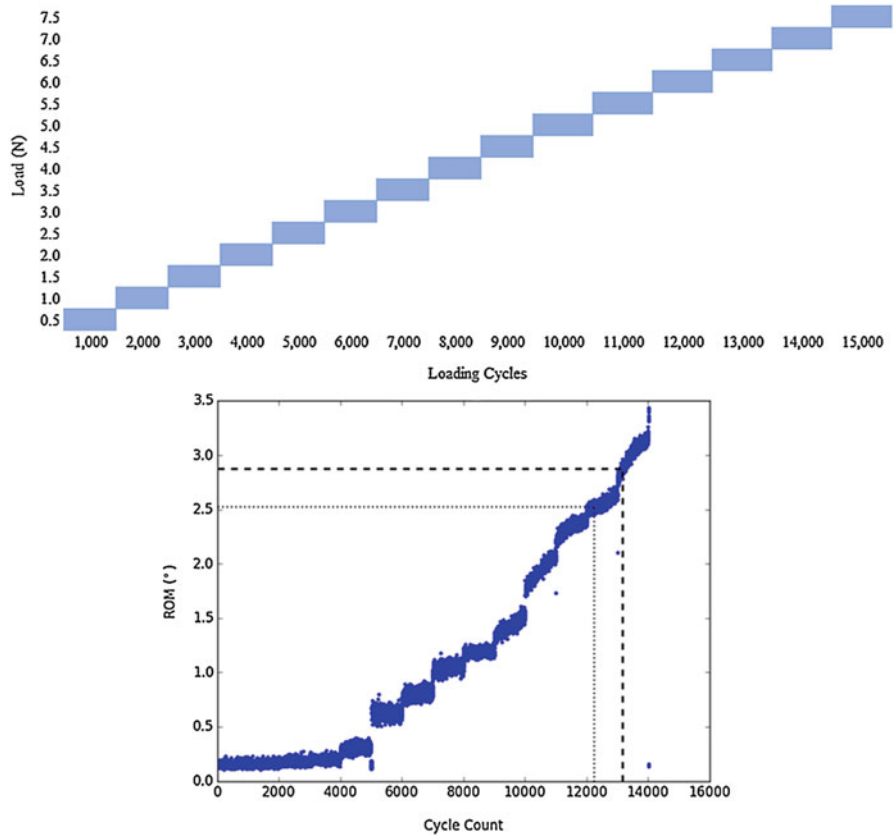

Fig. 3 Example of a stair-step loading scheme (top) and angular corresponding angular measurements produced by cyclically loading an FSU according to this loading protocol (bottom)

cyclical loading at a low magnitude with steady increases as the test progresses) may be employed to ensure that fatigue failure is achieved. This enables the gradual loading of the BII and allows for the inclusion of failure load as an additional outcome measure to compare the fatigue performance of the given constructs. Figure 3 illustrates a stair-step loading protocol and the angular measurements corresponding to the cyclical loading of an instrumented FSU according to the given protocol.

Pedicle Screws

The loads applied to pedicle screw constructs are generally based on the peak forces measured on a spinal fixator during walking (Rohlmann et al. 1997). When forces are applied at a constant magnitude, they typically range from a 50–200 N of force. Stair-step loading protocols for cyclical loading of pedicle screws employ a minimum of 20–50 N force historically, which is increased by small increments ranging anywhere from 0.1 to 20 N until failure is achieved. Maximum applied forces in stair-step loading protocols have been reported as high as 550 N (Bostelmann et al. 2017).

Pedicle Screw Constructs

Protocols designed to evaluate pedicle screw constructs tend to parallel the biomechanics literature for standard flexibility protocols. In the cervical spine, bending moments between 1.5 and 2.5 Nm are achieved through the application of up to 200 N of eccentric loads or in a pure moment

fashion using a spine tester (Cheng et al. 2011; Duff et al. 2018; Koller et al. 2015). For tests centered around the lumbar spine, larger bending moments of up to 10 Nm are induced through the application of eccentric loads ranging from 100 to 600 N (Agarwal et al. 2016; Wilke et al. 2006, 2016; Shimamoto et al. 2001). Stair-step loading protocols are especially used in the lumbar spine to force fatigue failure before the specimen degrades. These protocols generally start with loading magnitudes ranging from 100–300 N or 3–9 Nm and bending moments of up to 600 N or 18 Nm of force.

Interbody Devices

Protocols designed to evaluate the performance of interbody devices are intended to gradually stress the bone implant interface. As such, the magnitude of applied loads is often below those applied in traditional in vitro biomechanics tests, which range from 7.5 to 10 Nm in all modes of loading. When applying a stair-step loading protocol, the initial magnitude may be as low as 0.5 Nm which is gradually increased until failure has occurred (Cheng et al. 2018). Alternatively, authors have described the consistent application of up to 5 Nm loads until failure has occurred (Freeman et al. 2016). To evaluate the effects of combined loading, follower loads of up to 400 N and compressive forces of up to 1200 N have been described.

Failure Criteria

A cyclical loading experiment may be stopped based on a set number of loading cycles or predetermined failure criteria, which are metrics used to determine when fatigue failure occurs and can be unique to a given experimental protocol. Notably, the metric in question must be continuously monitored throughout the experiment in order for an experimental protocol to have a stopping condition based on a predefined measure of fatigue failure. Examples include actuator displacement or optoelectronic motion data. Failure may also be assessed after cyclical loading has been conducted to the desired number of loading cycles.

These criteria are used to evaluate the strength of the BII and quantify the number of loading cycles applied to induce failure, allowing for comparison of the fatigue strength across cohorts. When possible, failure criteria should be derived from clinical assessments of construct failure, such as radiographic assessments or motion measured using dynamic flexion-extension radiographs. Failure criteria may also be based on the determination of key events in the life cycle of a testing construct. Common significant events include the identification of a bony fracture, hardware deformation, or sharp change in construct stiffness.

Pedicle Screws

Screw loosening has been associated with other complications including hardware failure, pseudoarthrosis, non-union or progressive kyphosis. Currently, there is no standardized classification system for clinicians to evaluate screw loosening; however, according to a recent literature review conducted by Galbusera et al., the most common assessment of screw loosening is a radiographic assessment of the BII (marked by the presence of a radiopaque zone extending 1 mm or more from the screw in all directions) (Galbusera et al. 2015).

Screw loosening may occur due to exceedingly high loads, microfractures at the BII, or bony remodeling as a result of stress shielding. In vitro cyclical loading of pedicle screws may be used to assess failure due to the application of loads exceeding the bone screw interface (potentially resulting in a sharp increase in screw motion) or the accumulation of microfractures within it (identified by a slow and gradual increase in motion) (Bostelmann et al. 2017).

In vitro fatigue failure of pedicle screws is defined by the amount of displacement, measured directly by attaching tracking bodies to the screw head to measure angular displacement or indirectly by tracking the displacement of the test system. Measurement of screw angulation is

preferred as this provides more physiologically relevant data, while stopping criteria based on the displacement of the test fixture does not directly translate to screw displacement. This is especially true in testing constructs where pedicle screws are loaded eccentrically and displacement of the axial ram accounts not only for screw displacement but rotation about the axis of the hinge joint and deformation of the lever arm as well (Bostelmann et al. 2017). If the stopping criteria cannot be based on a continuous measurement of angular screw displacement or other fatigue metric, it is recommended that the data be post processed to determine when fatigue failure occurred.

Recent literature has defined fatigue failure of a pedicle screw during cyclical loading to be associated with anywhere from 6 to 8° of angular motion or an increase in the angular displacement of greater than 1° over a short period of time (Akpolat et al. 2016; Baluch et al. 2014; Lindtner et al. 2018). A limit of 10–15 mm of displacement may be applied when stopping criteria are based on the axial displacement of the test frame used to apply a cyclical compressive force (Bostelmann et al. 2017).

Pedicle Screw Constructs

Fatigue failure of pedicle screw constructs is largely related to screw loosening, bending, pull-out, or rod failure (Wittenberg et al. 1992). From an in vitro perspective, success of a pedicle screw construct is given by the stability of the spinal construct as a whole, often measured in degrees of relative motion between vertebral bodies. This is largely due to the fact that the forces generated during in vitro testing are not sufficient to damage the instrumentation in question. Wilke et al. have developed a series of success criteria to evaluate when fatigue failure occurs in vitro; they are facilitated by repeated stability measurements performed in series with blocks of cyclical loading. Here, loosening or failure is defined as either a visible fracture, motion which exceeds baseline instrumented stability by a factor of three, or motion which exceeds the value corresponding to the intact state (Wilke et al. 2006, 2016).

Numerous studies have been conducted to evaluate pedicle screw constructs without the inclusion of a fatigue failure criteria. In this case, success of a construct is determined by how well it performs in comparison to a control cohort based on a clinical standard of care (Cheng et al. 2011; Agarwal et al. 2016; Duff et al. 2018; Shimamoto et al. 2001).

Interbody Devices

Failure of the BII for an interbody device may lead to decreased stability, device subsidence, or device migration, and as such failure criteria should be established for all three possible options. Stability is most often measured through range of motion, and as such increases in motion beyond a specific threshold are often used to determine when failure has occurred. Various research groups have their own definition as to what constitutes an increase in motion large enough to be considered failure; however, all of these researchers agree that failure should be based on a baseline stability measurement. For example, Cheng et al. define failure as a 110% increase in ROM, based on the idea that a 10% increase in segmental ROM could have a substantially negative impact on arthrodesis (Cheng et al. 2018). As mentioned in the previous section, Wilke et al. argue that a return of ROM to the values measured at the "intact" stage of testing, before instrumentation, is performed should also be considered failure.

Cage migration may be considered clinically relevant when it exceeds 3 mm in any direction (Abbushi et al. 2009). Failure with respect to subsidence may be considered clinically relevant when subsidence exceeds 3 mm as well; however, it is often difficult to actively monitor cage subsidence during cyclic loading. As such, subsidence failure criteria are often based on the displacement of the test machine, as described by Alkalay et al. In those instances where subsidence is based on machine displacement failure, criteria are often much higher, on the order of 10 mm (Alkalay et al. 2018). This relatively large criteria

compared to the 3 mm threshold for clinical relevance is due to the inherent flexibility of the construct, as not all 10 mm of displacement may be attributed to cage subsidence, but rather plastic deformation of the specimen in addition to any subsidence.

Cyclical Loading of Spinal Constructs Literature Review

Basic Science

Cyclical loading studies help to further our basic understanding of the spine in addition to providing evidence on the in vitro performance of spinal instrumentation. Numerous studies have been conducted on cadaveric tissues evaluating their response to repeated loads and damage accrued from low magnitude repetitive loads to further understand spinal injuries and determine ideal boundary conditions for in vitro evaluation of instrumentation. The number of loading cycles a specimen may tolerate and the appropriate magnitude and rate of loading are integral to this process. In doing so, we can ensure that any damage created during experimental procedures can be attributed to the test article rather than the testing conditions.

Schmidt et al. used compressive cyclical loading data from 6 previously published works to generate a lumbar spine injury risk model based on fatigue failure data collected from 105 cadaveric samples subjected to varying loading magnitudes and lengths (Schmidt et al. 2012). All but one of these specimens consisted of a single FSU, subjected to compressive loads until failure or runout was achieved. As expected, age and sex were both significant predictors for the risk of failure. Notably, Schmidt found that the applied stress has a stronger influence than the number of loading cycles on the failure probability of a vertebral segment – a finding that gives credence to the use of stair-step loading protocols and underscores the importance of reporting failure loads when conducting cyclical loading experiments.

Liu et al. set a tremendous foundation for modern cyclical loading studies through their novel methodology, notably replicated in 2018 by Alkalay et al. in their investigation of performance of interbody cage designs (Alkalay et al. 2018; Liu et al. 1983). Through their compressive study, Liu hypothesized that clinical instability is the result of fatigue failure of the soft tissue structures of a spinal segment. Liu first identified the instantaneous center of rotation for each FSU by identifying the stiffest loading axis and aligning this axis with the loading axis of the MTS machine. Up to 10,000 cycles of compressive forces were then applied to this location at 0.5 Hz (ranging from 37% to 80% of the ultimate failure load for the respective index level). Failure loads used to determine the loading conditions for each specimen were based on those values reported in the literature. Furthermore, they divided the 11 FSU's that were loaded until failure into two groups: abrupt failure ($n = 5$) and gradual failure ($n = 6$). Abrupt failing specimens were classified as unstable and were associated with large changes in axial displacement. Gradually failing specimens were classified as stable with a consistent linear increase in displacement. Liu further characterized the damage caused to each vertebral body through radiographic imaging (abrupt failure specimens suffered endplate fractures which originated peripherally and propagated towards the center of the vertebral body) and morphological characterization facilitated by digestion of the organic matrix with sodium hydroxide to isolate the bony structures (the unstable group lost their structure and essentially disintegrated into small pieces of bone). This is opposed to those specimens from the stable group which maintained their structure after removal of the organic matrix. As such, recorded displacement values from the unstable group were attributed to bony failure while displacement in the stable group was attributed to creeping deformation of the intervertebral disc.

Parkinson et al. has further corroborated these results with their work relative to the cervical spine by evaluating the injury risk to both bony structures and soft tissue in response to dynamic flexion-extension and compressive loading (Parkinson and Callaghan 2009). Specimens were cyclically loaded and divided into five cohorts based on the magnitude of applied load

(ranging from 10% of ultimate failure load to 90% of the ultimate failure load). Loading was performed until failure (>9 mm vertical displacement) or runoff (12 h or 21,600 cycles) was achieved. Throughout testing, the compressive load, vertical displacement, and angular motion were collected to facilitate determination of a precise failure event, and the authors also quantified the cumulative moments and compression to achieve failure using trapezoidal integration. They concluded that failure was most often identified by examining the compressive stiffness of the construct and noted that a sharp decline in stiffness was associated with an increase in vertical displacement. Similarly to the work of Liu et al., this study found the magnitude of loading had a significant effect on the fatigue life of the constructs, with an average injury cycle of 14,400, 5,031, 155, 22, and 4 for the 10%, 30%, 50%, 70%, and 90% loading cohorts, respectively. Only 5 of the 46 specimens included in the study survived to the runout criteria of 21,600 loading cycles: 4 from the 10% loading cohort and 1 from the 30% loading cohort. Furthermore, the specimens in the 10% and 30% loading cohorts sustained a significantly larger cumulative compressive load than specimens from the 50%, 70%, or 90% groups. Post fatigue injury analysis revealed 34 instances of fracture, with the large majority of these injuries occurring within the endplate.

Both the Liu and Parkinson studies emphasize the importance of including multiple measurement techniques in studies designed to evaluate the fatigue performance of spinal instrumentation. By showing that an abrupt increase in recorded displacement is associated with radiographic and morphological evidence of bony failure, these studies support the inclusion of failure criteria based on abrupt changes in displacement or stiffness of the tested construct. The disintegration of samples which suffered bony failure after removal of the organic matrix proves the accumulation of microcracks in the trabeculae of vertebrae after cyclic loading. These results also provide insight into the number of cycles a cadaveric specimen can be expected to withstand, allowing for better understanding of construct efficacy through the window of cycles to failure.

Considerable work has also been put into studying the viscoelastic nature of trabecular bone. The Pankaj lab performed a series of experiments to develop a finite element model of the BII in order to evaluate the interface deformation as a function of cycle number and loading frequency (Xie et al. 2019; Manda et al. 2016). An idealized 2D plane-strain construct represented interactions between trabecular bone, a screw, and a 1 mm thick cortical shell in response to 300 N cyclic loads applied at seven different loading frequencies from 0.1 to 10 Hz for a total of 2,000 cycles. The trabecular bone volume was also varied to study the effect of bone density on displacement of the BII. The results of these models show that displacement at the BII is a function of both cycle number and loading frequency. At a low cycle number, slower loading rates produce more deformation; however, at higher cycles (above 500), faster loading rates produce much greater deformation. Unsurprisingly, the study also demonstrated a correlation between bone volume fraction and displacement, with lower volume fractions showing higher displacement compared to models run according to the same parameters but with a higher volume fraction. It is important to understand how the applied loading rate, number of applied cycles, and bone density influence reported outcomes, and the results of these studies as well as other similar reports should be considered when planning or evaluating cyclical loading research.

Pedicle Screws

One of the keystone designs for spinal fixation comes from the polyaxial screw system which was designed to connect the vertebrae to a rigid rod construct for spinal stabilization. Screws were designed with spherical heads enclosed within a housing that allowed for extreme mobilization within multiple axes relative to the housing. The ball joint allowed for use in most spinal surgeries because of its flexibility and ability to adapt to the most severe degenerative diseases. The system was placed above and below the vertebrae to bridge the fusion, giving it strength while

arthrodesis occurs. Rods were then connected to the polyaxial screws to prevent movement for ultimate stability. If rigid fixation is not maintained, complications may arise from screw breakage or loosening. Changes to the system's approach, screw diameter, length, pitch attempt to overcome many obstacles the original design imposed.

One area of focus in pedicle screw placement is maximizing fixation strength through pedicle screw trajectory. Using traditional fatigue studies to compare pedicle screw pullout strengths, Blauch et al. sought to determine fixation strength of laterally directed, cortical pedicle screw under physiological cyclical loads compared to a traditional approach. Lateral trajectory was designed to minimize soft-tissue dissection during instrumentation while providing improved spinal fixation (Baluch et al. 2014). Seventeen vertebral levels in total were obtained from three cadaveric spine specimens (T11-L5). Radiographic testing ensured no prior trauma or fracture, and pQCT was obtained for each level to determine bone mineral density (mean 202 mg/cm^3). Alternating sides of each level were instrumented with cortical then laterally and medially directed screws (tercet Triple-lead and Preference 2 Pedicle Screws). Each screwhead was connected to a 5.5 mm rod and secured via setscrews. Once in the testing apparatus, each screw underwent cyclic cranio-caudal toggling under increasing physiological loads until 2 mm head displacement was recorded and uniaxial pullout of each toggled screw was performed. The load (N) and toggle cycles to each pedicle screw movement were recorded and compared between the two techniques. Notably, cortical screws required 184 cycles to reach 2 mm of displacement compared to 102 cycles for traditional screws. Moreover, the force necessary to displace these screws was much greater for cortical than that of traditional pedicle screw trajectory; however, no statistical difference in axial pullout strength between toggled cortical and traditional pedicle screws was found. The results supported the hypothesis that laterally directed pedicle screws have greater resistance to cranio-caudal toggling than traditional trajectories – demonstrating the efficacy of alternative pedicle screw trajectories for spinal fusion surgery.

Akpolat et al. conducted a similar investigation to perform fatigue studies on specimens with poor bone quality to assess efficacy of the cortical bone trajectory (CBT) vs. the standard pedicle screw fixation (Akpolat et al. 2016). They postulated that the use of a hinge joint does not accurately represent physiological loading and therefore designed a new fixture based on ASTM1717 to allow for pure moments to be applied to the construct for fatigue testing purposes to better simulate physiologic screw loading and motion. CBT and standard trajectory pedicle screws were inserted in the same vertebrae and cyclically loaded to failure. A 5.5 × 130 mm rod was used to connect the screws to another screw mounted in a polyethylene block, intended to represent the superior vertebral level. Both the block and vertebral body were loaded into the testing fixture. Two equal and opposite forces were applied to generate pure moment bending through hinge forces designed to limit shear forces which may induce axial pullout forces. Loosening was monitored optoelectronically via reflective markers and infrared cameras, so relative motion between the vertebral body and pedicle screws indicated motion at the bone-screw interface. Six cadaveric lumbar spines were obtained using 12 vertebrae. Bone mineral density was obtained for each vertebral level. Each vertebral body was instrumented with screws from the cortical bone trajectory (4.5 × 25 mm) and standard pedicle screw trajectory (6.5 × 55 mm). A load was then applied under displacement control at 1 Hz in sagittal bending at 4 Nm. Appropriate force was determined by measuring the distance from the rod to the hinge joint. The construct was loaded for 100 cycles or until 6° of loosening was observed. Once fatigue testing was completed, the screws were pulled out axially at 5 mm/min. Standard pedicle screws had (1) significantly longer fatigue life than cortical bone trajectory screw (3592 +/− 4564 and 84 +/− 24, respectively), (2) showed better resistance to motion (6.9 +/− 4.8° of motion at 100 cycles and 15.2 +/− 5.5°, respectively), and (3) had significantly higher

pullout strength than CBT screws (776 N +/− 370 vs. 302 N +/− 332, respectively). Damage to the bone along its shaft by rotating around a fulcrum, located at the pars, pedicle isthmus, or the junction of the pedicle and superior endplate was the primary limitation of the CBT screws – laminar anatomy may prevent proper CBT screw insertion trajectory.

While imperfect, pedicle screw fixation has been considered the gold stand in posterior spinal stabilization and fusion for many years, with screw loosening at the bone-screw interface in an aging osteoporotic population (generally the highest source of spinal fixations) as an especially notable complication (Halvorson et al. 1994). Screw designs like fenestrated pedicle screws for bone cement applications, pre-cemented pedicle screws, in situ augmentation and augmentations to pedicle screw diameters have attempted to limit poor outcomes. Pedicle screw augmentation was designed for limited applications in spinal fusion and was focused on specific conditions like osteoporosis (Weiser et al. 2017b). The most widely used techniques are pedicle screw insertion in non-cured cement and in situ-augmentation with cannulated fenestrated screws. Bostelmann et al. focused on assessing the different augmentation techniques to explore pedicle screw loosening under physiological cyclic cranio-caudal loading (Bostelmann et al. 2017). While previous tests focused on axial pullout strength to determine anchorage, it does not simulate the in vivo nature of cranio-caudal loading and failure of pedicle screws. Two test groups were created, each containing 15 vertebral bodies (L1–L5, three of each level per group). High viscosity bone cement was used for all augmentation. Pedicle screws were placed on both the right (instrumented with solid pedicle screws in standard orientation with no bone cement added) and left side (cannulated and augmented with bone cement) of the vertebral bodies for the first test. For the second round of testing, the right pedicle screws were enhanced with the cement first technique, while the left were inserted with cannulated fenestrated screws within situ augmentation. Screws were tested using cranio-caudal cyclical loading started at 20–25 N and loading increased 0.1 N per cycle (1 Hz) for a total of 5,000 cycles or fatigue failure with stress X-rays were taken to determine screw integrity. In the first group, augmented screws showed significantly higher load cycles compared to control pedicle screws. Completed stress X-rays determined much lower screw toggling for the augmented screws than that of the solid pedicle screws. The second group of testing determined high load cycles until failure for cement first augmentation compared to in situ augmentation were not significantly different. Stress X-rays for this group revealed screw toggling for in situ augmentation vs. cement first augmentation was not significantly different. This test demonstrates the strength added for augmented pedicles screws compared to those with standard orientations. The significantly higher load cycles and failure loads add considerable strength to weakened osteoporotic bone. For all augmentation techniques tested (cement first, in situ augmentation, percutaneous application), no effects were exhibited on failure of these pedicle screws. The screws that did fail by cranio-caudal cyclical loading occurred via a "windshield-wiper effect" through the superior endplate. This is typically seen in clinical practice with osteoporotic patients.

Kueny et al. conducted a study to better understand the complications with aging osteoporotic bone on pedicle screw loosening at the bone-screw interface focusing on three different fixation techniques: traditional prefilled augmentation, screw injected augmentation, and unaugmented screws with increased diameters, while also determining whether pullout testing can be translated to physiological fatigue testing (Kueny et al. 2014). Thirty-nine osteoporotic lumbar vertebrae were instrumented with pedicle screws covering four testing groups: (1) screw only, (2) prefilled augmentation, (3) screw injected augmentation, and (4) unaugmented screws with increased diameters. Toggling testing was performed using cranio-caudal cyclical loading (1 Hz). The initial compression forces started at 25–75 N and was increased in a stepwise fashion by 25 N every 250 cycles until 5.4 mm of screw head displacement was noted. Once completed, the contralateral screw was subjected to pure axial pullout (5 mm/min). All

instrumentation techniques were compared to control. Screw injected augmentation increased fatigue force by 27% ($p = 0.045$), while prefilled augmentation reduced fatigue force by −7% ($p = 0.73$). Both of these techniques increased pullout force compared to control ($p < 0.04$). Increase in screw diameter (1 mm) increased pullout force by 24% ($p = 0.19$) while inducing the least amount of stiffness loss at −29% from control. They concluded that the highest biomechanical stability lies within the augmentation of the injected pedicle screws. Strong considerations should be noted from these studies indicating utilization of screw injected cement augmentation along with maximal screw diameter for increased biomechanical stability in osteoporotic patients.

Lai et al. further investigated the optimal screw diameter for osteoporotic bone (2018). Larger screws may provide more fixation strength but risk purchase failure during instrumentation, while smaller diameters minimized pedicle fracture but compromise stability. Focus was directed towards screw diameter and pullout of pedicle screws after fatigue loading in osteoporotic vertebrae. Five human cadavers were harvested for testing on 27 osteoporotic vertebrae (T3–T8). Two different size polyaxial pedicle screws were instrumented into each pedicle (5.0 mm × 35 and 4.35 mm × 35). Specimens were then randomly distributed into three groups: (1) control group, (2) fatigue group of 5,000 cycles, and (3) fatigue group of 10,000 cycles. This was accomplished with peak-to-peak loadings of 10–100 N at 1 Hz. After fatigue loading was completed, each specimen was subjected to axial pullout tests at a rate of 5 mm/min and the maximum pullout strength (N) and stiffness (N/mm) were obtained. During fatigue testing, displacement curves were used to determine microfracture analysis. No specimens incurred microfractures during the 5,000 loading cycles, but during the 10,000-cycle group, some specimens experienced discontinued curves and abrupt jumps – they were further categorized into two subgroups with and without microfractures. No statistical difference was noted between pedicle height and width from the 5.0 mm and 4.35 mm screw groups. Micro-CT and X-ray showed lateral breaches in most specimens. Specimens with no abrupt jumps in their loading displacement curve showed no noticeable changes along their screw trajectories. Those with abrupt jumps showed radiolucent lines between bone and screw interfaces after fatigue loading. Pullout strength of the 5.0 mm group (363.3 (138.3) N) was statistically higher than those of the 4.35 mm group (259.0 (159.3) N). The 5,000-cycle group pullout strength was reduced to 33.25 (165.2) N, but the 4.35 mm group increased to 316.1 (106.0) N. The pullout strength between the 5.0 mm group and 4.35 mm group was not statistically significant after 5,000 cycles. The pullout strength between the two screw diameters in the 10,000-cycle group was significantly decreased to 208.9 (90.1) N in the 5.0 mm group and 229.3 (99.1) N in the 4.35 mm group. No statistically significant change in pullout strength between the two groups were found. 5.0 mm screws at 10,000 cycles without microfractures showed pullout strengths that were not statistically significant to those with one microfracture. 4.35 screws at 10,000 cycles without microfractures show statistically higher pullout strengths than those with microfractures. Pullout stiffness in the 5,000-cycle loading group of 5.0 mm screws increased to 679.1 (290.8) N/mm and one of the 4.35 mm groups increased to 583.5 (215.8) N/mm. The pullout stiffness of the 5.0 mm group is higher but not statistically significant. In the 10,000-cycle group, the pullout stiffness decreased to 405.7 (236.2) N/mm and 444.5 (238.0) N/mm between the 5.0 mm and 4.35 mm screws. For the 5.0 mm screws in the 10,000 cycle groups, the pullout stiffness was not statistically significant between fracture and microfracture subgroups, even though slightly higher in the group without fractures. The same goes for the 4.35 mm screws in the 10,000-cycle group. Non-fracture pullout stiffness was slightly higher but not statistically significant. For bone mineral density vs. pullout strength and stiffness, the 5.0 mm screw groups were statistically significantly correlated with BMD in the control group and 5,000 cycle loading group but not in the 10,000-cycle loading group. For the 4.35 mm group in all loading conditions, the pullout strength and stiffness were not

statically correlated with BMD. This study provides evidence for the preferential use of smaller over larger diameter screws as the only positive outcome from using a larger diameter screw in osteoporotic patients is immediate strength after implantation. After considerable fatigue loading, this study did not show any added fixation strength for larger diameter screws. The results show that smaller diameter screws may be more beneficial in osteoporotic patients in reducing risk of surgical breaching of the pedicle cortical layer while providing comparable fixation strength to larger diameter screws. Further studies are likely needed in this area, especially with testing in the cranio-caudal cyclic loading fatigue testing of the prior two articles.

Pedicle Screw Constructs

Pedicle screw constructs have been one of the foundational pillars to spinal instrumentation; their presence permits the creation of immediate stability with the additional benefit of long-term fusion. There has been focused investigation into how the specificities of pedicle screw construct design may be tailored to improve the efficacy of these constructs in response to cyclical loading protocols. The works presented below provide an example of these experiments and what we can learn from them as a research community.

Irrespective of concerns regarding bone mineral density, pedicle screw constructs may cause significant unintended damage to adjacent levels due to rigid body constructs, abnormal forces, stress shielding, and hypermobility – a notion widely reported in the literature. This phenomenon was investigated by Agarawal et al. in which they assessed the significance of rod rigidity when with respect to screw loosening in a fatigue model (Agarwal et al. 2016). They postulated that less rigid rods may confer the advantage of minimizing these aforementioned complications. They utilized two groups of cadaveric lumbar spines, one with pedicle screws connected to titanium rods and the other connected to PEEK rods. Specimens were subjected to 10 Nm of pure moment in flexion and extension and later the L4–L5 segments from each were segmented and tested with cyclical loading up to 100,000 cycles followed by post-fatigue kinematic analysis. The titanium rod construct demonstrated a significant increase in flexion and extension ROM in pre/post-fatigue kinematic analysis, whereas the PEEK group did not show any significant difference, thereby potentially demonstrating an indirect association between rod material flexibility and fatigue.

Wilke et al. utilized both a pedicle screw and lamina hook system to evaluate its long-term efficacy (Wilke et al. 2016). As Wilke mentioned in their manuscript, the advantage of a pedicle screw is the primary means of rigid bone fixation, although bone mineral density is a limiting factor, especially in osteoporotic or osteopenic patients. Meanwhile, the lamina hook system provides direct connection to the lamina itself and possibly confers reduced risk of damage to neighboring structures, with the added patient benefit of reduced harm to anatomic structures if revision is indicated. To do this, the authors utilized a small sample of cadaveric thoracolumbar specimens and pedicle or lamina hook systems. The samples were subsequently placed into 100,000 cyclical loading (flexion/extension, lateral bending, and compression) cycles with moments of 3–66 Nm or until failure criteria was met: (1) failure at bony structure, (2) exceeding of the threefold ROM of the primary stability after implantation in flexion plus extension, and (3) reaching of the ROM based on the intact state before implantation both in flexion plus extension. Both implant systems demonstrated a significant reduction in ROM in all motion planes. Moreover, the pedicle screw and the lamina hook system were comparable in terms of loading cycles reached before failure (30,000–32,500, respectively) and corresponding moments (24 Nm and 25.5 Nm, respectively). The conclusion garnered from this exercise was that both pedicle screw and lamina hook constructs provide substantial and comparable characteristics – providing a potential biomechanically comparable alternative for patients with lower bone density.

The authors noted that basing failure criteria off baseline measurements of construct stability

may influence the study outcomes, specifically related to the number of cycles to failure. In instances where failure is determined based on a percentage increase relative to the baseline condition, a higher initial ROM would translate to a higher ROM in degrees but may have a higher level of instability and not be relevant clinically. For this reason, it makes sense to return to an intact ROM of motion to account for baseline ROM after fixation.

While biomechanics models have proven effective at delineating basic science characteristics of the spine, it is important to also recognize their importance in establishing and influencing clinical decision-making. Cheng et al. developed a cyclical loading methodology for cadaveric cervical spine models and further demonstrated the potential for pedicle screw constructs and biomechanics testing to influence clinical guidelines for patients in their postoperative course (Cheng et al. 2011). This study was also significant for use of cadaveric cervical spine columns, which may be subjected to significant physiological stressors due to daily movement, that were fused both posteriorly and laterally. A C5 corpectomy was performed and the cervical columns were fused from C3–C7 with posterior instrumentation and screws placed in the lateral mass of the vertebrae. Flexion/extension, lateral bending, axial torsion were each cycled to +/− 2.5 Nm at 1 Hz and axial compression cycled between 0 and 150 N. All testing was performed under continuous load control protocol and a sinusoidal waveform corresponding to 200 s/cycle. Cheng found that there was a significant change in pre- and post-fatigue cycling in axial torsion (pre-cycling mean 22.9 +/− 15.3, post-cycling mean 27.5 +/− 21.3, $p = 0.0030$) but none in flexion/extension, lateral bending, or axial compression. The aforementioned result led to the recommendation of potentially limiting axial torsion in the immediate postoperative course to decrease risk of instrumentation failure.

Interbody Devices

The use of interbody devices to increase anterior column support has improved spinal fusion outcomes. However, the potential for subsidence and cage migration necessitates biomechanics research to determine the risk of these complications based on various aspects of interbody cage design and fixation technique. Alkalay et al. performed a series of cyclic loading experiments to determine the influence of cage design on the long-term stability of TLIF constructs with three different cage designs: (1) a unilateral oblique cage (UOL) placed anteriorly, (2) an anterior conformal shaped interbody (ACS) intended to match the geometry of the endplate, and (3) bilateral linear implants (BLL) (Alkalay et al. 2018). An MTS machine was used to apply compressive loads ranging from 400 to 1200 N through the instantaneous center of rotation of each lumbar FSU at a rate of 2 Hz. Loading was performed until 20,000 loading cycles or 10 mm of displacement was achieved. All of the specimens tested survived for the entirety of the loading regime, with no more than 6 mm of recorded displacement. In addition, all three cohorts showed a continual increase in displacement throughout cyclical loading, with the rate of displacement highest in the first 500 loading cycles. This result indicates that 500 cycles at a constant loading rate may be a sufficient period to generate damage at the BII and could be used to validate stair-step loading protocols. This conclusion correlates well with basic sciences studies related to aseptic loosening which indicate there is an initial period of rapid loosening followed by a slow and steady increase in motion (Xie et al. 2019). The authors found that the compressive stiffness of the BLL cohort decreased at a significantly higher rate compared to the ACS and UOL cohorts and attribute this difference in cohorts to the centralized position of the BLL implants as opposed to the UOL and ACS implants, which are located closer to the endplate periphery where bone quality is superior (Alkalay et al. 2018). These results reinforce the notion that the majority of implant subsidence occurs within the first few weeks postoperation.

As stand-alone interbody devices continue to gain popularity, the diversity of cage fixation techniques has advanced in parallel. New fixation techniques require rigorous characterization to

determine their fatigue capacity and elucidate common failure patterns and risk categories based on patient demographics like bone quality. These results are of particular interest to the FDA as they continue to evaluate the safety of these devices. Indeed, the FDA's Office of Science and Engineering Laboratories have conducted a number of studies centered around the ability of these novel fixation techniques to retain fixation for extended periods (Palepu et al. 2017, 2018; Nagaraja and Palepu 2017). Screws placed across the endplate and into the vertebral body are often used to fix stand-alone interbody devices; however, bone quality varies across both the endplate and within the trabeculae of the vertebral body and may have a negative impact on the efficacy of these screws and other fixation strategies that rely on bony purchase within the endplate. Palepu et al. used a combination of high resolution micro-CT imaging and cyclical loading to evaluate the stability of integrated fixation cage screws based on their trajectory and bone quality (Palepu et al. 2018). Three different screw trajectories based on commercially available designs were evaluated: lateral to medial (LM), mid-sagittal (MS), and medial to lateral (ML). After a 3.5 mm pilot hole was drilled and micro-CT scans were performed, 5.5 mm screws were placed and subjected to cranio-caudal cyclic loads of 10–50 N for 10,000 cycles. The maximum load was increased by 25 N every 5,000 cycles until the 25,000 cycle mark was reached. Testing was stopped prior to 25,000 cycles if the screw displacement exceeded 5 mm. The authors found significant differences between the bone quality surrounding screws of the three trajectories, with the ML trajectory having greater total bone volume and bone volume fraction compared to MS and LM trajectories. Screws placed according to a MS trajectory had significantly higher bone volume fraction compared to LM screws. The higher bone quality surrounding ML screws translated to improved fatigue capacity with specimens from the ML cohort sustaining significantly higher counts of cycles to failure compared to both LM and MS screws.

The same authors furthered this work with another study focused on determining how stand-alone interbody devices compare to current clinical standards of constructs that combined interbody support with anterior plating to achieve fusion (Palepu et al. 2017). Lumbar segments L2–3 and L4–5 were instrumented with either an integrated fixation cage with four screws (two superior and two inferior) or a standard interbody cage with anterior plate secured with four screws. Both constructs were subjected to 5,000 cycles of 3 Nm flexion-extension loading at 1 Hz followed by 15,000 cycles of 5 Nm flexion-extension loading. Measurements of construct stability (ROM and lax zone) in response to flexion-extension, lateral bending, and axial rotation were performed in the intact condition, implanted baseline, 5,000, 12,500, and 20,000 loading cycle time points. The authors found both constructs demonstrated comparable stability in response to all modes of loading at all time points. Both constructs were able to significantly reduce ROM from the intact condition and saw significant increases in motion at the 12,500 and 20,000 loading cycle when compared to the instrumented baseline for both flexion-extension and lateral bending motions.

A 2016 study conducted by Freeman et al. addressed a similar research question: is there a difference in the fatigue performance of interbody devices placed through an anterior approach as opposed to an oblique approach (Freeman et al. 2016). The authors instrumented lumbar segments (L2–3 and L4–5) with one of two interbody devices, an ALIF and OLIF. Both interbody devices were of the similar design and employed the same fixation strategy, a curved anchor plate which is impacted across the endplate into the vertebral body. Specimens were subject to 30,000 cycles of moment loading, alternating between flexion-extension and lateral bending loading patterns according to a protocol similar to the hybrid or follower-load methodologies previously described Panjabi and Patwardhan (Panjabi 2007; Patwardhan et al. 1999). A custom follower load system was used to apply a cumulative 400 N compressive load in conjunction with ±5 Nm pure moments at a 1 Hz loading rate. The authors reported no instances of fatigue failure and minimal subsidence averaging 0.8 mm and 1.4 mm in the anterior and oblique cohorts respectively, with no significant

differences between the cohorts. Similar to the work of Alkalay et al., this study found that the majority of implant subsidence occurs early in the cyclical loading protocol, in this instance before the 2500th cycle. Device migration was also minimal with an average of less than 1 mm of anterior migration.

Cheng et al. have evaluated a number of interbody devices using the same protocol in an effort to build a library of data on the long-term efficacy of these systems. To accomplish this goal, standard measures of stability are conducted in series with stair-step cyclic loading protocols intended to gradually load the BII. Measures of flexibility are performed in the intact, instrumented baseline, mid-fatigue (5,000 loading cycles), and post-fatigue time points in addition to continuous tracking of segmental ROM throughout cyclic loading. Pure moment cyclical loading is applied in either flexion-extension, lateral bending, or axial rotation with an initial loading magnitude of 0.5 Nm which is increased by 0.5 Nm every 1,000 loading cycles until failure is achieved. Cheng defined failure as an increase in ROM to a value corresponding to 125% of baseline instrumented ROM. To date, these experiments have been conducted on interbody devices with various methods of integrated fixation including anteriorly impacted fins, curved anchor plates, endplate hooks, vertically driven anchor plates, and screw-based designs. These designs were associated with fatigue lives of 15,600, 13,124, 12,826, 14,052, and 12,500 respectively.

It is important to note that the three previously described experimental protocols used to evaluate the fatigue life of various interbody devices produced varying results. This illustrates how variations in experimental techniques may affect the reported outcomes. For example, although its effects are not well understood from a fatigue perspective, the inclusion of a follower load is known to increase the compressive load carrying capacity of the lumbar spine in static measures of stability (Patwardhan et al. 1999). Unless devices are tested in a head to head comparison, it is difficult to compare their ability to retain fixation for extended periods of time.

Conclusion

Fatigue testing of instrumented spinal constructs is a valuable tool in furthering our understanding of how instrumentation is able to maintain long-term stability. These studies provide evidence as to how long instrumented spinal constructs may be able to maintain stability in the absence of biological healing. The nuances of how these studies are conducted, including everything from the type of machine used to apply loads to how well specimen hydration is maintained, could have significant effects on the results of these studies and readers should therefore consider the differences between various manuscripts when comparing results between various laboratories. Future work is necessary to determine how these constructs respond to more complex loading schemes.

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FDA Premarket Review of Orthopedic Spinal Devices

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Contents

Abstract

Spinal implants are regulated by the Food and Drug Administration (FDA) in the Center for Devices and Radiological Health (CDRH). This chapter focuses on the premarket activities at CDRH that help determine the safety and effectiveness of orthopedic spinal devices prior to reaching the market. The specific topics discussed in this chapter include:

- FDA organizational structure and medical device classification
- The main FDA premarket submission types
- The types of evaluations used to assess the performance of spinal devices prior to reaching the market including mechanical testing, cadaver testing, computational modeling, animal testing, and clinical trials

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Spinal implant · Premarket evaluation · Medical device regulation · FDA classification · Premarket notification – 510 (k) · Premarket Approval – PMA · Biomechanical testing · Computational modeling · Animal testing · Clinical trials

Organizational Structure of the FDA and CDRH

FDA-regulated products account for approximately 20 cents of every dollar of annual spending by US consumers (Fact Sheet: FDA at a Glance). The FDA traces its founding back to the establishment of a consumer protection agency within the US Department of Agriculture in 1906 with the passage of the Pure Food and Drug Act, which prohibited the manufacture and sale of adulterated food products and poisonous drugs. The Federal Food, Drug, and Cosmetic Act (FD&C Act), enacted in 1938, replaced the 1906 law and further tightened controls over drugs and food and extended control to include medical devices and cosmetics. Importantly, the Medical Device Amendments of 1976 amended the FD&C Act to give the FDA authority to evaluate medical devices prior to the devices being marketed. The FD&C Act has been amended several additional times and today authorizes the FDA to regulate medical devices, human and animal drugs, foods and dietary supplements, and cosmetics. These products are regulated in CDRH, the Center for Drug Evaluation and Research (CDER), the Center for Veterinary Medicine (CVM), and the Center for Food Safety and Applied Nutrition (CFSAN). The Public Health Service Act (PHS Act), first passed in 1944, extends FDA's authority to include regulation of biological products. The Center for Biological Evaluation and Research (CBER) regulates vaccines, blood products including devices such as blood separators, human tissues for transplantation, and cellular and gene therapies. Lastly, the Family Smoking Prevention and Tobacco Control Act, passed in 2009, established the Center for Tobacco Products (CTP) which regulates the manufacturing, distribution, and marketing of tobacco products. The most current set of rules administered by the FDA can be found in Title 21 of the Code of Federal Regulations (CFR).[1]

The mission of CDRH is to protect and promote public health and to ensure that patients and providers have timely and continued access to safe, effective, and high-quality medical devices and safe radiation-emitting products. To accomplish this mission, CDRH plays several roles in the total product life cycle of regulated medical devices and radiation-emitting products. These roles include providing evaluation of the safety and effectiveness of various devices and diagnostic tests prior to their market release, monitoring the safety and effectiveness of devices after they have reached the market, ensuring compliance with medical device laws and regulations, when necessary, taking action against firms that violate these laws. Additionally, CDRH performs research studies that aid in developing appropriate evaluation strategies, testing standards, and communications for healthcare professionals and patients.

Device Classification

Medical devices are defined in Section 201(h) of the FD&C Act. A device is:

"an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component part, or accessory which is:

1. recognized in the National Formulary, or the United States Pharmacopoeia, or any supplement to them,
2. intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals, or,

[1]The electronic code of federal regulations can be accessed here: www.eCFR.gov

3. intended to affect the structure or any function of the human body of man or other animals, and

which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes."

As noted above, the Medical Device Amendments in 1976 amended the FD&C Act to give the FDA authority to impose premarket approval requirements for medical devices and called for devices to be divided into classes with varying amounts of control required for each class in order to provide reasonable assurance of safety and effectiveness. CDRH categorizes medical devices into one of three classes based on their level of risk. As device class increases from Class I to Class III, the regulatory controls also increase with Class I devices subject to the least regulatory control and Class III devices subject to the most stringent regulatory control as defined by Part 513 (a)(1) of the Federal Food, Drug, and Cosmetic Act:

- **Class I (low to moderate risk)**: Devices are subject to a comprehensive set of regulatory authorities called general controls[2] that are applicable to all classes of devices.
- **Class II (moderate to high risk)**: Devices for which general controls, by themselves, are insufficient to provide reasonable assurance of the safety and effectiveness of the device and for which there is sufficient information to establish special controls[3] to provide such assurance.
- **Class III (high risk)**: Devices for which general controls, by themselves, are insufficient and for which there is insufficient information to establish special controls to provide reasonable assurance of the safety and effectiveness of the device.[4]

Table 1 contains examples of orthopedic spinal devices in each of the three classes.

Premarket Submission Types

The regulatory class to which a device is assigned guides the type of premarket submission required to obtain FDA marketing authorization. Additionally, CDRH grants approval of and oversees clinical trials of significant risk, investigational devices conducted in the United States, through submissions called investigational device exemptions (IDE), which allow clinical evaluation of devices which have not yet been cleared for marketing in the United States.

Premarket Notification (510(k))

The premarket notification or 510(k) process, named after Section 510(k) of the FD&C Act, is generally the regulatory process by which CDRH evaluates Class II medical devices (FDA 2014a). As previously mentioned, most Class I and a few Class II devices are exempt from 510(k) requirements subject to the limitations on exemptions. If a device falls into a generic category of exempted Class I devices as defined in 21 CFR Parts 862–892, FDA "clearance" before marketing the device in the United States is not required. However, generally before marketing a Class II device, a submitter must receive a letter from the FDA which clears the device for marketing by stating that the FDA finds the device to be substantially equivalent to a similar

[2]All medical devices are subjected to general controls which include, for example, registration and listing, medical device reporting, and good manufacturing practices

[3]Special controls can include activities such as special labeling requirements, demonstration that the device components are biocompatible, or non-clinical performance testing such as mechanical testing or electromagnetic compatibility

[4]Certain types of devices classified into Class III that were in commercial distribution in the United States prior to May 28, 1976 (i.e., preamendment devices), may be cleared through the 510(k) process until the FDA issues an order requiring them to go through the premarket approval process or reclassifying them into Class I or Class II

Table 1 Classifications of orthopedic spinal devices

Classification	Examples
Class I: Generally exempt from premarket review	Manual surgical instruments used in orthopedic spinal device procedures such as retractors, scalpels, rongeurs External orthotic braces
Class II: Devices generally requiring 510(k) submission and intended for stabilization until fusion occurs	Pedicle screw systems Intervertebral body fusion devices Vertebral body replacements Spinous process plates Anterior/lateral plating systems Surgical instruments specific to Class II implants such as device inserters or trials
Class III: Devices generally requiring PMA submission and intended for non-fusion use or are drug/device or biologic/device combination products	Total disc replacements Interspinous process spacers Intervertebral body fusion devices used with any therapeutic biologic (e.g., BMP2) Device-specific surgical instruments provided with Class III device

legally marketed device with the same intended use and similar technological characteristics (also referred to as a predicate device).

Within a 510(k) notification, submitters must compare their device to one or more predicate devices to demonstrate that the new device is as safe and as effective as the predicate device. Substantial equivalence of a new device can be claimed to a device that has been previously cleared through the 510(k) process, a device marketed prior to May 28, 1976 (preamendments device), a device which has been reclassified to Class II from Class I or III, or a device which has been granted marketing authorization via the De Novo classification process (discussed below). Examples of Class II orthopedic spinal implants that are subject to the 510(k) process include pedicle screw systems and intervertebral body fusion devices. Figure 1 shows the distribution of various orthopedic spinal device types submitted to the FDA through the 510 (k) process between 2008 and 2017.

Modifications to a 510(k) cleared device may or may not require a new 510(k), depending on the significance of the changes (FDA 2017). Examples of modifications that may require a 510 (k) include but are not limited to a change to the device geometry or material type, a change in indications for use, changes to the environment of use such as the use in a magnetic resonance (MR) environment, or changes in sterilization or cleaning. A new 510(k) must be submitted if it is determined that a modification to a 510(k) cleared device is significant enough not to be covered under the existing 510(k). It is possible that submission of a Special 510(k), a submission which includes only summary information resulting from the design controls process, may be appropriate if the modification does not affect the intended use of the device or alter the fundamental scientific technology of the device.

Premarket Approval (PMA)

A Premarket Approval (PMA) as described in 21 CFR 814 is generally the process by which the FDA evaluates the safety and effectiveness of Class III medical devices. Contrary to the 510 (k) premarket notification process, in which a submitter can leverage existing information on predicate devices including applicable clinical data, a PMA application must provide sufficient valid scientific evidence to independently demonstrate a reasonable assurance of safety and effectiveness of the device. PMAs typically involve data from clinical trials of the specific device that support both safety and effectiveness, as well as detailed manufacturing information for the device. Many orthopedic spinal devices intended for non-fusion applications, such as total disc replacements and interspinous process spacers, are reviewed and approved through the PMA process. Table 2 lists the orthopedic spinal device original PMAs approved by CDRH between 2002 and 2017.

Unlike a 510(k), a PMA holder must report all design, manufacturing, and labeling changes

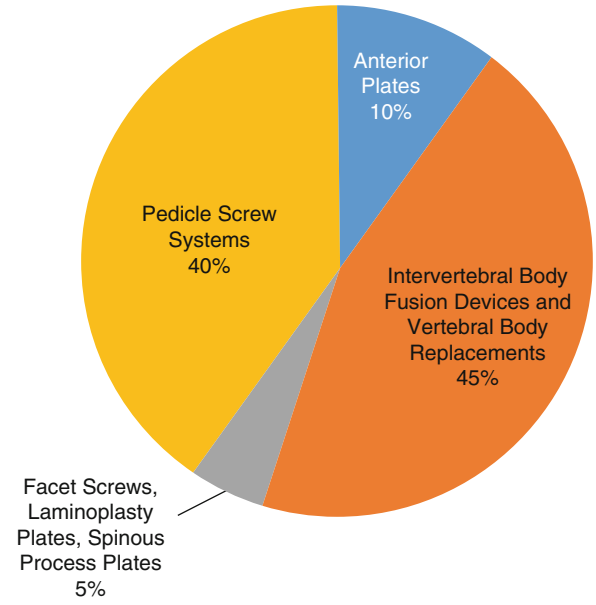

Fig. 1 Percentage of orthopedic spinal device 510(k)s received by CDRH from 2008 to 2017 (2452 total submission). (Information on orthopedic spinal devices cleared through the 510(k) premarket notification process can be found in a searchable database on the FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfpmn/pmn.cfm)

made to the approved device to the FDA via PMA supplements and PMA annual reports once a PMA is approved (FDA 2011; FDA 2014b).

Humanitarian Device Exemption (HDE)

The Humanitarian Device Exemption (HDE), as described in 21 CFR 814 Subpart H, is a marketing application for a humanitarian use device (HUD) and intended to benefit patients in the treatment of diseases or conditions that affect small (rare) populations. A HUD designation is reserved for those devices used in the treatment or diagnosis of a disease or condition that affects or is manifested in no more than 8000 individuals in the United States per year and for which there is no other comparable device that is legally marketed for the same intended use, other than another approved HUD. An HDE is exempt from the effectiveness requirements of Sections 514 and 515 of the FD&C Act and instead requires demonstration of safety and *probable benefit*. Additionally, HDE applicants are barred from selling their devices for a profit unless the device is intended and labeled for the treatment or diagnosis of a disease or condition that either (1) occurs in pediatric patients or in a pediatric subpopulation, and such device is labeled for use in pediatric patients or in a pediatric subpopulation in which the disease or condition occurs, or (2) is intended for the treatment or diagnosis of a disease or condition that does not occur in pediatric patients or that occurs in pediatric patients in such numbers that the development of the device for such patients is impossible, highly impracticable, or unsafe (FDA). Examples of orthopedic devices that received HDE approval include The Tether - Vertebral Body Tethering System (HDE number H190005) and the Minimally Invasive Deformity Correction (MID-C) System (HDE number H170001) which are non-fusion spinal devices intended to treat idiopathic scoliosis.[5]

Evaluation of Automatic Class III Designation (De Novo)

As previously described, all novel devices that have not been previously classified by the FDA are "automatically" determined to be Class III

[5]Information on orthopedic HDE approvals can be found in the searchable HDE database on the FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/hde.cfm

Table 2 Original Premarket Approval (PMA) applications approved for orthopedic spinal devices (2002–2017)

Device type	PMA number	Applicant	Device
Interspinous process spacer	P040001	Medtronic Sofamor Danek	X-STOP Interspinous Process Decompression System
	P110008	Paradigm Spine	Coflex® Interlaminar Technology
	P140004	Vertiflex	Superion Interspinous Spacer
Cervical total disc replacement	P060018	Medtronic Sofamor Danek	PRESTIGE Cervical Disc System
	P060023	Medtronic Sofamor Danek	BRYAN Cervical Disc Prosthesis
	P070001	Synthes Spine	ProDisc-C Total Disc Replacement
	P090029	Medtronic Sofamor Danek	PRESTIGE-LP Cervical Disc
	P100003	Globus Medical	SECURE-C Cervical Artificial Disc
	P100012	NuVasive	NuVasive PCM Cervical Disc System
	P110002	LDR Spine	Mobi-C Cervical Disc Prosthesis (one-level indication)
	P110009	LDR Spine	Mobi-C Cervical Disc Prosthesis (two-level indication)
Lumbar total disc replacement	P120024	Aesculap Implant Systems	ActivL Artificial Disc
	P040006	DePuy Spine	Charite Artificial Disc
	P050010	Synthes Spine	ProDisc-L Total Disc Replacement device

Additional information on orthopedic spinal device PMA approvals can be found in the searchable PMA database on the FDA website: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma.cfm

regardless of risks associated with the device. However, there may be low to moderate risk devices for which there is no legally marketed predicate device, but for which special or general controls are sufficient to provide a reasonable assurance of safety and effectiveness. For these devices, an applicant may submit a De Novo request for the FDA to evaluate the automatic Class III designation and consider whether a lower level of regulatory controls may be appropriate. Devices that are classified through the De Novo process into Class II may be used as predicate devices for future 510(k) submissions. An example of a granted orthopedic device De Novo request is an intraoperative orthopedic strain sensor (De Novo number DEN180012).

Investigational Device Exemption (IDE)

An investigational device exemption (IDE), as defined in 21 CFR 812, is an exemption that allows for an unapproved device to be shipped lawfully without complying with other requirements of the FD&C Act that would apply to marketed devices (e.g., registration and listing or quality system requirements except for the requirements for design controls). More simply, an IDE allows a significant risk device that has not received marketing authorization for a particular intended use to be investigated in a clinical study to collect safety and effectiveness information that can potentially be used to support a future marketing application. All clinical studies for evaluation of a new device or use of an existing device for a new intended use should include:

(1) An investigational plan approved by an institutional review board (IRB). If the study involves a significant risk device, the IDE must also be approved by the FDA.
(2) Informed consent from all patients.
(3) Labeling stating that the device is for investigational use only.
(4) Monitoring of the study.
(5) Required records and reports (FDA).

FDA's *Guidance Document for the Preparation of IDEs for Spinal Systems* provides information on the design of clinical trials for orthopedic spinal devices (FDA 2000). Note that the FDA often requires non-clinical evaluations (discussed in the remainder of this chapter) to be completed at the time of IDE submission as they may offer preliminary assurance of safety prior to implantation in human subjects.

Premarket Submission Device Evaluations

The success of orthopedic spine surgery depends on many factors including surgeon technique, patient characteristics, and performance of the orthopedic spinal implant. This chapter is primarily focused on the factors related to performance of the orthopedic spinal implant. A well-designed orthopedic spinal implant should have the following characteristics:

- Mechanical strength: The spinal device should be strong enough to endure the forces and moments it will be subjected to over its implanted lifetime.
- Device function: The spinal device should enable or restrict motion as intended. For example, fusion devices are typically designed to restrict motion, while non-fusion devices are often designed to allow motion similar to the healthy spine.
- Tissue-implant integrity: Many spinal devices depend on a strong interface between the spinal implant and bone both initially after surgery and over time through the development of a fusion mass or through bone ingrowth into the device.
- Safe implantation: The spinal device should have a surgical technique that allows safe access to the spine and does not result in unintended damage to bone or other anatomical structures.

In addition to the device characteristics listed above, all premarket submissions for orthopedic spinal devices should include information on the ability to sterilize the device, information demonstrating that the device is biocompatible (i.e., that the final, finished form of the device does not cause an inappropriate local or systemic reaction) and that the proposed labeling provides adequate instructions for use. While inclusion of biocompatibility assessment, sterility/reprocessing information, and draft labeling are generally necessary in all premarket submissions for orthopedic spinal devices, the information required for these elements will not be discussed in this chapter as the requirements are not unique to orthopedic spinal implants.

There are scientific methods available to assess each of the characteristics listed above ranging from simple mechanical bench tests to complex, randomized clinical trials. In this section, we will discuss common spinal device evaluation methods such as mechanical bench testing, cadaver testing, computational modeling, animal testing, and clinical trials. We will discuss the device characteristics each of these methods assess, including advantages and limitations of each method. We will also discuss how the FDA uses this information in the regulatory review process.

Mechanical Bench Testing

Mechanical bench testing involves the attachment of an orthopedic spinal device to a test machine and application of static or cyclic forces, moments, and/or linear or angular displacements. This type of testing is used to evaluate the susceptibility of spinal implants to experience failure modes such as yield, fracture, bone-implant interface failures, and excessive wear. Additionally, mechanical bench testing is used to characterize device function, such as stiffness or mobility, to help ensure that the device will perform as intended once implanted. For example, pedicle screw systems are subjected to static and cyclic mechanical testing to ensure adequate strength to resist the loads and moments they will be subjected to throughout the expected use life of the device. In addition, mechanical testing is utilized to ensure a pedicle screw system will provide adequate stiffness to stabilize the spine in order

to promote development of a fusion. The FDA provides recommendations for the mechanical testing of various spinal implants in guidance documents specific to implant types (FDA 2004, 2007, 2008).

Mechanical testing is one of the most common evaluation methods used to assess the performance of spinal devices, as the monetary and time costs are relatively low. With the exception of finite element analysis (FEA), mechanical testing represents one of the lowest cost methods of device evaluation compared to most other types of evaluation including cadaver testing, functional animal models, or clinical trials. Mechanical testing is particularly useful for the comparison of devices, which is the core concept of the 510 (k) process. For example, a company seeking clearance of a new intervertebral body fusion device through the 510(k) process may perform axial compression, compression-shear, and torsion testing on the new device to evaluate how the device performs as compared to a legally marketed predicate device. This mechanical comparison helps to establish that the new device will have adequate strength and stiffness to perform its intended use. In essence, the comparison of mechanical testing information in a 510 (k) premarket notification allows the FDA to apply the long history of clinical use of one device to another substantially equivalent device, thereby eliminating the need for clinical trials in most cases to show that the new or modified device is as safe and effective as the predicate device.

Standardized test methods are critical to performing the mechanical testing comparisons discussed above. Standards development organizations (SDOs), specifically ASTM International and the International Standards Organization (ISO), develop mechanical testing standards for orthopedic spinal implants by utilizing the expertise of spinal device manufacturers, third-party testing laboratories, physicians, and regulatory agencies from around the world. These standards are written through a consensus process in order to allow for the mechanical characterization and comparison of orthopedic spinal devices across different companies throughout the world. Without standard test methods, there would be substantial variability between device testing performed across different laboratories, and the device evaluation and regulatory process would be far more burdensome for both device manufacturers and regulatory agencies. A well-developed standard test method offers the user confidence that the test results will be repeatable assuming consistent manufacturing of the device and reproducible across different test laboratories. In addition, the user can feel confident that differences in test results between devices are due to differences in device performance and not variability in the test method. In order to ensure test methods are repeatable within a given test laboratory and reproducible between different test laboratories, ASTM International sponsors precision and bias studies of their test standards. These studies typically involve sending identical test specimens to several test laboratories to be tested per a given standard. The results are then compiled and compared, and the variability within individual laboratories and between laboratories is assessed. Subsequently, additional studies may be conducted, and revisions to the standard may be made in order to reduce variability within and between test laboratories. Precision and bias studies have been performed on orthopedic spinal device standards such as *ASTM F1717 – Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model,*[6] and the results are published within the standard.

Pedicle screw systems and intervertebral body fusion devices used in the previous examples represent devices used to stabilize the spine while a fusion develops. As previously stated, these devices are evaluated through the 510(k) process by comparison to predicate devices. However, standardized mechanical testing is also useful for non-fusion devices reviewed through the PMA process. In these cases, mechanical testing can reduce the burden associated with conducting clinical studies by providing an assessment of long-term device performance in a relatively short amount of time. While clinical studies offer

[6]ISO and ASTM standards mentioned in this chapter are published on an annual basis and are available via the organizations' websites: www.astm.org and www.iso.org

the most realistic environment for device assessment, clinical studies have a finite duration and do not cover the entire intended life of the spinal implant. Accelerated mechanical testing can be performed to simulate long-term use of the implant. For example, ISO 18192-1 – *Implants for Surgery – Wear of Total Intervertebral Spinal Disc Prostheses – Part 1: Loading and Displacement Parameters for Wear Testing and Corresponding Environment Conditions for Test* contains methods for performing wear testing on total disc replacements. The standard test method suggests performing ten million cycles of combined flexion-extension, lateral bending, and axial rotation and states that this approximates 10 years of in vivo function. Therefore, by performing this wear testing to supplement a clinical trial, additional confidence can be drawn that the device will last substantially longer than the length of the clinical trial (e.g., 5 years or less).

One common limitation of mechanical testing is that the test may not accurately replicate the complex and highly variable loading scenarios in the human body. For this reason, the utility of many mechanical tests is not in the precise simulation of a physiologic condition, but rather in its ability to characterize specific aspects of device performance particularly in comparison to similar devices. This is important to consider when determining the acceptance criteria for a mechanical test. The two most common sources for acceptance criteria for mechanical tests are (1) test results from a currently marketed device and (2) expected physiologic loads (Graham and Estes 2009). Due to the high variability in physiologic loading scenarios and the fact that the mechanical test may not be accurately replicating physiologic loading, it is often recommended that test results be compared to another similarly designed device tested in the same manner (ASTM Standard F2077 2014, "Test Methods for Intervertebral Body Fusion Devices" 2014; Graham and Estes 2009; Peck et al. 2017, 2018). Attempting to create test methods that better simulate the physiologic conditions may lead to more accurate loading on a spinal device during testing but also may lead to test results that are more difficult to interpret and compare across devices. As an example, *ASTM F1717 – Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model* and *ISO 12189 – Implants for Surgery – Mechanical Testing of Implantable Spinal Devices – Fatigue Test Method for Spinal Implant Assemblies Using an Anterior Support* are mechanical testing standards for the testing of pedicle screw systems (and other devices that primarily reside outside the anterior spinal column). ASTM F1717 involves testing the device in a scenario without anterior column support that would almost always be present in vivo from either the intact anterior spinal column or other spinal implants such as vertebral body replacement devices. The benefit of testing in this manner is that all of the load is transferred through the device and the results are easier to interpret and compare to other devices. A limitation of testing in this manner is that the device loading may not be entirely indicative of clinical use. ISO 12189 attempts to address this by adding anterior support to the testing model in the form of a spring intended to replicate the stiffness of the anterior spinal column structures. This method may result in loading on the device that is more physiologically realistic, as load is now shared between the device being tested and simulated anterior structures. However, load sharing with the simulated anterior column support makes it difficult to determine how much load is actually being applied to the device being tested. There has been some debate in the literature regarding which method is more appropriate (Graham et al. 2014; Villa et al. 2014). In most cases, the FDA prefers the use of ASTM F1717 as the loading on the device during testing can be easily determined and comparisons can be made between devices. There are cases where alternate test methods to ASTM F1717 are necessary, such as during the testing of low stiffness devices that cannot resist the bending loads applied under ASTM F1717. However, in these cases the use of ISO 12189 is still limited by the inability to easily determine the load that is borne by the device itself during testing.

In summary, mechanical testing is one of the most common performance evaluation methods for spinal implants and is present in some form in nearly every premarket application for a spinal implant submitted to the FDA. Mechanical testing

is relatively low cost compared to some of the other evaluation methods and is often repeatable and reproducible making it potentially ideal for comparisons of devices to one another. However, mechanical tests often do not fully replicate complex physiologic loading environments; therefore, testing should not be considered to represent a true simulation of in vivo conditions. Despite this limitation, the advantages of mechanical testing and the need to assess device strength, stiffness, and wear resistance prior to implantation in humans will ensure that mechanical testing remains a cornerstone of the performance evaluations of spinal devices. Table 3 lists the current mechanical testing standards for spinal devices that have been developed by the ASTM International and ISO (International Standards Organization) standards development organizations.

Cadaver Testing

Cadaver biomechanical testing is useful for assessing the performance of spinal devices, particularly when other non-clinical models are not suitable to address a specific question. For example, bone-implant interface assessments often use test methods that utilize uniform density polyurethane foam as a surrogate for bone (e.g., subsidence testing per ASTM F2267 or screw pullout testing per ASTM F543). However, the polyurethane foam does not incorporate the regional variations in bone density that exist in human vertebrae. Therefore, cadaver testing may be more advantageous when assessing bone-implant issues since cadaveric spinal segments represent human spinal anatomy and disease/aging conditions. Since cadaver testing can incorporate bone and disc quality for different disease and aging states, cadavers are the most realistic non-clinical model for assessing adverse events related to the tissue-implant interface such as screw loosening, device subsidence, device migration, or bone fracture. Numerous publications have used cadaveric biomechanical testing to measure the risk of pullout of pedicle screws from vertebral bone (Bianco et al. 2017; Cunningham et al. 1993; Frankel et al. 2007; Lehman Jr. et al. 2003; Pishnamaz et al. 2017). For spinal cages and total disc replacement devices specifically, cadaver test methods have been employed to understand adverse events such as subsidence into the vertebral body and migration of devices beyond the intervertebral space (Briski et al. 2017; Cho et al. 2008; Labrom et al. 2005; Pitzen et al. 2000). Furthermore, cadaver testing incorporates load sharing with other tissues (e.g., bone, cartilage, tendons/ligaments) to provide a more accurate representation of spinal device function (e.g., stability, in situ behavior) compared to other non-clinical testing options. For example, range of motion testing is commonly used to assess stability of an implant in physiologically relevant conditions such as flexion-extension, lateral bending, and axial rotation of the spine. Several previous publications have used cadavers to compare range of motion of a spinal device to the intact condition or to another device (Beaubien et al. 2010; Cain et al. 2005; Kornblum et al. 2013; Kuzhupilly et al. 2002; O'Leary et al. 2005; Oxland and Lund 2000; Voronov et al. 2014). For devices with novel or complicated surgical techniques (e.g., minimally invasive placement of screws or intervertebral body fusion devices), ease of implantation can be assessed with cadavers (Dixon et al. 2017; Kim et al. 2004; Luo et al. 2017; Ma et al. 2012; Ryken et al. 1995).

Cadaver biomechanical testing also has several limitations that can influence results and should be carefully considered when developing a cadaver test method and interpreting the results. One important consideration is that cadaver tissue cannot mimic biological response to the implant. For example, bone growth during spinal fusion is not captured in cadavers. Therefore, long-term assessment of the interaction of an intervertebral body fusion device with the surrounding tissue will not be captured with cadaveric testing. In addition, soft tissue and bone degradation occurs in ambient conditions, which limits biomechanical testing duration. This is important as most spinal implants undergo cyclic loading during daily activities such as walking, sitting, or standing. Adverse events such as device loosening, migration, and subsidence may occur gradually over time due to these daily activities and may be better assessed

Table 3 Consensus standards for mechanical testing of spinal devices

Device type	Standard	Methods used to assess
Pedicle screw systems and anterior plating systems	ASTM F1717 – *Standard Test Methods for Spinal Implant Constructs in a Vertebrectomy Model*	Static and fatigue strength of pedicle screw/hook systems and anterior plate constructs consisting of hardware necessary to span two spinal levels (e.g., pedicle screws and rods)
	ASTM F1798 – *Standard Test Method for Evaluating the Static and Fatigue Properties of Interconnection Mechanisms and Subassemblies Used in Spinal Arthrodesis Implants*	Interconnection strength of pedicle screw system components (e.g., pedicle screws, hooks, cross-connectors, etc.) to the rod under various loading modes
	ASTM F2193 – *Standard Specifications and Test Methods for Components Used in the Surgical Fixation of the Spinal Skeletal System*	Strength of individual spinal implant components such as screws, rods, and plates using methods such as cantilever bending and 4-point bend tests
	ASTM F2706 – *Standard Test Method for Occipital-Cervical and Occipital-Cervical-Thoracic Spinal Implant Constructs in a Vertebrectomy Model*	Static and fatigue strength of occipital-cervical-thoracic system constructs. The methods are derived from those in ASTM F1717 but include test setups that allow the attachment of occipital components
	ISO 12189 – *Implants for Surgery – Mechanical Testing of Implantable Spinal Devices – Fatigue Test Method for Spinal Implant Assemblies Using an Anterior Support*	Static and fatigue strength of pedicle screw systems and plating systems in a construct that includes a simulation of the anterior anatomical structures
Intervertebral body fusion devices and vertebral body replacements	ASTM F2077 – *Test Methods for Intervertebral Body Fusion Devices*	Static and fatigue strength of intervertebral body fusion devices in axial compression, compression-shear, and torsion loading modes
	ASTM F2267 – *Standard Test Method for Measuring Load Induced Subsidence of Intervertebral Body Fusion Device Under Static Axial Compression*	Propensity of an intervertebral body fusion device to subside using polyurethane foam as a surrogate for the vertebral body.
Artificial total disc replacements	ISO 18192-1 – *Implants for Surgery – Wear of Total Intervertebral Spinal Disc Prostheses – Part 1: Loading and Displacement Parameters for Wear Testing and Corresponding Environment Conditions for Test*	Wear of cervical and lumbar artificial disc replacements under loads and motions the device is expected to experience in vivo. The ISO and ASTM methods were developed by the separate SDOs independently but share many of the same principles
	ASTM F2423 – *Standard Guide for Functional, Kinematic, and Wear Assessment of Total Disc Prostheses*	
	ISO 18192-3 – *Implants for Surgery – Wear of Total Intervertebral Spinal Disc Prostheses – Part 3: Impingement-Wear Testing and Corresponding Environmental Conditions for Test of Lumbar Prostheses Under Adverse Kinematic Conditions*	Impingement wear and damage of lumbar artificial disc replacements to determine how the device behaves when operating at the limits of its designed range of motion
	ASTM F2346 – *Standard Test Methods for Static and Dynamic Characterization of Spinal Artificial Discs*	Static and fatigue strength of cervical and lumbar artificial disc replacements in axial compression, compression-shear, and torsional loading modes
Motion-sparing pedicle screw-based systems	ASTM F2624 – *Standard Test Method for Static, Dynamic, and Wear Assessment of*	Static and fatigue strength and wear characteristics of devices that reside outside of the disc space implanted across a single

(continued)

Table 3 (continued)

Device type	Standard	Methods used to assess
	Extra-Discal Single Level Spinal Constructs	level. This standard was developed primarily for motion-sparing devices
Motion-sparing facet replacement systems	ASTM F2694 – *Standard Practice for Functional and Wear Evaluation of Motion-Preserving Lumbar Total Facet Prostheses*	Wear of motion-sparing lumbar facet replacement devices under loads and motions that the device is expected to experience in vivo
	ASTM F2790 – *Standard Practice for Static and Dynamic Characterization of Motion-Preserving Lumbar Total Facet Prostheses*	Static and fatigue strength of motion-sparing lumbar facet replacement devices
Disc nuclear replacements	ASTM F2789 – *Standard Guide for Mechanical and Functional Characterization of Nucleus Devices*	Static and fatigue strength of disc nucleus replacements as well as various characterizations of device behavior such as swelling and lifting force
	ISO 18192-2 – *Implants for Surgery – Wear of Total Intervertebral Spinal Disc Prostheses – Part 2: Nucleus Replacements*	Wear of nucleus replacement devices under loads and motions the device is expected to experience in vivo

through long-term fatigue testing. However, cadaver specimens may be unable to endure the number of testing cycles required to simulate these activities. Although fatigue testing in cadavers has been performed to assess longer-term performance of spinal implants, it is a more challenging test to perform due to tissue degradation over time. A previous publication found that cadaver spine range of motion increases linearly in axial rotation, lateral bending, and flexion-extension over 72 h when exposed to ambient testing conditions (Wilke et al. 1998b). Therefore, cadaver fatigue testing is typically performed to a maximum of 24 h (up to 180,000 cycles at 0.5–2 Hz) to minimize degradation effects, particularly range of motion changes due to loss of hydration of the intervertebral discs in cadaver spine segments (Cook et al. 2015; Ferrara et al. 2003; Freeman et al. 2016; Heth et al. 2001; Hitchon et al. 2000; Lu et al. 2000; Palepu et al. 2017; Pfeiffer et al. 1997; Trahan et al. 2014; Vadapalli et al. 2006a; Wang et al. 2005).

Another disadvantage of cadaveric biomechanical testing is heterogeneity in the cadavers used for testing. Variability is observed in donor demographics such as age, gender, and race. In particular, it is difficult to obtain donors that are less than approximately 60 years old with normal bone mineral density. In general, cadavers obtained for biomechanical testing are elderly individuals with low bone quality (i.e., osteopenic or osteoporotic based on T-scores). In addition, various conditions (e.g., osteophytes, Schmorl's nodes) may be present and can affect bone (cortex, endplate, trabecular bone) and/or soft tissue (intervertebral disc, ligaments, tendons) quality. Therefore, cadavers available for biomechanical testing may not be representative of the intended patient population for a specific device. The substantial heterogeneity in cadavers typically leads to high variability in biomechanical testing results. For example, the average coefficient of variation[7] (COV) for screw pullout strength in studies using polyurethane foam was 8.8% (Hsu et al. 2005; Nagaraja and Palepu 2016; Thompson et al. 1997), which is substantially lower than an average COV of 37.5% (Beaubien et al. 2010; Helgeson et al. 2013; Nagaraja et al. 2015) for cadaveric screw pullout studies (Table 4). Furthermore, range of motion testing in cadaveric spine segments (e.g., functional spine units) had an average COV of 42.8%, even greater than cadaveric screw pullout studies (Cain et al. 2005; O'Leary et al. 2005; Palepu et al. 2017).

[7]Coefficient of variation for a given test result is the standard deviation normalized to the mean. This parameter allows for comparisons of variability across tests

Table 4 Coefficient of variation in published spine biomechanics studies

Screw pullout testing – foam	6.1% (2.3–10.2%) (Nagaraja and Palepu 2016)	13.3% (7.8–19.6%) (Thompson et al. 1997)	6.9% (3.8–10.0%). (Hsu et al. 2005)
Screw pullout testing – cadaver	29.1% (26.8–31.3%) (Helgeson et al. 2013)	35.8% (28.4–43.8%) (Nagaraja et al. 2015)	47.6% (36.9–64.6%) (Beaubien et al. 2010)
Range of motion testing – cadaver	37.6% (17.2–64.7%) (O'Leary et al. 2005)	39.7% (22.4–73.3%) (Cain et al. 2005)	51.1% (24.4–71.4%) (Palepu et al. 2017)

The large standard deviations observed in cadaveric testing may mask a true difference in outcomes between devices due to the heterogeneous set of cadavers used for testing. High variability is an important consideration in the regulatory framework, particularly when comparing a device to another device in the 510 (k) process. A lack of statistical difference between groups should not be interpreted to imply equivalence between two devices, but rather the variability inherent in the cadaver testing may be large enough to prevent observing differences between groups. In addition, obtaining and testing a large number of specimens to achieve a desired level of statistical confidence and reliability is difficult, particularly when comparing between two devices. Therefore, it is important to reduce this variability through cadaver preparation and screening. Nondestructive characterization such as visual inspection or image analysis (e.g., DEXA, micro-CT, MRI) can provide valuable information regarding the anatomy and quality of the vertebral structures to aid in excluding samples that do not meet pre-specified criteria. For example, BMD or T-scores from DEXA scans can be used to exclude osteoporotic cadavers. For devices that interface with vertebral endplates and/or trabecular bone, three-dimensional micro-CT imaging can be used to exclude samples with endplate sclerosis or Schmorl's nodes. Visual assessments are also particularly useful for identifying macroscopic abnormalities such as scoliosis, osteophytes, or disc degeneration. Degeneration within the nucleus or inner annulus can be assessed with magnetic resonance imaging (MRI). For cadaver tests intended to compare the performance between two or more devices, it is important to make the cadaver groups as similar as possible. Demonstrating similarity in cadavers can be achieved by stratifying cadavers into groups based on key factors (e.g., BMD, anatomical features, age, trabecular bone volume fraction) that influence the performance metric(s) of interest. For example, bias may be reduced by selecting cadaveric vertebrae with similar endplate thicknesses and trabecular bone volume fractions when comparing subsidence resistance between a subject and predicate interbody device. In addition, variability may be reduced by normalizing results to a parameter that can act as an internal control. For example, ROM after device implantation can be normalized by the preimplantation ROM (i.e., intact condition) to more directly understand the stability obtained due to device implantation (Kornblum et al. 2013). Another method of reducing variability is testing devices on the same cadaveric sample, if possible. For example, previous studies have performed matched pair testing (e.g., pullout of screws on the same vertebrae) to reduce variability and increase the statistical power and thus more directly compare two devices (Helgeson et al. 2013; Nagaraja et al. 2015). Although these methods aid in minimizing variability between cadaver groups, the inherent variability within and between cadaver spines cannot be completely eliminated.

Another limitation with cadaver testing is the lack of standardized methods for cadaver spine biomechanical testing. Cadaver studies reported in literature have variable testing protocols that currently prevent comparisons of results between different testing facilities. In order to address interlaboratory variability in cadaver test

protocols, previous publications have provided general recommendations for multi-directional cadaver testing such as loading magnitude, control mode (load/torque vs. displacement/angle), preloads (e.g., follower loads), use of a passive/active sliding table for pure moment loading, and reporting of spinal stability parameters (Crawford et al. 1998; Goel et al. 2006; Hanlon et al. 2014; Panjabi 1988; Patwardhan et al. 2003; Wilke et al. 1998a). However, fatigue testing introduces additional considerations such as testing frequency, physiologic loading modes and magnitudes, and duration that are inconsistent between testing facilities.

Overall, cadaveric testing of spinal implants is important not only in research/academic environments, but also can be a powerful tool during product development. In a regulatory setting, biomechanical testing can be used to assess device implantation, device function, and the bone-implant interface. However, heterogeneity between cadavers and variability in testing procedures are important limitations that currently prevent broad utilization of cadaver testing results in regulatory submissions. Careful consideration of these factors is critical when interpreting cadaveric testing in a regulatory framework. To increase the use of cadaveric testing in regulatory submissions, future work should focus on developing standardized cadaver selection and testing procedures where possible for spinal devices.

Computational Modeling (Finite Element Analysis)

There are several advantages to using computational modeling when evaluating spinal devices. Finite element analysis (FEA) can assess changes to a spinal device design quickly and can be accomplished relatively inexpensively compared to mechanical testing of various design iterations. In addition, FEA can assess local mechanics (e.g., stress concentrations), which cannot be determined from experimental mechanical testing. Although mechanical test methods provide a relative comparison between two devices, FEA can incorporate spinal structures to more accurately replicate the clinical scenario and understand interactions at the bone-implant interface. In fact, there have been many publications that have used FEA to understand the biomechanical environment surrounding spinal implants (Dreischarf et al. 2014; Goel et al. 2005; Newcomb et al. 2017; Polikeit et al. 2003; Trautwein et al. 2010). Another important advantage is that FEA can simulate complex physiologic loading (e.g., multi-axial loading) that may be difficult or even impossible with bench testing. However, an adequate understanding of expected in vivo loading conditions is necessary to simulate physiologic loads.

During spinal device development, FEA is used extensively to optimize device design in order to achieve desired performance and assess whether certain failure modes are mitigated. For regulatory submissions, FEA has also been used to assess device strength and function, particularly to determine the worst-case implant size for mechanical bench testing; thus, a least-burdensome approach is utilized so that mechanical testing is not performed on every size implant within a system. Additionally, when failures occur after approval or clearance, a root cause analysis is performed to assess these failures and subsequently determine a corrective action plan. FEA can be used in these situations where the knowledge gained from simulations is useful for reevaluating the design inputs and assessing potential design changes to ultimately improve device performance and safety. The FDA published a guidance document (*Reporting of Computational Modeling Studies in Medical Device Submission – Guidance for Industry and FDA Staff*) on reporting of FEA studies intended to support a regulatory submission (FDA 2016). Table 5 provides a summary of FDA recommendations in an FEA report.

Two important items recommended in this guidance document are verification and validation of the computational model to demonstrate that the simulation adequately represents the intended reality. A subcommittee within the American Society of Mechanical Engineers (ASME) is developing verification and validation (V&V) activities for computational modeling within

Table 5 Recommended format for FDA submissions of computational modeling studies

Section	Contents
Executive summary	Overview of the report including the use of modeling with respect to regulatory submission, scope and quantity(s) of interest (QOI) of the analysis, validation activities, results, and conclusions
Background/ introduction	Description of the context of use for the modeling study, device description, and intended use environment
Code verification	Description of the software quality assurance (SQA) and numerical code verification (NCV) performed
System geometry	Description of the device and/or tissue geometry and the method used to create the computational representation of device/tissue
Constitutive laws	Constitutive relationships used to describe the behavior (e.g., linear elastic) of the device material (s) and surrounding anatomy (if applicable)
Material properties	Inputs necessary to fully characterize the behavior (e.g., elastic modulus) of the device or tissue
Boundary and initial conditions	Diagram/schematic of the location and direction of the imposed boundary conditions (e.g., forces, displacements) including constraints
Mesh	Description of the type and number of elements used for the mesh and a convergence analysis used to demonstrate that the QOIs are independent of element size
Solver	Description of the software used in the computational analysis
Validation	Validation study that supports the context of use by comparing QOI (s) between model and comparator (e.g., physical testing, in vivo study, literature)
Results	Presentation of the quantitative results (e.g., von Mises stress/ strain, fatigue safety factor)
Limitations	Discussion of major limitations to the computational model
Discussion/ conclusions	Overall conclusions of the modeling study and how the objective(s) have been met with respect to the results

different medical device product areas (e.g., orthopedics, stents). Establishment of an adequate level of V&V is necessary for FEA simulations that are intended for regulatory evaluation. This subcommittee has developed a framework called the "risk informed credibility assessment method" which can be used to help determine the appropriate level of V&V necessary to support using the computational model for regulatory decision-making within a specific intended use of the model (e.g., determine worst-case implant size). For example, if the risk is determined to be low based on this method, credibility of the FEA may be established by comparing the force-displacement behavior of experimental testing per a standard test method (e.g., ASTM F1717) to the simulation results of that same test. This validation activity provides objective evidence whether the FEA results are representative of the physical test method. However, validation activities will depend on the level of credibility needed based on the risk and intended use of the model. Although there have been recent efforts to include validation activities in spinal device publications using FEA, many of these investigations model a single spinal anatomical structure with one set of tissue properties and are typically validated with limited experimental data (Campbell et al. 2016; Grauer et al. 2006; Kallemeyn et al. 2010; Vadapalli et al. 2006b; Wagnac et al. 2012). A recent publication reported the results of a multi-center study to compare eight previously validated FE models of the lumbar spine (Dreischarf et al. 2014). This study found that interlaboratory variability in mechanical parameters was low and fell within published in vitro ranges. These findings demonstrate that validated FE models can accurately estimate the response of the lumbar spine. Another challenge of FEA is accurately modeling interconnections between different components in a spinal construct. For example, polyaxial pedicle screws pose challenges to modeling the polyaxial mechanism (e.g., degrees of freedom) and the interaction (e.g., frictional contact) between the screw tulip, rod, and set screw components of this construct. Assumptions and simplifications to the computational model (e.g., geometry, material model, boundary

conditions) are typically used but may limit the applicability of the results and conclusions.

Overall, computational modeling, such as FEA, is a powerful tool that is used throughout the total product life cycle of medical devices. Spinal device manufacturers have used computational modeling in implant design, some premarket submissions, and making iterative changes to device design based on post-market monitoring. However, additional computational modeling V&V efforts are needed in the spinal device area to serve as a source of valid scientific evidence and ultimately play a greater role in regulatory decision-making. Further collaboration within the spinal device medical community is needed to establish a framework for model credibility and develop best practices for computational modeling of spinal devices.

Animal Testing

Animal testing is routinely used to address questions related to biologic response. Many of the standard biocompatibility evaluations referenced in the FDA Guidance and the associated ISO 10993 series of standards utilize animal models to evaluate potential hazards. When considering new materials for use in spinal implants, the biological response to particulate for novel materials is compared to the response generated by common orthopedic device materials using a similar animal model. With specific relevance to spinal devices, Cunningham et al. developed a rabbit model to examine the biological responses to epidural application of particles released from bearing surfaces or resulting from implant interconnection loosening (Cunningham et al. 2003). To date, more than 10 types of biomaterial particles, representing the mostly commonly utilized orthopedic implant materials including stainless steel, titanium alloy, cobalt chromium alloy, ultra-high-molecular-weight polyethylene (UHMWPE), and polyether ether ketone (PEEK), have been evaluated using this same rabbit model (Cunningham et al. 2013; Rivard et al. 2002). Based on the results of the aforementioned studies, it is known that particles of a phagocytosable size (between 1 and 10 μm) may be expected to be the most reactive particle types. Particles of smaller size (< 0.5 μm) were less inflammatory and resulted in less cellular injury as they were able to be taken up by the cells with the extracellular fluid through pinocytosis. Therefore, it is important to consider not only the device materials, but also the size and morphology of the particles expected to be generated by a device when evaluating the biologic response to wear debris, which may be determined based on the results of device fatigue or wear testing.

While animal testing may be used to address questions related to biocompatibility of the device materials or particulate that may be generated by the device as discussed above, animal testing is also used to address questions related to the functionality of a device. It should be noted that some animal tests may include assessments of both device biocompatibility and function. Functional animal testing can be used to assess development of an intervertebral fusion, bone integration into a porous coating, wear and durability of a device, or propensity of a device to migrate or expulse. An ideal animal model is one that adequately mimics the anatomical structures, physiologic loads, and relevant biological processes (e.g., bone remodeling) of a human. Common examples for large animal models used to evaluate spinal devices are sheep, goat, pig, and baboon (Abbah et al. 2009; Anderson et al. 2004; Cunningham et al. 2004; Di Martino et al. 2005; Drespe et al. 2005; Kotani et al. 2002). Drespe et al. summarized the various animal models used for spinal fusion studies stating that goats are suitable for cervical fusion studies and sheep for lumbar studies because their vertebrae are similar in size to the cervical and lumbar vertebrae in humans, respectively. In addition, Drespe et al. stated that primates have the greatest genetic similarities to humans and also approximate the human upright posture (Drespe et al. 2005).

Functional animal testing offers the advantage of being able to study a spinal implant in vivo without risks to humans. For this reason, animal testing results are often submitted to the FDA to demonstrate initial safety and/or effectiveness of a novel spinal implant prior to initiation of a clinical

trial. Additionally, because animals can be sacrificed, extensive local and systemic evaluations can be performed at various time points after implantation. For example, if intervertebral fusion is being assessed by the animal model, the spine of the animal can be removed and mechanically tested at various time points after device implantation with verification of bony fusion through histology at different time points.

Overall, selection of the most appropriate animal model for a given situation is important for scientific and ethical reasons. In fact, the FDA recommends that spinal device manufacturers discuss animal study protocols with the FDA prior to initiation of the study to ensure that the most appropriate animal model is chosen and that the protocol developed is suitable to address the relevant scientific question. Alternatively, it may be determined that no animal study should be performed depending on the scientific questions that need to be addressed. No animal test is fully representative of a human, and models that have characteristics most representative of humans (e.g., the baboon) tend to be very expensive and have the most serious ethical considerations. It is therefore important to balance many factors when determining whether an animal study can help provide safety and effectiveness evidence that would be translatable to humans, and if so which animal model is most appropriate.

Clinical Trials

In general, spinal device clinical trials involve the implantation of an investigational device into humans to assess the safety and/or effectiveness of the device in treating a particular spinal pathology. Clinical data are typically provided in original PMAs for Class III devices as these devices are considered to have higher risk and/or incorporate new intended uses or new technology. De Novo submissions often include clinical data to help demonstrate that a novel device or intended use that is automatically designated as Class III is actually low to moderate risk and that special and general controls are adequate to assure safety and effectiveness. Clinical data are also sometimes necessary in 510(k) submissions for Class II devices to help demonstrate substantial equivalence when other assessment methods (e.g., mechanical bench testing, cadaver testing, animal testing) are unable to adequately answer the question at hand. Unlike the other evaluations discussed in this chapter which rely on assumptions/simulations of the clinical setting, the advantage of clinical data is that experience is gained about an orthopedic spinal implant in the environment in which the device is used. However, collection of clinical data for orthopedic spinal devices is often very expensive and time-consuming.

Clinical data concerning spinal implants may be derived from a variety of sources and study designs ranging from case reports to randomized clinical trials. However, in order for the clinical data to be utilized in a regulatory submission to make a determination of device safety and effectiveness, the data must constitute valid scientific evidence. Valid scientific evidence is defined in 21 CFR 860.7(c)(2) as "evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories conducted by qualified experts, and reports of significant human experience with a marketed device, from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of the device under its conditions of use." This section of the CFR also states, "Isolated case reports, random experience, reports lacking sufficient details to permit scientific evaluation, and unsubstantiated opinions are not regarded as valid scientific evidence. . .." The amount and characteristics of the clinical data which are necessary depend on the questions that need to be answered. For example, if the safety and effectiveness profiles of a new technology are not well understood, a multicenter, prospective, randomized clinical trial may be necessary. Alternatively, there are instances where more is known about the performance of a particular technology and only limited clinical data specifically tailored to answer a narrower set of questions are required.

Study Evaluations

During a clinical trial for an orthopedic spinal device, study subjects are evaluated prior to the surgical procedure, intraoperatively, and at predefined time points postoperatively. Study assessments are primarily focused on the safety and effectiveness of the investigational device and surgical implantation procedure and include evaluations from the patients' perspective through the use of patient-reported outcome measures. Common assessments for orthopedic spinal device studies include:

- Pain and function evaluations, such as the Oswestry Disability Index (Fairbank and Pynsent 2000) and the Neck Disability Index (Vernon and Mior 1991), are used to assess changes in relevant pain symptoms experienced by the patient as well as assessments of the patient's ability to perform activities of daily living (e.g., walking, tying shoes). General health and disease-specific patient-reported outcome measures are used to objectively document the response to surgical intervention.
- Neurologic assessments (e.g., reflex, motor, and sensory evaluations) are performed to assess whether the procedure or device caused neurological damage.
- Medical imaging evaluations are utilized to assess the status and function of the device, bone/implant interface, and presence or absence of a solid arthrodesis if fusion is a goal of the surgical procedure.
- Adverse events are collected and categorized by seriousness, severity, and relationship to the device or procedure.
- Patient satisfaction measures are used to assess how satisfied the patient is with their outcome.
- Additional assessments are determined on a case-by-case basis depending on the intended use or technological features of a device.

Individual Patient Success

In clinical trials for orthopedic spinal devices, the success of a spinal procedure for a given patient is most commonly assessed using a composite primary endpoint. The individual components of a composite endpoint for a spinal device trial generally include pain, function, neurological status, subsequent surgical interventions, serious adverse events, and radiographic success for both the investigational and control groups. A predefined success criterion is identified for each component of the composite endpoint prior to initiating the clinical trial. Examples of success criteria include the following: pain and function scores must improve by a certain absolute amount or percentage, neurologic status must maintain or improve from preoperative status, there should be no serious device or procedure-related adverse events, there should be no significant subsidence or migration (based on pre-specified quantitative criteria) of the device seen on medical imaging, and depending on the device type and intended use, there should be no unplanned subsequent surgical interventions. If all of these criteria are met at the agreed-upon assessment time point (typically 2 years post-operation for a spinal device study), the patient is considered a success in the study. However, if one of these criteria is not met, the patient is considered a failure in the study.

Overall Study Success

Determination of overall study success in a clinical trial for a spinal device most commonly involves comparison of the proportion of patients that achieve individual success between the investigational and control groups. It is important to select an active control intervention with proven efficacy compared to a placebo (Mirza et al. 2011). There are two common types of predefined, statistical evaluations performed: non-inferiority and superiority. If non-inferiority is demonstrated, this means that the proportion of patients determined to be a success in the investigational group was statistically shown to be not inferior to the control group by a pre-specified margin. This type of study is appropriate when studying two comparable procedures such as anterior cervical discectomy and fusion (ACDF) with an intervertebral body fusion device filled with autograft bone graft compared to ACDF with an intervertebral body fusion device filled with a bone void filler or a therapeutic biologic. Once non-inferiority to the control is established,

superiority compared to the control can be tested. If superiority is demonstrated, this means that the proportion of patients experiencing success was statistically shown to be higher than the control group. Superiority evaluations are important if the investigational device treatment has additional inherent risks associated with it as compared to an active control treatment. For example, if the investigational treatment involves the use of a spinal device and the control treatment does not require the use of a spinal device (e.g., the control treatment is a spinal injection procedure), superiority is expected to be shown in the investigational group to offset the inherent risks associated with implantation of a spinal device. Superiority evaluations are also performed if a company wants to show their device to be better than an alternative treatment regardless of risk level.

Medical Imaging

One of the biggest advantages of clinical trials is their ability to assess the device in the actual environment in which it is used. While most of the clinical assessments collected in a clinical trial are related to the primary purpose for the surgical intervention (e.g., relief of pain, increase in function), it is also important to assess the status and function of the device and its relation to surrounding tissues. However, once the device is implanted, inspection of the device in vivo raises challenges. Medical imaging is necessary to view the device and surrounding bone and soft tissues and potentially correlate device status to adverse events such as new or increased pain. In clinical trials, medical imaging is generally performed according to a pre-specified imaging protocol, to assess various factors such as:

- Loosening of a device at the bone-implant interface.
- Changes in device position – device migration, expulsion from the disc space (if applicable), and subsidence of the device into bone can be visualized.
- Changes in device condition – imaging can be used to assess whether the device has fractured, excessively worn, or otherwise experienced damage.
- Fusion status – assessment of fusion status can be performed by evaluating motion across the spinal segment (or lack thereof) and the presence of bridging bone.
- Motion-sparing device function – assessment of device function for motion-sparing spinal devices such as a total disc replacement can be performed by assessing whether the device appears to be functioning appropriately during spinal motion (e.g., flexion-extension motion).

Imaging modalities utilized postoperatively can include plain film radiographs (X-rays), computed tomography (CT) scans, and magnetic resonance imaging (MRI). Each of these imaging modalities offers unique advantages and limitations, and a combination of imaging modalities may be used in clinical studies for orthopedic spinal devices. For example, X-rays are the most common method used in clinical trials because X-ray machines are widely available and images can be quickly obtained on the patient in various positions. However, X-rays cannot adequately visualize certain radiolucent polymeric materials commonly used to manufacture spinal devices. To address this issue, medical device manufacturers often add metallic radiographic markers to the polymeric components in order to visualize the components on X-ray. Additionally, X-rays provide a 2-dimensional representation of a 3-dimensional environment which can make it challenging to assess the true position and status. CT scans can be utilized to create a 3-dimensional reconstruction of the implant and surrounding region. Therefore, CT scans are useful to inspect the implant and surrounding bone in more detail, but the frequency of scans must be minimized due to the amount of radiation exposure associated with the use of this imaging modality. As MRI does not use ionizing radiation, it is often the initial imaging study obtained to evaluate spinal anatomy. However, imaging artifacts present from metal components may limit the utility of this imaging modality for many orthopedic spinal implants. Overall, medical imaging is often the primary method used to assess the condition of a spinal device while implanted and is therefore a critical assessment during clinical trials.

Conclusions

In order to market a new Class II or Class III spinal device in the United States, spinal device manufacturers are generally required to submit a premarket application to the FDA to receive marketing authorization. These submissions contain many types of data including mechanical testing, animal testing, cadaver testing, and clinical data intended to demonstrate the safety and effectiveness of a new spinal implant prior to marketing. Each type of evaluation has limitations that should be well understood prior to selecting a method to answer specific safety and/or effectiveness questions. For patients to have timely access to safe, effective, and high-quality medical devices, a balance between scientifically sound review processes and minimizing the burden on the industry to obtain regulatory approval is needed.

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Recent Advances in PolyArylEtherKetones and Their In Vitro Evaluation for Hard Tissue Applications

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Contents

Abstract

The advent of thermoplastic semicrystalline polymeric materials in the design of medical devices has allowed for the widespread use of polymeric interbody spacers for spinal arthrodesis to treat spinal degeneration. These polymers come from the PolyArylEtherKetone class of materials which are inert, readily machined, and serializable and have mechanical modules closely matching bone. Unfortunately, the inert nature of this class of materials may prevent osseointegration and can potentially generate a negative immune response. To overcome the inert character of PolyArylEtherKetones, researches have investigated several approaches to improving the biological properties of this important class of material. This review summarizes the history of PolyArylEtherKetones within the context of spinal arthrodesis and the recent approaches to improving the osseointegrative properties of this polymer.

Keywords

Polymer · Biomaterial · PEEK · PolyArylEtherKetone · Osseointegration

Degenerate issues of the spine affect nearly 20% of the American population (Brinjikji et al. 2015; Buser et al. 2018; Ravindra et al. 2018). Of that group, nearly 5% require surgical intervention to restore stability, reduce pain, and reestablish health function (Weinstein et al. 2006; Friedly et al. 2010; Martin et al. 2019). This means that nearly 400,000 spinal arthrodesis procedures take place annually.

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Spinal degeneration is caused by a series of factors including genetic predisposition, lifestyle and injury, weight management, as well as chronic disorders including diabetes and inflammation (Elfering et al. 2002; Steelman et al. 2018). With better management of many health conditions, coupled with longer expected life spans, the probability of degenerative disc disease occurring in the United States has risen and the number of surgical interventions to relieve this medical challenge has followed suit (Mihailidis et al. 2017; Kurucan et al. 2018).

Degenerative issues of the spine cause pain due to a loss of vertebral tertiary structural integrity due to the degeneration and potentially, instability (Mobbs et al. 2013; Battie et al. 2019). This loss of structure induces non-native conformation of vertebra translating into pressure on the spinal cord with symptoms ranging from pain to immobility (Donnally et al. 2020). The degeneration may occur at any point in the spinal column including the cervical, lumbar, thoracic, and sacroiliac joint.

While surgical intervention to stabilize degenerative issues has benefited from advances in materials, alternative pain management approaches are initially considered before surgical intervention is offered (Vaishnav and McAnany 2019; Winebrake et al. 2020). Hence, surgical intervention to stabilize and fix a motion segment may be the only viable medical approach available to patients to allow for redress to their health challenges. The goal of surgical intervention is to stabilize the degenerated tertiary vertebral structure by providing a means of fusion through the damaged disc space (Vaishnav and McAnany 2019; Lykissas and Aichmair 2013; Yavin et al. 2017). By allowing spinal arthrodesis to occur between two adjacent vertebrae through the intra-disc space, relief from pain and return of motor function can occur, thus making spinal arthrodesis a critical medical intervention.

The goal of spinal arthrodesis is to fix two adjacent vertebrae together by forming a de novo bone mass at the interface of the end plates (Spoor and Oner 2013; Baliga et al. 2015). Generally speaking, the approach requires exposure of the region of interest on the spine. Surgeons remove damaged disc and implant a temporary adjunct to fixation and may add additional bone growth supporting matrixes to aid in stability until arthrodesis occurs. Typically, fusion of two vertebra takes place over a period of 6–12 months with initial detectable bone deposition taking place as early as 2–3 months (Lee et al. 2011). The design and use of the temporary adjuncts to fixative devices play an important role in induction of fusion, radiological diagnosis of arthrodesis progression, and support of vertebra faceplate. (Danison et al. 2017) These adjuncts are hard metals, plastics, or ceramics that are meant to support the vertebra till new de novo bone is formed (Nouh 2012; Patel et al. 2019).

This chapter focuses on methods to improve the spinal arthrodesis outcomes through innovation in polymer materials used as temporary adjuncts to fusion. Included in this review are approaches for next-generation composites, changes to surface structure, and changes to surface chemistry. While advances in metallic implant devices have played an important role in recent clinical results, this review will not cover the use of metal implants. Detailed reviews on these implants can be found here (Ni et al. 2019). Furthermore, impact of spinal arthrodesis due to use of various bone growth extenders including allografts and synthetic bone void fillers has been well documented in the literature. Finally, the surgical approach can play an important role in device design as well as recovery post-spinal surgery. While important, this is the focus of other reviews and will not be covered in this review.

It was recognized in the late 1950s and early 1960s that spinal arthrodesis was a legitimate and effective tool to treat degenerative disc conditions and was first used in lumbar spinal fusion with metallic implants pioneered by Cushing (Prolo 1969; Bydon et al. 2011), Dommisse (Dommisse 1959), Boucher, (Boucher 1959) and others (Winter and Lonstein 1999). Initial surgical approaches for fixative devices to create space between degraded discs utilized sterilized autograft bone. While autograft bone alone is somewhat effective, major challenges to device fracture, sizing, placement, and device migration made the initial approach a suboptimal solution and the quest for new materials (Gupta et al. 2015; Buser et al.

2016; Fernandez de Grado et al. 2018; Sohn and Oh 2019).

Metallic implants were a breakthrough, as these implants could be machined and precision shapes could be readily prepared on commercial scales (Chong et al. 2015; Phan and Mobbs 2016; Tarpada et al. 2017). Initial medical devices custom made for spinal arthrodesis were comprised of stainless steel (DeBowes et al. 1984; Bagby 1988). The use of stainless steel allowed for some degree of customization in terms of device size and shape, but due to x-ray and MRI reactivity imaging, vertebral fusion and potential for challenges in future imaging studies limited the appeal of this material (Rupp et al. 1993; Kumar et al. 2006; Knott et al. 2010). Furthermore, an additional issue arose due to the use of stainless steel implants. It was found that the interface between the vertebra plates adjacent to the implant had a propensity to crack/shatter due to a mismatch between the tensile strength of metal and the bone (Ordway et al. 2007; Herrera Herrera et al. 2013; Choy et al. 2019).

While the promise of spinal arthrodesis as a tool to treat degenerative spinal conditions had begun to be achieved through the use of metal implants, the quest for new materials that were radiolucent and had strength indexes better matched to native cortical bone had begun to correct defects identified in metallic implants. At the time, circa 1980, a new polymeric material had begun making headway in advanced engineering applications due to the polymer's strength and inert nature (Parker et al. 2012; Manoukian et al. 2019). This polymer, PolyEtherEtherKetone (PEEK), held several advantages over traditional metals including radiolucency, easily machined from various sized rodstock, and had a strength profile closely matching that of bone (Kurtz and Devine 2007; Selim et al. 2018). Once identified and approved for use as an adjuvant to fusion by the FDA, PEEK has remained dominate in the spinal arthrodesis pace with only recent challenges from innovations in titanium-based devices (Li et al. 2016; Pelletier et al. 2016; Seaman et al. 2017).

The current space of devices serving as temporary adjuncts to fixation in spinal arthrodesis has rapidly expanded with devices having a litany of shapes, compositions, and surface treatments (Jain et al. 2016; Phan and Mobbs 2016). The goal of these new devices is to create a material that encourages rapid and effective bone growth to minimize wound healing time through the promotion of spinal arthrodesis. Recently, PEEK use has suffered from the perception that the material has inherent limitations that are not present in metal-based systems (Toth et al. 2006; Torstrick et al. 2017a). These limitations relate to the polymer's inert surface chemistry that prevents cell adhesion and growth.

While each material has inherent limitations, the goal of scientists and engineers has been the creation of an ideal implant. An ideal implant is one that would promote arthrodesis, while matching mechanical properties of bone, and have radiolucent properties to allow for visualization of wound healing and bone ongrowth (Martz et al. 1997; Kadam et al. 2016). These properties have thus far proved elusive in a single material, leading to cost-benefit analysis choices to be made in device selection by the surgeon.

When comparing radiolucency, electron-dense materials, such as metal like stainless steel and titanium, prevent the penetration of x-ray beams and interfere with MRI imaging. This radiopaque property leads to errors in quantification of bone ongrowth, an imaging of arthrodesis limiting outcome measurement post-surgery (Hayashi et al. 2012; Thakkar et al. 2012). Polymers such as PEEK do not suffer from this limitation. To compensate for metal's limitation, additive manufacturing of metallic implant with void space and low density has been proposed (Wilcox et al. 2017).

The implant used as an adjuvant to fusion must be capable of supporting the vertebra until the formation of a bony mass occurs (Cole et al. 2009). If the material has a mechanical strength greatly exceeding that of bone, the potential for the faceplate of the vertebra to crack or for the implant to sink into the vertebra is possible (Proietti et al. 2013; Tang et al. 2014), thus defeating the goal of surgical intervention, as the failed implant will not provide sufficient relief of pain and pressure removal from the spinal cord. If the implant is too weak, it may shatter, causing pain

and potential further damage to an already degenerated wound (Chou et al. 2016). The mechanical strength of an implant can play an important role in spinal arthrodesis (Hoshijima et al. 1997; Steffen et al. 2000). PEEK implants have a mechanical strength closely matching that of native bone compared to metallic implants that have a known risk of bone fracture due to mechanical strength mismatch. (Heary et al. 2017)

The ultimate goal of spinal surgery is to fix a degenerative spine. This is accomplished by the fusion of two adjacent vertebrae, (Gittens et al. 2014) making osteogenic promotion a crucial property of the implant material. Implants used as adjuncts to spinal arthrodesis must provide a matrix that allows for mineralization, bone ongrowth, and support for cell deposition. (Agarwal and Garcia 2015; Lewallen et al. 2015) Materials that have good surfaces for cell adhesion include those with surface charge or surface functional groups that allow for protein and cellular interaction (Mastrogiacomo et al. 2005; Stevens 2008; Amini et al. 2012; Qu et al. 2019). Materials that are neutral and without cell binding motifs generally are poor biomaterials due to their inability to promote cell ongrowth and adhesion. PEEK suffers in this category, as it is a neutral hydrophobic inert polymer with no native motifs for cell binding and growth. (Toth 2012) This is in contrast to typical metal-based implants that have a native surface charge that allows for cell and protein deposition and growth (Shayesteh Moghaddam et al. 2016; Gao et al. 2017).

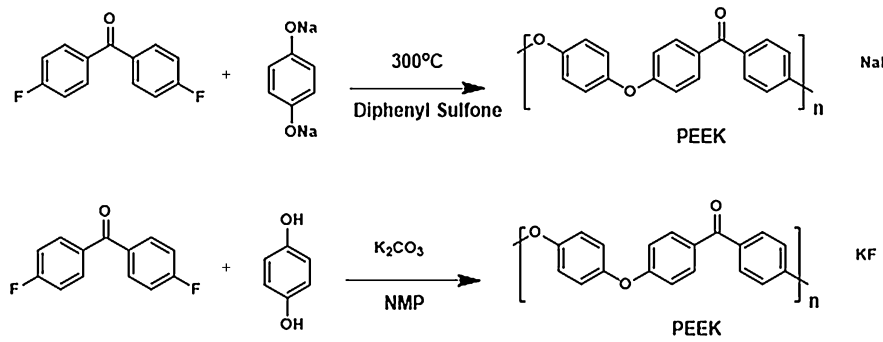
A devices materials properties and device design must therefore be balanced between (a) radiolucency, (b) mechanical strength, and (c) device osseointegration as no currently available device is capable of excelling in all three categories (Sohn and Oh 2019; Warburton et al. 2019). Therefore, research into metallic implants has focused on improving the radiolucency and better matching mechanical strength to that of bone. Research to improve PEEK's properties has focused on changing the bone-PEEK interface to increase osseointegration while still retaining PEEK's positive mechanical and imaging attributes (Torstrick et al. 2016; Walsh et al. 2016; Honigmann et al. 2018).

Industrially, PEEK is synthesized with a step-growth polymerization with AA BB type monomers with a phenol or phenolic salt and a halogenated benzophenone (Scheme 1). The reaction requires high temperatures, organic solvent, and generated alkyl halide salts. These polymers must be precipitated to remove unreacted monomers, solvent, and generated salts. Unfortunately, the residual starting material and generated salts are toxic and may induce biological effects. Once isolated, the polymer pellets are dried and the rods are extruded and can be machined into medical devices.

Despite PEEK's poor cell growth characteristics, this material has found widespread adoption and use and has been implanted in millions of patients globally. The adoption and use of PEEK was heavily influenced by the shortcoming of the initial medical devices used as temporary adjuncts to spinal fixation, as these materials were radiopaque and were not matched with bone's mechanical properties, resulting in a higher probability of poor medical outcomes (Kurtz and Devine 2007).

Historically, PEEK's commercial development by Vitrex (in the mid-1980s) occurred around the same time as issues with metal implants were becoming apparent. It was realized that good spinal arthrodesis required a strong material that supported vertebra without inducing stress fractures while still allowing for direct imaging to monitor wound healing. Furthermore, the use of a material readily manufactured from rodstock available in a variety of dimensions was a boon to device designers. These advantages lead to the first PEEK spinal devices developed by AcroMed in the 1990s (Wenz et al. 1990; Brantigan and Steffee 1993). PEEK was accepted as a material with desirable properties and found widespread adoption by all major medical device manufactures.

Since PEEK's initial use as a medical device, manufacturers have studied approaches to increase bone ongrowth, custom composites, and novel structural elements (Reid et al. 2019; Zhang et al. 2019; Buck et al. 2020; Enders et al. 2020). Recent innovations that are currently in clinical use have focused on PEEK's unique features, described herein. This has led to the creation of



Scheme 1 Synthesis of PEEK with: (**a**) Hydroquinone sodium salt or (**b**) Hydroquinone with potassium carbonate

spinal cages capable of expansion on implant to facilitate minimally invasive surgery (Alimi et al. 2015a; Kale et al. 2017; Zhang et al. 2018). Expandable cages are not possible using metal-based devices due to the rigid nature of metal. PEEK rodstock is formed from extruded PEEK pellets. Therefore, the opportunity to incorporate additives to form a composite that has increased bone ongrowth potential is afforded (Evans et al. 2015; Zhong et al. 2019; Petersmann et al. 2020). Finally, coating of PEEK with a thin metallic layer in order to increase the cell ongrowth potential of the implant has recently been introduced into the market (Gardon et al. 2014; Yang et al. 2015; Hasegawa et al. 2020). These innovations point to a strong appetite for next-generation evolved PEEK-based devices that retain the polymer's advantages but incorporate new functionalities for improved cell ongrowth and eventual fusion.

Although PEEK implants have found widespread adoption and use as temporary adjuncts to fusion as a material, PEEK has significant limitations not found with metallic implants. PEEK's major limitation relates to its inert hydrophobic character and lack of surface functional groups that promote cell binding. Typical polymer-based scaffolds optimized to support cell growth have an overall surface charge, or they may possess binding motifs for cell surface interactions (Polo-Corrales et al. 2014; Nikolova and Chavali 2019; Richbourg et al. 2019). For example, in simple in vitro assays, it is clear that PEEK does not support cell proliferation and has relatively low early- and late-stage osteogenic proliferation markers compared to titanium or positive control tissue culture polystyrene (Olivares-Navarrete et al. 2015; Cheng et al. 2018). Clinically, the formation of a fibrous layer around PEEK indicates a foreign body response (Anderson et al. 2008; Torstrick et al. 2016; Walsh et al. 2016). Due to this lack of surface charge and cell interacting groups, it is theorized that spinal arthrodesis may be delayed.

There is an emerging body of preclinical and clinical evidence related to heretofore unknown liabilities associated with PEEK (Walsh et al. 2016; Kao et al. 2014). This evidence is represented by both *preclinical* and clinical studies demonstrating PEEK's inability to support the proliferation of osteoblasts, leading to longer times required to successful vertebral fusion. A recent series of evidence has emerged that points to a potential immunogenic effect caused by PEEK's implantation. (Boyan et al. 2014; Krause et al. 2018)The immunogenic effect of PEEK, while only recently realized, may be due to a foreign body response or leaching of impurities from synthesis in PEEK pellets (Kurtz 2012). The immunogenic effects of PEEK are still being explored and have not been widely confirmed in the peer-reviewed literature. Clinical evidence has emerged that rates of pseudarthrosis in medical procedures that utilized PEEK intervertebral bodies as spacers are greater than in cases that used metallic spacers (Sardana et al. 2019; Teton et al. 2020). While this recent evidence does not preclude the use of PEEK, the questions raised have led to a surge of innovations in PEEK design to overcome the emerging liabilities.

Due to PEEK's importance as a material in spinal arthrodesis, extensive research in several solutions are currently employed to overcome PEEK's hydrophobic inert character to improve cell ongrowth and remove any potential immunological limitations. In terms of risk and reward, these approaches include the physical modification of PEEK, preparation of PEEK composites, and modification of PEEK's surface with new chemical functionalities. Physical modification of native PEEK is readily translated to a clinical setting without any risks to moving outside of the FDA 505(B)2 regulatory pathway, but this approach also limits the device to retaining PEEK's inherent cell interface weakness. Generation of PEEK composites using two FDA cleared materials has the potential to introduce a cell ongrowth component to the polymer implant but introduces liabilities for machining due to changes to device mechanical properties and a potential for regulatory oversight under non-505 (B)2 pathways. Finally, introduction of novel surface chemistry to modify the cell-PEEK interface has the greatest potential for changing how the body "sees" the implant but embodies the greatest risk for clinical translation.

Physical modification of PEEK through new PEEK cage design is considered the lowest risk approach and aims to accomplish surgical convenience and increase PEEK's surface. Upon implantation via in situ expansion with devices like the StaXx XD™ (Alimi et al. 2015b), the FlareHawk devices allow for more surface contact and areas for bone growth to occur using a relatively more minimally invasive approach. These devices accomplish their expansion via incorporation of an expandable metallic core that upon implantation is opened. NuVasive has recently demonstrated the clinical viability of a novel surface, porous PEEK, created via the etching of salt crystals emended into PEEK's surface yielding a material with the highest clinically available surface area for cell growth and proliferation (Torstrick et al. 2017b; Carpenter et al. 2018).

New materials are being designed to overcome the current clinical challenges known to PEEK. The goal of this research is the creation of a material that promotes cell growth while retaining bone strength matching and radiolucent properties. Critical to these efforts is to design a material that retains the best of PEEK, remains straightforward to machine and manufacturer, yet promotes cell growth and adhesion. There are two major categories of next-generation PEEK materials covered in this review: (1) filled PEEK composites, wherein PEEK remains chemically unmodified but is filled with inorganic minerals that promote cell growth, (2) surface-modified PEEK, PEEK's surface is modified with surface relative motifs that introduce a functional charge that allows for inherently better cell growth.

Of the innovative PEEK materials, filled PEEK composites have been present longest and have seen some recent clinical success. This class of material takes advantage of the extensive amounts of inorganic materials that may have known positive cell adhesion properties and combines them with PEEK to make a hybrid material that can support cell growth (Walsh et al. 2016). These materials are made through co-extrusion of PEEK pellets mixed with inorganic filler to a form hybrid rodstock that can be machined into desired spacer design (Ma and Guo 2019). Only inorganic filler materials are possible due to the relatively high temperatures required for PEEK extrusion. There are several key parameters that impact the properties of the extruded material and the eventual cell ongrowth properties. These include the inorganic crystal size, composition, and loading (Zhong et al. 2019; Ma et al. 2014; Kutikov et al. 2015; Zhu et al. 2019). All have influence over final device stability, biocompatibility, machinability, and material properties.

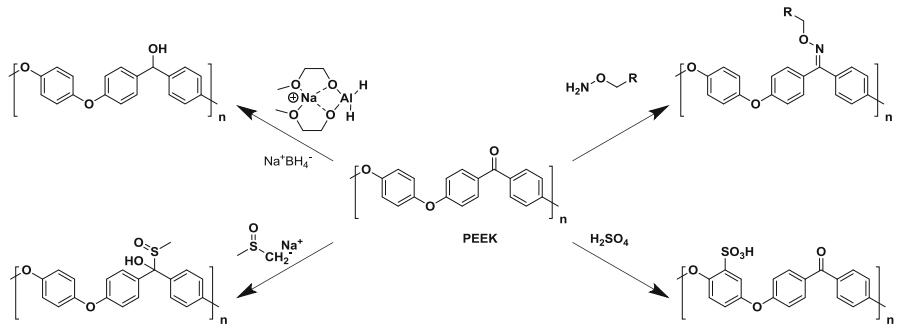
Examples of two recently developed and FDA-approved PEEK composites are PEEK OptimaHA® and ZFuse®. PEEK OptimaHA® is a PEEK composite filled with ~5 micron hydroxyapatite crystals at an ~20% loading. This material has shown clinical evidence of superiority vs PEEK with faster fusion times while retaining radiotransparency. ZFuse® is a PEEK zeolite (aluminosilicate) composite with an ~10% zeolite loading. Zeolites are inorganic sorbent materials capable of sequestering inorganic and organic small molecules. The introduction of zeolites

into PEEK may aid in the sequestering of the impurities found in PEEK. In addition, the introduction of zeolite into PEEK may provide surface charges that enable cell binding and growth to occur. While ZFuse® devices have not undergone clinical evaluation, this material has recently gained clinical approval for use in spinal applications. In a large animal study, the use of ZFuse® was found to lower local tissue inflammatory markers. These two newly approved PEEK-based biomaterials' impact on the medical device space has yet to be determined as implant makers begin the process of testing and potentially fielding devices based on these composites.

When considering how a biomaterial implant imparts its effect, both the bulk and surface properties must be considered (Ikada 1994; Angelova and Hunkeler 1999; Lucke et al. 2000). The bulk properties will influence device strength and stability, while the device surface interfaces directly with the body and influences cell attachment and biological response properties. Therefore, the direct chemical derivation of PEEK's surface to introduce cell binding groups can impart the desired biological response utilizing currently available PEEK manufacturing technology without impacting material mechanical or physical properties (other than hydrophilic and surface charge) (Poulsson et al. 2019; Wang et al. 2019). Changing PEEK's properties through direct surface modification is a new approach to creating next-generation materials with inherently improved cell growth properties (Kassick et al. 2018). Scheme 2 demonstrates possible reactions of PEEK found in the literature.

Unfortunately, the synthetic toolbox available to modify PEEK's backbone has been limited due to this polymer's lack of readily modified functional groups on its backbone (Franchina and McCarthy 1991; Díez-Pascual et al. 2009; Shukla et al. 2012). Two recent chemical-based approaches have broken through this barrier to create surface-modified PEEK. These approaches are the introduction of sulfonic acid moieties onto the aryl ring via etching with concentrated sulfuric acid. (Wang et al. 2019; Shibuya and Porter 1992; Chaijareenont et al. 2018) The introduction of the anionic surface charge promotes protein binding and deposition, creating an environment conducive to cell growth. In vivo evidence has emerged demonstrating the superiority of sulfonic acid-modified PEEK compared to native PEEK for support of bone ongrowth. (Zhao et al. 2013; Ouyang et al. 2016) A limitation to the sulfuric acid modification of PEEK is the potential for over-modification of the PEEK, (Daoust et al. 1994) leading to a rapid deterioration of the polymer's mechanical properties. Additional surface modification approach is the borohydride reduction of the ketone group of PEEK to an alcohol introducing a slight increase in hydrophilicity (Erik et al. 2016); additionally this approach allows for covalent medication of the reactive alcohol group (Fukuda et al. 2018). For example, the cell binding motif GRGD was attached to PEEK in a three-step procedure wherein the ketone was reduced to an alcohol PEEK was silanized and then reacted with the peptide GRGD to improve cell binding (Zheng et al. 2014). A recent breakthrough is the realization that the ketone groups of PEEK could be directly modified with compounds bearing aminooxy or hydrazine moieties forming a stable link via formation of a Schiff base. This approach was used to introduce peptides, amino acid mimetics such as the P15 peptide, and charged functional groups onto the surface of PEEK (Kassick et al. 2018). While only tested in vitro, the materials show great promise with significantly greater signs of both late-stage and early-stage mineralization and cell binding and growth. These new biomaterials have the most complex regulatory path forward but have demonstrated the greatest ability to support cell ongrowth and proliferation, potentially heralding the future of polymer-based medical devices.

The rapid assessment of a biomaterial's osteoconductive properties in vitro allows for straightforward go/no-go points. Therefore, in vitro assays are an excellent tool to establish if a surface modification or composite strategy imparts positive bone growth. Although advances in real-time PCR allow for assessment of osteogenic mRNA expression levels (Jadlowiec et al. 2004; Koch et al. 2005; Tuzmen and Campbell 2018), direct phenotypic expression of bone tissue biomarkers remains the gold standard for biomaterial assessment (Lian and Stein 1995; Yang et al. 2018; de Wildt et al. 2019). While the literature is



Scheme 2 Chemical modification of PEEK

replete with a host of variables in experimental design including a broad range of cell types used in cell line (Chin et al. 2012; Burmester et al. 2014; Yoo et al. 2016; Hwang and Horton 2019), primary (Noori et al. 2017; Lopes et al. 2018; Fu et al. 2019), and induced stem cells (Pirraco et al. 2010; Mattioli-Belmonte et al. 2015) and experimental conditions (Black et al. 2015; Dang et al. 2018; Levin et al. 2018), the major goal of these experiments is the measure of early phase bone biomarkers such as alkaline phosphatase and late phase presence of calcium deposits and collagen I (Lopes et al. 2018; Zadpoor 2015; Turnbull et al. 2018). Additionally, in vitro experiments allow a materials immunological profile to be screened and characterized (Chen et al. 2016). The lack of standard experimental conditions prohibits clear comparison between differing different literature reports highlighting the importance for the inclusion of positive control experimental cohorts. This will be an important area to standardize and correlate with in vivo data for a standard platform for new bone biomaterial assessment. This standard screen can lead to faster study of new materials, leading to improved patient outcomes.

Conclusions

PolyArylEtherKetones remain a critical implant material in bony tissue applications. Although PolyArylEtherKetone-based materials have found widespread use as adjuncts to spinal fixation, the future for these materials is questioned. The questions are based upon recent preclinical and clinical studies revealing that the inert nature of this material, while once heralded as a feature, can limit bone ongrowth and the potential to induce local inflammation, leading to pseudarthrosis. Fortunately, research into improving PolyArylEtherKetone osseointegrative properties has demonstrated promise for this material and the potential for these PolyArylEtherKetone derivatives' bright future as next-generation hard tissue implants while maintaining the critical design features of radiolucency, mechanical strength matching bone, and pro-cell ongrowth properties.

Cross-References

- Biological Treatment Approaches for Degenerative Disc Disease: Injectable Biomaterials and Bioartificial Disc Replacement
- Biologics: Inherent Challenges
- Bone Grafts and Bone Graft Substitutes
- Implant Material Bio-compatibility, Sensitivity, and Allergic Reactions
- Mechanical Implant Material Selection, Durability, Strength, and Stiffness
- Metal Ion Sensitivity
- Selection of Implant Material Effect on MRI Interpretation in Patients

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Selection of Implant Material Effect on MRI Interpretation in Patients

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Abstract

MRI is an important modality in the evaluation of the posttraumatic and postoperative spine. The use of MRI and its advantages over other modalities in evaluation of the spine with metal implants have been well documented in the literature (Sekhon et al., Spine 32(6):673–680, 2007; Malik et al., Acta Radilogica 42:291–293, 2001; Rupp et al., Spine, 1993; Rupp et al., J Spinal Disord 9(4):342–346, 1996; Tominaga et al., Neurosurgery 36(5):951–955, 1995). Although MRI is an established radiological method in spinal diagnostics, the clarity of images produced through magnetic resonance can be sensitive to the size and magnetic susceptibility of the materials used. Incompatible materials produce an artifact in the image, which can make assessments of adjacent osseous and neural structures difficult, if not impossible. Also, obtaining a high-quality diagnostic MR image in a patient can become challenging especially in certain postoperative patients as the image quality is affected by so many factors like the location of the device, implant materials, trajectory angle, etc (Sekhon et al., Spine 32(6):673–680, 2007). Therefore, at a minimum, implant materials not only must be MRI conditional (nonferrous) but also optimally allow meaningful diagnostic information to be obtained. Furthermore, implants should possess certain biomechanical properties such as weight-bearing strength, stiffness, biocompatibility, and resistance to corrosion and fatigue.

To that end, this chapter covers case studies that characterize the artifacts seen in magnetic resonance imaging (MRI) of the axial spine created by the constituent properties of the implanted material. These investigational studies are designed to characterize magnetic resonance image distortion associated with:

- Posterior pedicle screw systems
- Total cervical disc replacement intravertebral implants comprised of various materials

Keywords

MRI compatibility · Metallic implants · MRI artifacts · MRI image distortion · Geometric distortion · MRI magnetic compatibility

Pedicle Screw System

Metallic spinal implants like pedicle screws and rods are commonly used to provide stability and maintenance of spinal correction during a time in which bone fusion occurs. Combinations of different materials, like titanium (Ti) screws and cobalt-chromium (CoCr) rods, were recently adopted into clinical practice by spine surgeons. CoCr rods have the advantages of high stiffness and strengths required to correct rigid scoliotic deformities. While stainless steel (SS) has almost the same desirable mechanical characteristics, it produces high levels of artifacts in magnetic resonance imaging. In this study, implant volume and imaging parameters were kept constant to assess the artifacts produced by implants made of stainless steel, titanium, and cobalt-chromium. In this case study, postoperative MRI quality among three different constructs was compared: (1) Ti pedicle screws w/ Ti rods, (2) Ti pedicle screws w/ CoCr rods, and (3) SS pedicle screws w/ SS rods. This study was performed in two groups. The first study consisted of two human torsos to qualify the images, and the second study was performed in a phantom setup to quantify the artifact produced.

Study I

Two fresh-frozen human torsos (cervical-pelvis) were used for bilateral implantation at two levels as shown in Table 1. Torso A (81, male) and torso B (84, male) did not show any structural damage or bony deformity on radiographs.

Implantation in Torso: The EXPEDIUM® Spine System (DePuy Spine, Raynham, MA) with 5.5 mm rods was used for implantation. 6-mm-diameter and 45-mm-long pedicle screws made from stainless steel, titanium, or carbon fiber were used along with 5.5-mm-diameter rods made from titanium, stainless steel, cobalt-chromium, or PEEK.

Midline incision was made with muscle retraction, and pedicle preparation was performed utilizing a selection of awls, pedicle probes, ball tip feelers, and bone taps. Polyaxial crews were inserted into the pedicles. Appropriate length rods with the desired lordosis were selected and placed into the polyaxial screw heads. Different material constructs were implanted at levels based on a randomized protocol. Surgical incisions were sutured closed and the torso maintained in a supine position for MRI scanning. Each specimen was scanned with one of the four different implant groups using 1.5 T and 3 T scanners. A torso on the 3 T scanner is shown in Fig. 1. The six different pedicle screw and rod combinations used at the vertebral levels are shown in Table 1.

Study II

Phantom grids were used for precise quantitative measurement of the artifacts produced by different material as shown in Fig. 2. This method is similar to the ASTM F 2119-01 "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants" (ASTM F 2119-01).

Procedure: A plastic bin was assembled with a grid fixed at the bottom as a reference for quantitative measurement of artifacts. Different screw-rod construct combinations were assembled and then fixed in the plastic sheets and then suspended in a phantom bath normal to the grid. Constructs

Table 1 Specimen implantation levels

Specimen/torso	Upper level	Lower level
A	L1–L2	L3–L4
B	L2–L3	L4–L5

Table 2 Screw and rod combinations

Material	
Pedicle screw	Rod
Stainless steel	Stainless steel
Carbon fiber reinforced PEEK	PEEK
Titanium	Titanium
Titanium	Cobalt-chromium
Titanium	PEEK

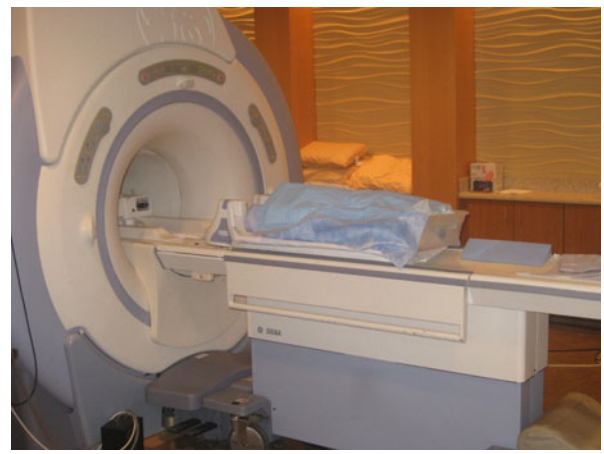

Fig. 1 3 T MRI scanner with implanted torso on coil

used for the phantom study are shown in Table 2. The phantom bath consisted of $CuSo_4$ solution (1–2 g/L), shown in Fig. 3, which reduces T1 and keeps TR at a reasonable level (Rupp et al. 1996). The bin was then placed on the same spine coil as the torsos and placed in the scanner as shown in Fig. 4.

MRI Imaging

MRI is a very useful diagnostic tool for spinal disorders due to its excellent soft tissue contrast. In this study, we compare MR artifact production by identical pedicle screws and rods with different materials: stainless steel (SS), titanium (Ti), cobalt-chromium (CoCr), carbon fiber reinforced PEEK (CFRP), and PEEK. Scans of instrumented constructs implanted in both the fresh cadavers and a phantom were then obtained.

The torsos and phantom were tested both on 1.5 T and 3 T MRI scanners. Parameters were varied according to standard clinical protocols, including echo time (TE), repetition time (TR), echo train length (ETL), number of excitations (NEX), bandwidth (BW), number of cycles (N Freq), phase (N Ph), phase direction (Ph dir), field of view (FOV), (Th), and slice gap (gap).

MR images were obtained using a clinical MRI system. A metallic object that displayed "weak" ferromagnetic qualities in association with a 1.5 T MRI system may exhibit substantial magnetic field interactions during exposure to a 3 T MRI system (Shellock et al. 2002). Problems presented

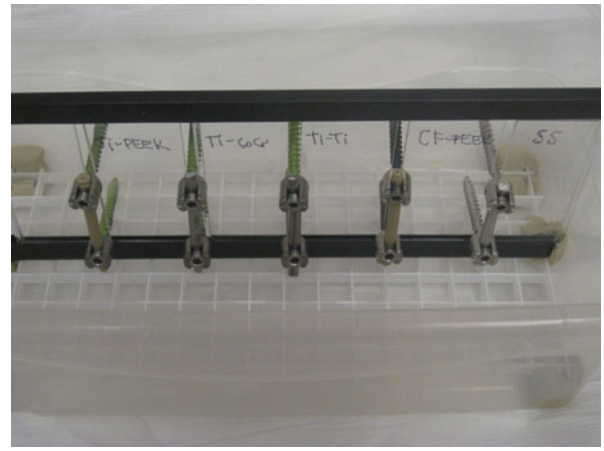

Fig. 2 Phantom construct, from left: Ti-PEEK, Ti-CoCr, Ti-Ti, CF-PEEK, SS-SS

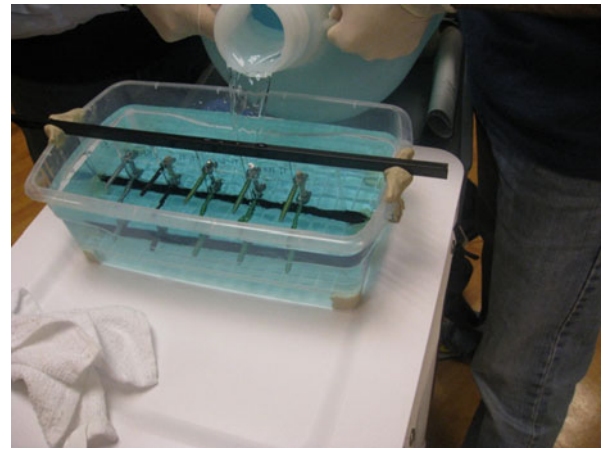

Fig. 3 Phantom setup with $CuSO_4$ solution

by 3 T systems for metallic implants include translational attraction and torque. Transitional attraction is what has been referred to as the *projectile effect* and results when an object moves toward the magnet at a high rate of speed. Torque, as it relates to MRI, is the shifting or twisting of the medical device or implant inside the patient's body. This movement is caused by the static magnetic field and can cause discomfort, injury, or death if the implant is displaced (Jerrolds and Keene 2009). Using muscle as a calibration standard at 3 T showed the highest accuracy value of 89 percent versus 80.5% at 1.5 T, whereas accuracies of the disc were 78.1% at both 3 T and 1.5 T (Zhao et al. 2009).

Images were acquired using a common 1.5 T MRI (Siemens Magnetom Espree 1.5 T MRI, Malvern, PA) and using 3 T MRI (General Electric Signa HDX 3.0 T MRI scanner, Milwaukee, WI) systems. T1 and T2 fast spin-echo (FSE) protocols typical for clinical images were acquired in the axial and sagittal plane.

IDEAL, a special GE software package, was used for artifact reduction. First, cursory analysis didn't find significant improvement with this package, but it is believed that there would have been a significant difference if we compared with scans with the fat saturation correction modality had been enabled. This software can reduce the fat signal by other mechanisms that are not magnetic field homogeneity dependent as well as providing a separate fat-sensitive image.

The hydrogen in fat has a slightly reduced resonant frequency due to its molecular environment. Normal clinical scans, especially with contrast, would be performed with fat saturation enabled to reduce the bright fat signal. Fat saturation options precede the pulse sequence with a saturation pulse tuned to the fat resonant frequency (which is 224 Hz below the 63 MHz frequency for 1.5 T systems or 448 Hz below the 127 MHz frequency for 3 T systems) in order to reduce the fat signal. Fat saturation, however, requires good magnetic field homogeneity, which is perturbed by the presence of metal implants. Hence, fat saturation correction modality is usually turned off when implants are present.

A list of the scan sequence and the specific materials used is shown in Table 3. The 3 T scans were performed at 41.67 Hz (clinically used) with change in bandwidth to 83.33 Hz with fat saturation turned off for better visualization. Field of view was maintained at 192–224 mm. Slice thickness was varied between 2 and 4 mm with slice separation of 1–1.5 mm. Abbreviations used for the description of the various parameters are shown in Table 4.

Four 1.5 T scans were performed with the distortion correction option enabled. The Siemens Magnetom Espree 1.5 T MRI, Malvern, PA, has a short and wide magnet bore, which adds to patient comfort, but reduces the area of magnetic field homogeneity which can distort images if not corrected.

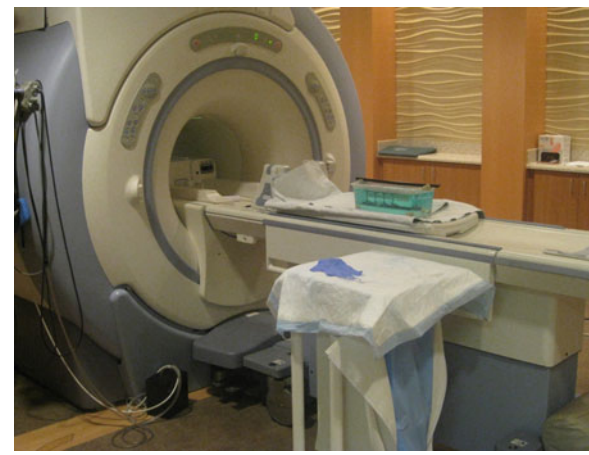

Fig. 4 3 T MRI scanner with phantom setup

Table 3 MRI scan sequence

MRI	Scan	Specimen/torso	Implanted level			
			Upper level		Lower level	
			Screw	Rod	Screw	Rod
3 T	Scan 1	A	SS	SS	Ti	Ti
	Scan 2		CF	PEEK	Ti	PEEK
	Scan 3	B	Ti	CoCr	SS	SS
	Scan 4		Ti	Ti	Ti	CoCr
1.5 T	Scan 5	A	SS	SS	Ti	Ti
	Scan 6		Ti	Ti	Ti	CoCr
	Scan 7	B	Ti	Ti	Ti	CoCr
	Scan 8		Ti	Ti	Ti	PEEK

	Configurations
SS – Stainless steel	SS/SS
Ti – Titanium	CF/PEEK
PEEK – Polyether ether ketone	Ti/Ti
CF – Carbon fiber	Ti/CoCr
CoCr – Cobalt-chromium	Ti/PEEK
Total scan = 10 (4 for each specimen and 2 for the phantom)	

Table 4 MRI parameter abbreviations

FRFSE	Fast-recovery fast spin-echo
ETL	Echo train length
NEX	Number of excitations
FOV	Field of view
Th	Slice thickness
Gap	Slice spacing
FR	Fast recovery
FC	Flow compensation
NPW	No phase wrap
TRF	Tuned R/F
SEQ	Sequential acquisition
ETL/sl	Number of echo trains/scanned slice
TF	Echo train length (turbo factor)
BW/pix	Bandwidth per pixel
Th	Slice thickness
FOV	Field of view
Gap	Slice spacing

BW/pix were used in the range of 117–170 Hz (clinically used) with increase of bandwidth for 290–651 Hz for implantation. ETL was kept in the range of 5–23 and 96 for few scans.

Axial scans were performed aligned with the disc spaces (separate series for each space). The "nonstandard" scans were performed with increased bandwidth.

Results

Phantom and torso scans showed that stainless steel causes the highest distortion of the MR images. Titanium does not contribute much for artifacts in the image. Titanium screws with cobalt-chromium rods produces larger artifacts than titanium screw with titanium rods. Nonmetallic implants like carbon fiber screw and PEEK rods do not cause image artifacts. Cobalt-chromium rods can cause artifacts at the junction where it meets the titanium screw head.

Study 1 was performed on torsos, where 1.5 T MRI examination revealed no visible metal artifact prior to the implantation of the spinal implants. After implantation, the images showed that specific neural structures (foramina and spinal canal) were unreadable in cases where stainless steel implant was used as shown in Fig. 5.

Study II was performed on a phantom grid that accurately measured the artifact sizes. The artifact sizes for 1.5 T were on an average greater in area for the stainless steel implants as opposed to Ti64 implants and the CCM rods. The artifact sizes for carbon fiber reinforced polymer (CFRP) screws were on an average less than titanium (Fig. 6).

For the 3 T scanners, the artifact sizes were on an average greater in area for the stainless steel

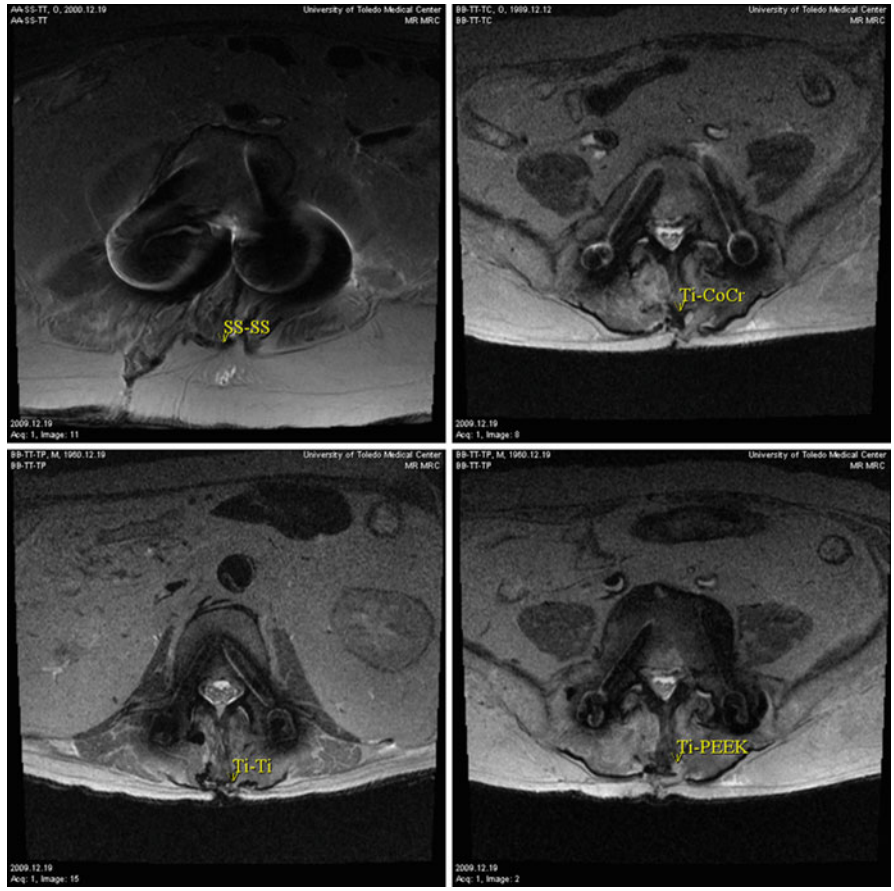

Fig. 5 1.5 T MRI of pedicle screw instrumented and rods

implants as opposed to Ti64 implants and the CCM. The artifact sizes for carbon fiber reinforced polymer (CFRP) screws were less than titanium.

There was a statistical difference in the artifacts and the quality of the images between 3 T and 1.5 T MRI. However, this difference was negligible for the CFRP implants.

Cervical Disc Devices

Materials used in the design of total disc replacement (TDR) devices are of utmost importance as they determine not only the mechanical stability and biocompatibility but also the amount of artifacts produced in magnetic resonance (MR) imaging of patients following surgery.

MRI is considered the diagnostic imaging procedure of choice for intervertebral disc herniation and disc degeneration (Practice parameters 1994), as it can provide exquisite morphologic detail of the disc abnormality (Herzog et al. 1995, Modic and Ross 1991). However, diagnosing a patient using MRI can become challenging as the quality of MRI is affected by previously mentioned factors. Artifacts may be far more important in the cervical spine than in the lumbar spine because of the relatively small size of the cervical vertebrae, which may cause image distortion into the adjacent level discs.

A variety of TDR designs today use a combination of metals and polymers. Metals used in cervical prostheses provide a base of support for the polymer surfaces as well as a surface for fixation to bone. The commonly used metals include stainless steel, titanium carbide alloy,

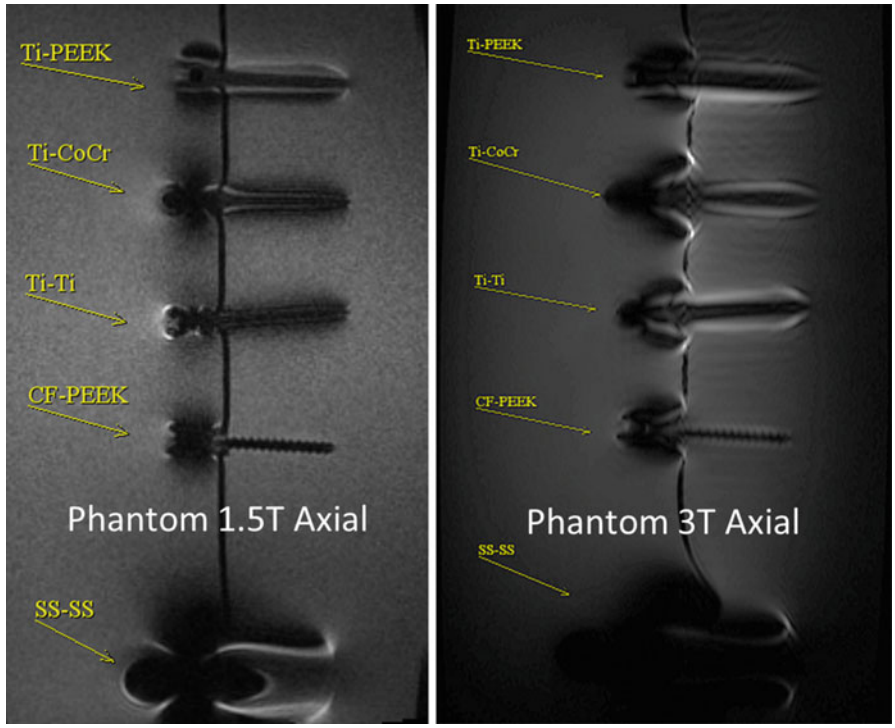

Fig. 6 Phantom 1.5 and 3 T axial views illustrating the significant artifacts associated with SS screws and rods

cobalt-chromium-molybdenum alloy (CoCr), and traditional titanium alloys. Polymers include polyurethane and ultrahigh molecular weight polyethylene. Polymers provide a low-friction surface for articulation as well as some degree of "shock absorption" (Oskouian et al. 2004).

The usage of titanium-based spinal implants is increasing. One of the many reasons is that titanium produces less MR susceptibility artifacts when subjected to MR imaging (Malik et al. 2001). Other advantages of using titanium include improved biocompatibility, increased resistance to corrosion and fatigue, and decreased hypersensitivity response by the body when compared to other nickel- or chromium-containing alloys like stainless steels and cobalt-chromium (Malik et al. 2001). Titanium implants also satisfactorily fulfill the requisite biomechanical demands. The usage of cobalt-chromium alloys has also been reported in literature for several other reasons of which one is its minimal wear (Tranelis 2002; Link et al. 2004; Ernstberger et al. 2007). In another study, H.D. Link et al. concluded that metal/polyethylene material combination is the best and the most suitable for an artificial cervical disc and preferred the proven combination of a highly polished cobalt-chromium alloy component articulating against an UHMWPE sliding partner (Link et al. 2004). Stainless steel on the other hand has met the biomechanical requirements but is a barrier to optimal imaging evaluation. In addition, stainless steel alloys corrode the most of all the alloys used in arthroplasty.

To date, titanium, cobalt-chromium, and stainless steel all have been used in the manufacturing of cervical arthroplasty devices. Previous studies have highlighted the advantages of using Ti alloys (Sekhon et al. 2007; Malik et al. 2001; Tominaga et al. 1995) from an MRI perspective, but there are very few studies comparing titanium and cobalt-chromium alloys (Sekhon et al. 2007; Ernstberger et al. 2007). These studies have examined the extent of cobalt-chromium (CCM) and titanium (Ti64) artifacts in cadaver spines and attested to the importance of artifact effects. However, the present case study not only emphasizes the

important impact of material selection in MRI interpretation of patients with cervical disc devices but also compares the amount of distortion produced by these devices on the adjacent segments.

Therefore, we conducted two studies to assess the extent of MRI artifacts produced by artificial cervical disc replacement devices on adjacent neural structures and to evaluate the influence of scanning parameters with respect to artifact size. In the first study, we used fresh human torsos to evaluate the extent of obscurement of periprosthetic tissues. The second study employed phantom grids to make precise quantitative measurements of the artifacts produced by CCM and Ti64 devices.

The ASTM F 2119-01 testing protocol provides a more controlled environment for precise study of artifacts from different materials and scanning parameters (ASTM F 2119-01).

For both studies, the DISCOVER™ artificial cervical discs provided by DePuy Spine Inc. (Fig. 7) were used. The CCM and Ti64 materials are compliant with the ASTM standards: ASTM F75-07 Standard Specification for Cobalt-28 Chromium-6 Molybdenum Alloy Castings and Casting Alloy for Surgical Implants (UNS R30075) and ASTM F136-02a Standard Specification for Wrought Titanium-6 Aluminum-4 Vanadium ELI (Extra Low Interstitial) Alloy for Surgical Implant Applications (UNS R56401). Disc implants were stored at room temperature in plastic bags and all tests were performed at room temperature.

Study I

In Study 1, three fresh-frozen human torsos (head-pelvis), two females and one male with an average age of 60 years, were used. CT and MRI scans of the torsos prior to implantation were taken at room temperature to evaluate visible metal artifact prior to spinal implantation. Images were obtained for a single-level implantation at C5–C6 or C6–C7 and bi-level implantation at C5–C6–C7 with identical devices made of either Ti64 or CCM. An experienced arthroplasty surgeon performed all the implantations on the specimen. Apart from making artifact measurements using a display software, hard copy images were also presented to an independent radiologist to evaluate the distortion of MR implant image itself and distortion of the MR image of adjacent neural structures (foramina and spinal canal). Approximate artifact measurements were performed in Study I to show that CCM resulted in larger artifacts and to see the effect of increasing bandwidth on the artifact size.

Study II

Study II was performed to make precise quantitative comparisons between artifacts produced by Ti64 and CCM which was relatively difficult due to variability in torso anatomy and void spaces. A phantom was used to evaluate the metal artifacts produced by the disc devices. Two artificial cervical disc replacements (Ti64 and CCM) were suspended in a phantom bath, which consisted of

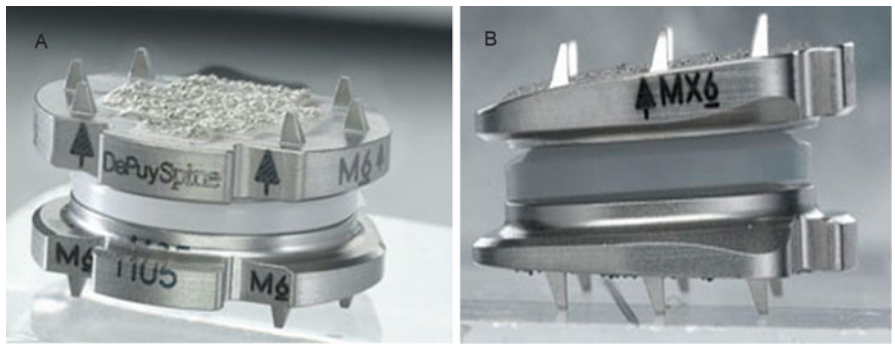

Fig. 7 Different views of DISCOVER artificial cervical disc, featuring titanium alloy (Ti64) and polyethylene components. (**a**) Oblique view; (**b**) Side view

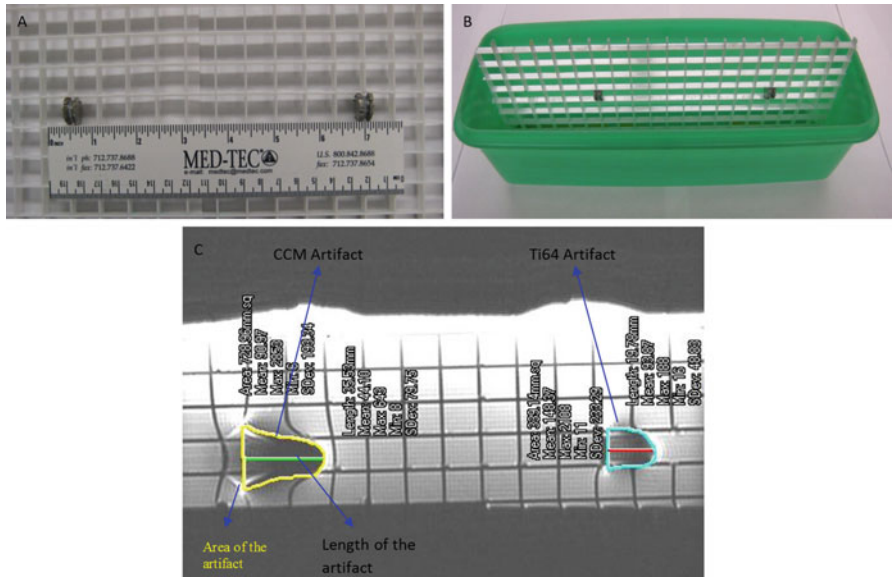

Fig. 8 Image showing disc placement and artifact measurement on the phantom grid. (**a**) The two discs (Ti64 and CCM) were placed sufficiently far apart (distance >4 cm) so that there is field homogeneity and no overlap of artifacts produced by the two discs. (**b**) Discs were aligned the same way as with the human discs in a container that was filled with $CuSo_4$ (1–2 g/L) solution. (**c**) Length and area of the artifact produced by CCM are greater than Ti64 alloy disc

a plastic container filled with $CuSO_4$ solution (1–2 g/L) (Fig. 8). This method was similar to the ASTM F 2119-01 "Standard Test Method for Evaluation of MR Image Artifacts from Passive Implants" (ASTM F 2119-01). It quantitatively assessed the extent of magnetic resonance imaging artifacts of cervical disc replacement devices (made of titanium alloy (Ti64) or cobalt-chromium (CCM)) and evaluated the influence of scanning parameters with respect to artifact size.

CuSo4 (1–2 g/L) solution following ASTM F 2119-01 (ASTM F 2119-01) was used as it reduces T1 and keeps TR at a reasonable level. First, the two discs were placed over 4 cm apart, simulating a non-contiguous two-level instrumentation, and the artifacts were measured. The clearance between the two discs and each side of the container was kept at more than 4 cm to achieve adequate field homogeneity. Then the discs were kept at a distance of 1.5 cm (Fig. 7), simulating two contiguous functional spinal units instrumented with artificial disc devices, and MR images were obtained and artifacts were evaluated.

To study the influence of bandwidth on artifact size, images were obtained at increased bandwidths (2.02–62.5 kHz) with ETL kept constant. Conversely, images were obtained with the ETL increased (4–60) and BW kept constant. As a determinant of image quality, the signal-to-noise (S/N) ratio was measured as the ratio of image signal value at a fixed location within the phantom grid to the standard deviation of the signal outside of the liquid phantom.

MR Imaging

MR images were obtained using a common MRI system (GE Signa 1.5 T, General Electric Company, Milwaukee, WI). Fast spin-echo protocols typical for clinical imaging were acquired using a repetition time (TR) of 4000 mil sec and a minimum echo time (TE). Scan parameters used: a 256 × 192 matrix for sagittal, sagittal STIR, and axial sequences and an FOV of 24-cm and 3-mm-thick sections for all sequences. The following MRI sequence and parameters were included: T1-weighted sagittal (TR, 435 ms; TE, 14 ms; NEX, 4), T1-weighted axial (TR, 600 ms; TE, 14; NEX, 4), T2-weighted sagittal (TR,

4000 ms; TE, 102 ms; NEX, 4), and T2-weighted axial (TR, 485 ms; TE, 9 ms; NEX, 4).

Images were displayed and artifacts were measured using Aquarius-NET (TeraRecon Inc., Tokyo, Japan) software. Susceptibility artifacts were seen as a bright-displaced signal and a void of signal loss. Artifact size (area and length) was measured in the frequency encode direction from the hyper-signal region to the edge of the signal void. For all sequences, artifact size for each artificial disc was measured on two images that contained the most well-defined artifact, and the average value was taken. We measured the artifact along the short axis of the metal implant to be consistent in measurements. Artifacts measured on the sagittal images were used for quantitative comparison and those on the axial images for comparison of the extent of artifacts on the adjacent neural structures.

Results

In general, the results showed that artifact sizes were greater with CCM than those seen with Ti64. CCM produced greater amount of distortion at the index level as well as at the adjacent segments when compared to Ti64 (Fig. 8). Artifact size was reduced at increased BW but degraded the image quality. Increasing ETL did not seem to significantly vary the artifact size.

In Study I performed on torsos, CT and MRI examination revealed no visible metal artifact prior to the implantation of the spinal implants (Fig. 9). After implantation, the images showed that specific neural structures (foramina and spinal canal; the spinal cord was visible in both cases) but were less readable in cases where a CCM implant was used (Fig. 8). Alternatively, the Ti64 implant allowed uncompromised imaging of the spine with only

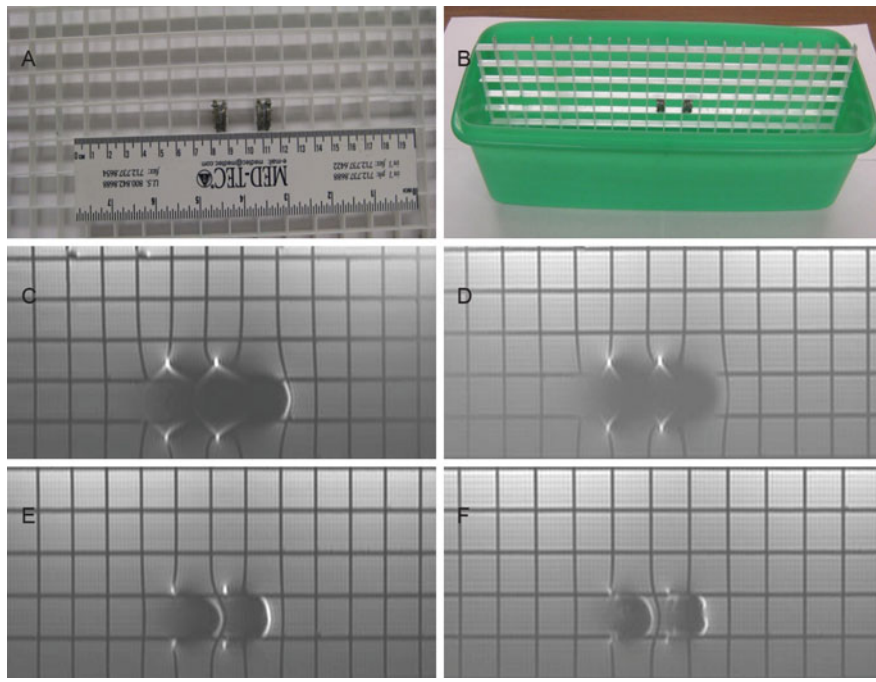

Fig. 9 Image showing disc placement and artifacts on the phantom grid with two similar types of discs separated by a distance equal to 2.5 cm which is approximately the distance between the center of the C5–C6 disc and center of the C6–C7 disc. (**a**) Placement of two Ti64 or CCM discs on the phantom grid with a separation of 2.5 cm. (**b**) Disc alignment in the container that was filled with $CuSo_4$ (1–2 g/L) solution. (**c**) Sagittal T2-weighted FSE image of bi-level CCM alloy disc obtained at 15 KHz BW. (**d**) When a similar image was obtained at 31.2 KHz BW using bi-level CCM alloy disc, the artifact size was comparatively lesser. (**e**) Image obtained with same scan parameters (15 KHz) but this time using Ti64 resulted in smaller size artifacts when compared to CCM (**c**). (**f**) The BW was increased to 31.2 KHz and artifact size was reduced when compared to (**e**)

minimal artifact production. The artifacts, in both cases, seem to skew more in the right direction (distorting the right foramen) as compared to the left in the axial images and downward when compared to upward direction in sagittal images (Fig. 8). However, the distortion caused in any direction was greater with CCM compared to Ti64. In case of dual CCM, the artifacts appeared to encompass over the entire index level, the adjacent level vertebra, and the adjacent disc while using Ti64 implant barely distorted the index level (Fig. 10).

Study II performed on a phantom grid accurately measured the artifact sizes (Fig. 11). The artifact sizes were on an average 58% greater in length and 44% greater in area for the CCM implants as opposed to Ti64 implants. Increasing bandwidth alone (Fig. 12 and Table 5) from 2.02 kHz to 62.5 kHz decreased the artifact size (lengths by 67% and areas by 78% for CCM and 70% and 81% for Ti64, respectively).

However, this increase in BW can degrade the image quality as seen (Table 6) by decrease in S/N (Figs. 13 and 14). Increasing the ETL did not seem to significantly vary the artifact size (Fig. 12 and Table 7).

Recent advancement in biomaterials has allowed the creation of the next-generation cervical total disc replacement with PEEK on ceramic articulated surfaces and plasma-sprayed titanium coating of the endplates to achieve better osteointegration and significantly reduce the artifacts. The 80 micron titanium plasma spray coating on the prosthesis endplates casts a minimal amount of artifact (Fig. 15).

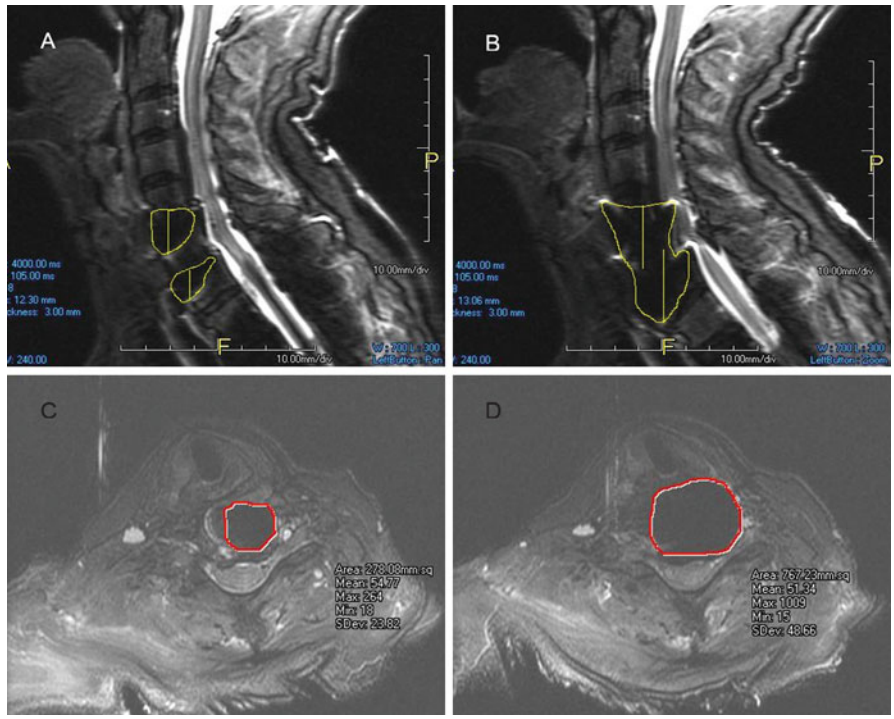

Fig. 10 MRI scans of one of a cervical spine showing image distortion produced by two adjacent (bi-level) artificial discs. (**a**) Sagittal T2 FSE image showing artifacts (length and area) produced by two adjacent levels (C5–C6–C7) Ti64 alloy discs. (**b**) A similar scan for two adjacent levels, CCM alloy discs clearly shows that the artifacts (circled) produced by CCM are greater in size and extending into the adjacent vertebrae. C6 vertebra is completely invisible in case of CCM. (**c**) An axial image with bi-level Ti64 alloy discs. (**d**) A similar scan obtained with bi-level CCM alloy discs clearly shows the artifact produced extends into the adjacent structures by a greater amount when compared to Ti64

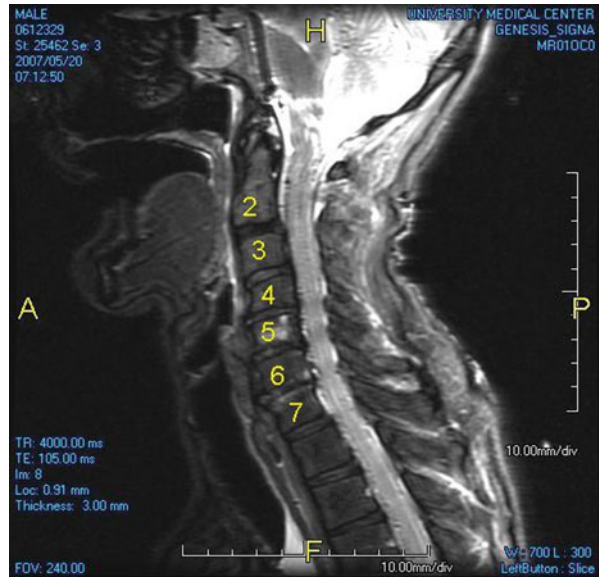

Fig. 11 MRI scan of one of a cervical spine prior to implantation of artificial cervical disc showing no visible metal artifacts at the intervertebral disc spaces of C2–T2

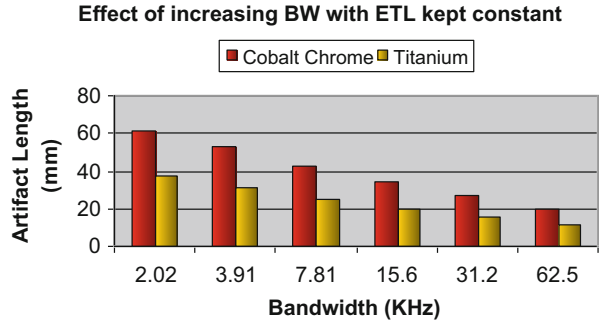

Fig. 12 Increasing bandwidth alone from 2.02 kHz to 62.5 kHz decreased the artifact size, lengths by 67% and areas by 78% for CCM and 70% and 81% for Ti64, respectively

Table 5 Artifact measurements with ETL kept constant. The use of CCM resulted in an average increase in artifact lengths by 58% and areas by 44% compared with Ti64 for identical scanning parameters. Increasing bandwidth alone, from 2.02 to 62.5 KHz, decreased the artifact size (lengths by 67% and areas by 78% for CCM and 70% and 81% for Ti64, respectively)

Artifact measurements with ETL kept constant					
ETL	BW	CC length	CC area	Ti length	Ti area
20	2.02	61.045	1788.495	37.545	888.9
20	3.91	52.7	1466.035	30.73	587.715
20	7.81	42.645	1078.375	24.875	439.49
20	15.6	34.145	703.045	19.78	319.99
20	31.2	27.505	485.72	15.605	221.28
20	62.5	20.185	387.635	11.43	166.705

Table 6 Variation of signal-to-noise ratio with bandwidth. The signal-to-noise (S/N) ratio was measured as the ratio of image signal value at a fixed location within the phantom grid to the standard deviation of the signal outside of the liquid phantom

BW	ETL	S/N	Normalized value
2.02	20	167	3.707977
3.91	20	131.3083	2.915498
15.6	20	76.7	1.703005
31.2	20	62.86	1.395709
62.5	20	45.03803	1

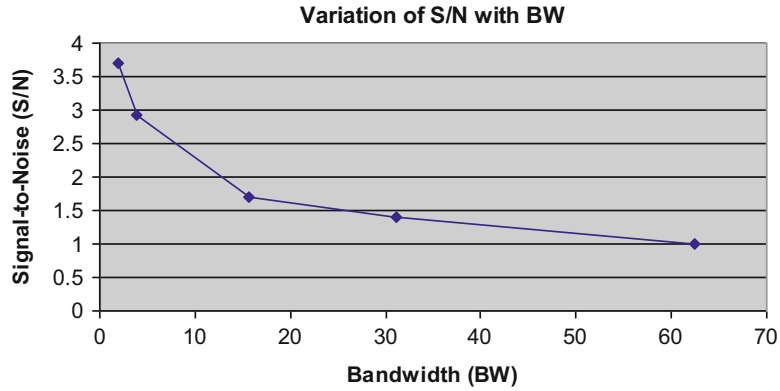

Fig. 13 Increasing bandwidth (BW) degraded the image quality as seen by decrease in signal-to-noise ratio (S/N)

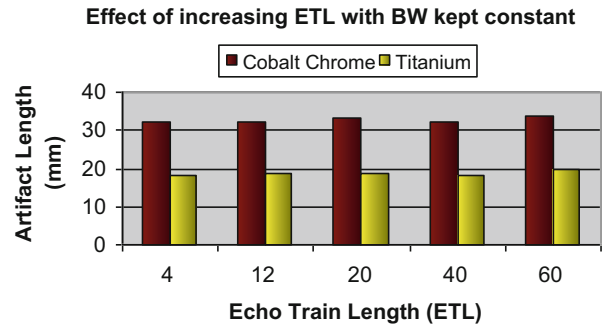

Fig. 14 Increasing the ETL did not seem to significantly vary the artifact size for both Ti64 and CCM

Table 7 Artifact measurements with BW kept constant. Increasing ETL alone did not significantly change the artifact size. Note: All lengths are in mm and areas in sq mm

Artifact measurements with BW kept constant					
BW	ETL	Length		Area	
		CC	Ti	CC	Ti
15.6	4	33.53	19.315	709.485	313.41
15.6	12	34.145	19.93	718.83	321.585
15.6	20	34.145	19.78	703.045	319.99
15.6	40	33.525	19.47	735.4	317.25
15.6	60	32.955	19.61	727.72	293.405

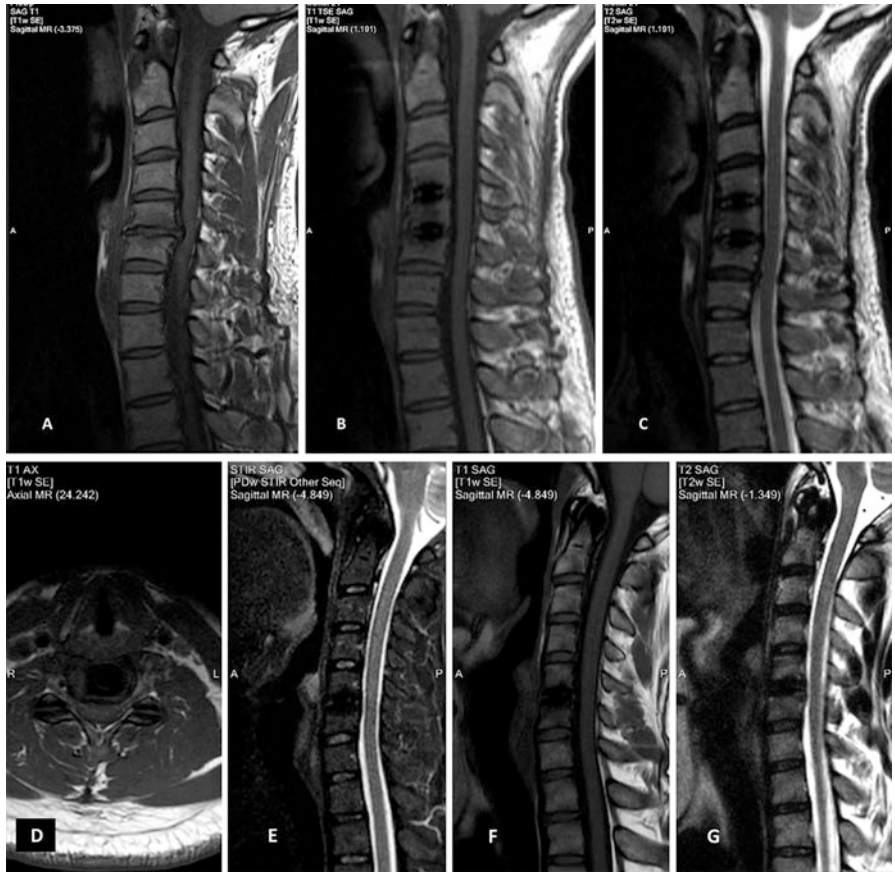

Fig. 15 Post-implantation MRI scans of double levels (**a**, **b**, **c**) or single-level (**d**, **e**, **f**, **g**) PEEK/zirconia-toughened alumina ceramic cervical artificial discs

Discussion

In the first section, we examined imaging artifacts in the lumbar spine. This pedicle screw study evaluated the artifacts produced by four materials Ti64, SS, CCM, and CFRP using 1.5 T and 3 T MRI scans. The ease of interpretation of MR scans with devices in place was evaluated. Approximate artifact measurements were performed in Study I and demonstrated that stainless steel produced in larger artifacts than all other materials yet CFRP produced the least artifacts. Precise quantitative measurements were performed in Study 2.

In the second section, we performed a cervical disc device study to evaluate the artifacts produced by two materials Ti64 and CCM commonly used in cervical arthroplasty and examined the ease of interpretation of MR scans with these TDR devices in place. In addition, we reported the effect of scan parameters on the artifact size.

In this section, we shall synthesize how the characteristics of the materials of implants and devices affect the quality of MR spine examination and how to optimize the images.

Pulse sequences appear to have some effect on the quality of the scans. Spin-echo sequences are less sensitive to field inhomogeneities and are preferred to gradient-echo sequences (Young et al. 1988). The protons located in the zone of field inhomogeneity diphase more rapidly than the others. In the conventional spin-echo sequence, the 180° pulse re-phases the magnetization, causing a

spin-echo signal to appear, and compensates for the de-phasing effect of the inhomogeneities of the main field and of most of the effects of patient-related susceptibility.

Using the gradient-echo techniques, there is no 180° re-focalization pulse. Thus, there is no correction for the de-phasing effect of field inhomogeneities. The loss of signal will increase, even with less intense magnetic fields. We did not measure the artifact on gradient-echo image, as it was very severe.

In one of the studies conducted by A.S. Malik et al., it was found that FSE sequences led to a decrease in perceptible MR artifacts. In this study, fast spin-echo (FSE) protocols typical for clinical imaging were used because FSE imaging, especially when performed with shorter echo spacing, increases the amount of T2-weighted information in the presence of metallic artifact because it decreases magnetic susceptibility effects (Rudisch et al. 1998). FSE pulse sequences seem to be more diagnostically useful than conventional spin-echo images, especially on T2-weighted images. Artifacts are not eliminated, but they are reduced enough to provide useful information. Moreover, these benefits are achieved in a shorter period of time. Spinal imaging with the fat suppression technique can also be degraded by the presence of metallic fixation (Leclet 1994).

The plane of the scan is a significant parameter in achieving clinically useful imaging studies. Theoretically, the artifact is greater along the long axis of the implant. For postoperative spine (instrumented) MRI, the sagittal plane is the best orientation because preference should be given to the slice perpendicular to the axis of the implant (Leclet 1994). For the current study, artifacts measured on the sagittal images were used for quantitative comparison, and those on the axial images were used for comparison of the extent of artifacts on the adjacent neural structures. Joined sagittal slices often make possible an interpretable median slice between the spinal instrumentation devices, which are often posterolateral (Leclet 1994). Acquisitions at the ends of the devices should be avoided. Slice thickness is not a determining factor.

Errors and misinterpretations of MRI images are inevitable (Leclet 1994). Artifacts impede interpretation by deteriorating the quality of the image and its informational content by masking the anatomical and pathological structures (Leclet 1994). Measurement of artifacts especially in human torsos can be difficult because of void spaces contained within it. To overcome this problem and predict the extent of artifacts into the adjacent structures, we modeled the in vitro study by separating the discs by about 1.5 cm, which is approximately the midsagittal height of the C6 vertebra (Fig. 13). Efforts were also made to minimize the error in measurement by firstly carefully selecting the void region and secondly by measuring artifacts in two images that contained the most well-defined artifact and then averaging them (Fig. 16).

Artifacts are signal intensities that have no relation to the spatial distribution of the tissues being imaged. There are four types of artifacts (Leclet 1994) (based on appearance): (a) edge artifacts (ghosting, chemical shifts, and ringing), (b) distortions, (c) aliasing (wraparound) artifacts, and (d) flow artifacts.

Motion artifacts (ghosting and smearing) often result from involuntary movements (e.g., respiration, cardiac motion and blood flow, eye movements, and swallowing) and minor voluntary subject movements. Motion artifacts appear only in the phase-encoding direction and appear as ghosts or smears. Motion artifacts can be flipped 90° by swapping the phase-/frequency-encoding directions. Flow effects can be reduced by using gradient motion rephasing (GMR) or synchronization of acquisition with motion rhythms or increasing the number of acquisitions (NEX) (Rudisch et al. 1998).

Metallic implant artifacts may be reduced by a number of imaging factors including shorter echo times, lower field strengths, higher readout bandwidths (BWs), and smaller voxel sizes. Techniques such as view angle tilt (VAT), orienting the long axis of the metal implants along the frequency-encoding direction, seem to reduce such artifacts (Kolind et al. 2004). Several studies examined the effect of various scanning parameters in order to reduce these resultant artifacts (Kolind et al. 2004; Tartaglino et al. 1994; Olsrud et al. 2004; Czervionke et al. 1988; Ludeke et al. 1985; Laakman et al. 1985; Orlando et al.

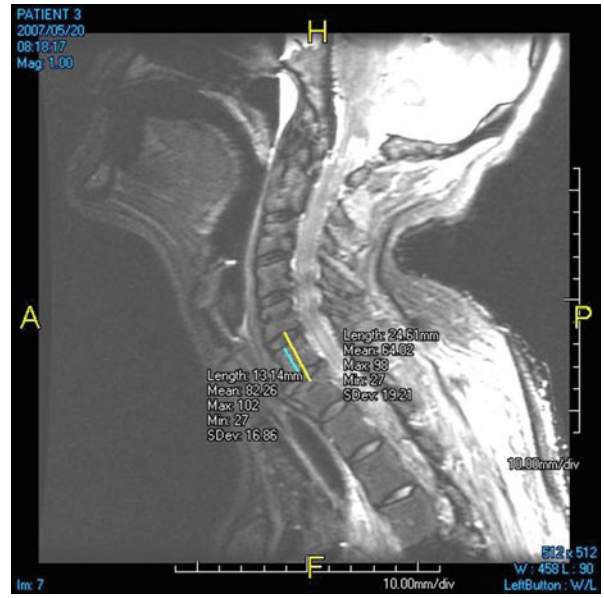

Fig. 16 MR image of one of the cadaveric specimens showing the midsagittal height of C6 vertebra measurement and the distance between the discs. C6 vertebra was about 13.14 mm and distance between the discs was about 24.16 mm

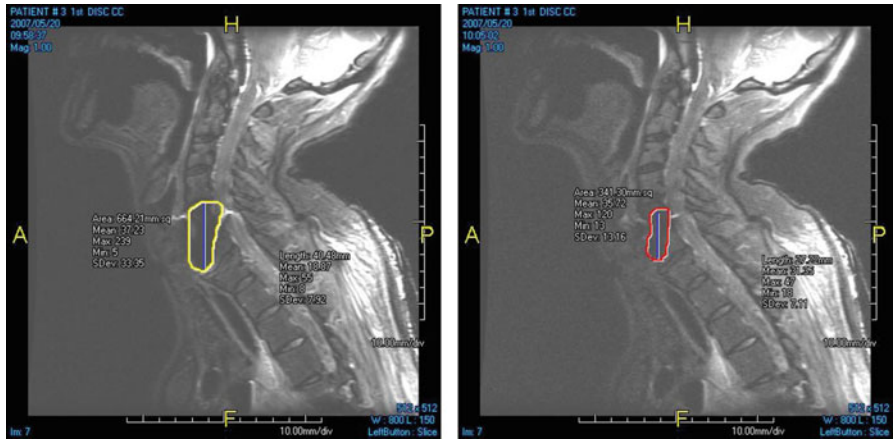

Fig. 17 Comparison of MR images at different bandwidths (BWs). (**a**) T2 FSE image – single level. (**b**) T2 FSE image – single level and higher bandwidth

1996; Farahani et al. 1990; Young et al. 1988; Vinitski et al. 1987, 1993). In one such study conducted by Shannon H. Kolind et al. (2004), it was found that artifact size could be reduced on an average of 60% by increasing BW from ±16 kHz to ±64 kHz. Although the scan parameters used in our study (Study II) were different, we found that increasing bandwidth alone (Fig. 10, 17, and Table 1) from 2.02 kHz to 62.5 kHz decreased the artifact size (lengths by 67% and areas by 78% for CCM and 70% and 81% for Ti64, respectively).

The bandwidth is defined as the sampling rate of the received RF signal at the processional resonant frequency of the hydrogen. The overall bandwidth as presented here can also be expressed as a frequency per pixel length by dividing the bandwidth by the matrix size, which is precisely 256 in these images. The 2.02–62.5 KHz therefore is equivalent to

7.9–244 Hz/pixel. As the sampling bandwidth is increased, the errors in the appropriate magnetic field strength result in a smaller spatial displacement of the signal and a resultant smaller artifact. In a related phenomenon, higher sampling bandwidths are also known to reduce chemical shift artifacts derived from fat. The primary cost with the increased bandwidth is an increase in the image noise.

The ETL, or the number of echoes obtained per excitation pulse, does not appear to have a significant effect on the size of the artifact, although very long ETLs may affect other scan parameter options and the presence of other artifacts.

When using CCM, a BW of 15.6 KHz or 31.2 KHz may be used for ease of readability of spinal MR images. Alternatively, the Ti64 allowed uncompromised imaging of the spine with only minimal artifact production for BWs 15.6 KHz and 31.2 KHz. The decision of selecting 15.6 KHz or 31.2 KHz is left to the discretion of the radiologist.

In a study conducted by Lali H. S. Sekhon et al. (2007), it was shown that titanium devices with or without polyethylene allow for satisfactory monitoring of the adjacent and operated levels. The results in our study were similar. Titanium devices induced more artifacts than CoCr alloys. The reason for this kind of behavior by the titanium materials may be explained as discussed below.

MR imaging localizes signals from hydrogen by varying the magnetic field across the object, causing a change in the resonant frequency dependent on position. The insertion of materials with significantly different magnet susceptibility properties from the surrounding tissues will distort the local magnetic fields, causing the signal to be improperly located. This susceptibility artifact can result in image distortion, as well as significant signal loss. The high ferromagnetic properties of the SS yielded significantly higher artifact than both CCM and Ti64. The magnetic susceptibility or paramagnetic properties of CCM produced higher artifacts than Ti64 but did not approach the level seen with the SS implants. CFRP and titanium which is a non-ferromagnetic metal did not exhibit as high a degree of deflection forces in a static magnetic field as ferromagnetic metals (e.g., certain stainless steel) (Zhao et al. 2009).

Conclusion

Magnetic resonance imaging artifacts are subject to a variety of influences, most notably implant material, implant volume, measurement criteria, and imaging parameters. In the cervical TDR study, of the two materials considered in our study, CCM resulted in significantly larger artifacts than Ti64. In the pedicle screw study, of the four materials considered in our study, stainless steel resulted in significantly larger artifacts than CCM, Ti64, or CFRP. MRI provides adequate visualization of neural structures at the operated and adjacent levels when CCM is used with Ti64 pedicle screws.

Today, titanium fixation implants and devices are recommended as a substitute for stainless steel in a patient who may need further MR examination. MRI provides adequate visualization of neural structures at the operated and adjacent levels when Ti64 is used which implies that the quality of the spinal MR images depends on the type of materials used to construct the implants or devices. Before beginning the MR study, the radiologist must critically review the X-rays showing the location and orientation of the implant. Only then is he able to adapt the MR acquisition technique.

Increasing the sampling bandwidth reduces the artifact at the expense of increased image noise, while changing ETL has relatively little effect on the susceptibility artifact. Since the extent of the artifact is primarily in the frequency-encoding direction, the extent and orientation of the artifact can be altered by swapping the phase and frequency-encoding directions of the data acquisition or by scanning in an alternate anatomical plane.

Of note, these results are true for cervical arthroplasty and may vary for thoracic and lumbar spine instrumented procedures. For example, Ortiz et al. (Orlando et al. 1996) showed that titanium implants of the thoracic and lumbar spine produce extensive artifacts that make interpretation of postoperative MRI studies extremely difficult, if not impossible. In their study, they

found that the MR images of titanium implants are superior than those obtained with stainless steel in some cases but were useless in other cases.

The results of the study show that MRI provides adequate visualization of neural structures at the operated and adjacent levels in devices containing titanium alloys. Neural imaging is required to define the pathologic anatomy when clinical neurologic symptoms are present, and this is typically best performed by MRI. Titanium and ceramic materials are the most MRI-compatible materials in use today and will afford the greatest versatility and visibility in postoperative imaging studies. Operational knowledge about MRI imaging techniques following spine surgery and metallic implant-induced artifacts can improve the quality of MRI postoperative studies now and in the future.

The findings of the study can be used in the selection of implant materials for optimal MRI interpretation of patients with cervical disc devices. The knowledge of artifact size and the amount of distortion caused into the adjacent structures and neural elements helps in the design of the devices that produce minimal artifact. The importance of artifacts depends on the volume and shape of the fixation device and therefore on the total amount of metal. The geometric distortions are more significant close to the extremities of the implant and in any region of sharp contour and shape change. All of these things need to be kept in mind during the design considerations for artificial cervical disc devices.

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Metal Ion Sensitivity

21

William M. Mihalko and Catherine R. Olinger

Contents

Abstract

Metal hypersensitivity to biomaterial alloys have been reported since the 1970s. While most reports have been in the total joint literature, in the last 10 years isolated spinal implant reactions have been reported. Much of this is because spine implants have been developed with bearing surfaces that may be a trigger for sensitizing patient from the local wear debris. Reaction to metal alloys and debris is a type IV hypersensitivity immunologic reaction in that it does not produce anaphylaxis. The adverse local tissue reactions (ALTR) around the implant can be substantial and lead to further surgery. The metal alloys used in spinal implants typically have an oxide passivation

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layer that can protect the body from these local reactions, but any type of fretting from modular connections of wear from a metal bearing can lead to exposure of the alloy below the passivation layer and be the trigger to the start of a reaction leading to ALTR.

Knowing the frequency of these sensitivities in the general population can help surgeons identify hypersensitive patients and notify them of the possible risk.

Keywords

Biomaterial · Metal alloy · Passivation layer · Hypersensitivity

Introduction

Metal hypersensitivity to biomaterial alloys has been reported since the 1970s. While most reports have been in the total joint literature, there also are case reports of spinal implant reactions in the last 10 years. Reaction to metal alloys and debris is a type IV hypersensitivity immunologic reaction that does not produce anaphylaxis. The adverse local tissue reactions (ALTR) around the implant can be substantial and lead to further surgery or significant morbidity. Knowing how common these sensitivities are in the general population, understanding the physiology of metal hypersensitivity, identifying appropriate testing protocols, and recognizing clinical signs of sensitivity can help surgeons properly diagnose this uncommon complication and notify patients of the possible risk of ALTR.

Metal Hypersensitivity Physiology

The pathophysiology behind metal hypersensitivity is a type IV hypersensitivity or delayed type hypersensitivity reaction. When a hypersensitivity reaction occurs, activated T-lymphocytes react to a foreign antigen presented via co-stimulatory molecules, which play a critical role in sustaining the chronic inflammatory response (Goodman 2007). Through this inflammatory cascade, T-lymphocytes CD4 and CD8 cells are activated and release a multitude of cytokines including IFN-gamma, IL-1, IL-6, and TNF-alpha (Merritt and Brown 1980).

The immune system can mount an adaptive or innate immune response to metal debris. The innate or nonspecific foreign body reaction is composed primarily of macrophages, foreign body giant cells, fibroblasts, and occasional lymphocytes. The aggressive inflammatory granulomatosis found in the monocyte-macrophage mediated clearance of debris is normally followed by the resolution of the reaction via the fibroblast mediated synthesis of remodeling the extracellular matrix. Metal implants may have osteoclasts that line the bone implant interface and in the presence of metallic or bearing debris the tissue may have high levels of proinflammatory cytokines, indicating an immune response that can put the longevity of the implant at risk (Goodman 2007). Animal models of exposed rabbits with implanted nickel demonstrated tissue reaction to screws with inflammatory cells and macrophages in induced sensitivity models (Merritt and Brown 1980). A combination of both innate and acquired immune response has been elucidated in the metal hypersensitivity reaction pathway.

In the case of metal hypersensitivity, the foreign antigen is metal debris from an implanted medical device. Metal wear degradation products combined with serum proteins form haptens. Haptens are then recognized via antigen presenting T-cells and initiate the activated T cell cascade. This activation of T-cells locally produces an inflammatory response and lessens circulating T cells. One study demonstrated that the serum analysis of patients with aseptic loosening showed decreased levels of circulating T-cells indicating an inflammatory consumptive process (Goodman 2007).

Proposed intracellular indigestible particles, via metal implant debris, together with elevated costimulatory molecule expression via antigen presenting cells and macrophages, promote T-cell inflammatory reactions in the surrounding tissues. Cobalt-chromium (Co-Cr) alloys are common metal compounds used in spinal implants. In

vitro proliferation of cellular responses to Co-Cr has been found to be significantly higher in patients with revision surgery for aseptic loosening compared to patients with revision for infection. Furthermore, patients demonstrated higher proliferative responses and cytokine production in response to Co-Cr challenge postoperatively after total joint replacement (TJR) than preoperatively (Goodman 2007).

Tissue samples from retrieved failed implants that formed pseudocapsules around metal implants have been analyzed for inflammatory cells. One study examined 123 tissue samples excised from reoperations for loosening, fracture, or mechanical irritation (infections were excluded). The removed pseudocapsule represented a crude joint capsule of scar tissue without defined layers. The inflammatory response to foreign bodies inside the fibrous tissue was characterized pathologically as granulation tissue. This inflammatory tissue was surmised to be from production of continual foreign material from wear particles. Patients with retrieved tissue from loosening had a marked tendency towards fibrosis, which gave rise to numerous lymphoplasmacellular infiltrations surrounding the implants (Willert and Semlitsch 1977). Metal hypersensitivity-induced osteolysis and aseptic loosening have been suggested to represent an underappreciated and ignored subset of failure mechanisms within TJR (Jacobs and Hallab 2006).

Knowing the mechanism behind these reactions in aseptic lymphocytic vasculitis-associated lesion (ALVAL) from metal-on-metal hip prosthesis is important since similar bearings are now being used in spinal implants. Patients deemed to have either a high- or low-wear pattern were identified and during retrieval had tissue analysis regarding the ALVAL score as determined by the histologic scoring of the synovial lining, inflammatory infiltrate, and tissue organization (low, 0–4; moderate, 5–8; high, 9–10). Tissues from patients who had revisions for suspected high wear had a lower ALVAL score, fewer lymphocytes, more macrophages, and more metal particles than tissues from patients who had revisions for pain and suspected metal hypersensitivity (Campbell et al. 2010). The characterization of the type of local tissue response and the patient's presenting symptoms of pain and dermatitis could help differentiate between metal type IV hypersensitivity reaction and metal-on-metal ion release from failed components (Verma et al. 2006).

Total joint literature has demonstrated periprosthetic pseudocapsule tissues harvested from failed TJR implants containing titanium and Co-Cr alloy to have pathologic demonstration of abundant macrophages containing titanium particles, numerous T-cells, but few B-cells. This pathologic evaluation was further used with tissue marker enzyme-linked immunosorbent assay (ELISA) studies in these samples for T-cell markers Cd11c, CD25, IL-2R, HLA-DR, CD35, CD36, CD2, and CD22. IL-2 was used as the main cell marker for activated T-cells in this population (Goodman 2007). The type IV hypersensitivity response surrounding failed arthroplasties has been supported by the presence of activated T-cells in vivo, and both pathologic and ELISA testing confirms their presence in these tissues.

Osteolysis mechanisms surrounding failed aseptic TJR have been investigated on the cellular levels. Receptor activator of nuclear factor-kappa B (RANK) production, determined by ELISA testing of harvested pseudocapsule tissue in failed implants, has been shown to be increased, as have abnormally high levels of RANK. The RANK-RANKL mediation has been shown to contribute substantially to aseptic implant loosening. Activation of this pathway via the type IV hypersensitivity response has been elucidated. Activated T-cells have been shown to express RANKL activating osteoclastogenesis. TNF-a and IL-1 are pro-inflammatory cytokines present in type IV hypersensitivity reactions that also upregulate the expression of RANK/RANKL (Holt et al. 2007).

Other cytokines have been demonstrated to contribute to bone homeostasis surrounding metal implants. IL-18 is a novel cytokine involved in the role of disturbance in bone homeostasis observed in numerous systemic disorders, specifically inflammatory arthritis. It initially was characterized in properties of acquired immune

response via activated T1 and T2 helper cells. After inflammatory responses are initiated, IL-18 is widely distributed, even in pseudocapsules from retrieved failed implants, as identified by PCR/ELISA testing (Goodwin et al. 2018).

The method of reaction to metal hypersensitivity in vivo may be a combination of several factors. Local inflammatory responses to the presence of metal alloys are recognized by the innate immune response, leading to T-cell activation, inflammatory cytokine production, osteolysis, and loosening via RANKL/RANK activation. Loosening of the implant-bone surface can lead to further wear debris and propagation of this cascade.

Implant Sources of Particulate Debris

Mechanisms that produce increased metal hypersensitivity require a nidus for metal debris. Metal implant wear can produce local tissue infiltration of metal ions and particles. Wear involves the loss of the material (mass) as a consequence of relative motion between two surfaces. Gravimetric wear is measured by the weight loss of the individual component after simulator or retrieval in vivo use. The amount of wear depends on two factors: the amount of force pressing the two materials together and the type or amount of lubrication between the two surfaces (Hallab 2009).

Wear is a mechanical or physical degradation of materials characterized as either abrasive or adhesive. The primary sources of articulating wear debris from hard-on-hard material couples, such as metal-on-metal articulations, generally produce less wear (volumetric loss) than metal-on-polymers. Corrosion is a chemical or electrochemical form of degradation of metal implants. Implant corrosion reduces structural integrity and causes release of by-products that interact locally and systemically. Stainless steel alloys generally corrode to a greater extent than cobalt or titanium. Fretting corrosion can take place at mechanical connections between implants. This is a common occurrence in spinal reconstructive surgery. With this kind of fretting in spinal instrumentation, chemical degradation is enhanced by mechanical factors such as a crevice and abrasive wear. Corrosion products typically are oxides, metal phosphates, metal salts, metal-ions bound to proteins, or organometallic complexes (Hallab 2009).

Implant debris types can be characterized as particles or ions. Particulate wear debris (metal or ceramic) exists from the submicron size up to thousands of microns in size. Soluble debris is limited to metal ions that are bound to plasma proteins. The most numerous particulate debris to measure is typically less than 1 μ in size. Particles generated in simulator studies of articulating spinal implants match the sizes and types of particles produced from hip and knee arthroplasty. Metal-on-metal articulations generally produce smaller-sized (submicron) fairly round debris, whereas traditional metal-on-polymer bearings produce larger (micron) debris that is more elongated in shape (Hallab 2009). Polymeric particles produced from implants generally fall into the range 0.23–1 μ. During articulating implant studies, 70– 90% of recovered particulates were submicron, with the mean size being 0.2–1 μ. Newer polymer implant debris from highly cross-linked polymers have demonstrated the production of smaller, more rounded debris in the submicron range as small as 0.1 μ (Hallab 2009).

Metal-on-metal particles are one to three orders of magnitude in number over those produced by metal-on-polymer articulating surfaces, but with far less volume. Cobalt alloy corrosion mechanisms also produce a chromium phosphate hydrate-rich material termed "orthophosphate," which ranges in size from submicron to aggregates of particles up to 500 μ. Low-angle laser light scattering (LALLS) can perform particulate characterization and increase the number of counted and sized particles from hundreds to millions. It is important to perform a number-based and volume-based analysis. Ability to accurately and comprehensively characterize implant debris is important where weight loss from the implant after a year of use (<0.2 mm^3 volume loss) could be attributed to the loss of a relatively few large particles or hundreds of millions of small particles (Hallab 2009).

For soluble metal ions, metal levels measured in people with disc arthroplasties have

comparable levels of circulating metal ions as people with TJR. Normal human serum levels of prominent implants metals are approximately

(a) 1–10 mg/mL AL
(b) 0.15 ng/mL Cr
(c) <0.01 ng/mLV
(d) 0.1–0.2 ng/Ml Co
(e) <4.1 ng/mL Ti

Recent studies of metal-on-metal total disc arthroplasty found serum levels of Co-Cr to concentrations of 3–4 ng/mL Co, 1–2 ng/mL for Cr (Guyer et al. 2011; Hallab et al. 2003; Seo et al. 2016). The concentrations of circulating Co-Cr metal in serum with total disc arthroplasty are similar to levels measured in well-functioning metal-on-metal THA. This has not been demonstrated in nonarticulating implants, where recent studies have failed to detect elevated amounts of Cr or Ni from stainless steel scoliosis rod fixation (Hallab 2009).

In vitro assessment of ion levels from spinal implants with 20% volumetric wear in comparison between serum and saline testing found 1000-fold more particles in saline testing, demonstrating a protective effect of serum proteins and demonstrating a worst case scenario in saline testing (Hallab et al. 2008).

Implant Debris Physical Attributes and Local Physiological Response

Particle-sizing techniques such as scanning electron microscopy (SEM) or transmission electron microscopy can determine the size of the wear particles ranging from nanometer to submicron range. New low-angle laser light scattering (LALLS) techniques sample millions to billions of particles that determine the significant portion of the total mass loss (the total amount of debris). A volume-based analysis that also can characterize implant debris with a number bases is very important, where different samples of particles look demonstrably very different when viewed as a volume-based distribution compared to number-based distribution. Collected metal particles are characterized for size and number by laser diffraction technology and have a mean diameter of less than 10 μ, usually approximately 1–2 μ with a size range of 1–10 [(Garcia et al. 2020)].

General particle characteristics on which local inflammation has been shown to depend are particle load (particle size and volume), aspect ratio, and chemical reactivity. (Bio Reactivity index: particle load x aspect ratio x material type x K unknown). Greater particle load can increase inflammation and is directly correlated to the concentration of phagocytosable particles per tissue volume. The degree to which equal numbers (dose) of large versus small particles (10 μ vs. 1 μ) induce an inflammatory response on a per-particle basis in vivo has not been thoroughly investigated. However, some studies have shown that in equal amounts of debris mass, small particles (0.4 μ) produced a greater inflammatory response than larger (7.5 μ) particles (Hallab 2009).

Elongated fibers are more pro-inflammatory than round particles. Currently, fibers can be categorized as particles with an aspect ratio greater than 3 to be more inflammatory. More chemically reactive particles are more pro-inflammatory. Despite reported differences, there is a growing consensus that metallic particles that are capable of corroding and releasing ions are associated with hypersensitivity responses, cytotoxicity, and DNA damage. Thus, they are more capable of eliciting proinflammatory responses than relatively inert polymers and ceramics (Hallab 2009).

To produce an in vitro inflammatory response, particles need to be less than 10 μ that are within phagocytosable range. Particle mean sizes of 0.2–10 μ are generally the most proinflammatory. The relationship between bacteria and aseptic loosening has been inferred because antibiotic-eluting bone cement and systemically administered antibiotics reportedly reduce the frequency of aseptic loosening (Hallab 2009).

Implant debris from wear causes local inflammation and granulomatous invasion of bone-implant contact that, over time, results in implant loosening and pain, necessitating revision in total joint arthroplasty. Implant debris is known to

cause inflammation, osteolysis, and, in some cases, hypersensitivity and concerns persist about implant debris becoming carcinogenic or toxic. Other systemic conditions from implant debris, such as renal failure, have been reported in patients with Co, Cr levels over 100-fold in comparison with individuals with stable prostheses with no aseptic loosening.

Metal debris becomes antigens for T-cell recognition. Once debris is ingested by macrophages and other peri-implant cells, host pro-inflammatory reactions occur, such as activation of metal reactive T-cells. Cobalt-chromium-molybdenum (CoCrMo) alloy debris form metal protein complexes that activate the macrophage inflammasome pathway. CoCrMo alloy debris has been shown to induce macrophage activation, which stimulates secretion of IL-1b TNFa, IL-6, IL-8, and upregulates NFKb and downstream inflammatory cytokines (Mitchelson et al. 2015). Titanium particles induced IL-8, monocyte chemoattractant protein-1 (MCP-1). The study demonstrated that osteoblast chemokine expression with increased NFKB inducing osteoblast activated periprosthetic osteolysis (Fritz et al. 2006).

Biologic reactivity to spinal implant debris has been clinically observed with all the hallmarks of traditional particle-induced osteolysis; granulomatous epithelioid membranes coating the metal implants have been reported, similar to the fibrous membranes associated with loose total hip replacements. Case reports of painful granuloma associated with spinal implant debris demonstrate that spinal implant debris-induced inflammation can result in bone destroying granuloma (Hallab 2009). There are relatively few reports of human retrieval studies of loose spinal implants, but granulomatous epithelioid membranes coating the metal implants, similar to the fibrous membranes associated with loose total hip replacements, have been identified. Metallosis often accompanies metal implant debris-related osteolysis, aseptic fibrosis, local necrosis, or loosening (Hallab 2009).

In a cohort of 12 loosened spinal implants, metallosis of the internal membrane was associated with the outer layer of membrane containing an infiltrate of leukocytes and macrophages and all 12 patients had radiolucency around part of the spinal instrumentation. During the study, 11 of 12 patients demonstrated elevated TNFa levels and an increased osteoclastic response in the vicinity of wear debris caused by dry frictional wear particles of titanium or stainless steel. The focal areas of osteolysis involved loose transverse connectors. Removal of the loose metal implants and tissue surrounding them in the fibro-inflammatory zones resulted in resolution of clinical symptoms in all 12 patients (Hallab 2009).

Particles activate macrophages that secrete TNFa, IL-1b, IL-6, IFNgamma, and PGE2, stimulating differentiation of osteoclast precursors into mature osteoclasts and increasing periprosthetic bone resorption. Wear debris particles also have been shown to compromise mesenchymal stem cell differentiation into functional osteoblasts, and particles can directly inhibit collagen synthesis by mature osteoblasts and induce apoptosis of osteoblasts (Hallab 2009). Protein chip assays of ELISA performed on resected inflammatory tissue surrounding failed arthroplasty demonstrates local increase in IL-6, IL-8 cytokines, driving local osteoclastogenesis and osteolysis (Shanbhag et al. 2007).

The release of IL-1b is a powerful inflammatory cytokine response. Co-Cr-Mo alloy particles were found to activate the inflammatory pathway in part through NADPH-mediated monocyte macrophage production of reactive oxygen species. Activation of the inflammatory pathway leads to cleavage of intracellular pro-IL-1b and pro-IL-18 into their mature forms and ultimately leads to their secretion of pro-inflammatory responses through autocrine and paracrine activation of NFKb, which initiates a powerful pro-inflammatory response. The identification of the inflammatory involvement in particle and metal ion-induced inflammation will likely provide new therapeutic strategies to pharmacologically treat implant debris-induced inflammation and hypersensitivity by specifically interrupting the initiation of the inflammatory response that leads to aseptic osteolysis (Hallab 2009).

Systemic Response to Metal Debris and Prevalence in the General Population

Debris-induced systemic effects with implant metals such as Co, Cr, V, and possibly Ni are rare and typically occur with extremely high serum levels of Co. Distant organ levels of cobalt have been found at necropsy with both total hip and knee implants (Arnholt et al. 2020; Urban et al. 2000, 2004). Isolated cases of cardiomyopathy, optic neuritis, and neuropathies from a failing implant have been reported after metal-on metal total hip replacements (Choi et al. 2019; Devendra and Kumar 2017; Garcia et al. 2020; Goodwin et al. 2018; Mikhael et al. 2009; Mosier et al. 2016; Runner et al. 2017; Sabah et al. 2018; Sanz Pérez et al. 2019). A review of the literature, however, does not produce reports of such high levels or systemic symptoms from spinal implants. Neuropathic effects have been reported around both well-functioning and failing articulating implants, but these were generated from a granulomatous response to implant debris and not directly from the implant debris. Inflammation of unknown etiology associated with spinal implants has been shown to resolve after implant removal (Hallab 2009; Zielinski et al. 2014).

Metal hypersensitivity is well documented in case reports and group studies, though overall it remains a relatively unpredictable and poorly understood phenomenon in the context of orthopedic spinal implants. The specific T-cell subpopulations, the cellular mechanism of recognition and activation, and the antigenic metal-protein determinants created by these metals remain incompletely characterized. Nickel is the most common metal sensitizer in humans, followed by Co and Cr. The prevalence of metal sensitivity among the general population is approximately 10–15%, with nickel sensitivity as the highest. Clinical studies of metal implant-related sensitivity link immunogenic reactions with adverse performance of metallic cardiovascular, orthopedic, plastic surgical, and dental implants (Merritt and Brown 1980). Dermatitis, urticaria, and itching, round red wheals, and/or vasculitis have been linked with the relatively more general phenomena of metallosis, excessive periprosthetic fibrosis, and muscular necrosis. Hypersensitivity reactions associated with stainless steel and cobalt alloy implants are more severe than those associated with titanium alloy components (Hallab 2009).

Specific types of implants with a greater propensity to release metal in vivo may be more prone to induce metal sensitivity, as has been shown in metal-on-metal total joint arthroplasty. Spinal implants have been rarely implicated in case reports or group studies of hypersensitivity; thus, metal lymphocyte transformation testing (LTT) prior to receiving an implant may be warranted for people with a history of metal allergy (Hallab 2009).

Toxicity investigations of implant-related metal toxicity include a variety of cell types, including fibroblasts endothelial cells and non-human osteoblast like cells, but these generally have been limited to in vitro studies and animal studies. Concentrations at which this will occur are not known and the degree to which soluble metals are able to contribute induced toxic effects will likely be difficult to distinguish from well-established pro-inflammatory effects of metal particles (Hallab 2009).

While reports of titanium hypersensitivity are absent in the total joint literature, there is a case report of one patient with titanium metal hypersensitivity following VEPTR rod insertion for congenital scoliosis confirmed with testing; symptoms improved with removal of the rod (Zielinski et al. 2014). Testing of a carbon coated VEPTR rod was undertaken with rod desensitization under the skin in the forearm for a 3-month trial. The patient tolerated the carbon rod and the metal rod was replaced with a VEPTR carbon-coated implant. No documented hypersensitivity was found following reimplantation with the carbon-coated implants (Zielinski et al. 2014).

Testing for Metal Hypersensitivity

In 2012 the dermatology literature published a report stating that all patients should be patch tested for skin sensitivity before any elective

surgery using a metal orthopedic device. A rebuttal of this practice was published soon after, pointing out multiple issues with patch testing as a gold standard for diagnosing metal hypersensitivity. The skin reactions are driven by a dendritic cell called the Langerhans cell. These cells are not what drive the deep tissue reactions that are seen around implants. There have been reports in knee replacement patients showing no correlation to skin patch results and outcomes of patients who test positive for the metal in the alloy of the implant (Bravo et al. 2016). There also are multiple reports of patients changing their skin patch test results from negative to positive after undergoing a total hip or knee replacement. The incidence of sensitization to metals in orthopedic implants by patch testing increased by 6.5% following hip and knee arthroplasty (Mihalko et al. 2012). Sensitivity to Ni, Co, Cr was 25% in well-functioning implants; this is more than twice the rate in the normal population. In patients with a failed or failing hip prosthesis, the rate of metal sensitivity rises dramatically to 60% or six times that of the general population (Hallab et al. 2001). Nickel is the metal that most often leads to hypersensitivity reaction and studies place the prevalence of nickel sensitivity in the general population between 8% and 25% (Mitchelson et al. 2015).

While a skin patch test may be helpful in the identification of a patient with a metal hypersensitivity, there remains no proof that routine screening will make a difference and may complicate treatment plans for many patients who otherwise will have no reaction to their implants after surgery. There are other options for identifying patients who may be at risk. Testing for hypersensitivity with lymphocyte transformation testing (LTT) in vitro involves measuring the proliferative response of lymphocytes obtained from peripheral blood by routine blood draw (Hallab 2009). Testing for metal sensitivity with metal-LTT testing generally is preferable since there is no subjectivity to the results as in skin patch testing. LTT testing is better suited for the testing of implant-related sensitivity because there is no risk of inducing metal sensitization using skin exposure, thus metal-LTT is highly quantitative (Hallab 2009).

Cutaneous patch testing is considered by some to be the gold standard for in vivo evaluation of delayed hypersensitivity reactions. It can be argued to be invalid because of the differences in antigen presentation between superficial and deep tissue responses in delayed type hypersensitivity reactions (Mitchelson et al. 2015). Some physicians also suggest that it can be subjective as far as grading dermal reactions from 1 to 3 (Merritt and Brown 1980).

One study has demonstrated that despite six positive skin tests before implantation of metal-on-metal (MOM) hip, five patients subsequently lost their sensitivity with repeat skin testing. All patients had good clinical outcomes with no evidence of loosening (Jacobs and Hallab 2006). Another disadvantage of patch testing is that the process of in vivo patch testing could potentially induce sensitization in a previously nonsensitized patient (Mitchelson et al. 2015). Patients' patch test results will shift from negative to positive after joint replacement surgery, suggesting that in vivo metal exposure can cause sensitization (Merritt and Brown 1980).

Postoperative patch testing has been advocated in patients presenting with suspected metal hypersensitivity implant failure in the absence of infection (Mitchelson et al. 2015). The rate of positive patch test results to metals is highest in patients with MOM implants and in those with failed prosthesis (Ooij et al. 2007). Regular preoperative skin testing is not supported; in patients with 21 positive patch results, hypoallergenic TKA components produced no hypersensitivity reactions (Mitchelson et al. 2015). A correlation has been established between patients who had poor outcomes after TKA and positive skin patch testing that indicated metal sensitivity (Maldonado-Naranjo et al. 2015). Routine screening for metal hypersensitivity prior to TKA is not supported by the literature.

Lymphocyte transformation testing (LTT) involves measuring the proliferative response of lymphocytes, following activation, by using a radioactive marker added to patients spun down lymphocytes along with the desired agent (the

metal ions) measured in counts per minute of stimulation (Hallab et al. 2001). LTT can be used as an alternative method to determine metal sensitivity by in vitro testing of sensitivity via venipuncture. It has been found to be more sensitive than patch testing and is highly quantifiable and reproducible. LTT does NOT confer sensitization to the patient as does patch testing, and LTT prior to arthroplasty may be effective as a preoperative screening tool for metal hypersensitivity.

In vitro leukocyte migration testing can be performed by capillary tube testing with leukocyte migration in response to antigen, membrane migration, leukocyte migration agarose technique, and collagen gel electrophoresis (Hallab et al. 2001).

Implantable metal testing for sensitivity has not established guidelines regarding the depth or duration of subcutaneous metal implantation as screening tests for hypersensitivity (Mitchelson et al. 2015). The timing of implantable metal testing is not supported in all TKA/THA patients and has only been found to be indicated in patients with a history of a metal allergy or previous aseptic orthopedic implant failure. Postoperative testing should be limited in patients with allergic contact dermatitis, arthralgia, and radiolucencies surrounding the implant or aseptic loosening without infection (Mitchelson et al. 2015).

Routine use of radiographs is supported for identification of periprosthetic radiolucent lines or aseptic loosening after TKA/THA (Mitchelson et al. 2015). Loosening or fracture of spinal implants has not been routinely documented in metal hypersensitivity reactions in the literature.

Risk Factors for Metal Hypersensitvity

One study of 28 TKA patients determined that those with hypersensitivity were more likely to be female; seven patients had a history of metal hypersensitivity before arthroplasty (Mihalko et al. 2012). Twenty-two patients had self-reported allergies, and skin patch testing was positive in 19 patients. Dermatologic symptoms resolved in patients who had revision with hypoallergenic implants with no further instability. A similar study found positive skin patch results in 68% of patients with reported metal allergy (Mitchelson et al. 2015). Another study found that 32% of patients who had TJR with no known prior history of metal allergies developed a positive leukocyte migration inhibition test of Ti, Co, Cr, or Ni 3 months to 1 year following surgery (Goodman 2007). Implant failure was reported to be up to 4 times greater in patients with a self-reported history of preoperative metal allergy compared with patients who did not have an allergy (Mitchelson et al. 2015).

Age, gender, and occupation are all risk factors for developing nickel hypersensitivity. Exposure to costume jewelry may account for the higher rates in women. Nickel sensitization has been reported to be present in 17–32% of women and 3– 10% in men. Cr is more common sensitization in men at 10% compared to 7% in women. Cr is associated with concrete exposure in the construction industry, leatherworking, and occupations involving cleaning. Co sensitization is common in hairdressers and textile industry workers. Nickel sensitization is associated with healthcare, agriculture, mechanics, and metal work.

One study demonstrated acquired hypersensitivity following Ti spinal implants and tattoos. Skin biopsy of reaction and surrounding tissues of TI spinal implants demonstrated high levels of Ni and Cr, Ti, skin testing was negative for Ni and Cr (de Cuyper et al. 2017).

The North American Skin Patch testing group reported 21% sensitivity to Ni 21% and 8% to Co and Cr in 5,000 patients (Merritt and Brown 1980). As more patients are repeatedly exposed to metal variants commonly used in orthopedic implants, the possibility of increased sensitivity reactions to these metals may rise.

Clinical Presentation of Metal Hypersensitivity

Metal hypersensitivity may result in localized or systemic allergic dermatitis, loss of joint function, implant failure, and pain. Pruritic erythematous,

eczematous, edematous, and sometimes exudative lesions may present over implant sites (Mitchelson et al. 2015). Symptoms ascribed to metal hypersensitivity include pain, swelling, cutaneous rash, patient dissatisfaction, and loss of function (Merritt and Brown 1980). The degree to which the known condition of metal hypersensitivity induced failure is not well known. No clear association between the prevalence of metal sensitivity and duration of implant in situ has been identified, and no clear objective lines have been found between pain-related failure in metal sensitive and nonsensitive patients undergoing revision (Hallab et al. 2001). This may represent an extreme complication or may be a more subtle contribution to implant failure overall (Hallab et al. 2001).

Metal hypersensitivity-induced allergic dermatitis, pain, and implant failure have clinically relevant laboratory markers associated with the conditions (Mihalko et al. 2012). Elevated levels of IL-6, INFa, and IL-17 are common identifiable markers in implant failure. Increased Ni and Ti have been demonstrated to increase expression of RANKL, macrophage colony stimulating factor, TNFa, and CCR4 receptors. Clinicians should have a high level of suspicion when patients present with arthralgia, periprosthetic radiolucent lines, or aseptic implant loosening. Ordering appropriate inflammatory laboratory markers during a workup for suspected metal hypersenstivity is necessary to determine the extent of the response (Mitchelson et al. 2015).

Metal Sensitivity to Spinal Implants

Spinal Implant Composition

Spinal implant composition is dependent on the implant function and location. Multiple implants ranging from pedicle screw instrumentation, metal on polyethylene disc replacements, and PEEK fusion grafts are implanted in patients undergoing spinal surgery for various reasons. Reports of metal sensitivity in patients with spinal implants are primarily single case reports or very small series (2–4 patients).

Disc Replacements

Disc replacements are metal and polyethylene combination implants used to replace symptomatic disc pathology while preserving the motion segment. In one study of 4 patients who had failed lumbar disc replacements, retrieval showed evidence of wear of the polyethylene cores, but the extent and severity varied among the four patients. Wear and fracture of the core were associated with osteolysis of the underlying sacrum. Histologic examination confirmed the presence of wear debris in inflammatory fibrous tissue. Evidence of failure prior to retrieval included subsidence, migration, undersizing, and reactionary adjacent fusion on radiographic analysis. The mechanism of wear was determined by adhesive wear of the central domed region of the polyethylene core and chronic rim impingement resulting in rim fatigue and fracture (Ooij et al. 2007).

In another report of four patients with TDR who had an uncomplicated initial postoperative course followed by worsening pain months after surgery, retrieval found an avascular soft-tissue mass was found to be causing an epidural mass effect scar and causing symptoms to re-emerge. Laboratory analysis of the tissue found lymphocytic reaction tissue, dominated by a large number of lymphocytes and small number of macrophages (Guyer et al. 2011).

Total Disc Replacement (TDR) Materials

The TDR can be composed of stainless steel alloys which confer greater ductility; Co-Cr alloys which confer increased corrosion resistance, hardest, strongest, and most fatigue resistance; or titanium alloys which good flexural rigidity and toughness and high corrosion resistance compared to stainless steel and Co-Cr (Hallab et al. 2003).

Polyetheretherketone (PEEK)

PEEK cages have a high biocompatibility profile and are radiolucent. One case report regarding chronic allergic response to interbody PEEK material reported diffuse erythema and itching, tongue swelling, and erythema in the throat following PEEK implantation. No significant

inflammatory tissue or response was found in the retrieval (Maldonado-Naranjo et al. 2015).

Device for Intervertebral Assisted Motion (DIAM)

DIAM is a silicone disc enveloped in a polyethylene terephthalate fiber sack. One case report described granulation tissue 5 years after DIAM. Histology demonstrated wear debris and chronic inflammation with a hypersensitivity reaction and subsequent bone osteolysis surrounding the implant (Seo et al. 2016).

Metal-on-Metal Facet Replacements

Two patients with MOM facet replacements were reported to develop local tissue reactions with pseudotumor formation, characteristic soft yogurt-like chalky white scars surrounding the implants (Goodwin et al. 2018).

Carbon-Coated Implants

Metal hypersensitivity was described in one patient after VEPTR titanium rod insertion for congenital scoliosis. No hypersensitivity was documented after reimplantation with carbon-coated implants (Zielinski et al. 2014).

Zirconium Rods

Plasma sprayed zirconium interface rods cannot be contoured, and significant implant brittleness precludes their use in deformity correction, limiting the use of zirconium for spinal implants (Zielinski et al. 2014).

ACDF Implants

Reported allergic reaction to PEEK implant and Ti ACDF plate and screws include system rash, congestion, dysphasia, and urticaria. Symptoms resolved once implants were removed, with no visible osteolysis (Urban et al. 2000).

Treatment

Treatment of metal hypersensitivity can range from symptomatic treatment to revision surgery. Reactions around the spine obviously play a different role than those in total joint replacement where symptomatic treatment of the dermatologic symptoms may resolve completely with a use of topical corticosteroid (Mitchelson et al. 2015). In the spine these reactions caused by proximity of vital neurologic structures need a more heightened awareness and investigation of possible deep tissue reactions. Metal artifact reduction sequence (MARS) MRI can help determine if a reaction is occurring and can help grade the reaction if any (Connelly et al. 2018). This can aid in the choice of an approach for treatment, which can be difficult depending on the purpose of the implant in place.

New technologies involving immune modulation have emerged, but are still investigative. The use of Nac, an antioxidant inhibitor of NFkB, can potentially be used to augment the inflammatory response via glutathione (GSH), which inhibits serine phosphorylation of iKB, thereby preventing the dissociation of NFkB induced cellular response to particulate debris. Reduction in the stimulation of NFkB leads to decreased osteolysis surrounding an implant (Willert and Semlitsch 1977).

Further use of disease modifying antirheumatic drugs (DMARDs) has expanded the pharmacologic treatment of metal hypersensitivity reactions. Numerous in vivo and in vitro animal model studies suggest that bisphosphonates may be a potential benefit for treatment of particle-induced osteolysis. Antitumor necrosis factor alpha (TNFa) therapy with etanercept has been reported to inhibit osteoclastic bone resorption; however, in an underpowered study it was found to produce no change in volumetric wear osteolysis compared to a placebo (Holt et al. 2007).

Conclusion

Over the last 10 years, metal hypersensitivity has been documented in patients with spinal implants with bearing surfaces that may be a trigger for sensitizing patients due to the local wear debris. Reaction to metal alloys and debris is a type IV hypersensitivity immunologic reaction that does not produce anaphylaxis and has led to increased

exposure. Realizing that 10–15% of the population has these sensitivities, identifying who is at risk, and noting clinical and radiographic signs of hypersensitivity can help surgeons notify their patients of the possible risk and determine appropriate treatment if required. Treatment can range from symptomatic treatment of dermatologic conditions to revision surgery and use of hypoallergenic implants.

Summary

While most reports of metal hypersensitivity have been in the total joint literature, in the last 10 years there have been a number of case reports of spinal implant reactions. Much of this is because spine implants have been developed with bearing surfaces that may be a trigger for sensitizing patients from the local wear debris. Recognizing the signs of metal hypersensitivity, becoming familiar with testing procedures, and identifying risk factors for hypersensitivity, in addition to knowing the frequency of these sensitivities in the general population, can help surgeons identify these patients and notify them of the possible risk.

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Spinal Cord Stimulation: Effect on Motor Function in Parkinson's Disease

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Contents

Abstract

Invasive high frequency electrical stimulation of the brain, deep brain stimulation (DBS), has become a standard of care intervention for improving motor symptoms in Parkinson's disease (PD). Although DBS has been shown to improve many of the cardinal motor symptoms of PD including dyskinesias, bradykinesia, tremor, and rigidity, DBS has not shown consistent benefit for gait dysfunction in PD. Spinal cord stimulation (SCS) is an older form of electrical neuromodulation and has been used in humans for decades to treat primarily chronic pain disorders. Over the past decade, there has been a growing numbers of animal and human studies suggesting that SCS may improve motor symptoms, especially gait dysfunction problems such as freezing, in patients with PD. SCS has no current regulatory approval for usage in PD motor symptomatology and many of the

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benefits of SCS in PD patient have been incidentally observed in PD patients who were implanted with SCS for chronic pain. This chapter will review the published evidence for SCS in PD and discuss possible mechanisms for motor improvement in PD in addition to pain alleviation.

Keywords

Spinal cord stimulation · Parkinson's disease · Deep brain stimulation · Gait · Thoracic level · Basal ganglia

Introduction

Parkinson's disease (PD) is a complex neurodegenerative disorder with myriad motor and non-motor symptoms. Medications, primarily in the form of dopamine replacement therapy, and deep brain stimulation (DBS) have proven successful in alleviating many of the most common PD motor symptoms. However, axial motor symptoms such as truncal postural abnormalities and gait problems such as freezing are often resistant to both medications and DBS. In fact, DBS is often withheld from PD patients with significant disability due to gait dysfunction and postural disability since DBS may not only prove ineffective but could potentially worsen such symptoms. Dissatisfaction with current DBS brain targets for axial symptoms in PD has led to exploration of new brain DBS targets such as the pedunculopontine nucleus (PPN) (French and Muthusamy 2018). Spinal cord stimulation (SCS) is an attractive neuromodulation technology for improving motor symptoms in PD for multiple reasons (Cai et al. 2020). First, SCS may be considered less invasive and risky since it does not require cranial surgery. SCS has a longer safety track record in humans due to its use for decades in chronic pain disorders. Moreover, SCS, unlike DBS, is able to be percutaneously trialed in a minimally invasive fashion prior to implant and this may facilitate better candidate selection for surgical implants. Further, chronic pain is a common yet underappreciated symptom in PD and SCS is most established for pain relief as shown in the Fig. 1. Finally, market forces have driven SCS technological innovation faster than that in DBS and consequently have generated a greater option of hardware and software technologies in SCS than in DBS. Although traditional tonic SCS engenders stimulation-induced paresthesias or tingling in parts of a patient's body, a recent innovation in SCS is paresthesia-free programming modes which lend themselves to blinded studies in both pain and movement disorders (De Ridder et al. 2010).

SCS was first used in humans for pain relief in 1967 (Shealy et al. 1967). The first report suggesting that SCS may be able to ameliorate motor aspects of a disease was seen in 1973 when a patient with multiple sclerosis receiving SCS for pain was noted to have improvements in weakness, speech, and swallowing after SCS implantation (Cook and Weinstein 1973). Over the past 30 years there have been multiple, mostly open-label studies of SCS in various movement disorders including dystonia (generalized dystonia, focal dystonia, and spasmodic torticollis), nonparkinsonian tremor, painful leg and moving toes (PLMT), and Parkinson's disease (Thiriez et al. 2014). The focus below will be on the published studies that have explored the gait and movement disorder consequences of SCS in patients with PD as well as in animal models of PD. We will also discuss recommendations for future study design to better investigate the motor function effects of SCS in PD.

Animal Studies

In 2009, rodent models of PD secondary to dopamine depletion with tyrosine hydroxylase inhibitor, alpha-methy-para-tyrosine, and 6-hydroxydopamine showed significant improvement in locomotion with SCS (biphasic square pulses at 300 Hz) applied to the upper thoracic levels. Fuentes et al. furthermore showed that SCS in these rat models altered both cortical and striatal local field potentials, suggesting that SCS, although applied to the epidural space within the spine, may provide motor benefit in PD by directly modulating brain function (Fuentes et al. 2009). Interestingly, SCS was shown to reduce aberrant synchronous

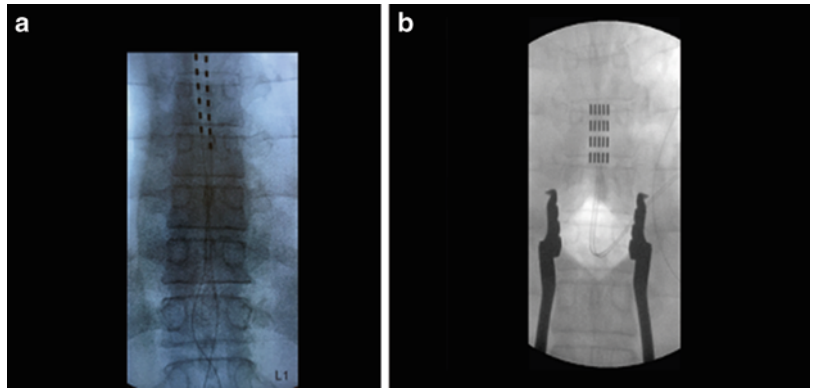

Fig. 1 Spinal cord stimulation leads: (**a**) 2 percutaneous or cylindrical leads (**b**) one plate or paddle lead

low-frequency oscillations in the basal ganglia which is similar to current theories for the therapeutic mechanism of DBS in PD (Beudel et al. 2019).

Moreover, in addition to dopamine depletion rodent models of PD, rats rendered parkinsonian by overexpression of alpha-synuclein (using unilateral injection of adeno-associated virus serotype 6 into the substania nigra) also were shown to improve use of their affected forepaw via SCS (Brys et al. 2017).

Santana et al. applied upper thoracic (T3-T4) SCS to a primate model of PD and observed improvements in freezing, hypokinesia, postural instability, and bradykinesia. Motor improvements were assessed by observers blinded to the SCS "ON" or "OFF" condition and the motor deficit which showed the highest improvement with SCS was freezing. The motor improvements in these primate models of PD treated with SCS showed a similar degree of motor improvement to that observed with UPDRS III motor score reduction with DBS in humans. They did not observe that altering the frequency of SCS led to differences in the motor improvements. Concurrent microelectrode brain recording in these animals showed that when SCS was activated, many neurons significantly decreased their beta rhythmicity (Santana et al. 2014). Thus, this study demonstrated that dopamine agonists, DBS, and SCS may also share the ability to improve parkinsonian motor symptoms by reducing excessive neuronal synchronization in the basal ganglia.

Yadav et al. reported that thoracic (T2) SCS applied just twice a week in bilateral 6-hydroxydopamine striatal lesioned rats significantly improved both posture and locomotion. Interestingly, similar to that observed in humans receiving subthalamic nucleus DBS for PD, SCS treated rats showed more weight gain compared to the control groups. Most significant in this study was the finding that striatal immunostaining for tyrosine hydroxylase, a marker for dopaminergic innervation, and substania nigra pars compacta neuronal cell count was significantly preserved in rats receiving SCS as compared to the controls (Yadov et al. 2014). Although requiring further study, this remarkable finding suggests that SCS may have a neuroprotective effect in PD.

Zhong et al. tried SCS at much lower levels in the spine, L2-S1, in a rat model of Parkinson's disease engendered by unilateral 6-hydroxydopamine lesion of the nigrostriatal pathway. During SCS, the lesioned rats which exhibited severe parkinsonism did show improved step initiation and step quality (Zhong et al. 2019).

Shinko et al. applied SCS to high cervical spinal cord (C1-C2) in unilaterally 6-hydroxydopamine lesioned rats and also demonstrated forepaw mobility improvement with SCS. Further support for neuroprotection with SCS was shown with tyrosine hydroxylase (TH) immunostaining which demonstrated preservation of TH-positive fibers in SCS treated rats. This group tried three different SCS frequencies (2 Hz, 50 Hz, and 200 Hz) and found that 50 Hz SCS engendered the greatest motor improvement and largest neuroprotective effect on dopamine cells within the striatum, particularly the substantia nigra pars compacta. They furthermore investigated the mechanism of TH-cell

preservation and showed that 50 Hz SCS significantly increased levels of the growth factor VEGF in the lesioned striatum (Shinko et al. 2014).

Human Studies

Despite heterogeneity in the location of SCS epidural electrode placement and programming parameters, preclinical studies overall with various parkinsonian animal models have shown improvements in motor function with application of SCS. Human studies thus far are comprised of case reports and small case series which can be divided into three groups: (1) patients with PD receiving SCS for motor symptoms, (2) patients with PD implanted with SCS for pain in which SCS was observed for benefits on motor symptoms, and (3) patients with PD implanted with DBS for which SCS was added as adjunctive neuromodulation to improve motor symptoms.

Thevathasan et al. published on 2 PD patients with moderate to severe motor impairments who received high cervical epidural SCS which were implanted surgically. One patient received SCS at 130 Hz and the other at 300 Hz. Ten days after surgery, the patients participated in a double-blind crossover study of the motor effects of SCS. The primary outcome was motor subsection of UPDRS (mean score of 2 blinded neurologists). Despite trying a range of SCS frequencies and intensities, there was no difference detected in the primary outcome measure of motor UPDRS. The authors speculated that perhaps the benefits of SCS seen in animal models of PD were secondary to SCS precipitating movements merely from its startling arousal effect (Thevathasan et al. 2010). This study has been criticized for the different frequencies chosen for each patient and for placing the SCS electrode in the high cervical spine, whereas most of the animal work showed benefit using thoracic spinal level SCS.

In contrast, Hassan et al. reported a single case of a 43-year-old woman with PD who underwent high cervical (C2) SCS for neuropathic upper extremity pain after trauma and was found to have significant improvement in her rigidity and tremor during SCS activation (Hassan et al. 2013).

The largest study of cervical SCS for PD to date was published by Mazzone et al. This study applied both tonic SCS and burstDR mode (burst rate 40 Hz, intraburst rate 500 Hz, pulse width 1000 microseconds) SCS. Tonic cervical SCS was applied to 6 PD patients (Group 1) suffering from low back pain and burst cervical SCS was implanted in 12 PD patients (Group 2) primarily to improve motor symptoms including tremor, rigidity, gait, and posture disturbances. Criteria for inclusion into the burst cervical SCS group included ineligibility for DBS, ineffectiveness of STN DBS, or decay of benefit from pedunculopontine DBS. The electrode tip was located at C2 (16 patients) and C2-C3 (2 patients). Group 1 patients had either a quadripolar electrode implanted (5 patients, Medtronic mod. 3487-A) or an octapolar electrode (1 patient, Medtronic mod. 3898), whereas group 2 patients all had an MRI-compatible octapolar electrode implanted (Abbott). In the Group 1, patients receiving tonic cervical SCS (3 months) were required to shown reduction in the UPDRS and Hoehn and Yahr scale (Mazzone et al. 2019).

The rest of the published human experience has highlighted thoracic SCS in PD. Nishioka and Nakajima described three cases of thoracic (T8-T11) SCS in PD patients in which SCS was implanted for low back and lower extremity pain. One patient had failed back surgery syndrome and the other two patients had lumbar stenosis. Gait was not examined, but SCS led to statistically significant improvements in both rigidity and tremor based on UPDRS. SCS improved pain in all patients but did not improve dementia or activities of daily living (Nishioka and Nakajima 2015).

Fenelon et al. reported a single patient with PD who underwent thoracic SCS for post-laminectomy pain syndrome. After 29 months of follow-up, UPDRS motor scores (off drug, on SCS) were reduced by 50% (Fenelon et al. 2012).

Agari and Date published on 15 patients (5 men, 10 women) with advanced PD (7 of which already had DBS) undergoing thoracic SCS for low back and/or lower extremity pain. The follow-up period was 12 months and motor function was evaluated with UPDRS, Timed Up

and Go tests, and Timed 10-Meter Walk test. Percutaneous leads with 4 or 8 electrodes were implanted using local anesthesia after a trial provided paresthesia coverage for more than 80% of the painful region. Posture, postural stability, bradykinesia, and gait showed significant improvement at 3 months, but the improvement decreased at 12 months. Timed 10-Meter Walk times were also improved at both 3 months and 12 months after SCS implant. No changes had been made to DBS settings if DBS or medications were present, so motor improvements in these patients were attributed to SCS (Agari and Date 2012).

More recently, Samotus et al. described five male patients with advanced PD and significant gait disturbances and freezing of gait who underwent thoracic SCS. The group used advanced gait analysis technology (Protokinetics Walkway) to measure gait parameters including timed sit-to-stand and automated freezing-of-gait detection via foot pressures. SCS programming combinations were tested over a 1–4 month period to find optimal programming settings for each patient. SCS led to significant improvements in mean UPDRS and step length, stride velocity, and sit-to-stand and also significantly reduced the number of freezing-of-gait episodes (Samotus et al. 2018).

Much of the remaining thoracic SCS data in PD patients involves patients already implanted with DBS. Pinto de Souza et al. treated four patients with PD and significant postural instability and gait disturbance with high thoracic (T2-T4) SCS. All patients had previously been implanted with bilateral subthalamic nucleus DBS. Timed-Up-GO and 20-meter-walk tests, UPDRS III, freezing of gait questionnaires, and quality of life scores were measured. Blinded assessments of gait were performed with sham stimulation as well as with SCS at 300 Hz and 60 Hz. Overall, it was reported that SCS at 300 Hz was well tolerated and led to significant improvement in gait. SCS at 300 Hz decreased freezing of gait, improved self-reported quality of life, and improved UPDRS motor scores (Pinto de Souza et al. 2017). Lima-Pardini et al. further investigated this group of four patients with more advanced biomechanical gait assessment tools. Testing was performed to determine effects of SCS on freezing of gait, postural reactive responses, and anticipatory postural adjustment (APA). The authors explained that APA is deficient in freezing of gait episodes and APA is crucial for normal gait. Freezing of gait was analyzed using wireless accelerometry and APA was quantified with a force platform. Overall, SCS engendered improvement in APA and freezing of gait but did not change postural reactive responses (de Lima-Pardini et al. 2018).

Lai et al. recently described a 73-year-old man with PD who underwent thoracic SCS for chronic low back pain. The authors describe an interesting accidental blinding that occurred when the SCS percutaneous lead dislocated and was replaced with a paddle lead. Despite SCS being below the threshold of perception for causing paresthesias, the SCS was shown to improve gait, suggesting that this is not a placebo effect (Lai et al. 2020).

Another case report by Akiyama et al. described thoracic SCS placed for painful camptocormia with Pisa syndrome in a 65-year-old woman with PD. Camptocormia refers to the exaggerated thoracolumbar flexion that occurs in PD, and Pisa syndrome is lateral trunk flexion also seen in neurodegenerative disorders such as PD. The patient was previously treated with DBS that did improve these truncal postural abnormalities for some time. However, the patient had reappearance of these truncal abnormalities and progressive resultant pain. SCS lead to immediate pain improvement and gradual improvement (after 10 days) in both her camptocormia and Pisa syndrome (Akiyama et al. 2017). This delay in postural improvement suggests that SCS may improve motor symptoms directly and not just indirectly from pain alleviation.

Additional small case reports and series have supported that thoracic SCS, both tonic and burst mode, can improve motor function in PD patients, particularly their gait and posture (Hubsch et al. 2019; Kobayashi et al. 2018). There is also some early evidence that burst mode SCS may additionally improve emotional symptoms and mental status in PD patients (Kobayashi et al. 2018). This is interesting since studies of brain imaging

during SCS for chronic pain suggest that burstDR SCS, unlike tonic SCS, modulates the medial pathway of pain involving the cingulate cortex and therefore may be able to positively influence emotions (Chakravarthy et al. 2019).

Overall, most of the human evidence has shown a beneficial effect of SCS, mostly thoracic level, on motor symptoms of PD and there is a growing body of evidence suggesting that SCS may be particularly beneficial for the levodopa-resistant motor symptoms of PD, such as gait and axial symptoms, which may be difficult to treat with basal ganglia DBS (de Andrade et al. 2016).

Possible Mechanisms of SCS in PD

The evidence that SCS provides benefits in PD, a neurodegenerative brain disease, provides further support that SCS a supraspinal site of action. Nashold et al., by studying the effect of SCS on EEG potentials, were the first to suggest that SCS works by blocking pain processing at the cerebral level rather than at the spinal cord (Nashold et al. 1972). Since SCS has been used for many decades to alleviate pain, it is natural to start with the assumption that SCS may be improving motor function in PD secondary to ameliorating pain in PD. Pain is an under-appreciated nonmotor symptom of PD and occurs through all stages of the disease. Moreover, pain has been found to significantly diminish quality of life in Parkinson's disease and may occur in >60% of PD patients (Skogar and Lokk 2016). Pain in PD is multifactorial and has been characterized in musculoskeletal, radicular/neuropathic, dystonia-related, akathitic, and central pain (Ford 1998). Most pain in PD is musculoskeletal and it is difficult to determine how much motor function in Parkinson's disease is influenced by chronic pain. The studies reviewed herein support that SCS can significantly and durably reduce pain in PD, especially pain involving the low back and lower extremities. However, there is evidence that SCS can produce motor benefits in PD independent of pain relief. Most of the research thus far has employed traditional tonic SCS, which consists of continuous square wave pulses at low frequencies (20–120 Hz) and at amplitudes chosen to create stimulation-induced paresthesias. At least two studies have suggested that there may be a latency between motor benefits and tonic SCS, despite immediate pain relief from the SCS, which supports that the motor function benefits of SCS in PD patients cannot solely be attributed to pain reduction (Mazzone et al. 2019; Akiyama et al. 2017).

Could the placebo effect be a mechanism behind the motor benefits observed in PD patient receiving SCS? The placebo effect is well-described and has been shown to be strong and durable with other implanted medical devices. The SCS literature has been criticized for a lack of blinding and placebo controls. However, it has been generally regarded that the inclusion of good placebo controls with tonic SCS is not possible since patients feel stimulation-induced paresthesias that would unblind them. Sham surgery or inactivated SCS implants could be considered for some reduction of the placebo effect in tonic SCS, yet there are significant ethical problems with adding placebo controls to surgical trials (Kjaer et al. 2020). The recent advent of paresthesia-free SCS programming modes, including burstDR mode, high density mode, and 10 kHz high frequency SCS, has opened the possibility of true double blinded SCS studies (Morales et al. 2019).

Animal models of PD have supported that SCS may be able to reduce abnormal synchronization in the basal ganglia, which has become a leading theory of the pathogenesis of PD. There is also evidence from PD animal models that SCS may be neuroprotective, particularly towards dopamine cells. DBS may also provide benefit by desynchronizing pathological oscillations in the brain of patients with PD; however, there is no strong current evidence that DBS is neuroprotective in PD (McKinnon et al. 2019). Reliable biomarkers of PD will be necessary to determine whether neuromodulation modalities such as DBS or SCS will be able to impart neuroprotection in PD.

It is intriguing to consider that SCS may be able to modulate the brain in the same way as DBS. Obviously SCS as a noncranial neuromodulation approach and would therefore be a potential

therapy for other brain diseases that may be considered as emerging from abnormal neuronal oscillations. Yadav and Nicolelis have argued that the spinal cord may be increasingly viewed as a "channel" that has the ability to transmit therapeutic electrical signals to the brain in PD and other neurological disorders (Yadov and Nicolelis 2017). A future strategy to determine whether SCS in humans with PD can also desynchronize abnormal basal ganglia activity might employ SCS and closed-loop DBS in the same patient; the SCS could be used to stimulate and the closed-loop DBS could be used to record from the basal ganglia without stimulating (Parastarfeizabadi and Kouzani 2017).

Finally, in addition to modifying brain circuits, SCS improves motor symptoms such as gait by its direct action on the spinal cord. Gait is a complex behavior which involves interaction between brain circuits and spinal pattern generation centers located within the spinal cord parenchyma. Local spinal circuits help to regulate limb muscle control and some have hypothesized that SCS improves gait by directly facilitating such local circuits within the spinal cord (Fonoff et al. 2019).

Future Directions

There are both animal and human studies supporting that SCS may have a significant therapeutic benefit in PD; however, these studies are limited by heterogeneity in spinal levels targeted by SCS, various hardware and software technology utilized for SCS, and lack of blinding and placebo controls. Another weakness of the human studies thus far has been the various metrics utilized for measuring motor improvement and the failure of routinely more objective measurements of motor outcomes such as gait. Although it has become a standard for assessing degree of PD severity and helping to determine candidacy for DBS, the United Parkinson's Disease Rating Scale (UPDRS) may be a poor indicator of gait and postural problems in PD. The UPDRS has good interrater reliability, but has been criticized for its inability to measure mobility in PD patients (Brusse et al. 2005).

Given the success of DBS in treating many of the motor problems associated with PD, future studies could focus on using SCS in PD patients with gait and postural problems as a chief complaint and to exclude PD patients with severe pain. Further studies of SCS in PD patients already implanted with DBS would be useful to determine whether there is a synergistic effect to these neuromodulation modalities. In addition, there is especially a need to perform high class evidence trials of SCS in PD patients who are not considered candidates for DBS. For example, presumably since SCS does not require cranial surgery, there should be less risk of cognitive decline with SCS, and SCS could be an option for those patients whose neuropsychological scores may preclude DBS implantation. To reduce bias from the placebo effect and to permit double blinding, it would be prudent to employ a paresthesia-free programming mode of SCS such as burstDR for all future studies of SCS in PD.

Based on the work in humans and animals thus far, it would make most sense to perform thoracic and not cervical SCS in patients with PD. Moreover, it would be helpful for SCS to be trialed percutaneously in PD patients similar to how it is currently trialed for chronic pain. A trial of SCS in PD could be used to help identify which candidates will respond the best to implantation and would be useful to set reasonable patient and caretaker expectations. Any trial of SCS in PD should include a "wash-out" period of SCS inactivation after implantation and between any change in programming settings.

Finally, future studies of SCS in PD could employ wearable sensory-based gait analysis systems to objectively assess gait parameters. Wearable sensor systems combining accelerometers and gyroscopes have been successfully tested in PD patients over the past decade (Schlachetzki et al. 2017; Brognara et al. 2019). These technologies are affordable, noninvasive and can provide multiple objective metrics about the complex gait behavior in PD patients including freezing of gait episodes. Furthermore, inertial sensors can be used by PD patients both in the clinic setting and at home and can therefore give clinicians a larger

snapshot of PD gait abnormalities without requiring expensive gait analysis laboratories. There is still a need for standardizing the measurement setup and selecting the most valuable gait parameters to evaluate in these patients. However, the quality, comparability, and reproducibility of neuromodulation research in PD could be significantly improved if such wearable motion sensors become a routine way to objectively measure motion. Furthermore, answering the question of whether neuromodulation in the form of DBS or SCS might change the progression of PD may be facilitated by long-term motion sensor monitoring of both nonimplanted and implanted patients.

Conclusion

Despite the well-established beneficial effects of DBS in PD, not all patients are candidates and DBS has known limitations in improving non-motor symptoms and axial motor symptoms such as gait disturbance. SCS is a promising new therapeutic approach based on animal and human studies. Although most of the current evidence is low level due to lack of control arms, the vast majority of studies have shown a motor benefits of SCS in PD despite different epidural SCS targets, heterogeneous programming parameters, and various SCS lead and battery technology. The recent development of paresthesia-free SCS programming modes and technological advances in wearable motion sensors has well-poised the field of neuromodulation for high level, blinded studies of SCS in PD.

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Intraoperative Monitoring in Spine Surgery

23

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Contents

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Abstract

Intraoperative neuromonitoring (IOM) has been introduced into the field of surgical medicine as a series of diagnostic modalities. IOM may help to prevent perioperative injury to the spinal cord and nerve roots during spine procedures. Neurophysiologists are trained specialists who work together with other members of the surgical team to create and record electrical signals within the nervous system closely related to motor and sensory function. Electromyography (EMG) and evoked potentials (EPs) are monitored throughout the operation, and surgeons are alerted when waveforms change and specific alarm criteria have been breached. A multimodality approach to spinal cord monitoring seems to be the most effective method of using IOM. The use of IOM has not been established as a standard of care, IOM continues to be used more frequently by surgeons across the world and its favorability continues to expand. The future of IOM as it relates to spine surgery will depend largely on the advancements in electrical technology and continued research on the effectiveness of IOM techniques within certain populations criteria.

Keywords

Intraoperative neuromonitoring · SSEP · TcMEP · EMG · Guidelines · Utility

History of Intraoperative Neuromonitoring

The advancement of surgical knowledge in the early 1970s created greater possibilities for the treatment of scoliosis and spinal deformity. However, these new innovations also posed great risks which could be detrimental to patient outcome. In an effort to recognize intraoperative harm to the patient, neuromonitoring was explored as a tool to reduce the instance of unintended injuries during surgical maneuvers. Intraoperative monitoring of the spinal cord for spinal surgery was initially developed by a group of surgeons who began stimulating and recording EPs for their own procedures (Tamaki and Kubota 2007). The field of intraoperative testing for the integrity of the nervous system has been given a number of abbreviations. In this chapter, it will be referred to as IOM.

At the inception, IOM was limited exclusively to somatosensory evoked potentials (SSEPs) which consisted of cortical and spinal recordings. In the following decade, Merton and Morton (1980) experimented on the effects of stimulating the motor and visual regions of the human cortex. Electromyography (EMG) had already been introduced much earlier in 1849 and was officially named in 1890 after Marey had successfully recorded the electrical activity of a voluntary muscle contraction in a human subject for the first time (Reaz et al. 2006). Pairing the progress of Merton and Morton with Marey led to the creation of transcranial motor evoked potentials (TcMEP), which made intraoperative tests for motor function available to surgeons.

Complications during spine surgeries typically result in a deficit to motor and/or sensory function. In most cases, the affected region of the body is at or distal to the sight of an injury to the nervous system. Hence, a severe injury to the cervical region may cause quadriplegia with loss of sensation. Neurophysiologists will generally select the SSEP, TcMEP, and EMG modalities for

monitoring surgery around the spinal column, spinal cord, or nerves. The combination of these modalities provide immediate feedback from the cortical, subcortical, spinal, and peripheral neurogenic structures which may be damaged in a procedure of spinal surgery involving large mechanical manipulation and placement of mechanical fixation devices.

The field of IOM has continued to progress over time, and it has allowed for more refined monitoring of various pathways in which neural tissues travel and interact. Even the most subtle and delicate features of the nervous system (e.g. spinal reflex synaptic activity, vision, and hearing) can be monitored under intraoperative settings. The use of IOM has enhanced an array of surgical approaches including: spinal cord mapping for tumor resection, cranial nerve monitoring for parotidectomy and thyroidectomy, nerve grafting procedures, provocative testing for awake brain mapping, musculoskeletal tumor cryoablation, microvascular decompression for hemi-facial spasm, thoracolumbar aortic aneurysm repair, and carotid endarterectomy. In this chapter, only those intraoperative modalities commonly found in spinal surgery will be discussed. A more comprehensive and inclusive understanding of neurophysiologic intraoperative monitoring can be found in other literature (Husain 2015) (Nuwer 2008).

Principles of Neurophysiology

The nervous system is comprised of neurons and other supporting cell types which create a network that communicates information within the brain, spinal cord, and peripheral nerves. Motor commands, sensory feedback, autonomic regulation, and other higher cognitive features are emergent properties of this system.

Charged ions circulating within and around a neuron create the foundational membrane potential that results from an electrochemical gradient between the intra- and extracellular fluid. When the dendritic tree of a neuron receives enough excitatory input to reach a threshold gradient at the axon hillock, the neuron proceeds to fire a single action potential down its axon and release a neurotransmitter onto downstream neurons, glands, or motor end plates. As an action potential propagates down an axon, it does so by a wave of depolarization. Information is coded within these electrical impulses through frequency and rhythm. IOM records these currents as they pass along specific pathways or evokes them by some form of stimulation.

Recording of Electrical Current

A general knowledge in electricity should be applied when understanding the practice of neurophysiology. The mechanisms of capturing EPs and EMG are based on differential amplification. This process requires two input electrodes referred to as active and inverted. Monitoring begins by creating a recording channel between these two electrodes. As charge flows between a pair of electrodes, the voltage within each electrode field varies. The voltage values are differentiated and the signal is magnified. A ground electrode is necessary for optimal signal acquisition along with low recording impedance. The grounded reference is placed remotely with electrical fields isolated from the other electrodes. The versatility of differential amplification allows for various types of electrical activity to be monitored with IOM including central and peripheral synapses, axon impulses, muscle activation, subcortical, and cortical activity.

In the case of all recordings, amplified signals are processed and digitized into a format that graphs upward peaks and downward deflections of voltage on the y-axis and time on the x-axis based on a sampling rate. Recording is sampled with respect to the Nyquist frequency, which is twice the value of the highest frequency of activity recorded. These recordings are put together similar to the way a movie pieces together a collection of consecutive images sampled over time. The result is a waveform that represents positive and negative fluctuations of charge. Obligate waveforms for each modality are correlated to specific generators within that pathway and indicate the overall status of these specific structures. They repeat consistently and are therefore able to be monitored for change.

Neuromonitoring can record continuously to allow for accurate temporal feedback during surgery. This method of IOM is used to identify nerve root irritation during pedicle screw placement. Continuous monitoring such as EMG or electroencephalography (EEG) requires constant attention of the neurophysiologist because symptomatic nerve firing may only be temporary, lasting a couple seconds. This type of monitoring focuses primarily on the presence of particular wave morphologies and general activity, opposed to changes in latency or amplitude of specific repeating waves which are seen in EPs.

Evoked potentials such as SSEPs and TcMEPs are captured within a specific time period. This time period is determined by the distance the current travels before passing into the recording field of an electrode. A trial is a single snapshot of recording channels generated after the application of stimulation. Obligate waveforms in different channels will have variation due to the distance between two input electrodes, the location of these electrodes along the pathway, and the type of activity being monitored. Evoked recordings of electrical potentials allow for monitoring of signal generators within a specific pathway.

Latency

Latency is an important characteristic attributed to the obligate waveforms of IOM. It describes the speed the current moves along a pathway and has units of milliseconds. For EPs, each waveform has a latency associated with a typical healthy adult. This value is based on nerve conduction velocity.

Many factors can influence the latency of responses including nerve thickness and myelination, perfusion to neurons, anesthetic interference with synaptic communication, and surgical injury. Patients with a previous history of myelopathy, diabetes, or other neurological conditions are expected to have greater latency in SSEP and TcMEP recordings in addition to low amplitude responses.

Amplitude

Amplitude is another aspect used to describe a waveform and has units of millivolts. The amplitude of a signal is measured by the difference in voltage between the upward and downward polarity of a wave. This characteristic is mainly determined by the strength of the patient's motor or sensory function prior to surgery.

A number of intraoperative factors can affect the amplitude of waveforms including the number of nerve fibers activated, anesthetic drug interference within synaptic pathways, perfusion to neurons, age, and surgical injury. Edema or large amounts of subcutaneous fat covering parts of the body may decrease the amplitude of recording channels due to the spatial distance between electrodes and the electric current, as seen in needle EMG. Larger needles may be used to access appropriate recording proximity (Daube and Rubin 2009). Patients with somatosensory or motor deficits prior to operation are expected to have lower amplitude responses.

Morphology

Morphology is the general shape of a waveform and can be used to describe complex multipeak waveforms such as those seen in muscle contractions after stimulation of the motor cortex or EEG. A loss of morphological value in a waveform may appear as a shift from polyphasic to biphasic. This is simply the shortening of a wave and the loss of positive and negative variation in the activity. Morphological data is used to subtly understand the underlying mechanisms, but it has not been promoted for the use of alarm criteria due to the variation in morphology that naturally occurs from surgical stress to the nervous system (Langeloo et al. 2007).

Delivery of Electrical Stimulation

The use of electrical stimulation to elicit nerve conduction has become a standard practice in medicine and the field of IOM. Nerve root differentiation, tissue identification, and EPs are all examples of stimulation-based monitoring. Electric charge can be administered through specialized electrode strips, a pair of electrodes, or a single hand-held stimulator.

Ohm's Law states that voltage equals the product of resistance and current. Constant voltage

stimulation is used in TcMEPs because resistance is not expected to vary much between individuals at the head region. Constant current is used in most other cases of stimulation because resistance is largely variable throughout the body. Stimulation intensities vary in IOM depending on the application. Bone has much a higher resistivity than soft tissue and fluid. Therefore, more stimulation is needed for TcMEPs than peripheral nerve stimulation. Corkscrew and needle electrodes have lower impedance than disk and adhesive electrodes and are often suggested for both stimulation and recording.

Stimulation can also be classified as anodal or cathodal depending on the polarity of charge that is applied. Unlike a battery, the stimulator's negative end is the cathode and the positive end is the anode. Neurons are preferentially activated in different anatomical regions based on the polarity of the charge introduced to the extracellular fluid. TcMEPs depend on anodal stimulation in which positively charged cations (+) are discharged under the anode and flow back toward the cathode. Pyramidal cell bodies depolarize as negative ions are pulled to the surface where cations (+) are being discharged. Cathodal stimulation, in which anions (−) are discharged from the cathode and flow toward the anode, preferentially activates axons because negative charges build up along the outer membrane and cause greater electric gradients and positive ions to move toward the cell membrane from the inside, thus causing depolarization.

Monopolar stimulation is useful when current can spread to surrounding tissue. These instances will identify the presence or absence of nerve bundles hidden under layers of fascia. Alternatively, bipolar stimulation applies a more localized current that can be specific in nerve activation. However, it is not as effective if used near pooled fluid which may cause current to dissipate.

Troubleshooting

The equipment used for a standard spine surgery consist of a computer, digital amplifier, stimulating and recording pods, electrodes, and possibly a hand-held probe when stimulated EMG is used. The wires connecting all these components together create the potential for technical error. IOM equipment should always be accessible to neurophysiologists in the event that changes in monitoring are noted of technical troubleshooting is required.

Electrical Interference

Electrical recording is not exempt from limitation. Even if all electrodes are placed correctly and the hardware is properly linked, differential amplifiers are subject to electrical interference. Mains electricity, also known as the power grid, emits a 60-Hz electrical frequency from all appliances, wires, or outlets. Electrocautery artifact completely obliterates any IOM recording with large amplitude and high frequency activity. The movement of an electrode tip from external pressure on the surface of the skin results in a low-frequency artifact termed a DC shift. Other interferences monitored in recording channels may be from fluoroscopy equipment, EKG, or other machines such as blood warmer or warming blanket heater.

Parameters for Signal Acquisition

In order to obtain the clearest and most accurate waveforms, neurophysiologists use a number of recording and stimulation parameters. Averaging is a method of processing consecutive trials to create a more precise waveform. The use of averages prevents the transient loss or disruption of a waveform to cause an alarm. Individual trials often appear noisy and vary from one to the other. Averages cancel out extraneous waves as the trials are summated, and the actual electrical impulses from the nervous system are distinguished. Signals may be clarified with digital smoothing and filters. A low-frequency noise filter can be used in all recording channels to quiet the electrical hum produced from the power grid. High-frequency filters help distinguish important waveforms from activity that may be present in other parts of the nervous system. Time-lock simulation is another technique used in IOM that keeps the stimulation and recording window of EPs consistent. It is also a way to eliminate "stimulation artifact" in EPs.

The charge applied during current delivery is the product of stimulation intensity and pulse width and it is given units of coulombs. Stimulation intensity is the quantity of energy being applied in volts or amperes. Raising stimulation intensity increases the depth and range of electrical current between the anode and cathode. Therefore, high stimulation intensities result in the activation of more nerve fibers within a fasciculus. Pulse width is the duration for which stimulation lasts. Most stimulation occurs in increments of microseconds. Supra-maximal stimulation refers to the technique of maximizing the charge delivered to ensure all fibers of a specific area are saturated and that complete nerve pathway activation is achieved. Safety of the patient becomes a risk with greater stimulation intensities and pulse durations, and neurophysiologists should adhere to a recognized protocol. The American Society of Neurophysiological Monitoring (ASNM) is a group of internationally recognized members who published an updated set of guidelines for IOM in 2009 that is used in many standard practices today.

Repetition rate (rep-rate) is the frequency of stimulating and recording an EP. Because the nervous system relies so heavily on the timing of currents and synapses to calculate information, adjusting rep-rate can optimize nerve activation. Pathways of the nervous system relay at different intervals, so their recording parameters differ. Patients with deteriorated nerve fibers require lower frequency simulations in order for the action potentials to summate and neurons to synapse in the correct fashion. Similar to the Nyquist frequency, rep-rate can also be useful to cancel out specific noise frequencies found in operating rooms.

Functioning within the Operating Room

IOM Setup

The preparation for monitoring begins before the patient has entered the room. A proper discussion of modalities and verification should take place with a surgeon present before any needle electrodes are placed. A reading neurologist must immediately confirm any changes or the status of IOM responses. Safety of the patient should come before any accommodations are made for neuromonitoring. Special attention should be brought to adhesive allergies, drug allergies, external shunts, pacemakers, or other metallic implants.

The application of subdermal needle electrodes occurs after induction, intubation, and approval from the other members of the surgical team. IOM setup may delay the positioning process due to limited patient access during this time from placement of other devices on the body (e.g., arterial lines, EKG, Foley catheter). A well-trained neurophysiologist should understand the priority of tasks and execute their setup with efficiency.

Anesthetic Effect on IOM

A continuous dialogue between the neurophysiologist and anesthesiologist is crucial to optimize neuromonitoring and patient safety. Anesthetic drugs have a major effect on synaptic activity in the entire nervous system. In almost all instances of IOM in spinal column surgery, anesthetic concentrations and regimes must be altered in order to allow for the nervous system to maintain specific functions. Temperature drops will cause neurons to decrease their activity in an attempt to protect the cell from energy loss and death. Changes in blood pressure and perfusion of neurovasculature structures can lead to transient signal loss (Sloan and Jäntti 2008).

Neuromuscular blockers prevent the activation of skeletal muscle. Therefore, EMG and TcMEP do not tolerate paralytics. Volatile inhalant agents act against cortical synapses and those within the spinal cord. Nitrous oxide is generally avoided because of the global depression in signals within all modalities (Liem 2016). Other drugs of consideration include benzodiazepines, barbiturates, and Propofol, which can diminish cortical activity at high concentrations. Systemic anticoagulants (e.g., Heparin) can result in delayed clotting at the sight of IOM needle electrodes.

Typically, monitoring continues until after the closure of skin or once the surgeon has verbally ended monitoring. After decompression, derotation, and hardware placement, the neurological structures of the spinal cord and nerve roots are no longer at large risk for further insult. The early dismissal of monitoring during case closure can allow for faster wake-up times and earlier neurologic exams, however prolonged monitoring may reveal a delayed change from a hematoma. The concentration of gases can be titrated more readily to alter anesthetic depth and is less expensive when compared to infusions of Propofol, which is often requested in the case of IOM (Gertler and Joshi 2010).

Baselines and Documentation

Baseline monitoring of EMG, SSEP, and TcMEP traces are recorded and stored before incision. Establishing baselines will depend on anesthetic cooperation and the extent of technical troubleshooting required. Baselines are used for comparison to responses monitored throughout the surgery. Any deviations in obligate waveform latency, amplitude, or morphology are quantified, and alerts are communicated based on a specific alarm criterion for each modality.

In the event that a patient has an unstable neurological condition, whether from trauma or degenerative instability, caution is necessary during the transition from hospital bed to operating table. Pre-positioning baselines can be obtained before the patient is placed into the prone position after induction and intubation. There are instances in which TcMEP and SSEP are lost due to the degree of cervical manipulation (Jameson 2017). Baselines are promptly set under low anesthetic values to ensure optimal neurologic function and response acquisition.

Communication with the surgeon and anesthesia staff is crucial throughout all of the procedure. Documentation by a neurophysiologist takes place throughout the entirety of monitoring. Time-stamped events of surgery, anesthesia, and other aspects of the operation allow for retrospective analysis of the case as it correlates to changes in IOM signals (ASNM 2009a). Thorough documentation of steps in the procedure offer evidence and proof that may be supportive in medicolegal situations. Any and all communication between the surgeon, neurologist, and anesthesiologist should be documented by the neurophysiologist.

Protocol for Intraoperative Change

Checklists are commonly used tools in medicine because they effectively organize priorities and can reduce harm or death in certain medical practices. As an effort to prevent error in the event of intraoperative changes in IOM waveforms, checklists have been proposed specifically for spinal deformity procedures. They can reduce the probability for human error and serve as a memory aid in highly crucial situations in a prompt fashion. Unfortunately, checklists are not a perfect way of addressing intraoperative change because every situation in the operating room will present in a different manner (Ziewacz et al. 2012).

In the event of intraoperative change, neurophysiologists are trained to alert the surgeon immediately. The surgeon then has the opportunity to try to determine if there is a correctable surgical cause of the neurophysiologic change. The neurophysiologists may then address the items outlined in the checklists. Documentation of surgical actions with anesthetic concentrations should regularly take place and IOM responses should be free of any technical errors from malfunctioning equipment or electrical interference (ASNM 2009a). The cause of intraoperative change should be considered by all members of the surgical team. IOM requires that a reading neurologist be available to confirm any observations to the operating physician.

Remote access to the case via digital network allows the machine in the operating room to be in other locations. A neurologist interprets the IOM data with the neurophysiologist. Clear communication between the anesthesia team, surgeon, and the neurophysiologist is vital to the success and ease of using IOM (Fig. 1).

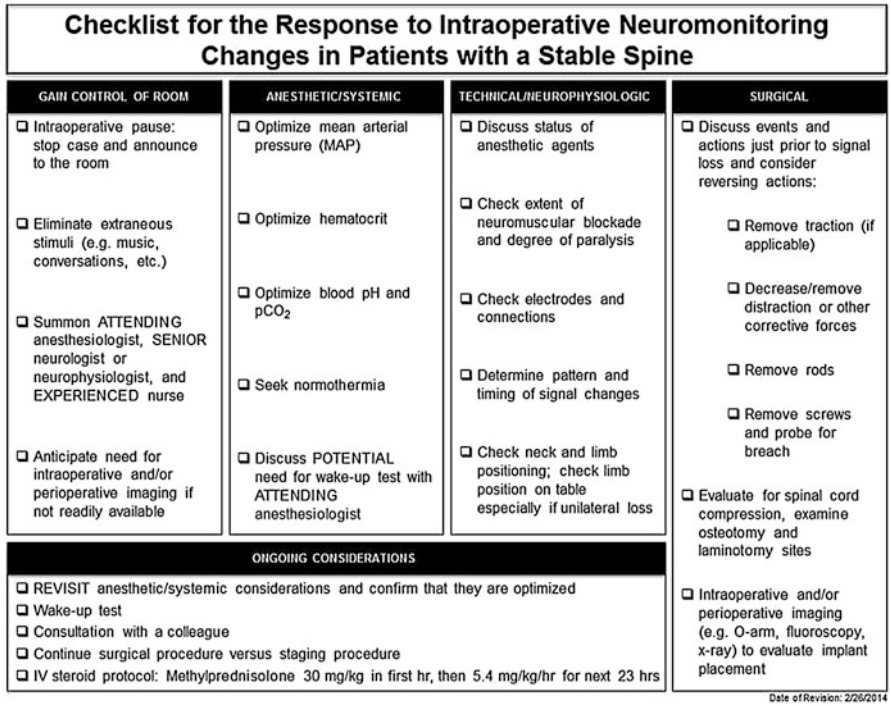

Fig. 1 Standard checklist for spine surgery created by Vitale et al. (2018).

Electromyography (EMG)

Neurophysiology

Electromyography is a standard technique used to observe and record the electrical impulses transmitted through muscle activation. It can be used intraoperatively to detect injury to nerve roots during decompression, hardware insertion, realignment of the spine, and tissue retraction. A clear understanding of muscle contraction physiology is necessary to interpret EMG accurately.

Alpha motor neurons within the gray matter of the corticospinal tract receive excitatory input from upper neurons. Action potentials propagate toward the neuromuscular junction and calcium influx occurs near the axonal terminal. This causes the release of the neurotransmitter acetylcholine which enters the synaptic cleft and binds to receptors on the motor end plate. Ligand-gated channels open and an influx of sodium creates waves of depolarization across the sarcolemma that travel throughout the muscle. This causes the release of calcium and activation of cross-bridge cycling.

As muscle fibers activate, compound muscle action potentials (CMAPs) occur as a result of synchronous co-contractions. CMAP do not always create a visible twitch. CMAP is directly reflective of muscle activation but can also give information on the irritation of specific nerve roots that innervate that muscle. Perturbation of the motor nerves distal to the spinal cord can cause spontaneous firing of action potentials along the axon and activates the release of acetylcholine and muscle contraction. This is often seen in EMG and is the reason why it is a useful tool in detecting any injury or sensitivity of nerve roots during parts of surgery.

Recording Methods

Paired needle electrodes inserted into bilateral muscle groups form channels for recording activity. An optional stimulator device may be used by

the surgeon to activate nerve roots or verify distance of the spinal cord from the pedicle space. The muscles chosen by neurophysiologist are easily identified anatomically and should be at least one spinal level above and below the site of surgery. Monitoring multiple levels of nerve roots is crucial because this method reduces the chance of false responses. For example, activity observed in the biceps brachii is more likely to originate from the C5 nerve root than the C6 nerve root, if there is also EMG activity in the deltoid channel. For example, C5 nerve palsy is a major complication for cervical spine operations, hence monitoring must be made as accurate as possible by monitoring adjacent levels (Nichols and Manafov 2012). Surgeons operating at or near the sacral plexus should consider monitoring the anal sphincter. Vodušesk and Deletis (2002) concluded that motor function of the sacral region is reflective of the integrity of the entire sacral plexus because of the anatomical nerve bundle which is comprised of efferent and afferent axons. Bladder, bowel, and sexual function can also be monitored through other IOM techniques, but these are not generally used in degenerative spine surgery (Table 1).

Spontaneous EMG

This modality is used in almost all instances of monitoring spine surgery. Spontaneous EMG is also termed "free-running" because it continuously records activity throughout the entire surgery. This offers excellent temporal resolution by changes in nerve function seen immediately as EMG pattern firing. When nerve roots experience injury from mechanical or thermal events, subsequent firing of high frequency bursts (termed "neurotonic discharges" or "A-trains") are seen in the recording of the same muscle levels (Holland 2002). Spontaneous EMG can also reveal a number of pathologies in nerve and muscle fibers, therefore creating activity which may not be caused from any surgical action. Surgeons may elect to decline intervention based on the alert of any kind during any time, such as rhythmic tibialis anterior activity seen during exposure. Although activity like this seems mistaken, patients with myelopathy and palsies experience fibrillation potentials due to muscle fibers losing contact with innervating nerves and spontaneously producing CMAPs as a result. An EMG baseline is taken after induction before the patient has been fully relaxed. Muscle activity in all channels is documented by the neurophysiologist.

Table 1 Common choices for EMG monitoring based on nerve root level. (Standard knowledge not requiring copyright permission)

Common EMG recording channels and their corresponding nerve root levels	
Nerve root	Muscle group
C3-C4	Trapezius
C5	Deltoid
C5-C6	Biceps brachii
C6-C7	Triceps brachii
C8-T1	Abductor pollicis brevis, abductor digiti minimi
T2-T6	Intercostal muscles
T7-T12	External oblique, rectus abdominus
L1-L2	Iliopsoas
L2-L4	Vastus medialis, vastus lateralis
L4-L5	Tibialis anterior
L5-S1	Biceps femoris, abductor hallucis longus
S1-S2	Gastrocnemius
S3-S5	Anal sphincter

Train of Four

The train of four (TO4) test is used to assess the degree of neuromuscular blockade (NMB). Four successive stimuli are applied through needle electrodes at a peripheral nerve. These stimuli produce a train of action potentials that propagate down the axon to the motor end plate of distal muscles. Recording the following CMAPs produced by these four stimuli notify the depth of patient relaxation. TO4 monitoring should always be done in the extremity from which EMG or EPs are being monitored. In most cases, the peripheral stimulators located at the wrist or ankle are used for a TO4. Often, these are the same electrodes used in evoking SSEPs and deliver cathodal stimulation. Typical parameters for this test are four supra-maximal bursts lasting 0.2–0.3 seconds are applied at a rate of 2 Hz (Nichols and Manafov 2012).

Paralytic is often requested during the exposure of the spine. During this time, EMG and TcMEP responses are not accurate. When

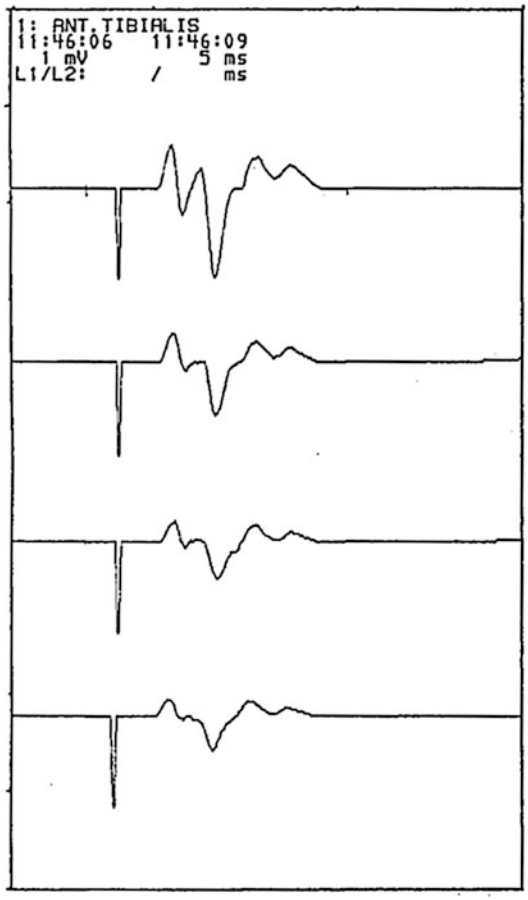

Fig. 2 TO4 test reveals four twitches with anesthetic fade. These results indicate adequate clearance of the NMB. (Holland 2002)

assessing the NMB from nondepolarizing relaxants (e.g., Rocuronium), a TO4 appears with fade. The amplitude of the first CMAP is the largest and they subsequently diminish. Four twitches of equal amplitude may not be achieved for a patient with a severe neurological condition. Baseline monitoring and continuous TO4 recordings provide the neurophysiologist with a good estimation of the extent of NMB. TO4 is interpreted largely by visual analysis (Fig. 2).

Triggered EMG

Stimulus triggered EMG is a surgeon-directed method to help to determine functional connectivity of nerve roots, or identify nerves from the surrounding tissue (e.g., tumors, scar tissue from revision, herniated disc). Nerve root testing, especially in the lumbar region, is not a good indicator of vertebral level; however, considering stimulation typically consists of a bipolar, cathodal stimulator that is held by the surgeon and an anode return is placed near the skin of the incision. Constant current is delivered at 1–3 mA for pulse durations of 0.2 ms at a frequency of 2 Hz. Surgeons direct the neurophysiologist during the stimulation to activate, deactivate, and adjust the intensity of the stimulator. The neurophysiologist provides positive or negative feedback seen in EMG channels and documents any observed activity. Previous studies have shown that nerve thresholds with these stimulation parameters are within 0.2–5.7 mA (Leppanen 2005) (Fig. 3).

Pedicle Screw Threshold Testing

Pedicle screw placement is a critical step in posterior spinal surgery. Stimulation of the pedicle hole, probe, tap, or screw with a ball tip probe can be useful in detecting a breach of the pedicle wall. Surgeons may choose to remove screws with a low threshold and stimulate the pedicle track with a probe, redirect the screw trajectory and replace the screw, or leave it out completely. There may be practicality in stimulating with the pedicle probe as it is driven into the pedicle wall using a real-time testing. In doing so, any alteration in trajectory of the live-probe can be made based on unacceptable low threshold before a violation of the pedicle walls occurs and the probe is fully seated. This is achieved by substituting the handheld probe with an alligator clamp connected pedicle probe. Screws can be stimulated after placement as well in these approaches (Rose et al. 1997).

The stimulation parameters for pedicle testing have been studied by many physicians, and there is a general consensus that cathodal stimulation at constant current offers the best result. Single pulses of stimuli lasting 100–200 microseconds are applied at a frequency of 2–3 Hz. Stimulation intensity is applied at low level and increased until a cutoff “threshold” value is reached. If EMG activity is observed before the threshold is reached, that is considered a positive response and suggests a breach in the

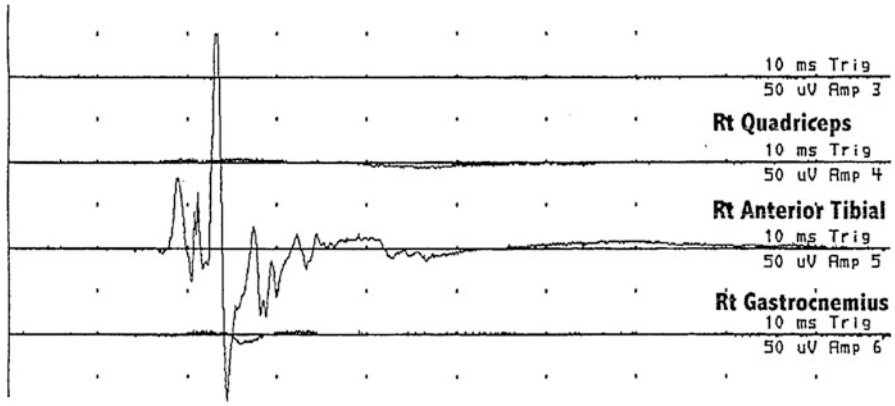

Fig. 3 Anterior tibialis activity recording after direct stimulation of the L5 nerve root. (Holland 2002)

pedicle. Higher thoracic levels are more difficult to monitor based on the level of deformity in the region and the ability to monitor the corresponding musculature (intercostal muscles). Recent publications have utilized the combination of pulse-train stimulation parameters in TcMEPs in addition to EMG monitoring of the lower limbs to test for malposition of thoracic level screws (Donohue et al. 2008).

The most appropriate threshold criteria and cutoff stimulation for pedicle threshold testing is of wide debate. There are a number of reasons why pedicle threshold testing may not be the most accurate assessment of neurological injury. Higher cutoff thresholds lead to a greater occurrence of false positives while lower threshold increase the incidence of false negatives (Skinner and Rippe 2012). For example, a 91% positive predictive value (PPV) with a 43% sensitivity and 99% specificity has been found when using a threshold cutoff of 5 mA in the lumbosacral region. Threshold cutoffs of 8 mA had sensitivity around 87% and specificity of 94% with a PPV of only 26%. Calancie et al. (1994) found that probe stimulation of the lumbosacral region to a threshold $\geq$7 mA with no EMG activity indicates good placement. A slightly higher threshold of 10 mA confirmed well placed screws. Surgeons may choose to stimulate up to intensities of 30–40 mA to confirm the adequate placement of screws. However, 15 mA of stimulation with no EMG responses is strongly suggestive of no postoperative deficit.

Misplaced pedicle screws may be clinically inconsequential and a safe zone may extend up to 4 mm depending on the anatomy. Small breaches of the pedicle wall could potentially cause current spread into the spinal cord or nerve roots and create an EMG alarm. However, these breaches are not typically clinically significant to deterioration of motor function. The conductivity of metallic screws and bone density can affect the impedance of charge delivery and therefore alter cutoff values as well. These factors contribute to inaccuracies between pedicle screw testing criteria and clinical outcomes. A study by Holland (2012) in cervical and thoracic pedicle screws found that 88% of medial breaches in the cervical spine can be detected by using a threshold of 15 mA. Medial breaches in the thoracic spine were detected 85% of the time while using a threshold of 6 mA. However, none of the screws detected by IOM correlated to postoperative deficits.

Although there is no technique to guarantee pedicle screw placement with 100% accuracy, there are many techniques to avoid symptomatic malpositioned screws. The traditional technique of pedicle screw placement relies on the surgeon's anatomical knowledge and confidence in finding the correct entry point; however, this method has been linked with failure rates of

15–42%. Plain radiographic CT scans also have a chance of being misinterpreted. Djurasovic et al. (2005) conducted a study comparing IOM threshold testing results with those from a posteroperative CT scan. They found 7 out of 11 instances where intraoperative screw stimulation detected unacceptable screws that were not identified on plain lateral radiographs.

The utility of IOM in pedicle screw placement is questioned because of the technological advancements in image-based navigation systems. Lee et al. (2014) compared various imaging approaches to pedicle screw placement and found that CT-based navigation, along with 2-d and 3-d fluoroscopy-based navigation, has a high accuracy for pedicle screw insertion. CT and 3-d navigation seem to be more accurate than 2-d navigation; however, a 96.7% accuracy was still found in 2-d fluoroscopy. Unfortunately there are technical limitations with these technologies as well, and a 3.3% failure rate has been observed. Intraoperative CT and fluoroscopy are not always available to surgeons because of a lack in hospital resources. The cost of imaging equipment and the need for lead shielding and a trained staff person are all considerations. This is contrast to the IOM technique which requires very little preparation and minimal interruption to the operating surgeon. Also, images of the bony anatomy have no direct reflection on the physiologic condition. EMG is able to detect the proximity of pedicle insertion to the neurologic tissue through current activation and weighs this information based on a standard threshold criterion.

Anesthetic Consideration

The main anesthetic concern for EMG monitoring is the NMB, which is established through the use of short- or long-acting paralytics. Reversal agents (e.g., Neostigmine, Sugammadex) allow for quicker recovery from paralysis. EMG may be performed with as much as 75% of receptors blocked. This percentage is not correlated to the loss of CMAP amplitude in a TO4 under paralytic. In fact, changes in EMG are only seen after 75% of NMB (Holland 2002). Minahan et al. (2000) studied the effect of NMB on pedicle screw testing and concluded that largest CMAP in a TO4 must not be more than 80% decreased from the baseline in order for optimal pedicle screw threshold testing. Surgeons who request a NMB for exposure should inform anesthesia of the appropriate time for reversal if they wish to monitor EMG. By monitoring the TO4, neurophysiologists communicate when the blockade has been adequately reversed.

Somatosensory Evoked Potentials (SSEPs)

Neurophysiologic System

SSEPs test the dorsal column-medial lemniscal (DCML) pathway, which is responsible for upper and lower extremity somatosensory function. This pathway is a series of large diameter afferent nerve fibers, which carry information from the periphery about fine touch and proprioception to the brain. The origin of these nerves is found in the muscle spindle receptors surrounded by skeletal muscle fibers. As the human body moves through space, a number of internal and external forces act on the musculature. Muscle spindles activate in response to static and dynamic changes in muscle length.

The activation of these afferent nerve fibers can also be achieved through stimulation over the axon. Afferent somatosensory nerves travel in the same common nerve bundle as efferent motor axons that innervate similar muscles. These “mixed nerves” split into a dorsal and ventral tract once they reach the spinal cord. The advantage of stimulating a mixed nerve is that visible twitches from the hand or foot ensure correct stimulation delivery during SSEP monitoring.

Proprioceptive nerve fibers enter into the dorsal root ganglia of correlating dermatome. The fasciculus gracilis and fasciculus cuneatus are white matter tracts of the DCML that carry upper and lower extremity sensation, respectively. A synapse in the medulla decussates the information and sends impulses into the thalamus and onto the contralateral

hemisphere. Therefore, the right side of the body is perceived in the left hemisphere and vice versa.

Recording Method

Stimulation electrodes 2 cm apart are placed in the wrist for upper extremity SSEPs, while lower extremity electrodes are placed in the ankle. Stimulation is applied over mixed nerves and both motor and sensory nerve fibers activate. Depending on the degree of NMB and patient condition, a twitch is not always observed. The activation of sensory fibers creates a wave of depolarization that flows proximally. Recording sites for SSEPs are variable depending on the training and technique of the neurophysiologist. However, in most setups, at least three channels of peripheral, subcortical, and cortical EPs are captured (ASNM 2009b).

The first recording along the sensory pathways is over a peripheral nerve or plexus that is just distal to the spinal cord. This type of axonal activity is termed a volley. For upper extremity SSEPs, electrodes are placed bilaterally behind the clavicle (Erb's point) or near the axilla. Two electrodes placed ~5 cm apart over each popliteal fossa are used for monitoring of the right and left lower extremity. Additional recording channels can be added to the lumbar or thoracic midline for lower extremity SSEPs. However, this activity is not frequently monitored.

The International 10–20 system is a method of measuring and describing the placement of electrodes for an EEG headset with a combination of letters and numbers. Capital letters are used to describe the region of the brain over which the electrode is placed. For example, C represents the central sulcus and F represents the frontal lobe. Z indicates midline. Odd numbers are located on the left hemisphere and higher order electrodes are placed more laterally. Therefore C1 and C3 would be placed over the left central sulcus, but would not lie in the same sagittal plane. References to the 10–20 system are used for the placement of cranial electrodes in all IOM applications. In order to monitor subcortical SSEPs of the upper and lower extremity, a channel is created between an electrode placed at the spinous process of a cervical vertebrae and an electrode placed midline at few centimeters rostral from the natural hairline. These locations are termed "Cs" and "Fpz," respectively. If placement of C lead is not possible due to the surgical field, it can be placed at the left or right auricular point (A1 or A2).

Cortical SSEPs are commonly monitored by electrodes placed over the left and right somatosensory cortex, 2 cm back from the central sulcus. Therefore these electrodes are given a prime mark because of their modified location (C3' and C4'). This channel is reversed depending on the stimulation side of the SSEP. This keeps the waveforms of each extremity in the same polarity so that waves are not flipped, which would make comparison more difficult. Upper extremity cortical SSEPs also use an alternative channel of C3' (right SSEP) or C4' (left SSEP) reference with Fpz. Lower extremity cortical SSEPs are also monitored with C3' and C4', but a perpendicular channel between Cz and Fpz is recommended (Nuwer and Packwood 2008).

Parameters and Technique

According to the recommended standards for SSEP monitoring set by ASNM (2009b), cathodal stimulation of rectangular pulses lasting 100–300 microseconds should be kept to 30–40 mA at a frequency of 2–8 stimuli per second. As in the case with all IOM application of stimulation, the charge deliver should not injure the patient in any way. Rep-rates that lie within 60 Hz frequency, such as 5.00 stimuli per second, should be avoided. Each pulse of stimulation creates one EP along the pathway. SSEPs in all four limbs can be interleaved by most IOM equipment. This technique cycles each limb at a rate so that averages are obtained most readily.

For surgeries above the C6 level, median nerves are suggested because this nerve has the largest cortical response from the upper extremity. Surgeries extending to C8 or instances where the patient is prone with the arms above the head, stimulation of the ulnar nerve is selected. Surgery in the thoracic and lumbosacral regions requires stimulation of the posterior tibial nerve, but the

peroneal nerve or the popliteal fossa can be used if the patient suffers from neuropathy. In most spine surgeries, both upper and lower SSEPs are monitored in order to control for global changes that may occur.

Peripheral channels assure that the DCML pathway is at supra-maximal stimulation because the amplitude of this response indicates the totality of afferent nerve fiber activation. Once maximum amplitude has been reached in the peripheral response, cortical and subcortical waveforms will not strengthen with additional stimulation.

Anesthetic Consideration

All anesthetic agents have some impact on the synapses between neurons. Therefore cortical SSEP activity diminishes before subcortical or epidural activity because of the large number of cell bodies and synapses in the neocortex. Halogenated gases (e.g., isoflurane, desflurane, sevoflurane) are commonly administered at minimum alveolar concentrations (MAC) of 0.5–1.0, with the addition of an analgesic agent (e.g., fentanyl, sufentanil, remifentanil) (Slimp and Holdefer 2014). MAC is a unitless measurement of vapor in the lungs that is required for 50% of the population to not respond to a surgical stimuli. Less potent gas (e.g., nitrous oxide) has higher MAC value because more is needed to keep a patient sedated. Nitrous oxide is not compatible with neuromonitoring; however, halogenated gases can be used as a part of a balanced anesthetic at low MAC.

Opiates show little effect on EPs at lower dosages, and muscle relaxants may improve SSEPs because there is less artifact from patient movement. Ketamine and Etomidate have been shown to increase the strength of cortical SSEP signals due to their mechanisms of cortical excitability and disinhibition (Sloan and Jäntti 2008). Other small concerns may be noted for SSEPs. Pulse oximetry is not always compatible when the stimulation of the wrist or ankle causes muscle twitches in the fingers and toes. Corkscrew electrodes at the scalp can be substituted for needle electrodes or disk electrode if a patient requires anticoagulation for the surgery and bleeding is expected.

Obligate Waveforms and Warning Criteria

The obligate waveforms of SSEPs are distinguished by the polarity (positive peak or negative dip) and latency. The latencies of these waveforms should be generally similar, but can have variation. Therefore, an individual baseline is recorded before incision, which is used to compare with the SSEPs throughout surgery. The last position of the ASNM (2009b) for alert criteria is an amplitude decrease of 50% or more or a latency increase of 10% or more in any obligate waveform (Fig. 4).

Cortical amplification is the process of thalamic input summating before it projects onto the cortex. Because of this, cortical recordings appear larger in amplitude than the subcortical and peripheral recordings (Slimp and Holdefer 2014). Subcortical and peripheral SSEP changes are considered more significant in spine surgery because insult to the system is likely in the spinal cord or nerve roots. The cortical channels will not be as affected by this damage because of thalamic summation and cortical amplification. As a result, an amplitude criterion is generally used in cortical and subcortical waveforms while latency is assessed in the periphery.

Causes of SSEP intraoperative change has been outlined by Gonzalez and Shilian (2015). Damage to the nerve roots will result in the change of subcortical and cortical waveforms. Peripheral channels distal to the site of injury would not show immediate decrement because the nerve underneath these electrodes is still intact. Therefore, insult to the SSEP pathway causes the loss of signal conduction proximal to the injury site. This is indicated by the loss of subcortical and cortical signals with no changes in peripheral response.

Global changes in SSEPs are usually a result of ischemic situations when the limb is malpositioned. Whenever the patient is positioned prone with the arms overhead, ulnar nerve SSEPs are used. It is the nerve at greatest risk for perioperative neuropathy from external pressure. However, up to one half of male patients may fail to perceive or experience clinical symptoms of ulnar nerve compression sufficient to elicit SSEP changes (Prielipp et al. 1999).

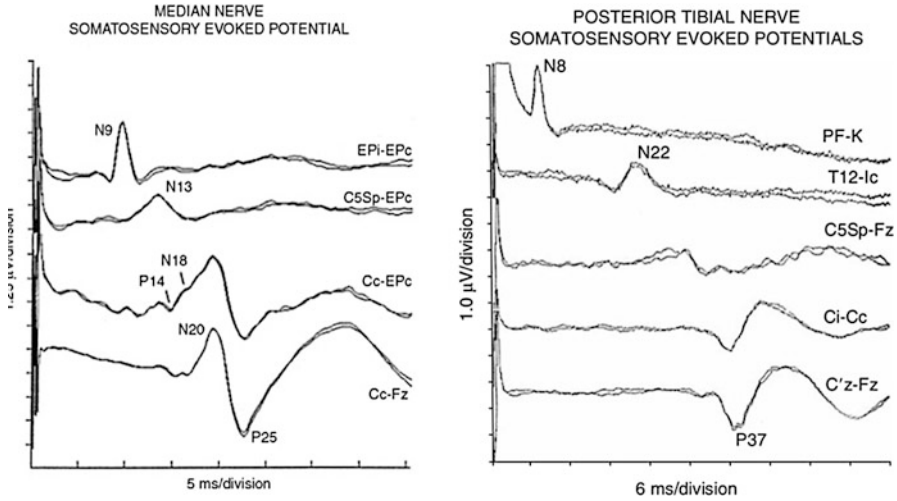

Fig. 4 Peripheral, spinal, subcortical, and cortical SSEPs of median (left) and posterior tibial nerves (right). (Nuwer and Packwood 2008)

Motor Evoked Potentials

Neurophysiologic System

Spinal cord function is not completely covered through the use of SSEPs alone. Motor evoked potentials allow for the monitoring of motor function via stimulation of the motor cortex. The lateral corticospinal tract is system of neurons originating in the motor cortices and terminating at the voluntary muscles throughout our entire body. Similar to somatosensory regions, the motor cortex is partitioned bilaterally on contralateral hemispheres in a homunculus arrangement.

Inputs from the basal ganglia, cerebellum, and the pre- and supplementary motor cortices excite the corticomotor neurons in the primary motor cortex. The axons of these cells outline the corticospinal tract as they travel through the internal capsule and cross hemispheres in the medulla oblongata. Depolarization along white matter continues inferiorly into the corticobulbar tract and the corticospinal tract. Excitation of alpha motor neurons at the ventral horn activates the physiological process of muscle contraction.

Indirect motor pathways (e.g., rubrospinal, reticulospinal, and tectospinal) consist of functions that heavily influence the corticospinal tract. These pathways do not have direct interactions with alpha motor neurons, but instead are connected through interneuronal synapses. These pathways have influence in facilitating a level of excitation in the corticospinal tract that makes TcMEPs possible (MacDonald et al. 2013). They are also responsible for what makes this system difficult to monitor.

Recording Method

TcMEPs deliver charge to the cortex through the skull. Other methods of evoking motor potential include direct stimulation of the cortex or deeper regions of the subcortical pathways. Stimulation electrodes for TcMEPs are placed 2 cm anterior to the central sulcus over the motor cortex and 4 cm anterior to SSEP head electrodes. A charge is delivered between these two electrodes to activate the left or right hemisphere.

Recording channels within the muscles are observed for the presence of CMAPs. Muscles that are more distal have greater latency because of the time it takes for the corticospinal tract activation to reach these motor units. Muscles are chosen in the upper and lower extremity to control for global change and confirm true positive results. Epidural recordings can also be

performed to monitor the descending portion of corticospinal tract within the spinal cord. In these instances, electrode pairs or strips are positions distal and proximal to the surgical site (Legatt et al. 2016).

Parameters and Technique

Anodal stimulation is used for TcMEPs most often with constant voltage delivery. The method of mutli-pulse, or pulse train stimulation, refers to a series of short consecutive shocks lasting about 50 microseconds. In awake subjects, 3 pulses with a 2 millisecond pause between each pulse successfully elicited motor activation at 25–50 volts. However, under anesthesia, the stimulation intensity required was as high as 400 volts (Calancie et al. 1998).

Neurophysiologists follow separate guidelines and no official protocol for stimulation parameters have been set forth. Calancie et al.'s (1998) original methods are still used but are often changed slightly. Double trains allow for two separate clusters of stimuli to be applied. Larger pauses between each stimulus can also reach 5 milliseconds. This technique of troubleshooting TcMEPs is often used because the timing of the excitation is crucial to successfully activating corticomotor nuclei. A maximum of 9 pulses can be given.

TcMEPs create patient movement, and surgeons must stop their actions and clear the surgical field every time. Bilateral bite blocks are mandatory in all instances of stimulating the motor cortex. Bite injuries are the most common complication with TcMEPs, appearing in 0.2% of all cases (Macdonald et al. 2013). Once the patient has been positioned prone, gauze padding should be confirmed secure before obtaining baselines by using a mirrored faceplate. Pacemakers and other electronic devices may also jeopardize the safety of collecting TcMEPs and are contraindicated. Patients with a history of seizures or superficial shunts should not undergo TcMEPs if the risk for harm is made greater by the stimulation.

Motor evoked potentials are used in spine surgery to monitor the connection of the corticospinal tract. It has been shown to be more sensitive for spinal cord compromise than SSEPs (Macdonald et al. 2015). Injury to the spinal cord will alter the CMAP in all muscle groups distal to the lesion. Therefore, nerve roots can be intact but the connection to the alpha motor neuron is blocked due to damage in the proximal corticospinal tract. TcMEPs do not provide the nerve root specific feedback that is monitored with spontaneous EMG. A damaged nerve root may not affect the CMAP of a muscle that has innervations from multiple levels of the spinal cord.

Epidural d-wave recordings represent the status of the corticospinal tract within the spinal cord from direct activation of the corticomotor neurons. The D-wave is recorded caudal and/or distal to the site of surgery and lies between the motor cortex and alpha motor neuron cell body. Therefore, no synapse occurs before the recording electrode. This makes D-waves less sensitive to general interference and yet very precise in determining the conductivity of the descending volley down the corticospinal tract (Deletis & Sala 2008).

Anesthetic Considerations

TcMEPs are the most sensitive to anesthesia than EMG or SSEPs. In a recent study by Acharya et al. (2017), over 50% total TcMEP alerts were accredited to anesthetic management. As aforementioned, TcMEPs prohibit the use of neuromuscular blocking agents to allow for CMAP activity. Reversal agents are administered to allow for enough time for the NMB to dissipate. By monitoring the TO4, neurophysiologists communicate when the blockade has been reduced optimally for TcMEPs.

Another concern for TcMEPs includes perfusion. The anterior aspect of the spinal cord, which contains the descending motor tract, is only perfused by one anterior spinal artery opposed to two posterior spinal arteries on the dorsal aspect. This makes TcMEPs more sensitive than SSEPs to decreases in blood pressure caused by anesthesia. Similar to SSEPs, needle or disk electrodes can be used at the head instead

of corkscrews if anticoagulant is planned for the surgery.

Total Intravenous Anesthesia (TIVA)

TIVA refers to a mixture of drugs other than inhalants to achieve the four elements of anesthesia: analgesia, amnesia, "sleep," and muscle relaxation. TcMEPs are very incompatible of inhalational agents because of their influence on the indirect motor pathways and the excitation of alpha motor neurons (Legatt et al. 2016). Interneurons do not remain stable with anesthetic gases, and TIVA should be prioritized for the most accurate TcMEP monitoring. Studies also show that TIVA regiments also carry an increased risk for intraoperative awareness (Gertler and Joshi 2010). As a result, anesthesiologists work together with neurophysiologists to create a balanced anesthetic that can include low MAC values of halogenated gas along with infusions of opiate and other amnesic drugs (Fig. 5).

Obligate Waveforms and Warning Criteria

The ideal waveforms for TcMEPs consist of robust CMAPs in all recording channels. Baseline CMAP latency, amplitude, and morphology vary depending on patient's health. TcMEPs are extremely sensitive to change due to the effects of anesthetic agents, perfusion of the spinal cord, and the activation of all the corticomotor neurons using appropriate parameters. Anesthetic fade over the course of a long procedure will often decrease the amplitude of EPs. A looser alarm criterion is used to prevent the instance of false positives, and an attenuation of 80% amplitude from baseline has been suggested for significant change (Langeloo et al. 2007). An all-or-none criterion is used in many instances of monitoring. Alternatively, increasing the stimulation intensity by 100 V or more to elicit the same responses as baseline qualifies as a standard criteria as well (ASNM 2009a) (Fig. 6).

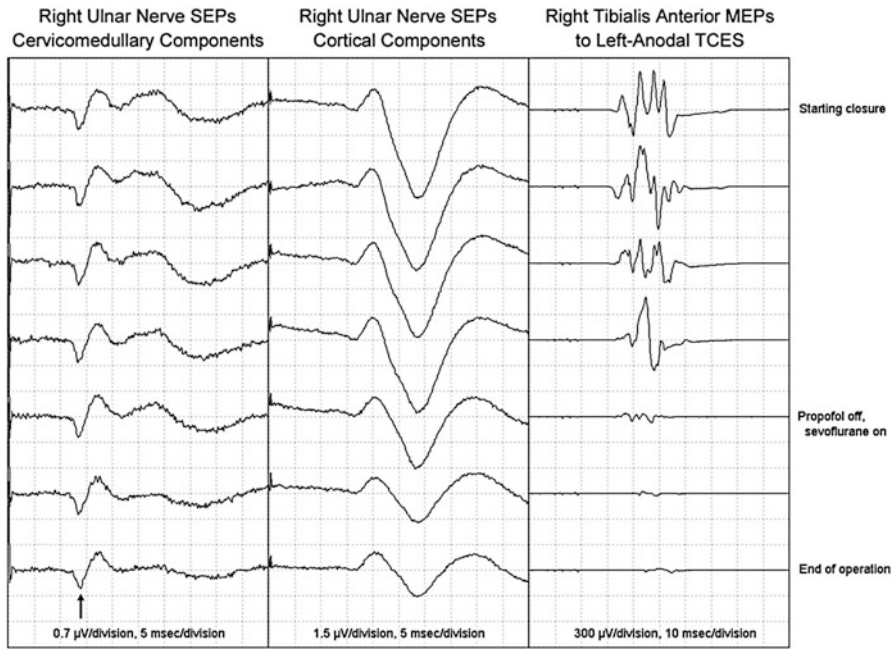

Fig. 5 SSEP and TcMEP amplitude and morphology diminishing as Propofol infusions were ended and anesthesia was switched to sevoflurane at the end of surgery. (Legatt et al. 2016)

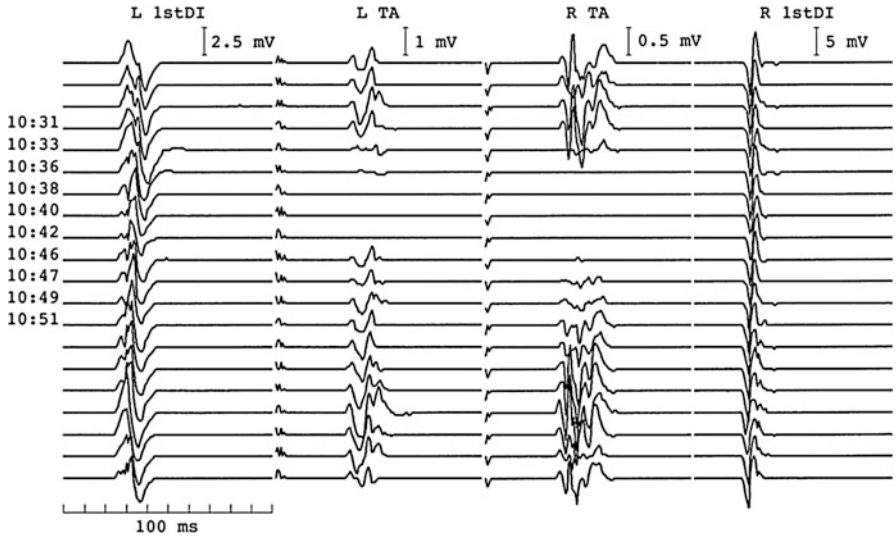

Fig. 6 Transient loss in TcMEPs from acute spinal cord ischemia during thoracoabdominal aneurysm surgery. Responses quickly recover after blood pressure was restored. MacDonald et al. 2013)

Utility of Neuromonitoring in Spine Procedures

Before deciding to use intraoperative neuromonitoring, the limitations of IOM should be known to spine surgeons. As previously discussed, the presence of IOM in the operating room can be cumbersome and result in surgical delay. Anesthesia protocol requires alteration and more closely managed throughout the case. Electrical recording has its own drawbacks as well. The variation in patient neuroanatomy and condition can make it difficult to distinguish the true utility of IOM for every situation. Preoperative condition will largely influence the efficacy of IOM in producing repeating and monitorable waveforms. The strength of baseline signals provide surgeons with an idea of how effective IOM will be during the rest of the surgery.

There is a wide debate on the effectiveness of neuromonitoring preventing or reducing neurological complications during spinal surgery, and that is accredited to a number of inconsistencies. Studies performed in this field are often retrospective and do not share the same independent variables. Differences in electrical recording and stimulation parameters between authors confound different conclusions as a result. The chosen alarm criteria used in different studies also affect the rate of sensitivity, specificity, and predictive value. The outcomes reported by recent authors vary along with their perspectives on the utility of IOM for spine surgery.

Ibrahim et al. (2017) used SSEPs, EMG, and TcMEPs and found three instances of false negatives in a study of 121 with a sensitivity of 57% with a specificity of 98%. In addition, they calculated that IOM has a PPV of 67% and an NPV of 97%. However, the three deficits that went undetected intraoperatively were eventually resolved after several weeks. This finding can be explained by neuroplasticity and the nervous system's ability to reorganize itself. Neira et al. (2016) found that TcMEPs were slightly more successful than SSEPs in spinal column surgery in detecting postoperative deficit, based on the findings in a population of children. This is in accordance with Zuccaro et al. (2017), who conducted a retrospective study on 809 pediatric patients in posterior spinal fusions, vertebral column resection, or other spinal surgeries. Each patient included in the study had one of the following diagnoses: idiopathic, congenital, or syndromic scoliosis, which included various neuromuscular syndromes. TcMEPs showed 100% sensitivity with 93% specificity and

SSEPs had 13% sensitivity with 100 specificity. These results were achieved using an alarm criteria of 50% decrease in the amplitude of TcMEPs or SSEPs with disregard to any latency alarm criteria.

Some physicians believe that IOM is a predictive tool to establish an increased risk for the adverse outcomes of paraparesis, paraplegia, and quadriplegia in spinal surgery. Tamkus et al. (2017) found the overall rate of IOM failing to predict a postoperative deficit was 0.04%. Animal studies reveal that surgical response to intraoperative change greatly reduces the risk of postoperative deficits, when compared to not intervening at all after a change in IOM responses. Neuromonitoring for human subjects has not been directly linked to decreasing the severity or rate of surgical injuries during spine operations because these studies raise ethical issues (Nuwer et al. 2012).

Multimodality Approach

Surgeons may choose to select their own modalities and alarm criteria for the procedure, or the neurophysiologist can suggest recommendations. A recent analysis on the field of IOM revealed that the most frequent unimodality monitoring consists of EMG, but SSEPs are also monitored alone. A multimodality approach of SSEP and EMG, or all three modalities including TcMEPs, appears to be the most preferential among surgeons. Trends in scoliosis surgery show that the use of neuromonitoring has steadily increased within the past decade, although the prevention of neurological injury has not significantly improved with the use of monitoring (Ajiboye et al. 2017).

IOM Services

The demand for neuromonitoring has risen and the field is projected to grow exponentially in the next decade. Neuromonitoring performed in medical centers is done by IOM staff or the use of a contracted neuromonitoring service. Qualifications of the neurophysiologist are beginning to become standardized, as this field continues to expand. A Certificate in Neurophysiologic Intraoperative Monitoring (CNIM) is the current specification preferred for neurophysiologists and it is credentialed by the American Board of Registration of Electroencephalographic and Evoked Potential Technologists (ABRET) (Nuwer 2015). Neurophysiologists should be properly trained and complete a certification process. Educational programs within universities that teach the knowledge and skills of neuromonitoring have become available in the past decade. Mergos et al. (2015) proposed a training curriculum for such programs which include theoretical study and clinical experience.

Conclusions

The historical evolution of surgical technology and the advancements in anesthesiology have supported the development of intraoperative neuromonitoring within the past several decades. The field of IOM has grown quite extensively and can be used in a variety of operative procedures. The diagnostic tests available through EMG can be used to inform the level of NMB, injuries to specific nerve roots, the identification of nerve tissue, and the integrity of pedicle screw placement. Spine surgeries often require the patient to be in a prone position with their arms stretched out over head. Monitoring SSEPs can prevent brachial plexus ischemia and detect injuries along the DCML pathway. SSEPs also give insight into the perfusion of the spinal cord, specifically the posterior aspect. TcMEPs test the connection between the motor cortex, corticospinal tract, and peripheral muscles. They are closely associated with overall motor function and can indicate the perfusion of the anterior spinal cord.

Ajiboye et al. (2017) performed a retrospective analysis between 2004 and 2011 and found a statistical increase of about 20% for the use of IOM. It appears that multimodality combinations are considered necessary for practical and effective neuromonitoring. Laratta et al. (2018) have

described the importance of an experienced multimodality approach to neuromonitoring in spine surgery. They emphasized that the efficacy of IOM depends on the familiarity of the surgeon and neurophysiologist with both the surgical procedure and the IOM modalities. The prompt detection of potential neurologic injury is accredited to a firm understanding of the surgical maneuvers and anesthetic concentrations. These authors point out that rapid intervention and successful outcomes can only be achieved through clear communication and interdisciplinary respect between the surgeon, anesthesia staff, and neurophysiologist.

Although neuromonitoring has been successful in predicting postoperative outcomes and eliminated the need for wake-up tests, it has not been proven to reduce the neurological complications associated with spine surgery. The future holds much promise for the field of neurodiagnostics and the application of IOM. Technological innovation coupled with standardization and uniform practice would yield more precise, physiologic feedback. As with all surgical techniques, the primary objective of IOM is to optimize patient safety to maximize postoperative outcomes.

Cross-References

- ▶ Pedicle Screw Fixation
- ▶ The Diagnostic and the Therapeutic Utility of Radiology in Spinal Care

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Oncological Principles

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Contents

Abstract

Surgical resection of neoplastic spinal pathology requires a multifactorial understanding and appreciation of the anatomy and biomechanics of the spinal column, pathologic characterization of the lesion, multidisciplinary options available, best guidelines for treatment, patient presentation, and feasibility of resection. When counseling patients with spinal pathologies, in my practice, I distill decision-making into three key questions: "(1) What is the tumor histology? (2) What is it doing to the patient neurologically and mechanically? (3) What are the patient's options?" The first question aims at identifying a conclusive radiographic and pathologic

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diagnosis. The second assesses the patient's symptomatology, clinical presentation, spinal stability, and systemic burden. These two dictate the final query – describing treatment options and indications/extent of surgical resection. This chapter aims to provide an overview of essential principles in spinal oncology.

Keywords

Spinal tumor · Spinal metastasis · Vertebral column tumor · Oncologic resection · Enneking system · Negative margins · Multidisciplinary care

Introduction

The management of spinal malignancies is one of the most complex clinical tasks encountered by the academic spine surgeon. Coarsely, spinal malignancies can be grouped along two main axes: (1) primary vs. metastatic and (2) intrathecal vs. extrathecal location. This division gives rise to four main lesion types: (1) intradural, intramedullary lesions, (2) intradural, extramedullary lesions, (3) primary vertebral column tumors, and (4) vertebral column metastases. Though metastatic disease of the vertebral column is far and away the most common lesion class, spinal oncologists must be prepared to address all four classes, including the goals of surgery (palliative, curative, etc.), the proper strategy for resection (en bloc vs. piecemeal), and the indications for instrumentation and reconstruction following resection. Here we address each tumor class in turn, focusing on preoperative patient selection, intraoperative surgical strategies, and the need for adjuvant or neoadjuvant therapy to mediate an optimal outcome.

Patient Evaluation

Magnetic resonance imaging (MRI), X-ray, and computed tomography (CT) are the cornerstone of imaging for spinal pathologies. X-ray often serves as the initial form of radiographic evaluation and may be beneficial to identify a lesion, motion, or alignment (Ilaslan et al. 2004; Greenspan 2004; Rodallec et al. 2008). Dynamic X-rays, such as flexion-extension films, are useful to assess sagittal translation, suggesting possible destabilization between adjacent segments. This may result in mechanical pain, exacerbated by motion, as can occur with lytic disease involving the facet joints (Ciftdemir et al. 2016). Disruption in the anterior vertebral line, posterior vertebral line ("George's Line"), spinolaminar line, and posterior spinous line may indicate adjacent segment motion (Horne et al. 2016). Alignment is assessed on standing 36-inch scoliosis films and should be considered in cases of extensive lesions resulting in spinal deformity, or possibility of deformity following iatrogenic destabilization and reconstruction (Mehta et al. 2015).

MRI is the gold standard to assess soft tissue and neural structures, with the ability to identify cystic or lobulated structures. In the presence of neurologic deficit, spinal cord and/or nerve root compression should be carefully identified. One must be mindful to rule out vascular abnormalities, vitamin deficiency (i.e., subacute combined degeneration), or immune conditions (i.e., multiple sclerosis). Generally, dense osteoblastic lesions are hypointense on T1-weighted and T2-weighted MRI, whereas osteoclastic lesions are frequently T1-hypointense and T2-hyperintense. Based on vascularity, most tumors enhance following gadolinium administration, which is especially useful to characterize epidural soft tissue invasion. CT is unparalleled to assess bone mineralization, ideal for the characterization of bony invasion, fracture, vertebral height loss, and the classification of osseous lesions (i.e., blastic, lytic, or mixed) (Rodallec et al. 2008; Kim et al. 2012a).

MRI and CT can be useful to provide diagnostic insight, but pathologic diagnosis should always be attempted in non-emergent cases. CT-guided needle biopsy should be repeated or a core biopsy attempted for nondiagnostic lesions (Sciubba et al. 2010; Aaron 1994; Laufer et al. 2013). For locally aggressive malignancies, such as chordoma, marking the percutaneous trajectory with methylene blue or a tattoo can minimize the

risk of tumor seeding to be included in the surgical resection (Mehta et al. 2015). PET-CT characterizes systemic burden, particularly necessary for suspected metastatic disease (Metser et al. 2004). Patients with spinal tumors most often present with pain, and/or neurologic dysfunction, requiring a thorough physical examination. Frailty and medical comorbidities are significant factors for surgical decision-making, with a substantial impact on postoperative adverse events and long-term function, and should be considered as well (Sciubba et al. 2010; Aaron 1994; Laufer et al. 2013).

Multidisciplinary Approach

Optimal treatment of spinal neoplasms relies on a multidisciplinary approach of surgeons, medical oncologists, radiation oncologists, interventional radiologists, pathologists, and neuroradiologists. These specialists play an integral role in not only the treatment of spinal lesions but should be involved early during patient evaluation to achieve the best outcomes (i.e., imaging, biopsy, and staging).

The indications for surgery depend on tumor type, clinical presentation, systemic burden, and response to chemotherapy or radiotherapy. In many centers, such options are presented in multidisciplinary conferences to determine the most appropriate treatment plan (Wallace et al. 2015; Kim et al. 2012b; Ropper et al. 2012; Kaloostian et al. 2014). Prior to surgery, neoadjuvant chemotherapy or radiation can play a critical role in feasibility of resection. Postoperatively, adjuvant therapy may substantially increase prognosis in both primary and metastatic lesions and may even delay recurrence for subtotally resected intramedullary tumors (Uei et al. 2018; Oh et al. 2013; Dea et al. 2017). Other tools for optimizing surgical outcomes include preoperative embolization for vascular lesions (i.e., renal cell carcinoma, pheochromocytoma, hemangioma, follicular thyroid carcinoma).

Access surgeons including general surgeons, vascular surgeons, oral maxillofacial (OMF), and thoracic surgeons may be consulted especially during technically demanding or high-risk exposures. This may involve surgical exposures to the upper cervical spine such as transoral or transmandibular circumglossal; to the thoracic spine such as thoracotomies, or sternotomies; and to the lumbar spine such as anterior transperitoneal or anterior retroperitoneal (Chiriano et al. 2009; Fourney and Gokaslan 2004; Walsh et al. 1997; Samudrala et al. 1999; DeMonte et al. 2001). Additionally, more extensive surgical resection may require complex plastic and reconstructive surgery closure to optimize aesthetic outcome and minimize the risk of postoperative infection (Chieng et al. 2015; Epstein 2013).

Primary Spinal Column Tumors

Primary tumors originate in the spinal column and are far less common compared to metastatic spine disease. Patients frequently present with progressively worsening back pain and/or neurologic deficit. Soft tissue extension to the surrounding subcutaneous tissue or muscle results in paraspinal pain, whereas spinal cord or nerve root compression results in myelopathy and radiculopathy, respectively (Ropper et al. 2012; Kaloostian et al. 2014; Dea et al. 2017).

Unlike metastatic spine disease, the focality of primary spinal lesions allows for the potential to surgically cure these patients of disease. Consequently, the goal of surgery for primary lesions is curative, when feasible, unlike metastatic lesions, which is palliative. Several factors are considered to decide the optimal treatment for these patients.

Enneking Classification System

The Enneking Staging System was proposed in 1986 for the classification of primary spinal neoplasms, with three characterizing factors (Enneking 1986): tumor grade (G), local extent (T), and the presence or absence of metastasis (M). Tumor grade is based on histopathological diagnosis of the lesion; local extent refers to lesions confined to the compartment

(i.e., intracompartmental vs. extracompartmental); and metastasis describes systemic burden. Benign lesions are given a grade of G0, with the stage denoted by Arabic numbering (i.e., 1,2,3) (Dea et al. 2017). In 2009, the Spinal Oncology Study Group (SOSG) proposed a modified version of the original staging system, with suggestions for appropriate treatment of benign and malignant primary spinal tumors (From Chan et al. 2009),

benign tumor stage (all grade G0, with no metastasis M0):

- Stage 1: Latent tumor, with well-defined margin, intracompartmental (T0), low biological activity, that often resolves spontaneously (i.e., non-ossifying fibroma). Surgical management not required for oncologic control but may be warranted for decompression or stabilization if symptomatic.
- Stage 2: Active tumor, with lytic bone destruction, intracompartmental (T0), often symptomatic, and can result in pathologic fracture (i.e., aneurysmal bone cyst). Treatment involves intralesional resection with the possibility for local adjuvant therapy.
- Stage 3: Aggressive tumor, without well-defined margins. High rates of recurrence with subtotal resection, frequently symptomatic (i.e., giant cell tumor). Optimal treatment consists of marginal en bloc resection.

Malignant primary spinal lesions, however, have grades from G1 to G2, and stages are denoted with Roman numerals (i.e., I, II, III):

- Stage IA: Grade G1 (low-grade malignant), intracompartmental (T0), without metastases (M0). Best treatment consists of wide en bloc resection.
- Stage IB: Grade G1 (low-grade malignant), extracompartmental (T1), without metastases (M0). Best treatment consists of wide en bloc resection.
- Stage IIA: Grade G2 (high-grade malignant), intracompartmental (T0), without metastases (M0). Best treatment includes wide en bloc resection with postoperative adjuvant therapy.
- Stage IIB: Grade G2 (high-grade malignant), extracompartmental (T1), no metastases (M0). Optimal treatment is wide en bloc resection with postoperative adjuvant therapy.
- Stage III: Presence of metastases (M1) is the key characterizing factor. May be low grade or high grade, intracompartmental, or extracompartmental. Treatment is palliative.

The feasibility of resection is further illustrated by the Weinstein-Boriani-Biagini classification (Dea et al. 2017; From Chan et al. 2009; Boriani et al. 1996, 1997), which defines the extent of vertebral involvement. The axial vertebral body is segmented into 12 sectors with 1 and 12 situated on the left and right side of the spinous process, respectively. In addition, lateral to medial involvement are defined by the following:

A. Extraosseous soft tissue
B. Intraosseous (superficial, cortical)
C. Intraosseous (deep, medullary)
D. Extraosseous within the spinal canal (epidural)
E. Extraosseous within the spinal canal (intradural)
F. Vertebral artery involved (cervical)

Case Illustration

Radiation-Induced Osteosarcoma

A 69-year-old white male with a history of radiation-treated seminoma was referred to our service with diagnosis of osteosarcoma of the lumbosacral spine. The patient initially presented to an outside facility with chief complaint of non-mechanical lower back pain with right radicular leg pain. Workup revealed a right-sided mass involving the right posterior L5 vertebral body, right pedicle, and right L5 and S1 facets. This led to a CT-guided biopsy demonstrating a high-grade (3 out of 3) osteosarcoma. The patient was referred to our center for further management.

During consultation, the patient reported radicular pain in the right L5 distribution, and motor testing demonstrated mild weakness in the right

extensor hallucis longus with commensurate decrease in the deep tendon reflex at the right ankle. PET-CT revealed the patient's disease to be localized, and recommendation was made for the patient to undergo en bloc resection of the L5 mass with preoperative embolization to minimize intraoperative morbidity (Fig. 1).

The patient elected to pursue this therapeutic regimen and underwent a three-stage operation to resect the lesion. During stage I, a posterior midline incision was made from L3 to S2 with subperiosteal dissection bilaterally over L3, L4, S1, and S2. The dissection over the sacral level was carried laterally to expose the iliac wings for instrumentation. Over the level of L5, subperiosteal dissection was carried laterally on the left side to expose the pedicle for instrumentation; dissection was restricted on the right side to maintain a muscular cuff around the lesion. An ultrasonic cutting device was then used to perform an L4 laminectomy and resect the inferior articulating process of L4 bilaterally. The pedicle and facet surfaces were also resected from the left L5 and S1 vertebrae to expose the descending S1 and S2 nerve roots. Left-sided hemidiscectomies were then performed at the L4/5 and L5/S1 levels, and the ultrasonic cutting device was used to create a parasagittal osteotomy through the L5 vertebral body. The osteotomy did not involve the anterior cortical surface to avoid injury to the IVC. Pedicle

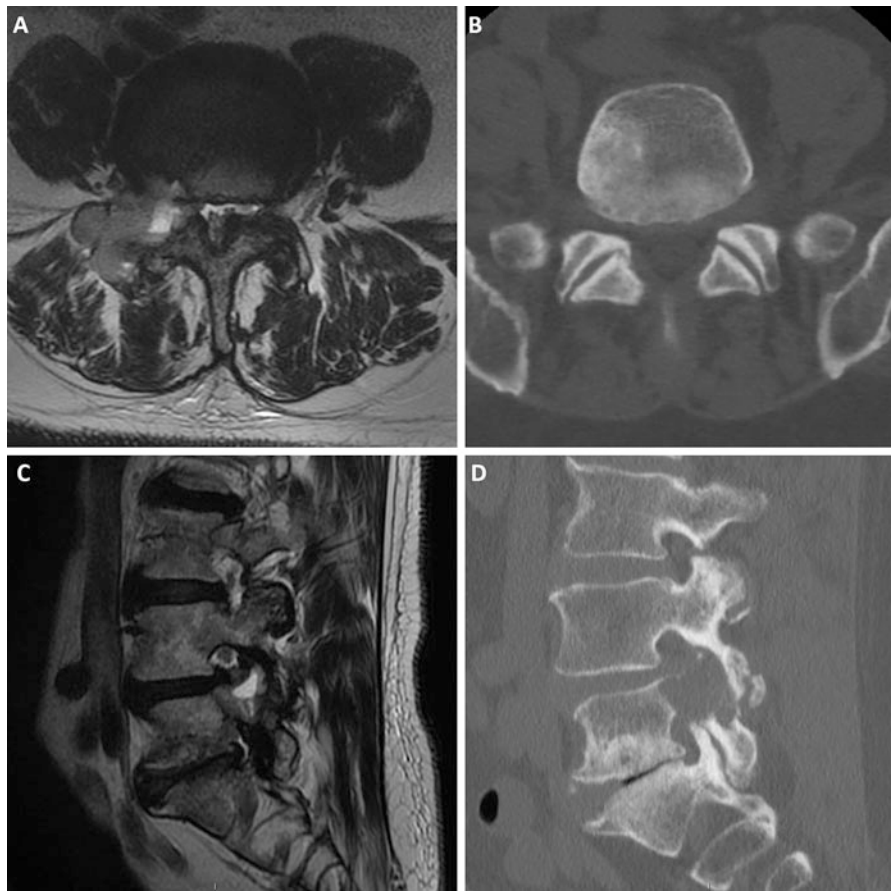

Fig. 1 A 69-year-old WM presenting from an outside hospital with nonmechanical back pain secondary to an aggressive (3 out of 3) radiation-induced osteosarcoma arising from the right L5 vertebral body. MR (**a** and **c**) demonstrated involvement of the right L5 root, and CT (**b** and **d**) demonstrated an osteoblastic lesion with poorly defined margins. PET (not shown) demonstrated no systemic metastases

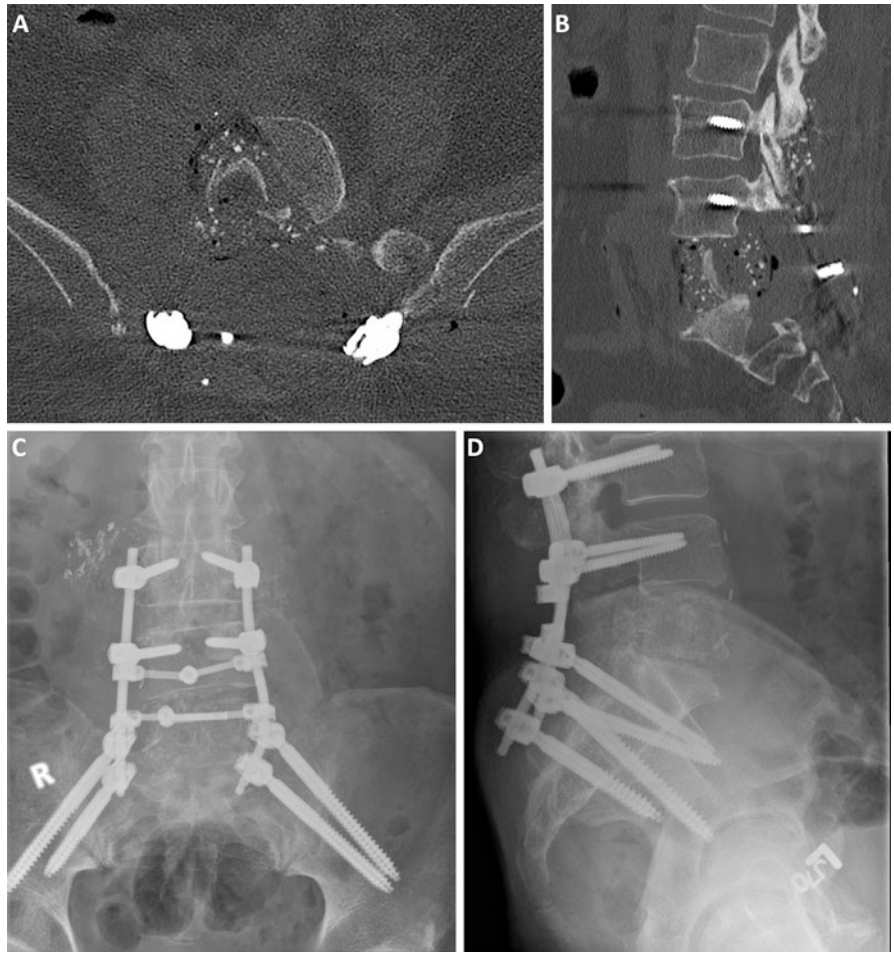

Fig. 2 Postoperative imaging demonstrating en bloc resection of the right L5 hemivertebrae (**a** and **b**). Standing radiographs acquired at 3 months (**c** and **d**) postoperatively demonstrate good positioning of the L3-pelvis fusion with no signs of anterior column insufficiency

screws were then placed bilaterally at L3 and on the left side of L4. Double iliac bolts were placed on the left side, and a 5.5-mm titanium rod was used to connect the left-sided instrumentation. Plastic surgery was consulted for wound closure, which was performed using adipocutaneous flaps in circumferential fashion.

During stage II, a right-sided retroperitoneal approach was employed. The patient was placed in the left lateral decubitus position on a beanbag with an axillary roll. An incision was made in the midaxillary line extending from the 12th rib to the iliac crest. The abdominal wall musculature was incised, and the peritoneal contents were deflected medially. A plane was developed between the abdominal musculature and the peritoneum, allowing identification of the right iliopsoas muscle and the great vessels. Bipolar coagulation and sharp dissection with Metzenbaum scissors were used to elevate the iliopsoas from the underlying spine. The segmental arteries were then ligated and transected to allow mobilization of the iliac vessels, IVC, and aorta. The L4/5 and L5/S1 discectomies that begun in stage I were then completed, as was the parasagittal osteotomy, mobilizing the rostral aspect of the tumor. Hemostasis was obtained, and the wound was closed in layers.

During the final stage of the operation, a posterior midline approach was again adopted. The prior incision was reopened to expose the lumbosacral junction. The right-sided S1 pedicle and superior articulating process were resected to expose the L5/S1 disc space and to allow identification of the L4 and L5 roots. The specimen was rotated away from the midline, with sequential sectioning of adhesions to the surrounding structure. The sympathetic branch of L4 and entire L5 nerve root were found to be involved in the tumor and were sacrificed to preserve negative margins. Further dissection freely mobilized the tumor, which was delivered en bloc, including a cuff of healthy paraspinal soft tissue. Hemostasis was obtained, and instrumentation was performed at the right L3 and L4 pedicles and right ilium, using the holes cannulated in stage I. Intraoperative testing suggested that a cage could not be safely seated in the corpectomy defect, and so no anterior column reconstruction was performed (Fig. 2). Iliac crest autograft was employed for arthrodesis, and the wound was again closed by the plastic surgery service using adipocutaneous flaps.

The patient's postoperative course was uncomplicated, and he was transferred to inpatient rehabilitation for recovery. Postoperative follow-up demonstrated that the wound was healing appropriately, and the patient's pain was well controlled. The patient passed shortly after the 3-month postoperative follow-up.

Metastatic Spine Disease

The vast majority of extradural spinal tumors are metastases, with the spinal column representing the most common site of skeletal metastasis. The greatest incidence of metastatic spine disease occurs in those from 40–65 years old, and symptomatic lesions are most commonly located in the thoracic spine (Sciubba et al. 2010; Aaron 1994; Laufer et al. 2013; Perrin and Laxton 2004; Fisher et al. 2010a; Bilsky et al. 2010; Posner 1987). These most often present with pain, followed by neurologic dysfunction, frequently originating from a primary breast, prostate, or lung cancer (Sciubba et al. 2010). Unlike primary spinal tumors, the aim of surgery of metastatic spine disease is palliative nature, to treat neurologic compromise, pain, and/or mechanical instability.

Neurologic Oncologic Mechanical Systemic (NOMS) Framework

A multidisciplinary algorithm for the management of spinal metastasis, the NOMS Framework, encompasses four clinical aspects to inform decision-making (Laufer et al. 2013):

- **N**eurologic: characterization of symptomatic epidural spinal cord or nerve root compression due to extradural metastasis
- **O**ncologic: pathologic diagnosis of the tumor, aggressiveness, and its response to treatments
- **M**echanical stability: "loss of spinal integrity as a result of a neoplastic process that is associated with movement-related pain, symptomatic or progressive deformity, and/or neural compromise under physiologic loads" (Fisher et al. 2010b)
- **S**ystemic: metastatic disease burden, stage, grade, medical comorbidities, benefits and suitability for surgery, prognosis, and risks

The neurologic factor is an extension of the epidural spinal cord compression scale (ESCC, Table 1), a 6-point grading system from axial MRI images, reliably validated by the Spinal Oncology Study Group (SOSG) (Fisher et al. 2010b). Low-grade compression is classified as Grades 0–1b that are generally suggested to undergo radiation, in the absence of mechanical instability. The oncologic assessment classifies tumors by normal response to conventional external beam radiation therapy (cEBRT), as radiosensitive or radioresistant. In the absence of mechanical instability, the authors advocate for cEBRT to treat radiosensitive tumors (i.e., lymphoma, seminoma, myeloma, breast, prostate, ovarian, neuroendocrine carcinoma), even in the presence of high-grade ESCC. Treatment of radioresistant tumors (i.e., renal, thyroid, hepatocellular, colon, non-small cell lung, sarcoma, melanoma)

Table 1 Epidural spinal cord compression scale (Tokuhashi et al. 2005)

Epidural spinal cord compression scale	
Grade	
0	Osseous only disease
1a	Soft tissue component effaces the dura without deformation of the thecal sac or abutting the spinal cord
1b	Soft tissue component deforms the thecal sac but does not abut the spinal cord
1c	Soft tissue component deforms the thecal sac and abuts the spinal cord, without cord compression
2	Spinal cord compression with CSF visible circumferentially around the cord
3	Spinal cord compression with no CSF around the cord

relies on the degree of ESCC. For low-grade ESCC, radioresistant lesions can be adequately managed by stereotactic radiosurgery (SRS) alone, unlike radioresistant high-grade ESCC, which is treated by surgical decompression and separation surgery.

Mechanical instability is an absolute indication for surgical stabilization or cement augmentation, regardless of radiosensitivity or other factors. Clinically, this commonly presents as mechanical pain exacerbated by movement, distinct from tumorigenic or biologic pain (Sciubba et al. 2010; Laufer et al. 2013; Bauer and Wedin 1995). The Spinal Instability Neoplastic Score (SINS), consisting of seven radiographic and clinical features, was developed by the SOSG to quantify instability due to metastatic spine disease (Tatsui et al. 1996). The greatest contributing factors for mechanical instability include metastatic lesions located at a junctional level (i.e., occiput – C2, C7 – T2, T11 – L1, L5 – S1), mechanical pain on clinical presentation, lytic lesions on CT, vertebral subluxation/translation, >50% vertebral body collapse from pathologic fracture, and bilateral involvement of the posterolateral elements.

Predictive Analytics

Predictive analytic scoring systems may play a role in decision-making for spinal tumors. Several scoring systems have emerged in the literature (Tokuhashi et al. 2005; Bauer and Wedin 1995; Tatsui et al. 1996; Katagiri et al. 2005; Tomita et al. 2001), in addition to machine learning prediction tools (Senders et al. 2018). These scoring systems take various factors into consideration: including performance status, primary tumor diagnosis, age, visceral/brain metastases, neurologic deficit, and number of vertebral metastases to predict survival for patients undergoing surgery. This may be instrumental for surgeons and clinicians to design the most appropriate treatment for patients with metastatic spine disease, in order to maximize quality of life and offer the most robust treatment. Algorithms have been recently proposed that consider tumor-specific and prognosis-specific survival to select the most accurate scoring system for a given patient (Ahmed et al. 2018).

Case Illustration

Mechanically Unstable Breast Metastasis to Lumbar Spine

A 39-year-old Caucasian female presented to our service with a primary complaint of right-sided mechanical back pain. She had a recent history of breast cancer treated with right-sided lumpectomy and axillary lymph node dissection followed by systemic chemotherapy (doxorubicin, cyclophosphamide, and paclitaxel) and hormonotherapy. Her disease was felt to be in remission, but outside imaging demonstrated a large lytic lesion of the L3 vertebral body and pedicle, which was biopsied and found to be consistent with ER-, PR-positive breast cancer (Fig. 3). Systemic imaging identified no other lesions, and a recommendation was made for the patient to undergo resection of the lesion with instrumented fusion.

The patient elected to pursue this intervention, which proceeded as a single-stage operation. The patient was placed prone, and a midline incision was formed over the L2–4 vertebral levels. Subperiosteal dissection was performed over these vertebral levels, extending laterally to the pedicles, which were cannulated and instrumented bilaterally at L2 and L4 and on the left side of

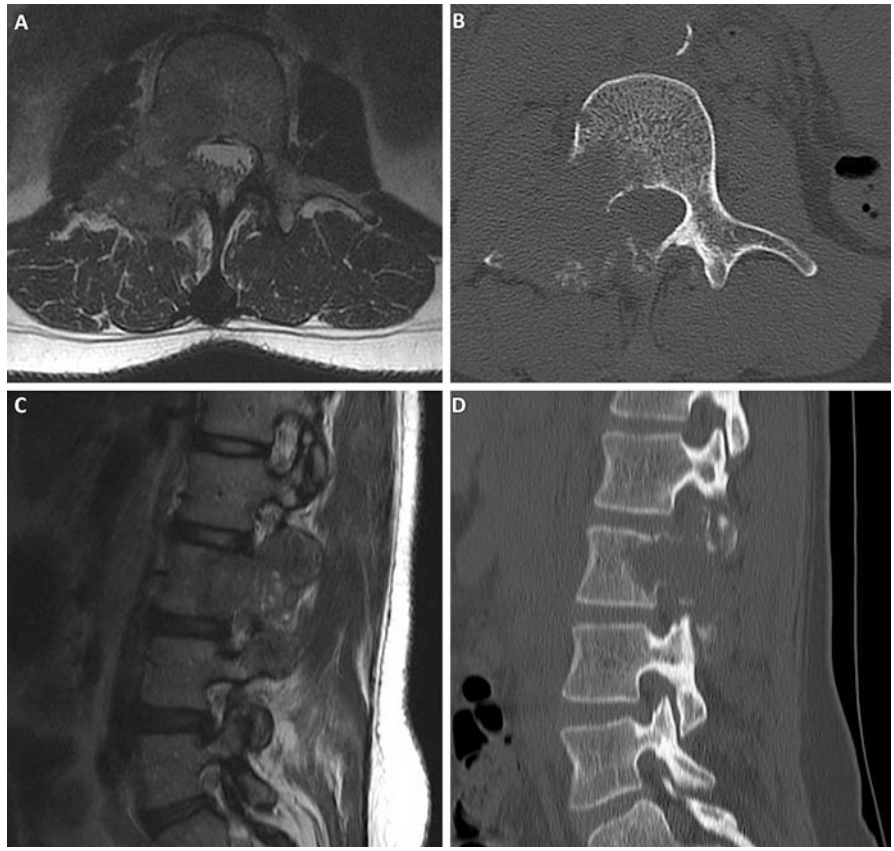

Fig. 3 A 39-year-old WF with a recent history of breast adenocarcinoma in remission presented with mechanical lower back pain. Imaging demonstrated a mass involving the right vertebral body, pedicle, and facets (**a** and **c**). The mass was lytic (**b** and **d**) with a SINS score of 8 (potentially unstable lesion)

L3. A laminectomy was then performed at the level of L3, along with a piecemeal transpedicular corpectomy of the right hemivertebra, resecting more than 50% of the body. During this, the L3 root was skeletonized and decompressed. The wound was washed with vancomycin for infection prophylaxis and solumedrol to reduce irritation of the L3 nerve root. Rods were placed bilaterally at L2–4, and following confirmation of positioning, the wound was closed in typical neurosurgical fashion (Fig. 4).

The patient's recovery was unremarkable, and she was recommended for adjuvant radiotherapy (3000 cGy in 10 fractions to the L3–5 vertebrae). She then underwent six cycles of systemic chemotherapy with docetaxel, trastuzumab, and pertuzumab. By the 3-month follow-up, the patient reported complete relief of her pain, and she remained neurologically intact. However, imaging at the 6-month follow-up demonstrated progression of disease, with new metastases involving the lungs, liver, and axial skeleton. As of last follow-up (10mo post-op), the patient remains neurologically intact, and her surgical site remains asymptomatic, though she continues to show progression of her disease, for which she is receiving trastuzumab emtansine.

Intradural Spinal Tumors

Operative Considerations

Intradural spine tumors represent 4–16% of all central nervous system neoplasms, consisting of ~60% intradural extramedullary (IDEM) lesions,

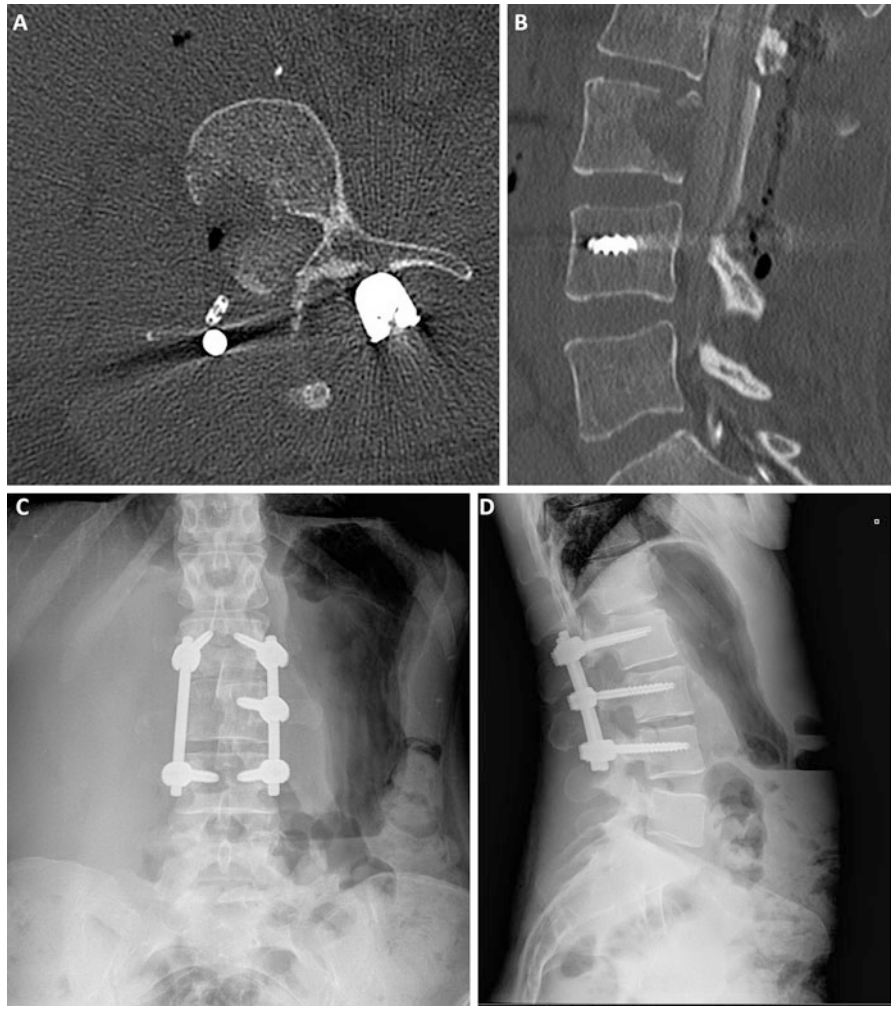

Fig. 4 Postoperative imaging demonstrating partial L3 corpectomy with adequate decompression of the thecal sac (**a** and **b**). Standing films acquired at 4-month follow-up (**c** and **d**) demonstrated good positioning of the hardware without signs of anterior column breakdown

~20% primary extradural lesions, and ~20% intramedullary lesions in adults (Hirano et al. 2012; Fehlings and Rao 2000). In pediatric patients, intramedullary, IDEM, and primary extradural lesions represent 40%, 10%, and 50% of spinal cord neoplasms (Fehlings and Rao 2000). Intradural lesions typically demonstrate indolent growth and slowly progressive neurological symptoms, with pain as the most frequent initial symptom (Samartzis et al. 2015). The majority of intramedullary lesions are benign or have a low-grade histologic diagnosis. These should be carefully distinguished from inflammatory, autoimmune, infections, or vascular conditions (i.e., multiple sclerosis, tuberculosis, granulomatous angiitis, Guillain-Barre, dural AV fistula, AVM) (Tobin et al. 2015).

Intraoperative ultrasound and neuromonitoring are critical for identification and preservation of neurologic function, respectively. Cavitron ultrasonic surgical aspirator (CUSA) is utilized for tumor debulking and resection. Neuromonitoring consists of continuous somatosensory evoked potentials (SSEP), serial transcranial motor evoked potential (MEP), and epidural (D-wave) evoked potentials (Fehlings and Rao 2000;

Samartzis et al. 2015; Tobin et al. 2015; Costa et al. 2013). Surgeons should monitor for the presence or absence of MEPs intraoperatively as well as the proportion of D-wave decrease. Intraoperative loss of MEPs and 50% reduction in D-wave amplitude have been associated wtih permanent postoperative neurologic deficit (Costa et al. 2013). Following tumor resection, laminoplasty has been demonstrated to reduce the risk of postoperative CSF leak (Nagasawa et al. 2011).

Intradural Extramedullary Tumors

Intradural extramedullary (IDEM) lesions include meningioma, schwannoma, neurofibroma, or malignant peripheral nerve sheath tumor (MPNST). Meningiomas are classically broad-based with a dural tail, isointense, homogenously enhancing, and more common in female patients, arising from arachnoidal cells of the meninges. Schwannomas are enhancing nerve sheath tumors, eccentrically located, commonly arising from the sensory nerve root, with T2-hyperintensity and possible cystic components (De Verdelhan et al. 2005; Turel and Rajshekhar 2014; Ahn et al. 2009). Myxopapillary ependymoma (WHO I) is typically located at the cauda equina, with contrast enhancement and T1-hyperintensity. These arise from the central canal, similar to traditional intramedullary ependymomas, but may seed via drop metastasis (Kucia et al. 2011).

Case Illustration

Symptomatic WHO I Meningioma

A 51-year-old Caucasian female presented acutely to our emergency department with an 8-month history of back pain and 2-month history of progressive lower extremity numbness with the subjective sensation of leg tightness and weakness. Neurological examination demonstrated minor weakness in hip flexion for the left lower extremity and clonus in the right lower extremity. Imaging demonstrated a 1.7 × 1.4 × 1.0 cm (craniocaudal, mediolateral, anterior-posterior) intradural extramedullary mass at the level of T7/8, posteriorly displacing and compressing the cord, with concomitant T2/STIR signal change consistent with cord edema. These findings were felt to be most consistent with meningioma, and given the patient's clinical picture, a recommendation was made for the patient to undergo operative management (Fig. 5).

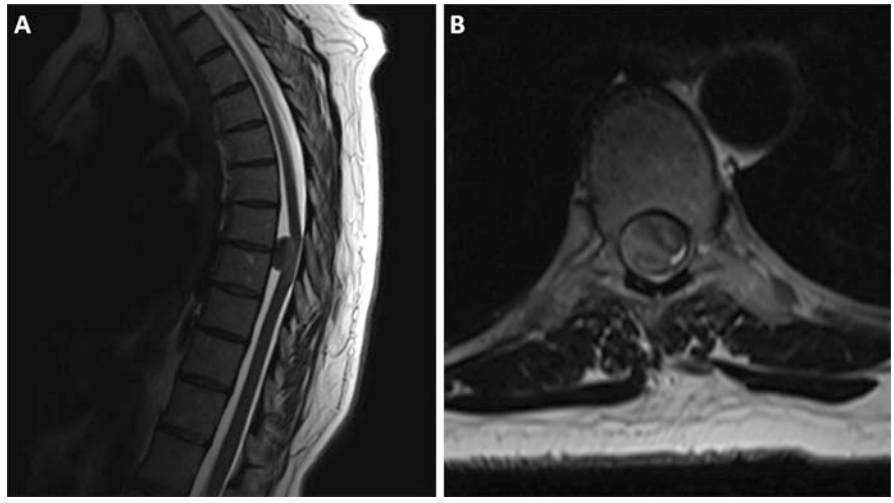

Fig. 5 A 51-year-old WF presented to the emergency department with a 2-month history of progressive BLE weakness. MR imaging (**a** and **b**) demonstrated a large intradural, extramedullary lesion at the level of T7/8 that significantly compressed the cord. Biopsy was consistent with WHO I meningioma

The patient underwent a single-stage operation using a posterior midline approach. Subperiosteal dissection was performed over the T6–8 levels, dissecting laterally to the facets. An ultrasonic bone cutter was then used to perform and en bloc laminectomy of the T6–8 levels; the laminae were delivered off the field and preserved for post-resection reconstruction. An ultrasound was then brought into the field to verify the tumor location. Under microscopic visualization, the dura was sharply incised in the midline using a #15 blade, and the flaps were retracted laterally using 4–0 silk sutures. Dissection of the arachnoid was performed using microscissors, revealing a left-sided lesion. A 5–0 Prolene suture was placed through the left-sided dentate ligament to allow manipulation of the cord, which was rotated to the right to better expose the lesion. The tumor was detached from the overlying arachnoid, followed by division of the dural attachment and separation from the adjacent cord. The lesion was delivered en bloc, and the dura was repaired with 5–0 Prolene. Valsalva demonstrated no CSF leakage, and fibrin glue was applied over the repair. The T6–8 laminae were then reattached with titanium plates, and the wound was closed in typical neurosurgical fashion (Fig. 6). The patient's

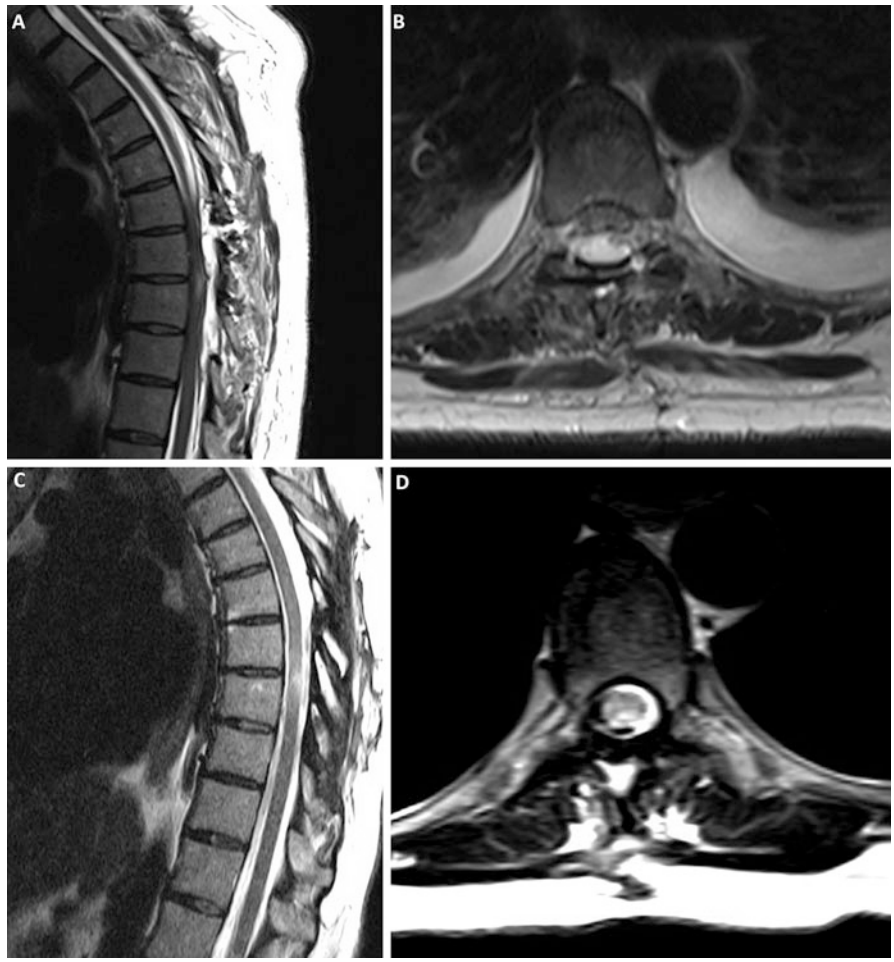

Fig. 6 Postoperative MR (**a** and **b**) demonstrated adequate decompression of the cord with residual cord deformity and T2 signal hyperintensity. MR acquired at the 4-month follow-up (**c** and **d**) showed improvement in cord deformity, though residual T2 signal hyperintensity was noted

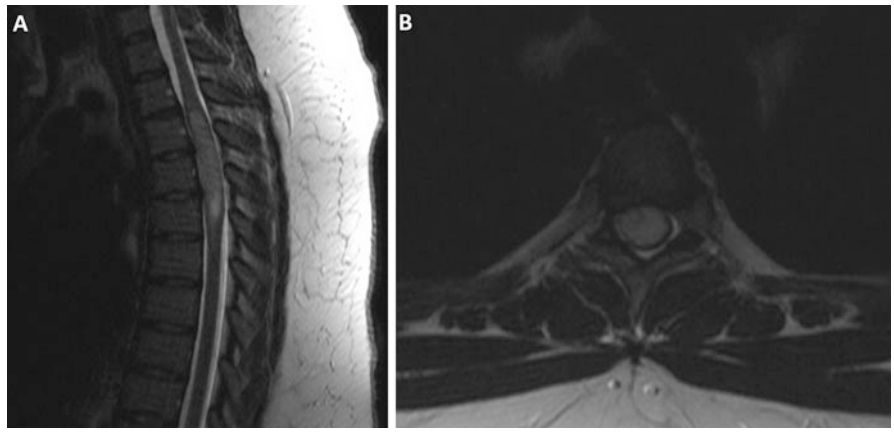

Fig. 7 A 26-year-old female presented with a 2-year history of nonmechanical upper back pain and progressive BLE weakness. MR imaging (**a** and **b**) demonstrated a large intradural, intramedullary lesion extending from T2/3 to T5/6. Histology of the surgical specimen was consistent with WHO III anaplastic astrocytoma

recovery was uncomplicated, and she was discharged on post-op day 3. At 3-month follow-up, the patient reported near-complete relief of her symptoms, with only residual circumferential numbness at the level of the lesion, which had been noted at discharge.

Intramedullary Tumors

Intramedullary lesions frequently present with a long history of symptoms, predominated by sensory dysesthesia (Samartzis et al. 2015; Tobin et al. 2015; Ferrante et al. 1992; Nakamura et al. 2008). Preoperative ambulatory status is graded by the McCormick Scale, from grade I to V (McCormick and Stein 1990). The majority of intramedullary lesions are ependymoma or astrocytoma. Astrocytoma represents ~30% of intramedullary spinal cord tumors and is the most common spinal cord tumor of children. Astrocytomas are generally hypointense on T1-weighted MRI; are hyperintense on T2-weighted MRI, eccentrically located, and cystic; and have variable enhancement (benign often enhances, i.e., WHO I juvenile pilocytic astrocytoma). In contrast, ependymomas are centrally located, originate from the central canal, and are the most common intramedullary tumor in adults, contrast enhancing, T1-hypointense, and T2-hyperintense. The "Rule of C's" can be a useful mnemonic to summarize ependymomas: cervical, contrast-enhancing, cavity (syrinx)-associated, cap of hemosiderin, and centrally located (Tobin et al. 2015; Ferrante et al. 1992; Nakamura et al. 2008).

More rarely, intramedullary hemangioblastoma, subependymoma, or intramedullary metastasis may also occur. Hemangioblastoma are subpial, highly vascular lesions, associated with a large syrinx with possible flow voids (Samartzis et al. 2015; Ferrante et al. 1992; Nakamura et al. 2008). Removal of these lesions is similar to that of an AVM, whereby arterial feeders are primarily coagulated with preservation of the dilated veins. Subependymomas are minimally enhancing lesions, located eccentrically, with T2-hyperintensity, often infiltrating the dorsal or ventral spinocerebellar tracts (Krishnan et al. 2012).

To avoid epidural bleeding and excess CSF obscuring the operative field, the dura is opened at the posterior midline before the arachnoid is incised. Myelotomy is performed at the posterior median sulcus, through either mapping of the dorsal columns or identification of vessels entering the spinal cord at this location. Due to the location of myelotomy, dorsal column dysfunction is a significant risk of the procedure (Samartzis et al. 2015; Tobin et al. 2015).

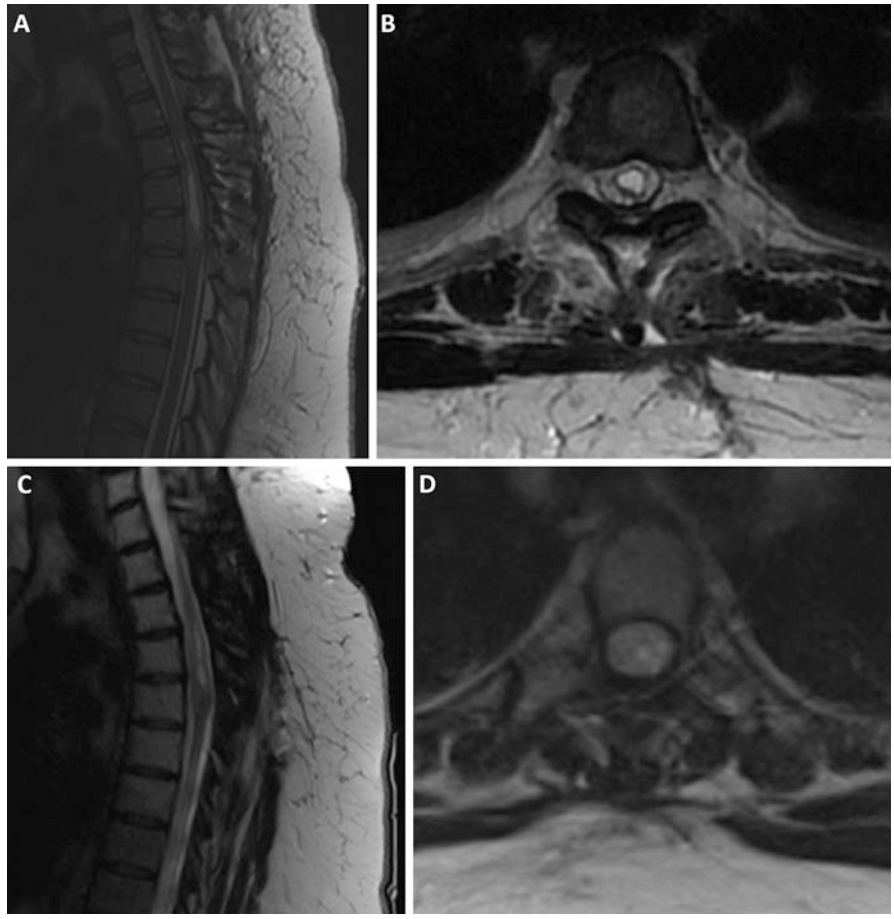

Fig. 8 Postoperative MR (**a** and **b**) demonstrated subtotal resection of the lesion with formation of large syrinx. Sequential follow-up MR demonstrated little change, with the most recent images (**c** and **d**) acquired at 41-month follow-up demonstrating slight decrease in the syrinx size

Case Illustration

Anaplastic Astrocytoma

A 26-year-old Hispanic female presented to our service with a 2-year history of progressive upper back pain accompanied by pain and tinging in her bilateral lower extremities. The patient also complained of urinary retention and progressive lower extremity weakness over the preceding 2 months, forcing her to employ knee braces and crutches for ambulation. Physical examination demonstrated mild weakness of the bilateral lower extremity, most pronounced in dorsiflexion and plantarflexion; she was also noted to be hyperreflexive in the bilateral lower extremities. Imaging demonstrated a 1.3 × 1.3 × 5.0 cm T2-hyperintense intramedullary lesion extending from T2/3 to T5/6, suggestive of an intramedullary neoplasm (Fig. 7). Surgical intervention was recommended, which the patient elected to pursue due to her worsening neurological symptoms.

Surgery was performed in a single stage using a posterior midline approach. The patient was placed prone on the Jackson table, and a #15 blade was used to incise the skin overlying the T2–5 vertebrae. Bovie cautery was used to carry the dissection through the subcutaneous tissues, and a subperiosteal dissection was carried out over the laminae, facets, and spinous processes

of the T2–5 levels. An ultrasonic bone cutter was then used to perform an en bloc laminectomy of the T2–5 levels; the specimen was delivered off the field and preserved for post-resection reconstruction. An ultrasound was then used to confirm the lesion position and to confirm that both the rostral and caudal poles were exposed. Epidural electrodes were then placed to demonstrate that stimulation of the area overlying the lesion led to no MEPs in the lower extremities. Under microscopic visualization, the dura was then sharply incised in the midline with a #15 blade, and the dural leaflets were tacked down laterally with 4–0 Nurolon sutures. The arachnoid was sharply incised and dissected laterally to expose the cord. A midline myelotomy was then performed with a #11 blade, extending the incision to the level of the rostral and caudal poles. This revealed a large lesion, which herniated through the myelotomy defect. Dissection proceeded by developing a plane between the tumor and cord parenchyma. Bipolar cautery and gentle suction were used to develop this plane circumferentially, and the tumor was resected en bloc. Hemostasis was obtained, and the dura was reapproximated using 5–0 Prolene sutures. Valsalva was performed to confirm a CSF tight seal. The laminae were then replaced and affixed with titanium microplates, and the wound was closed in typical neurosurgical fashion with interrupted 0 Vicryl in the fascia, 3–0 Vicryl in the dermis, and 4–0 Biosyn in the skin (Fig. 8).

Pathology revealed a WHO Grade III anaplastic astrocytoma with positive margins that was negative for R132H mutation in IDH-1. Postoperatively the patient was paraplegic and was discharged to an inpatient rehabilitation center on postoperative day seven. The decision was made to start the patient on temozolomide and forego radiation in order to increase the potential for spinal cord recovery. At 6-month follow-up, the patient was deemed neurologically stable with minimal recovery of neurological function in her lower extremities. Given her stable neurological status and positive surgical margins, the patient underwent conventional multifractionated radiation to the site of tumor (4500 cGy) at this time. The patient is alive at 53 months postoperatively with no evidence of disease recurrence.

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Bone Metabolism

25

Paul A. Anderson

Contents

Abstract

Poor bone mass is a common condition affecting over 50 million Americans. Consequences are fracture with increased morbidity and mortality compared to the no fracture population. The spine patients appear to be at high risk for poor health but this is often overlooked. Despite spine surgeons treating patients with

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fragility fractures, further osteoporotic care is rarely provided, thereby increasing the risk of secondary fractures. Secondary fracture prevention programs are comprehensive programs to identify those at risk and provide counseling, nutritional recommendations, physical therapy, and medication when indicated. Programs such as *Own the Bone* are highly effective and can reduce the risk of secondary fracture by 40%. Increasingly, evidence has also linked poor bone health to poor outcomes after spine surgery. Vitamin D deficiency is almost universal, and osteoporosis, when present, is associated with increased nonunion and hardware complications. A proposal for preoperative bone health optimization using methods similar to secondary fracture prevention has been recommended. In this program, if patients are osteoporotic, then, if possible, surgery should be delayed until bone health is improved.

Keywords

Osteoporosis · Secondary fracture · Secondary fracture prevention · Fracture Liaison Service · Spine surgery · Preoperative bone health optimization · Vitamin D deficiency

Introduction

Poor bone health status from osteopenia and osteoporosis is a major health concern throughout the world. Despite accurate diagnostic tests and effective treatments, osteoporosis care is lacking for the majority of patients. For example, primary care utilizes guideline-based assessment, and treatment is less than 10% of patients for primary osteoporosis prevention (Camacho et al. 2016; Cosman et al. 2014). Secondary fracture care after an osteoporotic-related fragility fracture occurs in less than 20% of patients and has not improved in the last 20 years (Balasubramanian et al. 2014).

The purpose of this chapter is to review the epidemiology of osteoporosis and its prevalence in spinal diseases. We will review updated definitions to identify osteoporosis and the consequences of osteoporosis on morbidity and mortality of spine patients, the effects on outcomes of surgery, and the results of secondary fracture prevention programs. Finally, preoperative bone health optimization programs will be introduced with the emphasis that spine surgeons can provide such care.

Epidemiology

Osteoporosis is a complex public health condition with a prevalence in 2011 in the United States of over 10 million people and over 40 million with low bone mass (osteopenia). By 2030 this is expected to increase to 14 million and 60 million people, respectively (Wright et al. 2014). Approximately 2.1 million fragility fractures occur yearly (Burge et al. 2007). This is greater than that for stroke, heart attack, and breast cancer combined. Costs of care for fractures exceed $19 billion per year and will increase dramatically in the future. Hospitalizations for fragility fractures in 2011 occurred in 325,000 patients with hip fractures and 246,000 for spine fractures (the second most common fragility fracture requiring hospitalization). The incidence of clinical vertebral fractures is related to gender and age. For example, 3.5% of females compared to 1.6% of males require hospitalization for fragility fractures (Burge et al. 2007; Ballard et al. 2018). In patients over the age of 80, fragility fractures resulted in 6.4% of all hospital admissions compared to 1% of patients in their 60s. Burge estimated that there will be a 75% increase in fractures between 2005 and 2025 in women and a 25% increase in men. Costs will increase in the same proportions (Burge et al. 2007).

Morbidity and Mortality of Fragility Fractures

Osteoporotic fragility fractures are life-changing events resulting in reduced independence, chronic pain, loss of function, diminished health-related quality of life, and increased mortality. Tajeu

found that after hip fracture, there is overall 28% mortality at 1 year which was 2.2 times higher than those without hip fracture. Disability and loss of independence were four times higher, and destitution was twice as likely after hip fracture when compared to control (Tajeu et al. 2014). Lau found the same findings in a large Medicare database study of 97,000 patients having vertebral fracture; mortality was over 2–3 times higher than expected depending on the age at time of fracture (Lau et al. 2008). Chen examined the social consequences after hospitalization for vertebral fracture (Chen et al. 2013). Forty percent were discharged to skilled nursing homes, and 15% required home health, whereas only 14% of patients were able to return home immediately.

Pain is also common after vertebral fracture. Chen found that baseline pain after fracture was of 7.8/10 and decreased to 3.4 at 6 months of follow-up (Amin et al. 2014). The baseline pain is greater than any studies for elective spine surgery. Health-related quality of life is also significantly diminished. Tosteson reviewed patients with hip and/or spine fractures using the SF-36 5 years after fracture (Tosteson et al. 2001). Only 13% of patients reported no limitations of activities of daily living (ADLs), whereas 25% of the spine fractures and over half the hip fractures have significant limitations of ADLs. Similarly, the SF-36 decreased by 1 standard deviation after spine fracture, 1.6 standard deviations for hip fracture, and 2 standard deviations for patients with combined hip and spine fractures. Svensson performed structured narrative interviews of octogenarians after vertebral fractures (Svensson et al. 2016). Patients consistently reported struggling to understand a deceiving body, breakthrough pain, and fear of isolation, dependency, and an uncertain future.

Secondary Fracture Risk

An important impetus for secondary fracture prevention is that one fragility fracture begets another. Hodsman reported a 12% increase in secondary vertebral fracture risk at 2 years, 16% by 5 years, and 25% at 10 years (Hodsman et al. 2008). Center followed patients for 16 years determining the incidence of secondary vertebral fracture. The risk per 1,000 patient years was 80 in females and 100 in males (Center et al. 2007). The relative risk of a new fracture in those with prior fracture was 2.5 in females and 6.2 in males. Kanis pooled placebo-controlled randomized controlled trials (RCT) for assessment of alendronate (Kanis et al. 2004). In the placebo group, 26% had prior fragility fracture. The relative risk of a new fracture in patients with prior fracture was 1.8 for females and 2.0 for males. Anderson reported results of a meta-analysis of nine RCTs of vertebroplasty versus control (Anderson et al. 2013). In the placebo treatment group, 18.8% of patients had a secondary fracture within 12 months of injury. Lindsay pointed out that the number of vertebral fractures significantly increased secondary fracture risk (Lindsay et al. 2001). Those patients with a single fracture had a 4% risk within 1 year, whereas those patients presenting with two or more fractures had a 25% risk.

Secondary Fracture Prevention

Osteoporosis care, even after fracture, is poorly managed throughout the world. The care is ideally suited for primary care, but unfortunately primary care physicians do not have the time to care for bone disease and are often confused by the many conflicting guidelines and complicated pathways (Binkley et al. 2017a). In 2004, the US Surgeon General reviewed bone health and osteoporosis throughout the United States noting that there was a gap between what we know and its application (American Orthopaedic Association 2005). Primary care physicians and orthopedic surgeons rarely discuss osteoporosis with patients having fractures. In response to the Surgeon General's report, the American Orthopedic Association (AOA) initiated the "Own the Bone" program in recognition of the failure of primary care (American Orthopaedic Association 2005). This is a quality improvement program to provide optimum secondary fracture prevention. In this model, fragility fractures are seen as a sentinel

event, an opportunity to encourage patients to obtain management of their bone disease.

In a systematic review of secondary fracture prevention programs, Ganda identified four types (Ganda et al. 2013). In Type A, a Fracture Liaison Service (FLS) coordinator is imbedded into the fracture team and assumes the entire care of bone health. In Type B, the coordinator is also imbedded in the fracture team but refers the follow-up osteoporosis care to the primary care physician (PCP). The initial consultation is provided at the time of fracture hospitalization. In Type C programs, the patient is seen, provided educational material regarding the need for further fracture evaluation care, and communication is sent to the primary care physician. Type D simply instructs the patient to obtain further osteoporosis care through their PCP. As would be expected, treatment is directly correlated to the intensity of effort. In the Type A program, 79% of patients receive DXA and almost all have recommendation for pharmaceutical therapy. In the Type B program, 59% of patients obtain DXA and 40% are prescribed medications. In Type C, 43% receive DXA and 23.4% pharmaceutical medications, and in Type D, only 8% of patients received any secondary fracture care (Table 1).

Although secondary fracture prevention is highly effective, over the last 20 years, no improvement in the incidence of patients receiving care has occurred. Leslie reported that from 1996 to 2006, there continued to be less than 20% receiving secondary fracture prevention (Leslie et al. 2012). Balasubramanian more recently reported that the percentage of patients receiving secondary fracture prevention is actually worsening with only 19% of patients receiving fracture prevention care which was less than occurred in 2001 (Balasubramanian et al. 2014). In men, only 10% received secondary fracture care. Flais identified causes for the lack of secondary fracture prevention (Flais et al. 2017). In 35% of cases, there was a lack of awareness on the part of the PCP that further care was needed, and in 17% of cases, there was a lack of awareness of the PCP that the patient even had a fracture. These are modifiable with a comprehensive care program.

Outcomes of Secondary Fracture Prevention

Secondary fracture programs have been shown to be effective. Bawa found that only 10.6% patients were treated with anti-osteoporotic medications after fracture (Bawa et al. 2015). However, this group had a 40% reduction in secondary fractures compared to non-treated patients (Bawa et al. 2015). In England and Wales, a quality improvement program to have all hip fracture patients receive secondary fracture prevention was instituted in 2005 (Hawley et al. 2016). Hawley reported a 30% reduction in secondary fracture risk (Hawley et al. 2016). Several studies from Australia comparing hospitals with fracture liaison services to those without document a secondary fracture reduction of over 50%

Table 1 Secondary fracture prevention programs

		DXA recommendations	Pharmaceutical recommendations
Type A	FLS coordinator Imbedded in orthopedic trauma team Assumes entire care of bone health	79.4%	46.4%
Type B	FLS coordinator Imbedded in orthopedic trauma team Refers bone health care to primary care	59.5%	40.6
Type C	Inpatient consult Education Communicates with primary care	43.4%	23.4
Type D	Education Refer to primary care	–	8.0

FLS Fracture Liaison Service

(Nakayama et al. 2016; Lih et al. 2011). Curtis calculated that the number needed to treat to prevent subsequent major fracture depending on initial fracture type and patient age was between 8 and 46, thought to be well within the acceptable range for cost-effective care (Curtis et al. 2010). Secondary fracture prevention is highly effective but has proven difficult to implement across populations. It is recommended that when spine surgeons treat osteoporotic-related fractures they assure that patients receive secondary fracture prevention.

Own the Bone Quality Improvement Program

One example of a secondary fracture prevention program is "Own the Bone" (Bunta et al. 2016; Dirschl and Rustom 2018). The goal of this program is to break the fragility fracture cycle. The introduction of the Fracture Liaison Service provides assessment, education, nutrition recommendations, elimination of toxins, and, when indicated, pharmaceutical management. The *Own the Bone* program identifies fragility fracture patients older than 50, consults during the "teaching moment," and initiates multi-disciplinary care. *Own the Bone* provides documentation in a registry and many educational opportunities for patients and providers. Over 250 programs are distributed throughout the United States, and over 50,000 patients have been entered in the *Own the Bone* program. The program is adaptable to all health-care settings, not just academic medical centers; more than 50% of the programs are in community-based hospitals or physicians' practices.

Diagnosis of Osteoporosis

The World Health Organization (WHO) utilizes bone mineral density from dual-energy x-ray absorptiometry (DXA) to classify osteoporosis (Camacho et al. 2016). This was a major improvement in the understanding, diagnosis, and treatment of this disease. Because of the differences in bone mineral density obtained, depending on the type of scanner, a statistical methodology is utilized. Patient bone mineral density is compared to young healthy female between 20 and 30 age years (T-scores) or age-gender matched controls (Z-scores). The T- and Z-scores are calculated using the formula:

$$\text{T or Z Score} = \frac{\text{BMD Patient} - \text{BMD Reference}}{\text{SD Reference}}$$

The WHO criteria for osteoporosis is a T-score less than −2.5. Osteopenia (or what is now called low bone mass) is a T-score of −1.0 to −2.5. Normal bone is greater than −1.0.

The use of the World Health Organization T-scores, although an advancement, is problematic as there is poor association with the fracture in over 50% of cases and does not aid in treatment decisions. Recent guidelines by the National Osteoporosis Foundation (NOF) and the American Association of Clinical Endocrinology have combined bone mineral density with established function (Camacho et al. 2016; Cosman et al. 2014). The criteria for osteoporosis is any of the following: T-score of −2.5; a recent fragility spine or hip fracture; low bone mass (−1.0 and −2.5) and a fragility fracture; and low bone mass and high fracture risk probability (FRAX).

More important than BMD to the diagnosis of osteoporosis is the fracture risk of the patient which is based on measurable risk factors and BMD. A number of instruments have been created to assess fracture risk. The Fracture Risk Assessment Tool (FRAX) probability assesses the 10-year risk of hip and major osteoporotic fracture based on 12 known risk factors. Risk factors include demographics, known risk factors for osteoporosis, and femoral neck bone mineral density T-scores. Fracture risk can be determined without DXA, although this is more often used to screen patients for the need for DXA. The FRAX identifies the 10-year risk of hip and major osteoporotic fractures (Table 2). The criteria for recommendation for pharmaceutical treatment are when the fracture risk for hip fracture is greater than 3% and major osteoporotic fracture greater than 20% (Camacho et al. 2016).

Table 2 Fracture Risk Assessment Tool (FRAX) risk factors

Age	Smoking history	Interpretation of FRAX
Gender	Alcohol consumption >3 units/day	Without DXA >9.5% 10-year risk of major fracture indicates need for DXA
Height	Inflammatory arthritis	Osteoporosis diagnosis >3% 10-year risk hip fracture >20% 10-year risk of major fracture
Weight	Glucocorticoid use (>5 mg prednisone daily)	
Prior fracture	Secondary osteoporosis	
Parent with hip fracture	Bone mineral density (DXA), T-score, or trabecular bone score	

Dual-Energy X-Ray Absorptiometry (DXA)

The gold standard to measure BMD is DXA. It is important that spine surgeons be able to interpret their own DXA like other diagnostic tests. The BMD is taken at three regions of interest (ROI): the proximal femur, the lumbar spine, and the distal 1/3 radius. Unless unavailable, the BMD of the proximal femur T-score is used to classify bone health (Fig. 1a–d). If the proximal femur is not available due to surgery or other bony abnormalities such as osteoarthritis, then the spine and/or distal radius is used. It is common to have discordant results between ROIs and this may have important implications. For example, lower third distal radius score with relatively normal hips and spine may indicate hyperparathyroidism.

Advances in Bone Densitometry

There are several adjuncts to bone mineral density testing that may aid in classification and directing treatment. A vertebral fracture assessment (VFA) can be obtained during DXA (Fig. 1e). The patient is turned in a lateral position and a low-energy x-ray from approximately T4 to L5 is obtained. This is a true lateral, with the x-ray beam always parallel to the disc spaces avoiding parallax. Utilizing the VFA, occult fractures can be identified using morphologic criteria of Genatt (Fuerst et al. 2009). It is estimated that at least 20% of patients having DXA scans may have occult spine fractures (Jager et al. 2011) and result in a change in their diagnosis to osteoporosis. The trabecular bone score (TBS) is a new software technology that assesses the microarchitecture of bone (Harvey et al. 2015). The TBS measures the heterogeneity between pixels of bone cross sections obtained from DXA (Fig. 1e). Osteoporotic bone will have voids between pixels compared to normal bone and thus high heterogeneity. TBS is assessed as follows: <1.23 is degraded microarchitecture; 1.23–1.31 is partially degraded; and greater than 1.31 is intact. The TBS is better than BMD-based T-scores for fracture prediction and can be used in FRAX (Schousboe et al. 2016). The trabecular bone score may be of more importance to spine surgery when considering instrumentation. Further research in the use a trabecular bone score to predict surgical outcomes is needed.

Opportunistic CT

Computed tomography (CT) is a frequent diagnostic test and may be used to assess bone quality. CT is based on x-ray attenuation determined for each voxel of tissue. Attenuation is dependent upon the density and atomic mass of atoms in the tissue thus, in the case of bone, to bone mineral density. X-ray attenuation is measured by the Hounsfield unit (HU) which is normalized based on air (-1000) and water (0). The Hounsfield unit is easily obtainable from all CT using the elliptical tool available on the picture archiving and communication system (PACS) (Fig. 2). A region of interest is drawn and the mean HU in that area is displayed. Cortical bone typically will have an HU of 500 and normal trabecular bone such as vertebral body greater than 150. Using CT obtained for other reasons to estimate bone health is termed "opportunistic CT" and can

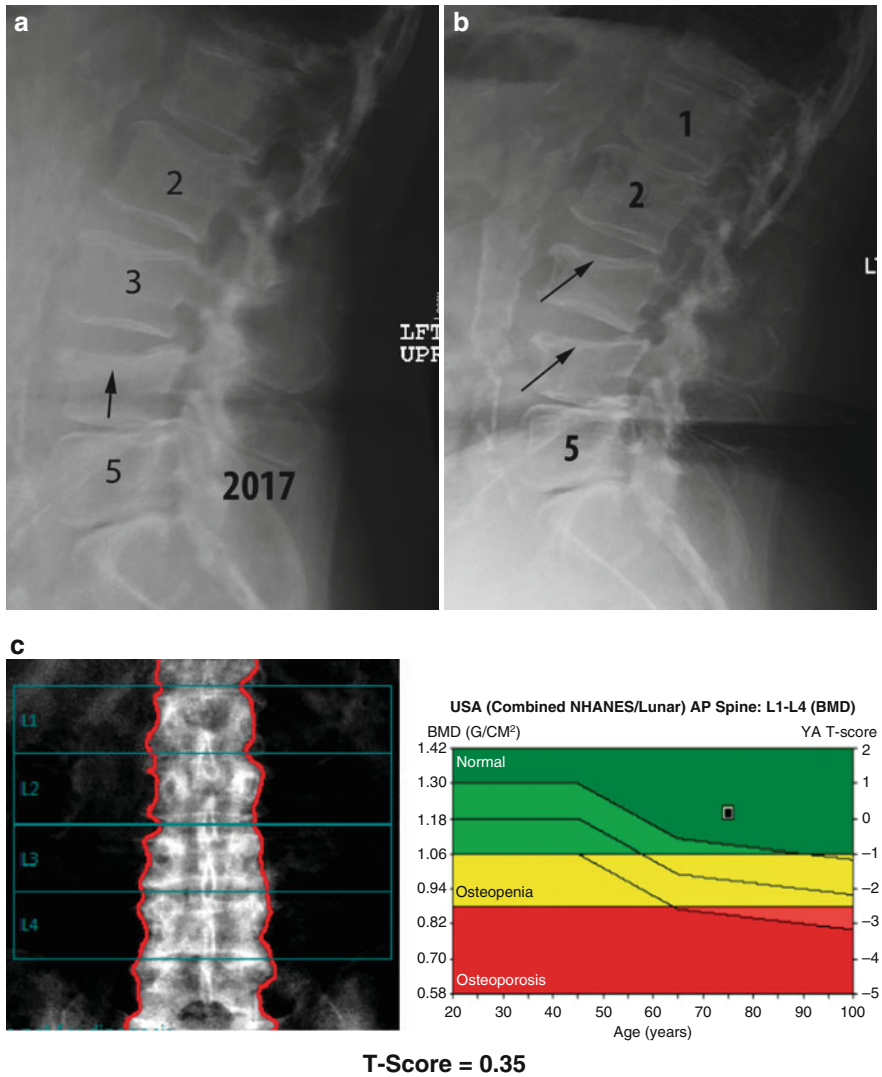
aid in determining those patients that need further evaluation and predicting failure of surgical procedures (Meredith et al. 2013; Schreiber et al. 2014; Pickhardt et al. 2013).

Thresholds for opportunistic CT have been established for the lumbar spine. Pickard recommended using a threshold of >150 HU to exclude osteoporosis and HU values less than 110 rules in osteoporosis. HU values of 135 or less suggest further workup or evaluation with DXA is needed and that there is a likelihood of low bone mass or osteoporosis (Carberry et al. 2013).

Treatment for Osteoporosis

Education

The treatment of osteoporosis begins with recognizing that osteoporosis is present in the case of a fragility fracture and may potentially be present in a preoperative spine surgery candidate (Table 3) (Camacho et al. 2016). Patients with osteoporosis should receive education regarding bone health and what they themselves can do to reduce further bone loss. Education should



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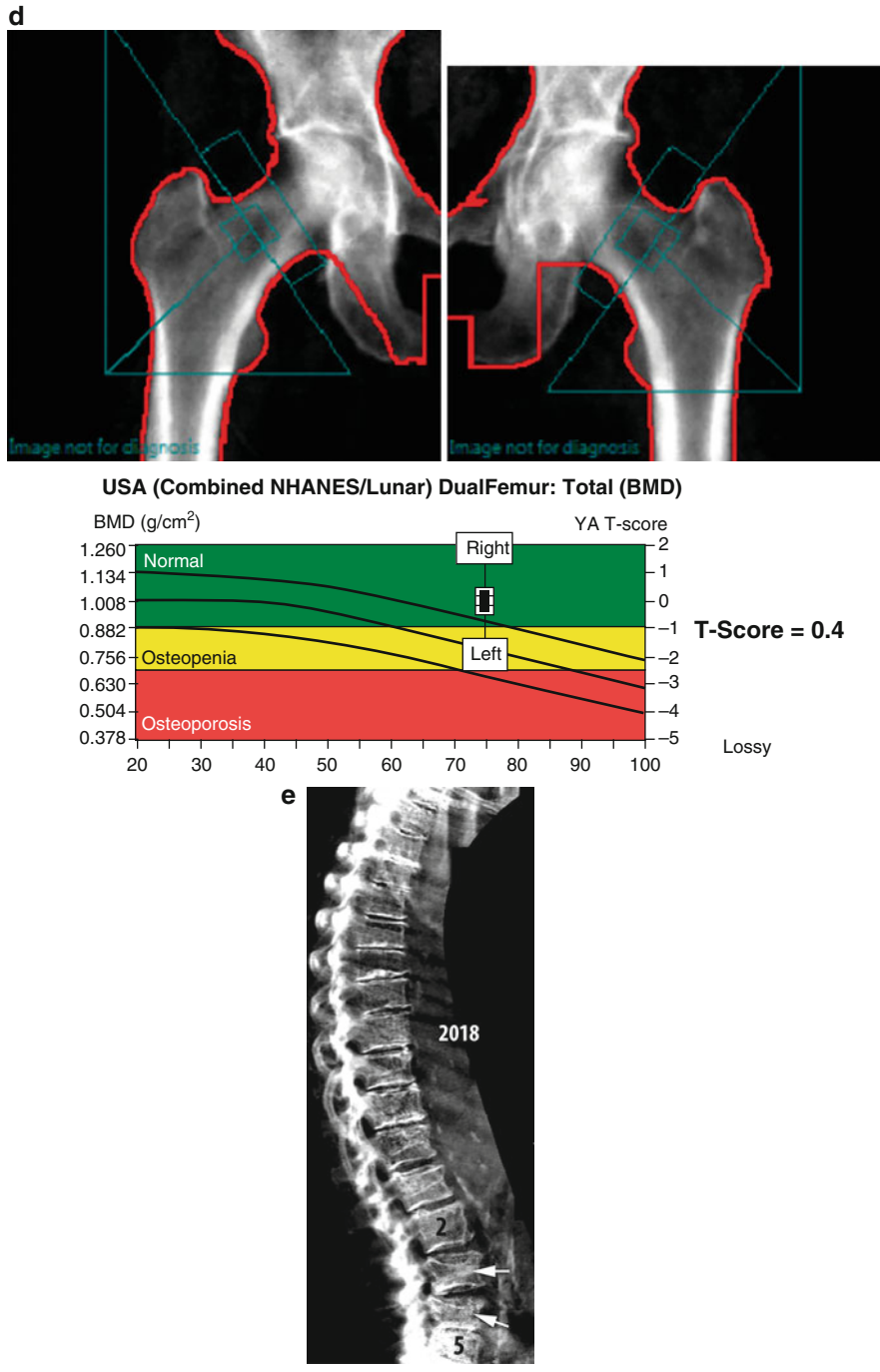

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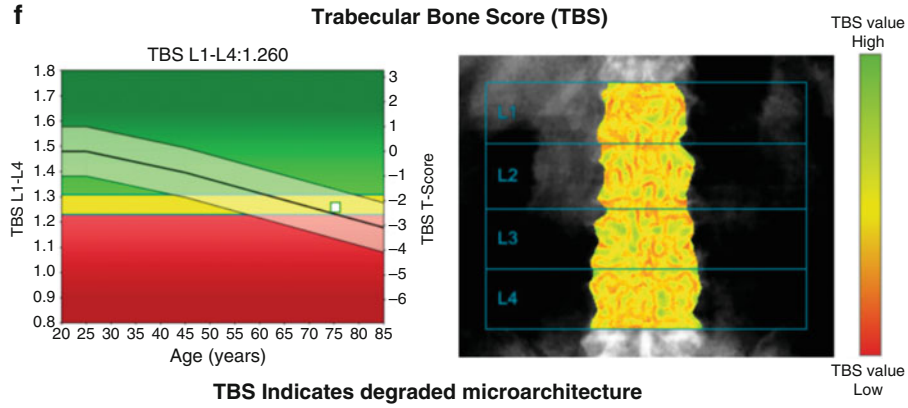


Fig. 1 (**a**) A 57-year-old female sustained a superior endplate fracture of L4 from a ground-level fall. No further evaluation was done despite a diagnosis of osteoporosis based on spinal fracture from ground-level fall. The patient did well with resolution of pain. (**b**) One year later she had a compression fracture of L3 after another ground-level fall (arrows). Laboratory evaluation revealed 25(OH) vitamin D of 12 ng/ml. (**c**) Spine DXA shows a T-score of 0.3. This is unreliable due to degenerative changes. (**d**) Hip DXA also shows normal bone mineral density. (**e**) Vertebral fracture assessment shows fractures at L3 and L4 (arrows). (**f**) Trabecular bone score (TBS) shows degraded bone microarchitecture

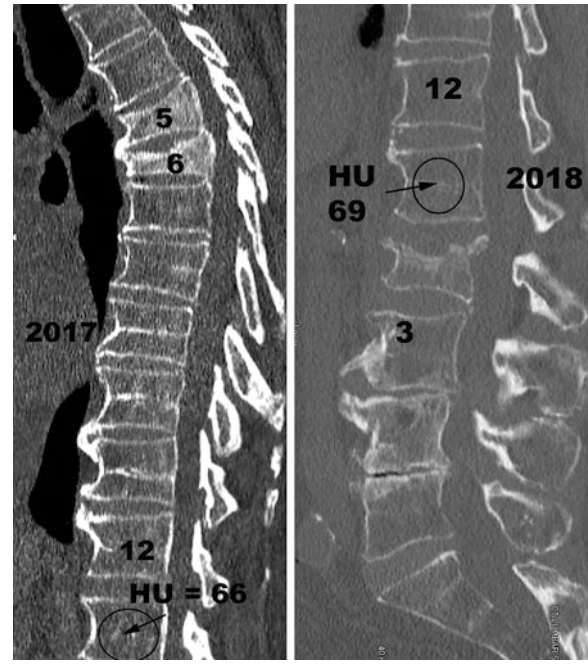


Fig. 2 Sagittal CT from 2017 and 2018. In 2017 fractures of T5 and T6 are present. An oval region of interest of L1 (ellipse) has a mean Hounsfield unit (HU) of 86 which indicated high probability of osteoporosis. In 2018 a new L2 fracture is present. The HU at L1 remained low

Table 3 General principles of osteoporotic care

1	Consider poor bone health
2	Patient education
3	Eliminate toxins
4	Provide nutrient supplements
5	Fall prevention and balance
6	Screen for secondary causes of osteoporosis
7	Assess for need for further testing (consider fracture risk)
8	Communication with primary care
9	Medications for high fracture risk

include the consequences of osteoporosis, identification of risk factors, and natural history. Toxins that affect bone health should be eliminated such as smoking and drinking in excess of two alcoholic beverages per day. Nutritional needs should be assessed. Osteoporotic patients are often underweight or morbidly obese. In addition, sarcopenia (loss of muscle mass and function) is common in osteoporotic patients (Tarantino et al. 2013). Therefore, weight-bearing exercises such as walking or jogging should be discussed. Fall risk should be assessed and, if warranted, fall prevention therapy recommended. During examination, fall risk can be assessed using the "timed up and go test" in which the patient should be able to arise from a chair without using his hands and walk 3 meters, turn around, and sit again. Patients who exceed 20 s are at increased risk of fall. Another test is grip strength using a dynamometer; men should have 15 kg and women 10 kg of grip strength. Fall prevention at home should be discussed including elimination of obstructions, with special attention to the bathroom where falls frequently occur at night.

Nutritional Supplementation

Vitamin D has important effects on bone physiology. Vitamin D promotes osteoblastic differentiation and osteoblastic-mediated mineralization. Vitamin D is involved in calcium regulation, and, when under hypocalcemic conditions, it increases the differentiation of monocytes to osteoclasts. In addition, vitamin D increases collagen crosslinking leading to stronger bones. Serum vitamin D is measured as the 25(OH) vitamin D. 25(OH) vitamin D is one of the many metabolites and is in the greatest concentration. It is felt to represent long-term stores of vitamin D. 25(OH) vitamin D is bound by acute-phase reactants and therefore may be lower immediately after surgery or trauma (Binkley et al. 2017b). Although the normal vitamin D level is unknown and remains controversial, most authorities agree that normal exceeds 30 ng/ml (Table 4) (Camacho et al. 2016). An insufficient condition is between 20 and 30 ng/ml and deficient is less than 20 ng/ml.

Table 4 Classification of 25(OH) vitamin D status

	25 (OH) vitamin D (ng/ml)
Normal	>30
Insufficient	20–30
Deficient	<20

Multiple studies have shown that the majority of patients preoperatively have vitamin D deficiencies or insufficiencies (Stoker et al. 2013; Ravindra et al. 2015a; Kim et al. 2013). Therefore, spine surgeons should consider treating all patients with vitamin D prior to surgery or after fracture. Vitamin D supplements vary in potency. Ergocalciferol (vitamin D2) is less potent and is not measured on some assays; therefore, it is not recommended. Cholecalciferol (vitamin D3) is more potent. The author recommends that all patients take 2000 U vitamin D3 daily. Preoperative patients who are insufficient should consume between 2,000 and 5,000 U daily. Deficient patients are prescribed 50,000 U vitamin D3 weekly for 6 weeks and then have levels rechecked.

In addition to vitamin D, adequate calcium intake is required. In adults, 1,200 mg of calcium intake is the recommended daily requirement (Camacho et al. 2016). This can be obtained through the diet largely through the consumption of milk products. An 8 ounce glass of milk or equivalent is approximately 250 mg. If dietary intake is insufficient, then calcium supplements should be recommended. Either calcium citrate or a calcium carbonate compound is effective. It is best if calcium can be obtained dietarily, rather than by supplements if at all possible.

Secondary Causes of Osteoporosis

Primary osteoporosis is the age-related loss of bone mass especially in females after menopause. Secondary causes from medical disease and medications are common and should be screened (Camacho et al. 2016; Cosman et al. 2014). Most important is to identify endocrine disorders such as hyperparathyroidism and hyperthyroidism, cancer especially multiple myeloma, and liver and renal disease. The author recommends screening with complete blood count, complete metabolic panel, 25(OH) vitamin D, intact parathyroid hormone, phosphate, and 24-h urine collection for calcium, sodium, and creatinine. Other tests will be dictated by results of history and physical examination.

Pharmaceutical Management

Pharmaceutical management is recommended in patients who have high fracture risk as assessed by FRAX (Camacho et al. 2016). Specifically, those patients who have a 3% or greater 10-year risk of hip fracture or 20% or greater 10-year risk of major fracture are considered candidates for pharmaceutical treatment. Two classes of medications are available: anti-resorptive and anabolic.

Anti-resorptive medications include bisphosphonates, calcitonin, denosumab, and estrogens. Bisphosphonates bind to hydroxyapatite on their resorptive surfaces preventing osteoclastic enzymatic breakdown of bone. In addition, they cause apoptosis of osteoclast cells. Denosumab is a monoclonal antibody inhibitor of the receptor activator of nuclear factor kappa-B (RANK) ligand. RANK ligand activation is required for activation of preosteoclast to osteoclast and is prevented by denosumab. Bisphosphonates and denosumab have consistently been shown to reduce fractures by 50–70% at 3 years for primary osteoporosis and after fracture (Camacho et al. 2016; Cosman et al. 2014).

Calcitonin is an older anti-resorptive medication; however, there is increased risk of cancer and this is rarely used today. Estrogens and estrogen analogs also have anti-resorptive effects but carry risk of venous thromboembolic disease and cancer so are rarely utilized for osteoporosis currently.

Two recombinant parathyroid hormone analogs are approved for osteoporosis: teriparatide and abaloparatide. The mechanism of action for anabolics is promoting osteoblastic differentiation, and they are highly effective at reducing risk of fracture in osteoporotic patients (Camacho et al. 2016; Cosman et al. 2014). The indications for which insurers will pay for the anabolic agents will vary. However, they are indicated after failure of anti-resorptive medications or in high-risk patients such as those with high FRAX risk scores or on glucocorticoids. The anabolic agents are delivered by daily injection and costs range from $1,800 to $3,200 per month for 18–24 months.

Complications of Medical Treatment of Osteoporosis

Bisphosphonates and denosumab have been linked to atypical femur fracture and osteonecrosis of the jaw. Atypical femur fractures are stress fractures located in the femoral subtrochanteric area (Shane et al. 2014). Initially there will microfracture of bone and then eventually a stress fracture will occur. This is often bilateral. Atypical femur fractures are directly related to duration of exposure (Camacho et al. 2016). In general, the increase is seen after 5 years of treatment or in cancer patients who are given large doses of the IV form of bisphosphonate. It is estimated that bisphosphonates prevent between 15 and 100 fractures for every 1 of atypical femur fractures. As a consequence, drug holidays are commonly prescribed (Camacho et al. 2016; Cosman et al. 2014). Specifically after 5–7 years, it is recommended that bisphosphonates be discontinued. Some loss of bone mineral density will occur after withdrawal of bisphosphonates, although fracture risk does not appear to be affected. However, in some patients, rapid bone loss occurs after drug withdrawal and therefore monitoring needs to continue. In very-high-risk patients, it is not

recommended to use a drug holiday (Muszkat et al. 2015).

Preoperative Optimization of the Spine Surgery Patient

Spine surgeons are increasingly recognizing the linkage of poor outcomes and complications to the presence of osteoporosis and, therefore, are considering preoperative bone health optimization (Lubelski et al. 2015). Preoperative optimization of bone health requires assessment, recommendations for nutritional support, elimination of toxins, assessment of fall risk, and potentially pharmaceutical management with a delay in surgery.

Vitamin D deficiency has been examined in patients undergoing spine fusion. Stoker found that only 16% of patients had normal vitamin D levels, Ravindra only 31%, and Kim none (Stoker et al. 2013; Kim et al. 2013; Ravindra et al. 2015b). The majority of patients were actually deficient, <20 ng/ml. In addition, osteoporosis and osteopenia are also quite common in the preoperative spine patient. Bjerke found that only 31% of patients had normal BMD, 59% were osteopenic, and 10% were osteoporotic (Bjerke et al. 2017). These were findings similar to Yagi and Wagner (Yagi et al. 2011; Fujii et al. 2013). Thus, the majority of adult patients undergoing spine surgery have vitamin D deficiencies and osteopenia or osteoporosis.

Outcomes in osteoporotic patients and vitamin D-deficient patients have been examined. Ravindra found that the time to fusion was significantly lower in patients who are vitamin D-deficient (Ravindra et al. 2015a). In addition, fusion success was 3.5 times less likely in the vitamin D-deficient than normal patients. Kim found an inverse correlation between the final Oswestry Disability Index and preoperative vitamin D levels; that is, patients with high baseline vitamin D have better recovery (Kim et al. 2012).

Osteoporosis is also linked to poor outcomes of spine surgery (Fig. 3). Bjerke reviewed 140 patients who underwent spine fusion and assessed bone mineral density using the WHO criteria (Bjerke et al. 2017). In the osteoporotic patients, nonunion occurred in 46% of patients compared to 19% and 18% in normal and osteopenic patients, respectively. Complications were also significantly worse in the osteoporotic group; 50% of patients had complications compared to 33% and 22% in osteopenic and normal, respectively. Oh evaluated cage subsidence after interbody fusion in 120 osteoporotic patients finding that the severity of osteoporosis strongly correlated with the severity of cage subsidence (Oh et al. 2017). Meredith linked prediction of proximal junctional fracture after spine fusion with baseline HU. HU of <135 strongly correlated to risk of fracture in two-thirds of patients (Meredith et al. 2013).

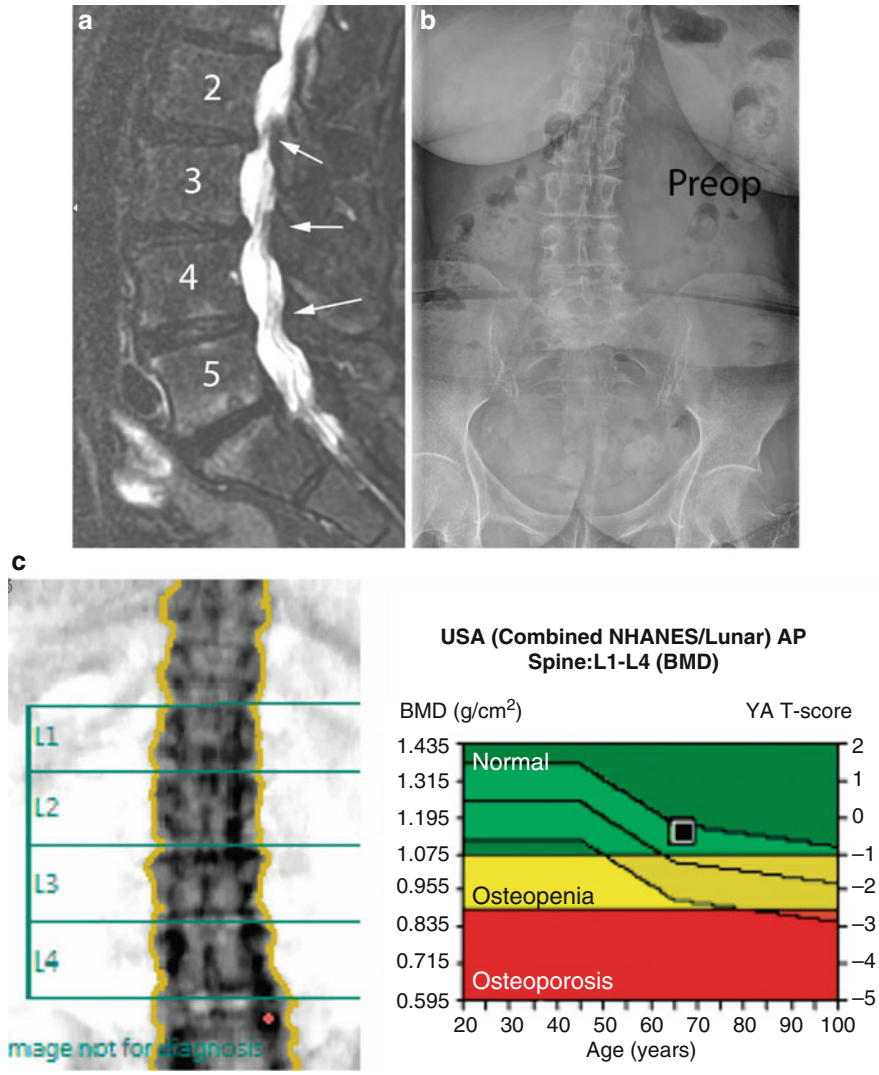
Mitigation of Poor Bone Health on Spinal Outcomes

Multiple randomized controlled trials have demonstrated improvement in clinical results, time to fusion, fusion success, and reduction of hardware-related complications in patients with osteoporosis who were treated with bisphosphonates (Stone et al. 2017). Similar results were seen with the use of anabolic agents which also show a positive effect on bone healing and reduction of bone-related complications, although no improvement in clinical outcomes was demonstrated (Stone et al. 2017; Ebata et al. 2017). Inoue randomized osteoporotic patients to teriparatide or control and assessed insertional torque of pedicle screws (Inoue et al. 2014). He found that even with only 2 months of treatment, there was a statistical improvement of insertional torque. This is consistent with investigations that show that even at 3 months, there are decreased rates of secondary fractures with treatment with anabolic agents (Kanis et al. 2004).

Preoperative Bone Health Program

No comprehensive preoperative bone health program has established efficacy. *Own the Bone* has developed an example program, although

efficacy also has not been established. It is recommended that patients older than the age of 50 years having thoracolumbar spine surgery be assessed for risk of osteoporosis as part of the preoperative workup when surgery is being scheduled. A checklist is reviewed based on current guidelines, and, if positive, the patient is scheduled for bone densitometry (DXA) (Table 5) (Camacho et al. 2016; Cosman et al. 2014). The risk factors include women older than 65 years, men greater than 70, history of inflammatory arthritis, glucocorticoid use (>5 mg of prednisone daily), diabetes mellitus, history of fracture after age of 50, and a FRAX score greater than 9.3% of major osteoporotic fracture. The FRAX is calculated without bone mineral density and is used to identify patients who need DXA. In addition, all patients are prescribed 2,000–5,000 units of vitamin D daily and 1,200 mg of calcium.



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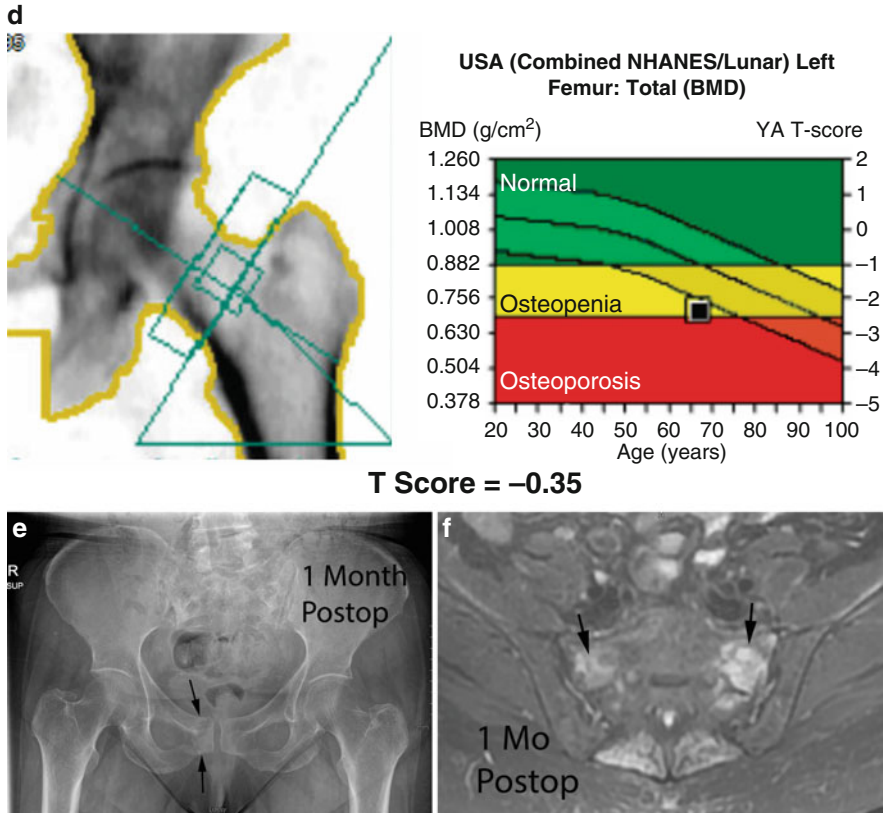

Fig. 3 (**a**) A 69-year-old female presents with neurogenic claudication from L2 to L5. Spinal stenosis is seen on T2-weighted MRI (arrows). (**b**) Her bone quality appears poor on anteroposterior radiographs. She was diagnosed 6 months earlier with osteoporosis but was untreated. (**c**) The spine DXA shows normal bone mineral density but should be ignored given her degenerative spinal disease. (**d**) The proximal hip DXA shows osteoporosis with a T-score −3.5. She was not treated for osteoporosis. (**e**) One month postoperative she presents with severe groin pain and left radicular pain and difficulty walking. Pelvic radiograph shows fracture of pubic rami (arrows). (**f**) Pelvis T2-weighted MRI shows bilateral sacral insufficiency fractures (arrows). She was subsequently started on vitamin D3, calcium replacement, and teriparatide daily injection

Table 5 Preoperative bone health assessment checklist to determine need for further evaluation and treatment

1	Females >65 years
2	Males >70 years
3	Inflammatory arthritis
4	Diabetes mellitus
5	Glucocorticoid exposure
6	Fracture after age 50
7	FRAX >9.3% (without DXA)
	Any positive criteria is evaluated by DXA

The DXA should be reviewed by the surgeon and a FRAX (with DXA) obtained. If the FRAX is greater than 3% for 10-year risk of hip or 20% risk of major osteoporotic fracture, then the patient is referred to a bone health specialist. This may be an established Fracture Liaison Service, bone health specialist, or primary care. Based on a high fracture risk, the patient should consider preoperative treatment and delay of surgery. In this case, in the author's opinion, an anabolic agent is used if insurance coverage can be obtained and the patient consents.

The surgical delay will depend upon many factors and is not evidence-based at this time. For patients with a low-risk requirement for bone healing such as laminectomy, surgical delay would only consist of 3 months. For patients who require bony fusion or who have more severe osteoporosis, a delay between 3 and 6 months

should be considered. For patients who require multilevel fusion, spinal osteotomy, or coronal sagittal plane deformities, then longer treatment of 9–12 months should be considered. After surgery the medication should be restarted.

Conclusion

Poor bone health is common and increasing in prevalence. There is a need for spine surgeons to become involved in the diagnosis and assuring that patients receive adequate treatment. Any patient over the age of 50 with a fracture requires critical evaluation for osteoporosis and probably medical treatment. In addition, surgical outcomes are strongly linked to poor bone health. These can be mitigated through the use comprehensive programs such as a Fracture Liaison Service. It is critical that spine surgeons first recognize that osteoporosis is a problem and then encourage patients to delay treatment if necessary so that surgical outcomes can be optimized and complications avoided.

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Part IV

Technology: Fusion

Pedicle Screw Fixation

26

Nickul S. Jain and Raymond J. Hah

Contents

Abstract

Pedicle screws and rods are a modern posterior spinal instrumentation system that has gained widespread adoption throughout the world as the gold standard for instrumentation of the spine over the last two decades. They provide significant advantages in that they provide rigid 3-column fixation of the spine from an entirely posterior approach without reliance on intact dorsal elements. However, there is a steep learning curve for their placement, and adequate training is required prior to their routine use. They are not without their own set of unique complications. Many modifications to pedicle screws exist to improve clinical

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outcomes including augmentation with cement, and a variety of novel technologies can be used to help improve accuracy in their placement including fluoroscopy, computer navigation, and robotics.

Keywords

Pedicle screw · Pedicle instrumentation · Transpedicular fixation · Navigation · Screw · Dorsal instrumentation

Introduction and History

Posterior spinal instrumentation has been used for decades to allow surgeons to correct spinal deformity, stabilize fractures and instability, and promote arthrodesis. They have provided surgeons many advantages including a more stable, low-strain environment for fusion procedures and more immediate stability in unstable conditions requiring fixation (Vanichkachorn et al. 1999). This allows for early patient mobility, often times eliminating the need of external orthoses. Many indications for posterior spinal instrumentation have been described including unstable thoracolumbar fractures, metastatic tumor resulting in spine instability, spondylolisthesis, scoliosis, and pseudarthrosis (Vaccaro and Garfin 1995a).

Scoliosis was previously often treated with posterior spine fusion without instrumentation. Complications included a reported 30–40% pseudarthrosis rate with progressive loss of scoliotic correction. Harrington first described a hook-rod posterior spinal instrumentation system in 1962 which allowed for distraction and compression of the spine and marked reduction in pseudarthrosis rates (1–15%) (Harrington 1962). The system provided excellent coronal plane correction but had no rotational stability or sagittal alignment control. This predisposed patients to develop a hypolordotic "flat back" but was protective against progressive kyphosis and neurological decline. Disadvantages included loss of fixation with hook disengagement in up to 20% of cases and an inability to perform short-segment fixation (Harrington 1988).

Luque in 1980 then described the first dorsal instrumentation that allowed for segmental fixation and short constructs using sublaminar wires attached to rods. The authors demonstrated decreased pseudarthrosis rates and stable fixation; however, the system did not have the ability to resist axial load. Other complications included durotomies, neurologic injury, and wire failure (Luque 1980). Cotrel and Dubousset modified this technique to use laminae or pedicle hooks to achieve segmental fixation; however, this required intact dorsal elements including the lamina and facet joints (Cotrel et al. 1988).

Pedicle fixation allows for segmental fixation of the spine while providing the ability to control axial displacement and functions independent of the presence or absence of the dorsal elements of the spine. Additionally, they are the only posterior spinal instrumentation that allows for entire 3-column fixation of the spine which provides significant biomechanical advantage. The first posterior-based screws were described in the 1940s by King as short transfacet screws with high pseudarthrosis rates (King 1944, 1948). Boucher then described a longer screw that crossed the facet joint in 1958 (Boucher 1959).

Roy-Camille first applied screws through the entirety of the pedicle attached to plates for thoracolumbar fractures, instability after tumor resection, and lumbosacral fusion (Roy-Camille 1970). Multiple newer and improved iterations were then developed in the following decades including the AO internal fixator, the variable spinal plating (VSP) system, the Cotrel-Dubousset Universal Spinal Instrumentation (USI), the Texas Scottish Rite (TSRH), and Isola systems all providing various advantages including variable angles to ease screw-rod connection. Newer, modern designs have increased adaptability with polyaxial heads, variable diameter rods, side-to-side connectors, and modern materials including titanium and cobalt-chrome alloys.

Pedicle screws are a versatile and powerful tool for posterior spinal instrumentation. They can resist load in all planes given their 3-column fixation nature and provide a powerful fulcrum for

correction of rotational, sagittal, and coronal plane deformities. Pedicle screws also allow for the surgeon to apply significant forces to the spine (including distraction, compression, and translation). They have a proven benefit in enhancing fusion rates and avoid the complications of entering the spinal canal of some of the predecessor posterior spine instrumentation systems (Lorenz et al. 1991). Additionally, they allow for earlier rehabilitation and obviate the need for postoperative external orthoses.

However, they are not without disadvantages. Pedicle screw insertion has a steep learning curve, and malpositioned screws can result in durotomies or neural injury if there is pedicle wall penetration. Their use increases operative time and cost. Additionally, they often require increased radiation exposure for both patient and surgeon, and they often obscure postoperative imaging. Additionally, the rigidity of fixation and placement of screws that violate adjacent segment facet joints may result in accelerated rates of adjacent segment degeneration. Despite these shortcomings, pedicle screws are still widely considered the gold standard for posterior spinal instrumentation today.

Anatomy of the Pedicle

The pedicle is the strongest part of the vertebra and has often been described as the "force nucleus" of the spine. The posterior elements of the vertebra converge and are linked to the anterior vertebral body and the anterior two columns of the spine by the cylindrical pedicle (Steffee et al. 1986). The pedicle is comprised of a strong shell of cortical bone with a cancellous bone core. Typically, the transverse width of the pedicle is less than the sagittal pedicle height with the exception of the low lumbar spine (Figs. 1 and 2).

Clinically, it is critical to understand the pedicle anatomy for accurate placement of screws within the pedicle. The coronal and sagittal angulation and the transverse diameter vary from level to level within the entire spinal axis. In the sagittal plane, cephalad and caudal angulation of the pedicle starts at neutral in the thoracic spine at T1 and increases to approximately 10° of cephalad angulation at T8 before decreasing back to 0° by T12 (McCormack et al. 1995). In the axial plane, beginning at T1, medial angulation decreases as one travels through the thoracic spine. In the lumbar spine, medial angulation in the axial plane increases from neutral at L1 to approximately 25–30° of medial angulation at L5. The width of the pedicle increases from L1 to S1 (Krag 1991), while the midthoracic pedicles (T4–T8) are typically considered the most narrow.

The inner diameter of the pedicle has been shown to account for 60% of the screw pullout strength and 80% of the longitudinal stiffness (Hirano et al. 1997). It has been correlated to the height of the patient. Typical screw sizes have been proposed as 4.5 mm diameter and 25–30 mm in length for T1–T3 and 4.5–5.5 mm in diameter and 30–35 mm in length from T4 to T10 (Louis 1996). Pedicles do have some plasticity and ability to undergo expansion however.

Many structures exist in close contact and surround the pedicle. Intrathecal nerve roots course along the medial aspect of the pedicle as the traversing root and have been shown to be 0.2–0.3 mm from the pedicle at T12 and touching the dura below L1. Exiting nerve roots then course beneath the pedicle and enter the neural foramen, occupying the ventral and rostral one third of the foramen (Benzel 1995a). Clinically, this is relevant as violation of the pedicle medially or caudally can injure the nerve root.

Design and Anatomy of the Pedicle Screw

The pedicle screw consists of a head, neck, body, and threads, each serving a distinct purpose (Fig. 3). The head of the pedicle screw facilitates attachment of the screw to longitudinal rods to provide fixation to adjacent segments or levels. Modern screws can have either monoaxial or polyaxial translating heads. Monoaxial screws have significant biomechanical advantages and reduce head-neck junction failure commonly seen in polyaxial screws; however some cadaveric testing has shown no differences between the two

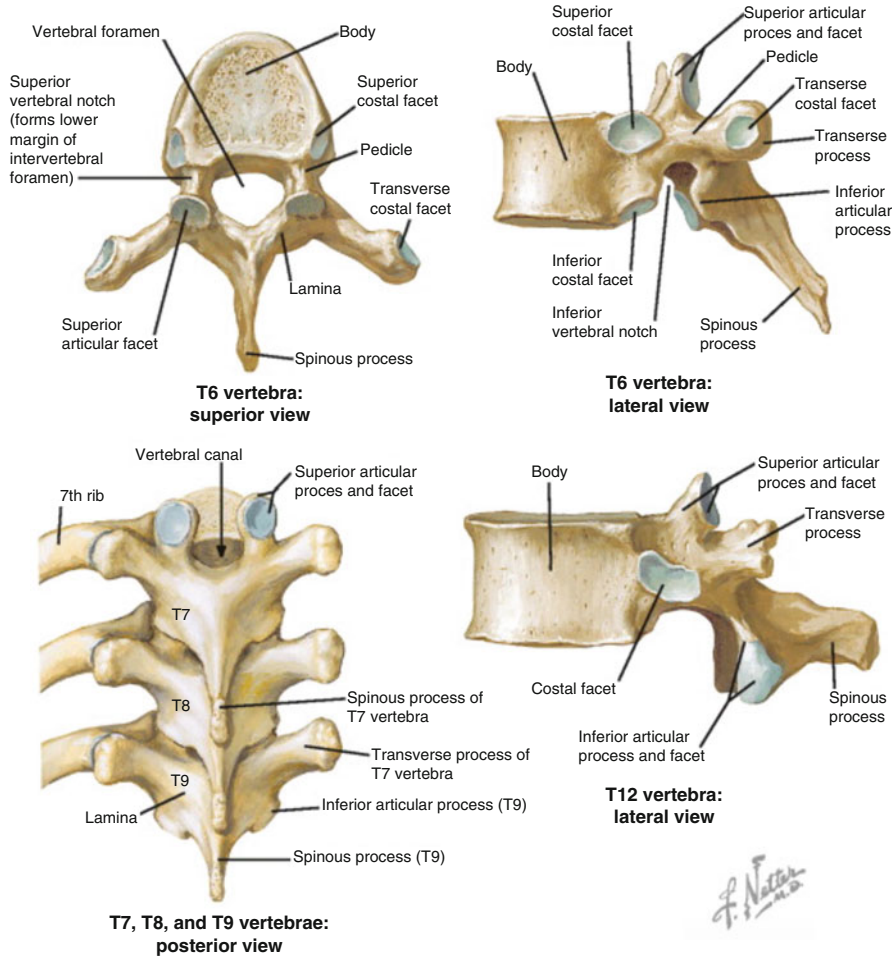

Fig. 1 Anatomy of the thoracic pedicle. (Reproduced from *Netter's Concise Orthopaedic Anatomy*, 2010 with permission from Elsevier)

in regard to construct stiffness (Fogel et al. 2003; Shepard et al. 2002). However, in exchange for this vulnerability to fatigue failure, polyaxial screws provide surgeons significant increased versatility and facilitate ease of rod to screw fixation and rod contouring across multiple levels. This helps limit implant-bone contact stress which can be increased when there is screw-plate or screw-rod mismatch. Additionally, the head-neck junction in polyaxial screws may be protective against pedicle screw breakage within a pedicle (Fogel et al. 2003).

The neck of the screw bridges the head to the body and is typically considered the weakest part of the screw. The body of a screw contains threads to obtain bony purchase. The bending or fatigue strength of a screw is proportional to the core (or inner) diameter of the screw body (Benzel et al. 1995). Liu and coauthors found fatigue strength of a screw increased 104% following a 27% increase in diameter (Liu et al. 1990).

The body of a screw can be conical or cylindrical (Fig. 4). Conical screws have been shown by some authors to have superior insertional torque with no difference in pullout strength (Kwok et al. 1996). However, other authors have advocated that conical screws, when backed out half to one full turn, lose significant purchase (Lill

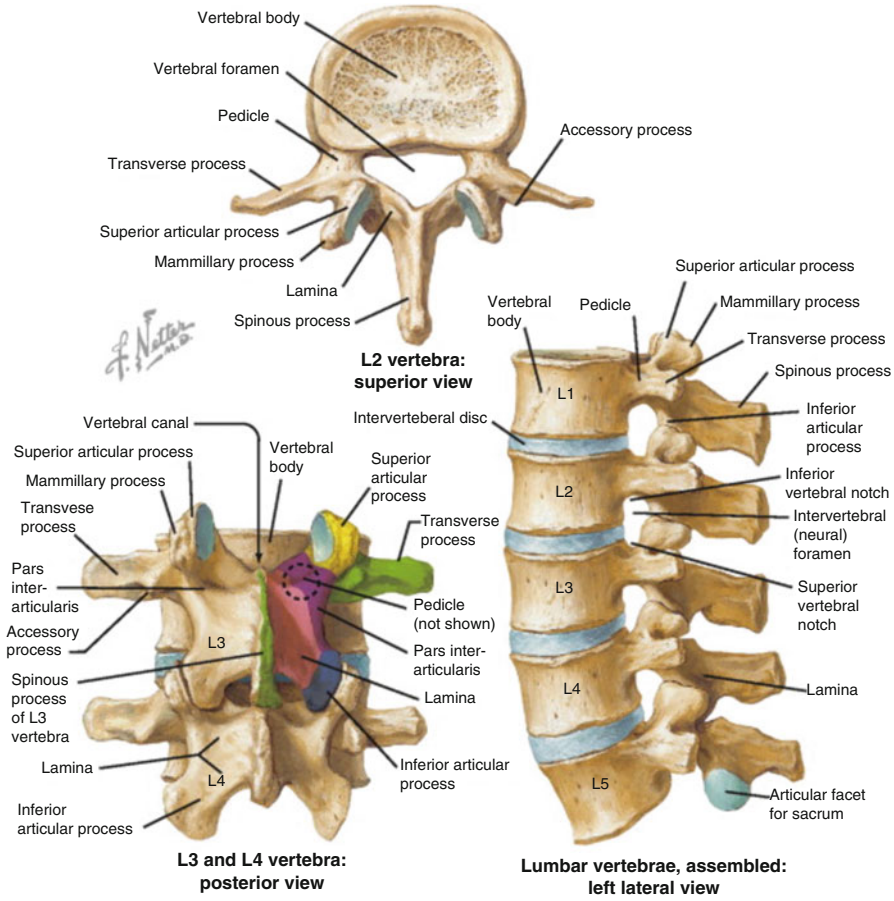

Fig. 2 Anatomy of the lumbar pedicle. (Reproduced from *Netter's Concise Orthopaedic Anatomy*, 2010 with permission from Elsevier)

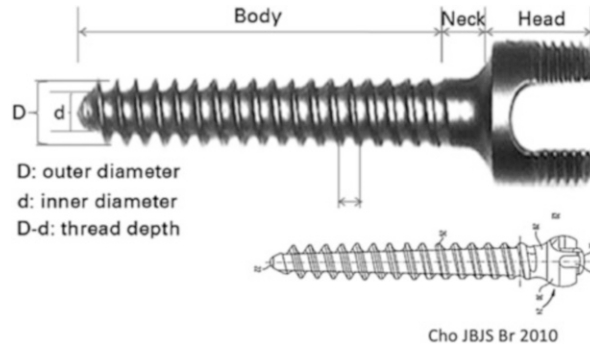

Fig. 3 Anatomy of the pedicle screw. (Reproduced from Cho et al. 2010 with permission from *J Bone Joint Surgery British*)

et al. 2006). The conical geometry of a screw may also be beneficial as 60% of the screw pullout strength is obtained from the cortical bone of the pedicle as opposed to the trabecular bone of the vertebral body (Shea et al. 2014). There has been significant debate between the two screw designs and their effectiveness with conflicting studies showing either no difference or biomechanical advantages of conical screws over cylindrical screws.

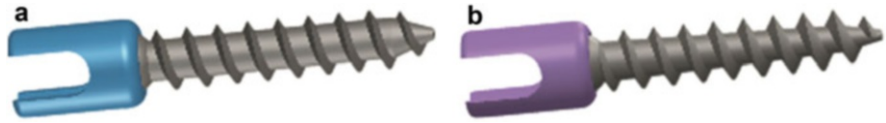

Fig. 4 Cylindrical versus conical screw design. (Reproduced from Shea et al. 2014 with permission from *Biomed Rest Int*)

The body of a screw can also be hollow to allow for screw passage over a wire in a cannulated fashion. This has been shown to be safe and effective but does decrease the bending strength of screws significantly when compared to solid bore-bodied screws. Threads are the portion of the body of the screw that allows for bony purchase. The difference in the inner and outer diameter of a screw is equal to the thread depth. The pitch is the distance between threads longitudinally across the body. Threads can be fully threaded along the entirety of the body of the screw or partially threaded across only a part and are typically cancellous type thread pattern given their fixation within the cancellous bone of the pedicle. However, some newer screw designs incorporate a dual-thread design with cortical threads dorsally along the screw to obtain cortical fixation within the pedicle and cancellous threads within the anterior column (vertebral body).

The pullout strength of screws is determined by the amount and quality of bone between the threads of a screw. Smaller thread pitches confer slightly stronger pullout strength as do deeper thread depths and more total threads (fully threaded). A general rule of thumb is that large outer diameters, small inner diameters, short pitch, and strong bone maximize pullout strength of the screw. These factors in combination with bone mineral density (BMD) help determine insertional torque of a screw which has been demonstrated to have a linear correlation with cycles to screw loosening (Zdeblick et al. 1993).

Modern pedicle screw systems typically have polyaxial heads, and diameters range from 4.5 to 8.5 mm for the thoracic and lumbar spines and lengths between 25 and 60 mm increments. They are typically made up of either stainless steel, titanium alloys, or cobalt-chrome-molybdenum alloys. Stainless steel (a nickel-chromium-iron alloy) was originally used due to its biocompatibility, low cost, and high stiffness in bending strength. However, modern screws have moved away from stainless steel as a material given their MRI incompatibility for postoperative imaging, higher corrosion rates, and the prevalence of nickel allergies. Titanium-aluminum-vanadium alloys (TiAlVa or Ti6-4) have been commonly used in bone implants given their lower modulus of elasticity than stainless steel that more closely approximates the modulus of bone. This has been hypothesized to decrease stress shielding of bone. Additionally, Ti alloys have high yield strength, are biocompatible, promote osteointegration, and are MRI safe. Cobalt-chromium alloys (CoCr) have also been more recently popularized given their superior stiffness and fatigue strength when compared to Ti alloys; however, they are often times significantly more expensive. Both titanium alloys and cobalt-chrome implants have low risk of corrosion when compared to stainless steel.

Various coatings have been added to screws in attempts to improve fixation. Hydroxyapatite coatings allow for bone ingrowth and provide thicker threads with increased initial friction and stability and have been shown to be useful in osteoporotic animal models (Sandén et al. 2001).

Biomechanics of Pedicle Screw Fixation

Spinal instrumentation functions to stabilize the spine, and its construct strength is determined by the mechanical load at which implants fail. Stiffness of a given spine construct is defined as the ability of fixation to resist axial compression as well as linear and circular moment forces.

These biomechanical characteristics of implants help define clinical success as implant failure typically leads to poor clinical outcomes.

Pedicle screws have been compared biomechanically to other dorsal spinal instrumentations. When compared to Harrington rods and Luque sublaminar wiring constructs, pedicle screw constructs have been shown to have greater torsional rigidity, overall construct stiffness and strength, and a significant reduction in the strain of flexion loading (Chang et al. 1989; Puno et al. 1987). They also have been shown to be superior in flexion-extension and lateral bending strength when compared to facet screw fixation (Panjabi et al. 1991a).

Dorsal pedicle screw systems allow for the surgeon to impart cantilever bending forces to the spine around a fixed moment arm which can provide distraction, compression, as well as tension band fixation of the spine. Since they extend past the instantaneous axis of rotation of the spine, they do allow for three-dimensional control of the spine. These constructs do become load bearing as well with adequate anterior column support for load sharing. Without additional anterior column support (i.e., corpectomy model), they can be vulnerable to construct failure (Yoganandan et al. 1990) (Fig. 5). Ensuring that maximal pedicle screw biomechanical advantage is achieved is critical to help avoid catastrophic implant failure or pullout.

Pilot holes in the dorsal pedicular cortex are used to begin cannulation of a pedicle and allow safe screw passage. Pilot hole size has been described to contribute to the insertional torque of a screw, critical for establishing both maximum pullout strength and preventing pedicle fracture. Battula et al. established the critical pilot hole size as 71.5% of the outer diameter of the pedicle screw was ideal in osteoporotic bone to optimize the balance between low insertional torque and high pullout strength (Battula et al. 2008).

Pedicle screws should be placed in a convergent fashion with medial angulation (Cho et al. 2010). This allows for a more lateral starting point resulting in longer screw lengths and reduced contact with the superior facet joint of the vertebra. Additionally, the convergence allows for an interlocking effect that increases resistance to torsional and lateral bending and up to 28.6% increase in pullout strength when compared to a straight-ahead technique (Barber et al. 1997).

They should also be placed parallel to the superior end plate to minimize screw breakage as the "straight-forward" technique paralleling the superior end plate has been shown to be biomechanically superior to the anatomic screw trajectory in the thoracic spine (Lehman et al. 2003; Youssef et al. 1999). An anatomic screw trajectory can be used as a salvage technique especially within the thoracic spine, when multiple screw attempts have been attempted and failed,

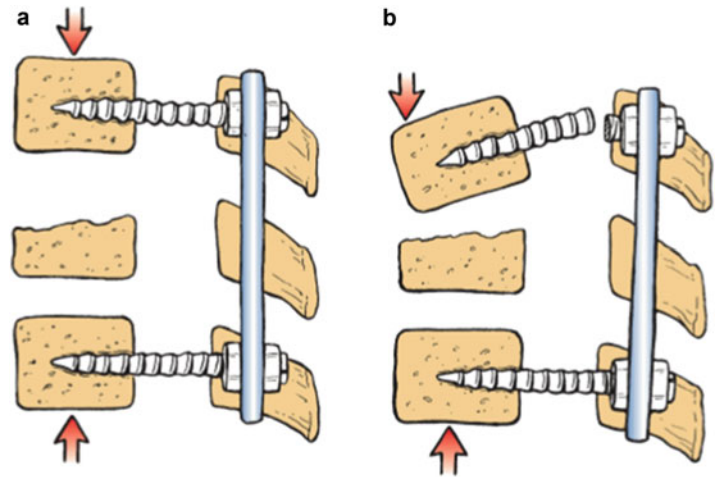

Fig. 5 Screw failure without anterior column support. (Reproduced from *Benzel's Spine Surgery*, 2017 with permission from Elsevier)

given its more cephalad starting point (Lehman et al. 2003).

Ideal screw length has been determined to be at least 60–70% across the body and total length of the pedicle. Screws placed to only 50% of anterior-posterior length of the pedicle had 30% less pullout strength than screws that spanned 80% of the width (Krag et al. 1988). Minimum engagement of at least the neurocentral junction is critical as it has been demonstrated to provide 75% of the maximum insertional torque of a screw (Lehman et al. 2003). Lateral fluoroscopy and a measured ball-tip probe can be used intraoperatively to aid in determining screw length, and care should be taken not to place screws longer than 80% of the length of the pedicle on imaging as this can penetrate the anterior cortex 10–30% of the time (Whitecloud et al. 1989a). While bicortical fixation spanning the entirety of the pedicle has been shown to improve pullout strength up to 25%, the dangers of anterior perforation to critical vascular structures are too great to advocate routine bicortical screw fixation. One exception is at the S1 level where anterior midline penetration and bicortical purchase are safe due to the capacious pedicle and absence of midline vascular structures at this level (Lonstein et al. 1999).

Ideal screw diameter should be such that the screw threads obtain purchase at the inner cortical portion of the pedicle which serves to decrease hoop stresses and cortical deformation. A screw diameter that is too large can result in risk of perforation or pedicle fracture, especially in weak or osteoporotic bone.

Indications for Use

Pedicle screws as dorsal spine instrumentation have many uses including fracture stabilization to allow early mobilization, even in the setting of posterior element injury, tumor instability, infection, spondylolisthesis, fusion assistance in degenerative conditions, and scoliotic deformity correction of the spine. Overall, they serve to provide rigid internal immobilization that allows mechanical support, early mobilization, and rehabilitation.

Contraindications to pedicle screw fixation include small pedicles, severe osteoporosis, and absence of adequate anterior column support (Orndorff and Zdeblick 2017).

Insertion Techniques

General

Placement of pedicle screws requires a thorough understanding of the anatomy of the pedicle for safe passage of a screw. In general, screws should not penetrate the pedicle and be placed away from critical neural and vascular structures as well as facet joints. An exception to this rule is the case of the "in-out-in" screw, typically reserved for severe deformity or congenital small pedicles. This method utilizes a far lateral entry point and is an extrapedicular tract through the transverse process into the pedicle (Perna et al. 2016). The dorsal cortex of the pedicle should be kept intact as much as possible to allow for maximal insertional torque and pullout strength (Daftari et al. 1994).

Freehand Technique

The pedicle screw entry point is identified by the surgeon using anatomic landmarks (described below) and careful review of preoperative imaging studies. Once a pilot hole in the dorsal cortex of the pedicle is made at the ideal starting point, typically a blunt-tipped gearshift probe can be used to cannulate the cancellous bone of the pedicle and allow for creation of a safe screw track within the cortical pedicle walls. Tactile feedback and experience are used in the freehand technique to establish this safe corridor. Typically, the pedicle probe is directed laterally for the first 15–20 mm of the pedicle before being removed and flipped 180° and then directed medially into the vertebral body once past the neurocentral junction. A sudden loss of resistance is often indicative of a cortical breach. The passing of the probe allows compaction of the cancellous bone during cannulation of the pedicle. Alternatively, a drill can be used to cannulate

the pedicle without significant difference in biomechanical properties of final screw placement (George et al. 1991). A ball-tip feeler or another pedicle sounder can be used to palpate the anterior, superior, inferior, medial, and lateral margins of the pedicle to verify pedicle cortical integrity and provide a depth measurement. This however has variable accuracy even among expert surgeons.

A tap can be used to create screw threads within the pedicle prior to screw placement; however it is not required as most modern screw systems are self-tapping. Self-tapping screws do have the disadvantage of increased insertional torque and pedicle fracture risk. Tapping has demonstrated improved screw trajectory but variable effects on screw pullout strength (Erkan et al. 2010; Pfeiffer et al. 2006). Line-to-line tapping (using a tap the same size as the screw) is not recommended as it reduces screw purchase and pullout strength. However, using a tap 1 mm smaller in diameter has been shown to have the same pullout strength as untapped pilot holes (Carmouche et al. 2005; Chatzistergos et al. 2010). Tapping is typically performed just within the cortical bone of the pedicle cylinder and not extended into the cancellous bone of vertebral body as tapping cancellous bone reduces screw-bone contact and pullout strength (Chapman et al. 1996). The pedicle is then gently probed after tapping again to confirm no cortical perforations. A screw is then placed.

Freehand pedicle screw placement has a steep learning curve and requires detailed understanding of an individual patient's anatomy as it is essentially a blind technique. Accuracy rates for freehand pedicle screw placement have been reported between 59% and 91% in the lumbar spine and 45% and 97% in the thoracic spine (Perna et al. 2016).

Cervical

Traditionally, posterior instrumentation of the subaxial cervical spine has been limited to lateral mass fixation, sublaminar or interspinous wiring, and translaminar fixation. While pedicle screw fixation has been commonly described at C2 and C7 with good safety and efficacy, pedicles at C3–C6 have often been considered too dangerous to attempt screw fixation due to the proximity of the vertebral artery and the cervical nerve roots as well as the significant variability in the cervical pedicle morphology between patients.

Panjabi et al. demonstrated anatomically the ability for the cervical spine to accommodate pedicle screws (Panjabi et al. 1991b). They quantified the C2 pedicle to be the largest, the C3 to be the smallest, and the increasing pedicle size up to C7. At C4, an approximate 45° medial angulation in the coronal plane is required for insertion, and it decreases sequentially to about 30° at C7. The sagittal angle (superior-inferior) is determined by review of the preoperative imaging of the individual patient.

Cervical pedicle screw fixation has been shown to have superior biomechanical properties in regard to loosening and fatigue testing compared to other dorsal cervical spine instrumentation. Indications for cervical pedicle screw fixation have been described as trauma-induced cervical fractures and/or dislocations, multilevel instability, tumor resection, osteoporosis, or absence of dorsal spine elements (Pelton et al. 2012).

Typical cervical pedicle screw size is 3.5–4.5 mm in diameter and requires careful study of preoperative imaging for length determination and to ensure a safe passageway. For C2, the pedicle starting point has been well established as 2 mm lateral to the bisection of a horizontal line through the mid-pars of C2 and a line vertically between the midpoints of the facets. The trajectory is typically 30–45° medial angulation and 35° superior angulation. Typically at C2 cannulation of the pedicle is done with a drill as opposed to a larger gearshift probe. Laminoforaminotomy can be added to allow for palpation of the medial border of the C2 pedicle to confirm the trajectory.

For C3–C7, there is more heterogeneity in the starting point, but many authors describe it as slightly lateral to the midpoint of the lateral mass and superior (closer to the cephalad inferior articular process) (Fig. 6). Laminoforaminotomy can be added to allow for palpation of the medial border of the pedicle to confirm the trajectory.

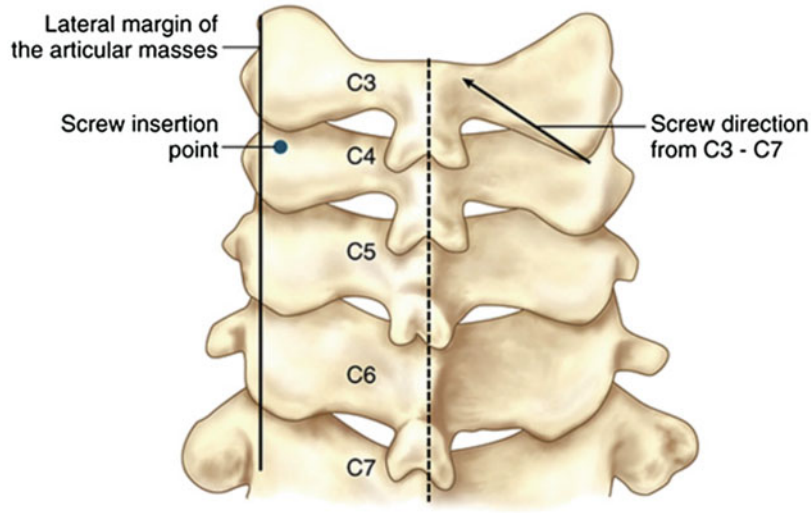

Fig. 6 Entry point for cervical pedicle screw placement. (Reproduced from Spine surgery. Operative techniques, 2008 with permission from Elsevier)

Cannulation of the pedicle can then be performed with a drill with set depth stops as the cervical pedicles are typically hard and hand-controlled instruments can slip or create too much downward pressure (Ludwig et al. 1999). At C7, some authors have described the pedicle entry point to be 1 mm inferior to the midportion of the facet joint above, with a 25–30° medial angulation and neutral sagittal plane (Ludwig et al. 1999).

Freehand technique is not usually recommended in the cervical spine, and image-guided assistance with fluoroscopy or computer-assisted stereotactic navigation is recommended as there is evidence to support improved safety (Ludwig et al. 2000).

Complications of cervical pedicle screw placement include misplacement, pedicle fracture, CSF leak, infection, nerve root injury, spinal cord injury, and vascular injury. Despite the serious consequences that can occur with cervical pedicle screw placement and previous anatomic studies suggesting vascular injury being the most likely complication of cervical pedicle screws, Kast et al. reported in their series of 26 patients with 94 total screws a 30% malposition rate with 9% being critical and 1 patient requiring revision surgery for nerve root symptoms. There were no vascular injuries. The authors described a significant learning curve for this technique that has also been reported by other authors (Kast et al. 2006; Yoshihara et al. 2013).

Thoracic

Much like the cervical spine, thoracic pedicle screws have a low margin of error due to the proximity of the spinal cord, lungs, esophagus, great vessels, and large intercostal and segmental vessels that are closely associated with the thoracic vertebrae (Vaccaro et al. 1995). Scoliosis increases the difficulty of accurate cannulation with altered trajectory from axial rotation and hypoplastic pedicles at the concavity of the curvature.

Progressing cephalad from T12, the starting points tend to be progressively more medial and cephalad up to T7, at which point they then shift to be more lateral and caudal (Parker et al. 2011; Xu et al. 1998; Chung et al. 2008). Typical medial angulation is 30° at T1–T2 and approximately 20° from T3 to T12. Sagittal angulation varies based on the level and patient, but a general rule is to cannulate the pedicle orthogonal to the dorsal spine.

Anatomic landmarks can also be used to identify the starting point and have been described as the midpoint of a triangle formed by the lower border of the superior articular facet, the medial border of the transverse process, and the pars interarticularis medially. Some authors have proposed a consistent starting point, as opposed to varying starting points, for the thoracic screws that are 3 mm caudal to the junction of the lateral aspect of the superior articular process and

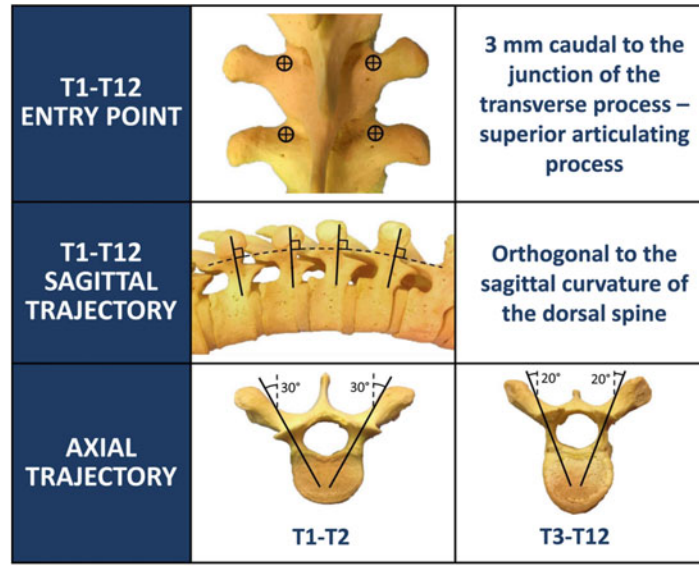

Fig. 7 One method of thoracic pedicle screw entry point localization. (Reproduced from Avila and Baaj 2016 with permission from *Cureus*)

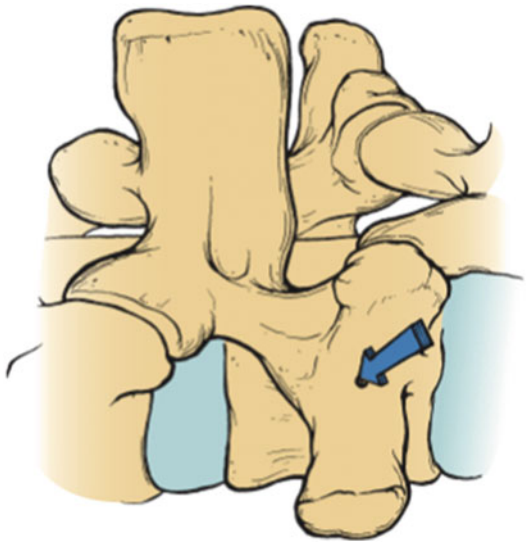

Fig. 8 Lumbar pedicle screw entry point. (Reproduced from *Benzel's Spine Surgery*, 2017 with permission from Elsevier)

transverse process (Avila and Baaj 2016) (Fig. 7). During decortication of the dorsal cortex, the surgeon can look for the pedicle blush of cancellous bleeding bone to ensure an accurate starting point.

The thoracic pedicles are most narrow between T4 and T9. Typical screw sizes are between 4.5 and 5.5 mm. Overall accuracy of freehand thoracic screws has been reported in the literature between 85% and 98% (Avila and Baaj 2016).

Lumbar

In the lumbar spine, the ideal pedicle screw starting point is the bony junction of the pars interarticularis, the transverse process, and the mammillary process or lateral facet joint. Alternatively, it can be described as the intersection of a vertical line bisecting the facet joint and a horizontal line through the midportion of the transverse process (Fig. 8). A laminoforaminotomy may also be used to palpate the medial wall of the pedicle from within the epidural space to allow guidance of the cannulation. Cannulation is performed as described above. Typical lumbar pedicle violations are lateral more commonly than medial or inferior.

In the lumbar spine, a novel pedicle screw tract known as the cortical screw has been described. It utilizes a more medial and caudal starting point and has a medial-lateral and caudal-to-cranial direction in order to increase screw-cortical bone contact to improve fixation in osteoporotic patients (Santoni et al. 2009). It does require some resection of the inferior spinous process and has been theorized to be weaker in axial rotation but does have advantages including potential increased fixation strength and less required muscle dissection (Rodriguez et al. 2014; Calvert et al. 2015). Screws are typically shorter in length and smaller in diameter but placed in a similar fashion as described above (Fig. 9).

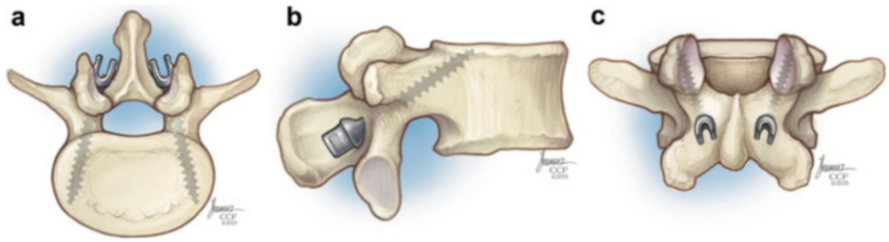

Fig. 9 Cortical screw trajectory for the lumbar spine. (Reproduced from *Benzel's Spine Surgery*, 2017 with permission from Elsevier)

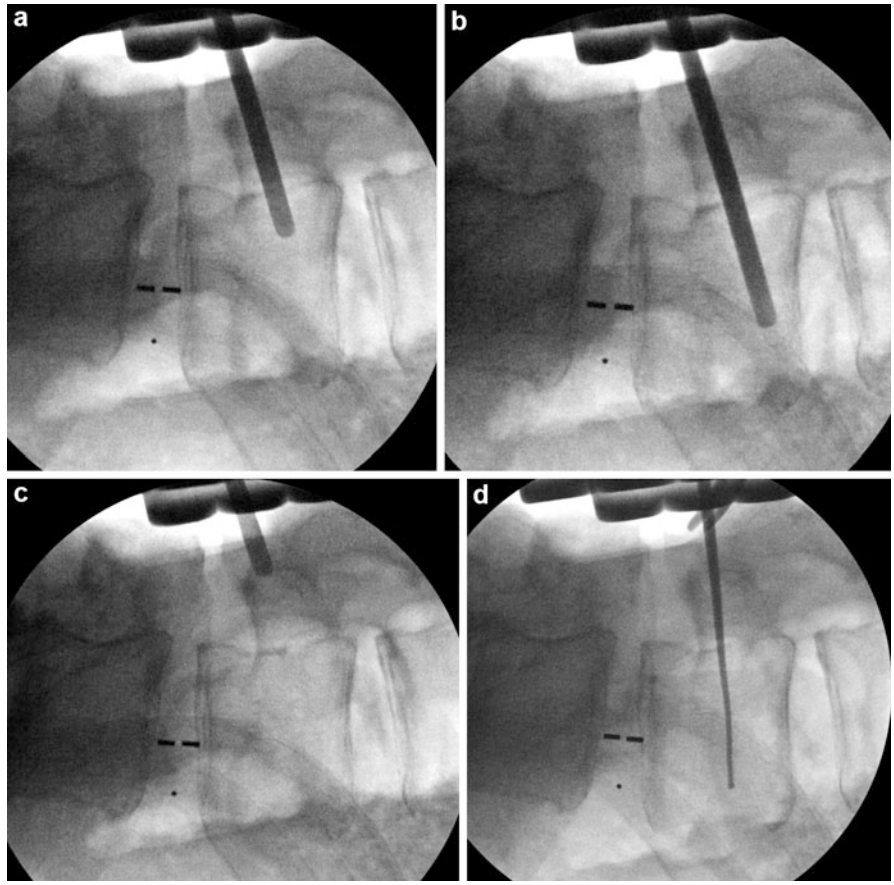

Fig. 10 Fluoroscopic-assisted screw placement. Cannulation was performed under lateral XR guidance followed by pedicle probing. Start points can be confirmed using AP and lateral fluoroscopic imaging

Fluoroscopic-Guided Technique

Intraoperative fluoroscopy can be used to aid pedicle screw placement as it provides 2D imaging of the entry point to the pedicle using radiographic markers as well as the trajectory of a pedicle to aid in cannulation. Using a combination of serial AP and lateral images with a parallel superior end plate, the pedicle cannula is started in the midpoint of the lateral most edge of the pedicle on the AP image and directed in the cranial-caudal direction of the pedicle on the lateral image (Fig. 10). While this can verify and increase accuracy rates of placement, it does not guarantee accurate trajectory.

Fluoroscopic-assisted pedicle screw placement accuracy rates have been reported to be similar to the freehand technique with one study reporting a 68.1% accuracy rate (Mason et al. 2014). 3D fluoroscopy software has more recently been implemented to allow consecutive images from different angles to create a 3D visualization to improve accuracy rates in fluoroscopic screw placement with the caveat of increased radiation exposure to the patient (Perna et al. 2016).

Percutaneous Screw Placement

Pedicle screws can also be placed via a Wiltse paraspinal approach percutaneously with the assistance of one or multiple of any of the abovementioned imaging modalities (fluoroscopy, intraoperative CT, computer-assisted navigation, or robotic-assisted systems). Purported advantages include reduced length of stay, earlier mobilization, decreased postoperative pain and blood loss, and earlier return to work. Principles for placement of pedicle screws percutaneously are no different than that of fluoroscopic or navigated screw placement and utilize imaging to guide the surgeon through the pedicle. Typically for fluoroscopic percutaneous screw placement, K-wires can be used after cannulation of the pedicle to maintain the pedicular track, and cannulated screws can be placed over these wires into the pedicle (Fig. 11).

Computer-Assisted Surgery and Navigation Technique

Computer stereotactic navigation techniques have recently been utilized to assist in pedicle screw

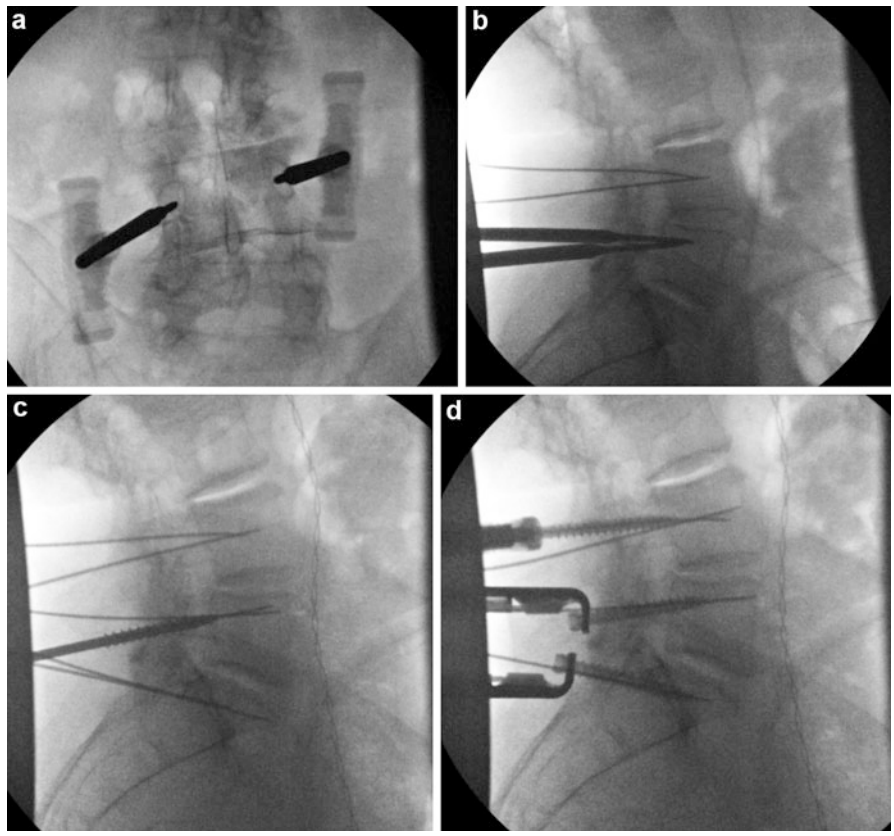

Fig. 11 Percutaneous screw placement: (**a**) Pedicle cannulation using a Jamshidi needle, (**b**) guide wire placement into cannulated pedicle, (**c**) cannulated tap using guidewire, and (**d**) cannulated screw placement over guidewires

placement by correlating a patient's preoperative or intraoperative acquired images to the patient's real-time surgical anatomy using fixed-point optical or electromagnetic markers. A computer model generation is then used to guide the surgeon in real time relative to the patient's anatomy (Fig. 12). Many authors have advocated for the safe and effective use of computer-assisted technology to make pedicle screw placement more reproducible by guiding the surgeon to the appropriate trajectory; however, effects on patient outcomes and benefit in reducing neurologic complications are unclear (Ughwanogho et al. 2012; Verma et al. 2010). The use of intraoperative cross-sectional imaging and referencing has gained popularity as it limits the inaccuracies that may develop due to patient repositioning when using computer-assisted navigation based on preoperative imaging. However, inaccuracy can still develop, and the further away one works from a reference frame, the less accurate the navigation system becomes (Scheufler et al. 2011). Disadvantages include increased radiation exposure to the patient, cost, and operative time. Overall accuracy of pedicle screw placement using navigated technology has been reported between 91.5% and 97.7%, which appear to be significantly higher than freehand or fluoroscopic placement rates, with the most benefits seen in the accuracy of thoracic pedicle screw placement (Puvanesarajah et al. 2014; Waschke et al. 2013). Additionally, repeat imaging using intraoperative CT scan can detect misplaced screws and allow the surgeon to correct them intraoperatively (reported at a rate of 1.8% in one series) (Van de Kelft et al. 2012).

Navigated optical technology has been expanded into robotic-assisted pedicle screw placement as well. Using preoperative or intraoperative imaging and appropriate patient fiducial markers, a robotic guidance arm can be used to guide pedicle cannulation trajectory and screw placement with increased reliability, reproducibility, and accuracy with potentially reduced radiation exposure. Disadvantages include significant cost, operative time, and learning curve.

Intraoperative Neuromonitoring (IONM)

Electrophysiological intraoperative testing can be useful to assess or confirm pedicle screw placement within a pedicle. Stimulation of pedicle screws or cannulation tools allows for electric currents to be transmitted into the pedicle. Cortical bone has a high resistance to electrical current resulting in minimal stimulation of nearby nerve roots if intact. Cortical breaches of the pedicle can allow for electric current to flow into soft tissues and allow for depolarization of nearby nerve roots which can be picked up on EMG recordings of specific myotomes in monitored extremities. Typically acceptable minimum thresholds of depolarization for safe screws are reported between 10 and 12 mA.

This technique of triggered EMG is useful in detecting misplaced pedicle screws as it has been shown to be highly specific; however, there is a high false-negative rate with only fair sensitivity with up to 22% of misplaced screws being

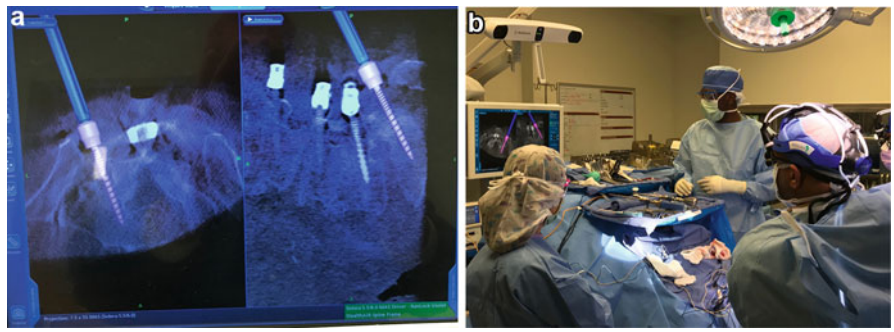

Fig. 12 Navigated screw placement and workflow

missed (Mikula et al. 2016). This technique, while primarily used for the lumbar spine given the lower extremity myotomes, has been described for monitoring thoracic nerve roots as well by selective myotome monitoring of the rectus abdominis for T6–T12 and the intercostal muscles from T3 to T6. This technique has been described for cervical screws as well as iliosacral screws.

While widely advocated for general use for safe placement of pedicle screws, there is a paucity of clinical data supporting improved clinical outcomes with routine IONM and EMG testing of screws (Reidy et al. 2001).

Pedicle Screw Outcomes

Pedicle screws first received US FDA approval as a class III device in 1995 but were frequently used prior to that throughout the world. Early transpedicular fixation screws were found by McAfee to have an approximate 80% survival rate at 10-year follow-up with 90% incidence of successful fusion in a mixed cohort of patients undergoing fusion with the early VSP device or the Cotrel-Dubousset transpedicular screw systems (McAfee et al. 1991). Yuan et al. established the safety of pedicle screw fixation in 1994 with a cohort of 303 surgeons with nearly 3,500 patients revealing very low rates (<1%) of implant failure, neurovascular injury, and dural tears in their cohort (Yuan et al. 1994). In 1998, the FDA downgraded pedicle screws to a class II device with increasing evidence of their safety.

Arthrodesis or fusion involves a surgeon-created artificial process of bone formation across a motion segment. It has a useful tool for spine surgeons to eliminate pathologic motion within the spine and provide stability to unstable segments. Fusion success is often directly proportional to construct stiffness and is dependent on a low-strain environment for primary or secondary bone healing and formation. Typically, a goal of <10% strain is desired in a construct. Wolff's law describes increased loads that result in increasing competitive strain. As bone adapts to load, bone formation occurs to add rigidity.

Pedicle screw constructs are ideal to provide a construct with adequate stiffness and provide a low-strain environment within the spine to allow for bone formation and fusion. Multiple studies have shown that pedicle fixation increases spinal arthrodesis rates. Louis in 1986 studied 266 patients in the lumbosacral spine who underwent instrumentation with pedicle screws and plates and found a 97% rate of successful fusion (Louis 1986). West et al. studied 62 patients undergoing spinal arthrodesis and found a 90% fusion rate and 2/3 of patients returned to full-time work (West et al. 1991). Zdeblick compared degenerative lumbar spine surgical patients with and without rigid pedicle screw instrumentation and found in short-term follow-up a significant difference in fusion rates (64% in uninstrumented patients and 95% in patients with pedicle screw and rigid rod instrumented fusions). However, clinical outcomes were not significantly different (87% good to excellent in uninstrumented, 95% instrumented) (Zdeblick et al. 1993; Zdeblick 1995). He also noted a significantly increased fusion rate in rigid screw-rod constructs when compared to semirigid plate and screw constructs. These findings were confirmed by Fischgrund et al. in 1997 in regard to improved fusion rates but no difference in overall clinical outcomes between instrumented and uninstrumented patients in the degenerative lumbar spine.

Complications

Pedicle screws, while consistently shown to be a safe method of posterior spinal instrumentation, are not without complications. Overall complication rates have been reported up to 25%; however, many are without significant clinical consequence, while others can be catastrophic.

Misplaced pedicle screws occur in various rates reported from 5% to 41% in the lumbar spine and from 3% to 55% in the thoracic spine and have been reported in up to 21% of posthumous cadaveric studies (Perna et al. 2016; Vaccaro and Garfin 1995b). The majority of misplaced screws are asymptomatic; however, medial-breached pedicle screws can cause nerve root

injury or irritation that can be symptomatic and require screw revision (approximate incidence of 0.5%). Misplaced screws are typically classified as screws greater than 4 mm of breach (Gertzbein and Robbins 1990) or by the thoracic safe zone criteria of up to 6 mm lateral breach and 2 mm medial breach as described by Belmont et al. (2002). Most case series have shown that less than 2 mm of breach is not associated with complications (Gelalis et al. 2012; Belmont et al. 2002). Superior or rostral breach can lead to superior adjacent-level disc penetration resulting in poor screw purchase. Inferior breach can lead to nerve root or dural injury. Lateral screw placement can lead to segmental vessel injury and poor screw purchase. Nerve root injury can occur in 2.5–7.5% of cases, and removal of malpositioned screws can lead to resolution (Ohlin et al. 1994). Dural tears have been reported to be about 2–4% (Robert 2000).

Screw pullout or cutout from the pedicle is very common and dependent on not only technical surgeon-controlled factors of insertion but also implant design and host bone mineral density (Chapman et al. 1996; Zindrick and Lorenz 1997; Coe et al. 1990). Pedicle fracture can also occur resulting in loss of fixation or injury to surrounding neurovascular structures.

Implant failure or fatigue has also been reported, and early pedicle screw systems such as the VSP system reported rates as high as 17.5% screw failure (Whitecloud et al. 1989b). As technology has improved including material science and surgeon understanding of pedicle screw fixation techniques, this rate has dramatically decreased.

Posterior spinal instrumentation (and pedicle screws in particular) does increase rates of surgical site infections (SSIs) when compared to uninstrumented fusions approximately twofold from 3% to 6%.

Pedicle screw systems can also cause direct irritation symptoms to dorsal soft tissues as they are relatively raised compared to the dorsal elements of the spine. This can lead to wound breakdown or painful bursitis, especially in thin patients.

Augmentation

With a rapidly aging population, an increasing number of spine fusion procedures being performed each year with pedicle screw instrumentation, the issue of bone mineral density has become increasingly important for surgeons to be cognizant of when planning pedicle screw fixation. Many strategies have been developed to help improve pedicle screw fixation in the setting of osteoporosis or osteopenia via pedicle augmentation.

Polymethyl methacrylate (PMMA) bone cement has been described to augment pedicle screw fixation and can increase screw pullout strength in osteoporosis from 50% to 250% (Becker et al. 2008). Typically 1–1.5 mL of PMMA is placed into the vertebral body after pedicle cannulation followed by immediate screw placement to allow for hardening of the cement around the screw. Alternatively, some cannulated and fenestrated screw designs allow for cement delivery through the screw itself (Fig. 13). This technique, while effective, does pose a safety risk as cement extravasation resulting in emboli or neurovascular damage has been reported. Alternatively, biodegradable bone substitutes such as calcium sulfate or phosphate have been used in a similar fashion as a potentially safer alternative without the exothermic reaction of PMMA (Rohmiller et al. 2002; Bai et al. 2001).

Novel screw designs to aid in screw fixation in osteoporotic spines have also been described in

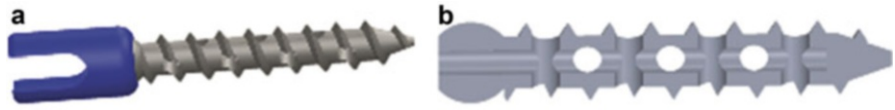

Fig. 13 Fenestrated screw design. (Reproduced from Shea et al. 2014 with permission from *Biomed Rest Int*)

an attempt to avoid PMMA use. Expandable screws that allow for finned expansion in the distal portion of a screw have been described with varying reports on the biomechanical properties of the expandable screw in different osteoporotic spine models (Cook et al. 2004; Koller et al. 2013; Gao et al. 2011; Liu et al. 2016; Lei and Wu 2006). A definitive advantage has not been shown over PMMA augmentation of traditional pedicle screws; however future research may demonstrate a clinical advantage.

Conclusions

Transpedicular fixation has been rapidly adopted among the spine surgery community in the last two to three decades due to its many advantages and ability to provide immediate three column stability to the spine and impart corrective forces all from a posterior-only approach. It is critical for surgeons to have a thorough understanding of the pedicle screw design options and flaws in order to achieve maximum fixation for a given scenario and avoid common complications of screw pull-out, pedicle fracture, or misplacement. Given the potential for catastrophic neurovascular injury during pedicle screw placement, adequate training must be obtained before attempting placement of these fixation devices. New technologies such as computer-assisted and robotic navigation can aid in the safe placement of pedicle screws, but their clinical advantage and value have yet to be definitively proven. As pedicle screw technology and design continue to evolve, their widespread adoption, safety, and efficacy are likely to continue to improve.

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Interspinous Devices

27

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Contents

Abstract

The purpose of an interspinous device is to distract adjacent spinous processes, thus producing flexion and limiting extension of that spine level. Interspinous devices can be designed for motion preservation or for fusion, and the device insertion is minimally invasive. The North American Spine Society (NASS) and the International Society for the

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Advancement of Spine Surgery (ISSAS) have provided indications and contraindications for the use of interspinous devices, with careful patient selection being paramount. The patient is typically placed in a prone position, and the interspinous device is inserted between the adjacent spinous processes to hold the spine in a slightly kyphotic position, thus increasing the canal diameter and reducing symptoms of neurogenic claudication. Complications, complication rates, and reoperation rates have been reported in a large retrospective study and in review articles. Complications can result from the design or intrinsic purpose of the device, incorrect surgical indications or patient selection, or incorrect device sizing. Outcomes of interspinous devices and how their outcomes compare with the outcomes of nonoperative treatment, bony decompression alone, and instrumented fusion have been reported.

Keywords

Clinical outcomes · Dynamic stabilization · Indications · Indirect decompression · Interspinous device · Interspinous fusion device · Lumbar spinal stenosis · Minimally invasive · Motion preservation · Surgical technique

Introduction

The purpose of an interspinous device is to distract adjacent spinous processes (Fig. 1), thus producing segmental flexion and limiting extension of that spine level (Ravindra and Ghogawala 2017; Gazzeri et al. 2015). This flexion can provide indirect decompression of the neural elements and thus alleviate the symptoms of neurogenic claudication caused by lumbar spinal stenosis (Ravindra and Ghogawala 2017; Gazzeri et al. 2014; Borg et al. 2012). Interspinous devices of appropriate design can be used alone, as a means of indirect decompression; in conjunction with bony decompression, as a means of stabilization with motion preservation; or as a fusion device. The procedure is minimally invasive, which makes it especially useful for older, higher-risk patients (Gazzeri et al. 2015), and can be used to avoid or delay more invasive procedures (Bonaldi et al. 2015).

Distracting adjacent spinous processes and inducing segmental flexion with an interspinous device have several anatomical effects (Gazzeri et al. 2014, 2015; Parchi et al. 2014; Gala et al. 2017). The spinous process distraction tightens the ligamentum flavum, thus preventing it from buckling into the spinal canal and causing stenosis. The distraction provides indirect decompression by increasing the spinal canal area and increasing the neural foramina area and height. The facet joints and posterior intervertebral disc are unloaded. Adjacent spine levels should not be affected (Parchi et al. 2014).

Interspinous devices can be designed for motion preservation or for fusion (Parchi et al. 2014). Furthermore, motion preservation devices can be static or dynamic. Static devices are rigid, thus disallowing any extension upon contact with both spinous processes (Fig. 1a). Dynamic devices are flexible and act like a compression spring between the spinous processes to prohibit excess extension (Fig. 1b).

Interspinous devices used for motion preservation allow for dynamic stabilization of the motion segment; stabilization is achieved, but with motion restricted rather than prevented as would occur with fusion (Lee et al. 2015; Bonaldi et al. 2015; Parchi et al. 2014). Motion is restricted in the directions that can cause pain, but is allowed in other directions (Lee et al. 2015; Bonaldi et al. 2015). Retaining motion at the treated level allows that segment to continue to contribute to the motion of the spine and prevents or reduces adjacent segment disease (Lee et al. 2015; Parchi et al. 2014; Serhan et al. 2011).

An interspinous fusion device (Fig. 1c) may be used as a less invasive alternative to pedicle screw-rod fixation (Bonaldi et al. 2015; Parchi et al. 2014). The interspinous fusion device holds the spinous processes in distraction and, with the addition of bone graft, facilitates development of a stable arthrodesis. Although biomechanical studies have indicated that interspinous fusion devices and pedicle screw-rod fixation

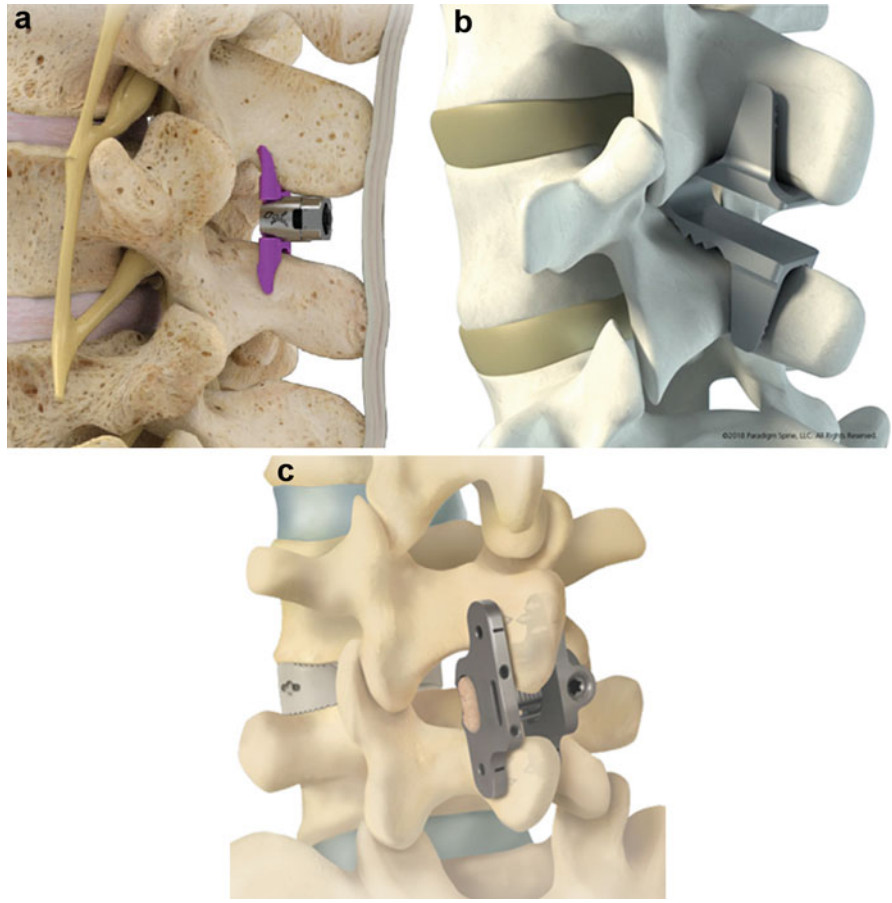

Fig. 1 Representative interspinous devices. (**a**) Static motion preservation device (Superion, Vertiflex Inc., Carlsbad, CA) (Vertiflex Inc. 2016). Note that the interspinous ligament is preserved. (Figure reprinted with permission from Vertiflex Inc.). (**b**) Dynamic motion preservation device (Coflex, Paradigm Spine, New York, NY). (Figure courtesy of Paradigm Spine). (**c**) Fusion device (Aspen MIS Fusion System, Zimmer Biomet Spine Inc., Westminster, CO) (Zimmer Biomet Spine Inc. 2016). Note the interbody cage at that level and the bone graft placed laterally through the device. (Figure reprinted with permission from Zimmer Biomet Spine Inc.)

appear to be similar in how they limit the flexion/extension range, interspinous fusion devices may be less effective in limiting axial rotation and lateral bending, as compared with bilateral pedicle screw-rod fixation (Bonaldi et al. 2015). An interspinous fusion device could be used stand-alone or in conjunction with an interbody cage (Parchi et al. 2014).

Interspinous device insertion has the advantages of a minimally invasive procedure (Pintauro et al. 2017). The device may be inserted with the patient under local anesthesia (Gazzeri et al. 2015; Borg et al. 2012; Parchi et al. 2014). Soft tissue damage, blood loss, and skin scarring are minimized, and operative time is reduced (Borg et al. 2012; Bonaldi et al. 2015). Because interspinous device insertion does not directly interfere with the spinal canal or neural foramina, dural tears or nerve root injuries are unlikely (Borg et al. 2012). Recovery time, complications, and length of stay are reduced, and the surgery could be performed on an outpatient basis (Bonaldi et al. 2015; Borg et al. 2012). Additionally, the procedure is reversible, if further decompression or fusion surgery is required later (Gazzeri et al. 2014, 2015; Borg et al. 2012).

Indications and Contraindications

North American Spine Society (NASS) Coverage Policy Recommendations for Interspinous Devices

The North American Spine Society (NASS) has provided coverage policy recommendations for each category of lumbar interspinous device: those to be used without fusion and with direct decompression (NASS Coverage Committee 2018), those to be used without fusion or direct decompression (NASS Coverage Committee 2014b), and those to be used with fusion for stabilization (NASS Coverage Committee 2014a). For lumbar interspinous devices to be used without fusion and with direct decompression (laminectomy), as an alternative to lumbar fusion, NASS provides indications and contraindications (Table 1). For lumbar interspinous devices to be used without fusion and without direct decompression, NASS also provides indications and contraindications but considers this coverage to be conditional pending further evidence (Table 2). For lumbar interspinous devices to be used with fusion for stabilization, NASS only states, "Interspinous fixation with fusion for stabilization is currently NOT indicated as an alternative to pedicle screw fixation with lumbar fusion procedures (NASS Coverage Committee 2014a)."

International Society for the Advancement of Spine Surgery (ISSAS) Coverage Indications and Limitations of Coverage

The International Society for the Advancement of Spine Surgery (ISSAS) has also provided indications and limitations of coverage for interspinous devices (referred to as interlaminar

Table 1 North American Spine Society (NASS) indications and contraindications for lumbar interspinous devices to be used without fusion and with direct decompression (NASS Coverage Committee 2018). (Reprinted with permission from NASS Coverage Recommendations, © 2014–2018, North American Spine Society)

Indications
Stabilization with an [interspinous device] without fusion in conjunction with laminectomy may be indicated as an alternative to lumbar fusion for **degenerative lumbar stenosis with or without low-grade spondylolisthesis** (less than or equal to 3 mm of anterolisthesis on a lateral radiograph) with qualifying criteria when appropriate:
1. Significant mechanical back pain is present (in addition to those symptoms associated with neural compression) that is felt unlikely to improve with decompression alone. Documentation should indicate that this type of back pain is present at rest and/or with movement while standing and does not have characteristics consistent with neurogenic claudication
2. A lumbar fusion is indicated post-decompression for a diagnosis of lumbar stenosis with a Grade 1 degenerative spondylolisthesis as recommended in the *NASS Coverage Recommendations for Lumbar Fusion*
3. A lumbar laminectomy is indicated as recommended in the *NASS Coverage Recommendations for Lumbar Laminectomy*
4. Previous lumbar fusion has not been performed at an adjacent segment
5. Previous decompression has been performed at the intended operative segment
Contraindications
[Interspinous devices] are ***not*** indicated in cases that do not fall within the above parameters. In particular, they are not indicated in the following scenarios and conditions:
1. Degenerative spondylolisthesis of Grade 2 or higher
2. Degenerative scoliosis or other signs of coronal instability
3. Dynamic instability as detected on flexion-extension views demonstrating at least 3 mm of change in translation
4. Iatrogenic instability or destabilization of the motion segment
5. A fusion is otherwise not indicated for a Grade 1 degenerative spondylolisthesis and stenosis as per the *NASS Coverage Recommendations for Lumbar Fusion*
6. A laminectomy for spinal stenosis is otherwise not indicated as per the *NASS Coverage Recommendations for Lumbar Laminectomy*

Table 2 North American Spine Society (NASS) indications and contraindications for lumbar interspinous devices to be used without fusion and without direct decompression (NASS Coverage Committee 2014b). (Reprinted with permission from NASS Coverage Recommendations, © 2014–2018, North American Spine Society)

Indications
Interspinous distraction devices without fusion may be indicated for the following diagnoses with qualifying criteria, when appropriate:
1. Degenerative lumbar stenosis:
(a) Associated with neurogenic claudication that is relieved by lumbar flexion
(b) Patients over 50 years old
(c) Failure of nonoperative treatment
(d) No more than 25° of degenerative scoliosis
(e) No more than a Grade 1 degenerative spondylolisthesis
(f) Open surgery (e.g., laminectomy) is not a medically safe treatment option because of comorbidities
Contraindications
Interspinous distraction devices are **NOT** indicated in cases that do not fall within the above parameters. In particular, they are not indicated in the following scenarios and conditions:
1. Degenerative spondylolisthesis of Grade 2 or higher
2. Degenerative scoliosis greater than 25° dynamic instability at the operative level
3. Symptoms are not relieved by flexion
4. Patient is medically suitable for a direct decompressive procedure (e.g., laminectomy)
5. Patient has primarily axial back pain that is unrelated to activity
6. Patients younger than 50 years old

stabilization) used with direct decompression (Table 3; Guyer et al. 2016). The ISASS awaits further data and review before providing indications and limitations of coverage for interspinous devices used without direct decompression.

Surgical Technique

Interspinous device placement can be performed from either a lateral decubitus or prone position. We prefer the prone position on a Jackson frame, as this setup seems to give better exposure and leverage with implant placement and also reduces radiation exposure to the patient and surgical team when using intraoperative fluoroscopy. The procedure described below is applicable to both motion preservation devices and fusion devices.

After the patient has undergone general anesthetic, he or she is placed in the prone position with all bony prominences well padded and checked by the surgeon. The patient's skin is typically prepped and draped in the usual fashion using chlorohexidine scrub. Fluoroscopy is then used to identify the appropriate surgical levels.

The skin is then anesthetized with 0.25% Marcaine with epinephrine, to aid with hemostasis and postoperative pain control. A 10-blade scalpel is then used to make a longitudinal incision over the length of the interspace; if a fusion procedure is to be performed, the incision can be extended over the length of the superior and inferior lamina. If multiple levels will receive an interspinous device, we recommend making a separate incision for each level, to reduce scarring and improve cosmesis. Once the skin incision has been made and hemostasis has been obtained, subperiosteal dissection is performed using Cobb elevators to expose the superior and inferior lamina. Great care is taken to avoid injury to the facet capsules and joints and to preserve the supraspinous and interspinous ligaments. Once adequate exposure is obtained, a self-retaining retractor is placed to hold the soft tissue out of the way for adequate visualization. At that point, a curved curette is placed under the superior lamina, and a lateral x-ray is taken to confirm the appropriate level.

Table 3 International Society for the Advancement of Spine Surgery (ISSAS) indications/limitations of coverage for interspinous devices (interlaminar stabilization) used with direct decompression (Guyer et al. 2016). (Reprinted with permission from the International Journal of Spine Surgery)

Indications
Patients who have all of the following criteria may be eligible for decompression with interlaminar stabilization:
1. Radiographic confirmation of at least moderate lumbar stenosis, which narrows the central spinal canal at 1 or 2 contiguous levels from L-1 to L-5 that require surgical decompression. Moderate stenosis is defined as >25% reduction of the anteroposterior dimension compared with the next adjacent normal level, with nerve root crowding compared with the normal level, as determined by the surgeon on CT scanning or MRI
2. Radiographic confirmation of the absence of gross angular or translatory instability of the spine at index or adjacent levels (instability as defined by White and Panjabi: sagittal plane translation >4.0 mm or 15% or local sagittal plane rotation >15° at L1–2, L2–3, and L3–4; >20° at L4–5 based on standing flexion-extension radiographs). Improved imaging technologies are able to better refine/detect previously undetected instability, and as these technologies become more established, surgeons should expect to refine with specificity and clear delineation of appropriate surgical candidates requiring stabilization
3. Patients who experience relief in flexion from their symptoms of leg/buttocks/groin pain, with or without back pain, and who have undergone at least 12 weeks of nonoperative treatment consisting of nonsteroidal anti-inflammatory drugs and at least one of the following: rest, restriction of activities of daily living, physical therapy, or steroid injections
Limitations (Contraindications)
Decompression with interlaminar stabilization is NOT indicated for patients with the following:
1. More than 2 vertebral levels requiring surgical decompression
2. Prior surgical procedure that resulted in gross translatory instability of the lumbar spine
3. Prior fusion, implantation of a total disc replacement, or complete laminectomy at index level
4. Radiographically compromised vertebral bodies at any lumbar level(s) caused by current or past trauma, tumor, or infection
5. Severe facet hypertrophy requiring extensive bone removal that would cause gross instability
6. Radiographic confirmation of gross angular or translatory instability of the spine at index or adjacent levels with sagittal plane translation >4.0 mm as spondylolisthesis or retrolisthesis
7. Isthmic spondylolisthesis or spondylolysis (pars fracture)
8. Degenerative lumbar scoliosis (Cobb angle >25° lumbar segmental)
9. Osteopenia and osteoporosis
10. Back or leg pain of unknown etiology
11. Axial back pain only, with no leg, buttock, or groin pain
12. Morbid obesity defined as a body mass index >40
13. Active or chronic infection – systemic or local
14. Known history of Paget disease, osteomalacia, or any other metabolic bone diseases (excluding osteopenia, which is addressed above)
15.Rheumatoid arthritis or other autoimmune diseases requiring chronic steroid use
16. Active malignancy: a patient with a history of any invasive malignancy (except nonmelanoma skin cancer), unless he/she has been treated with curative intent and there has been no clinical signs or symptoms of the malignancy for at least 5 years. Patients with a primary bony tumor are excluded as well
17. Known allergy to titanium alloys or magnetic resonance contrast agents
18. Cauda equina syndrome defined as neural compression causing neurogenic bowel or bladder dysfunction

Once the adequate level has been confirmed with fluoroscopy, the placement of the interspinous device begins.

The placement of the interspinous device depends on the implant chosen and on whether or not that implant involves preserving or resecting the supraspinous and interspinous ligaments (Fig. 2). The surgeon should have a definitive knowledge of the requirements of each device and surgical placement steps prior to the surgery. Typically, there is a step of trial sizing to choose the appropriate implant (Fig. 3). The appropriately sized implant will give good tension and distraction between the spinous processes, to

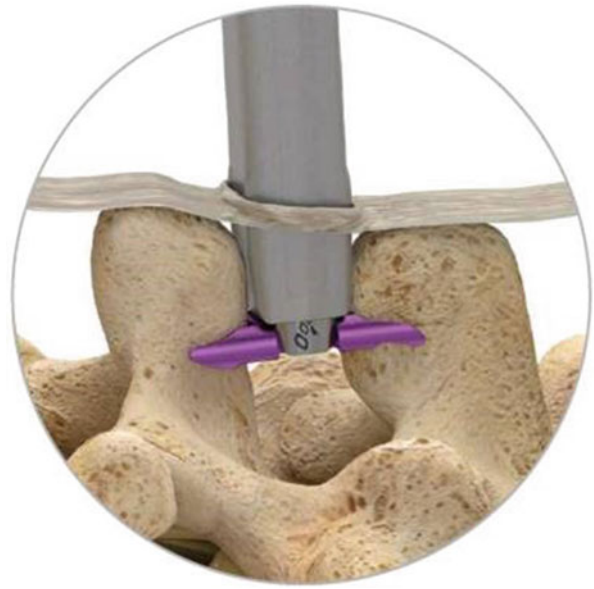

Fig. 2 Superion (Vertiflex Inc., Carlsbad, CA) interspinous device being inserted through the supraspinous ligament (Vertiflex Inc. 2016). (Figure reprinted with permission from Vertiflex Inc.)

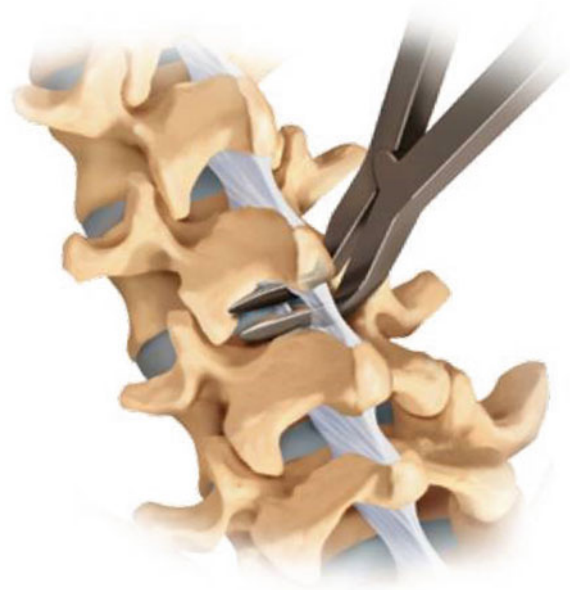

Fig. 3 Measurement of the interspinous separation distance, to select the appropriate rasp and implant size; note the preservation of the supraspinous ligament (Zimmer Biomet Spine Inc. 2016). (Figure reprinted with permission from Zimmer Biomet Spine Inc.)

widen the interspinous spaces and indirectly decompress the spinal canal. However, an oversized implant can lead to spinous process fracture and implant subsidence, while an undersized implant can result in inadequate decompression and poorer patient outcomes. Once the interspinous device has been successfully placed and locked in position, final imaging is used to confirm the appropriate level and good placement of the implant (Fig. 4).

If a fusion follows the interspinous device placement, dissection may be carried out further around the facet joints for additional exposure. The facet joints are then removed with a Leksell rongeur and decorticated with a high-speed burr. This local bone is saved as autograft to facilitate

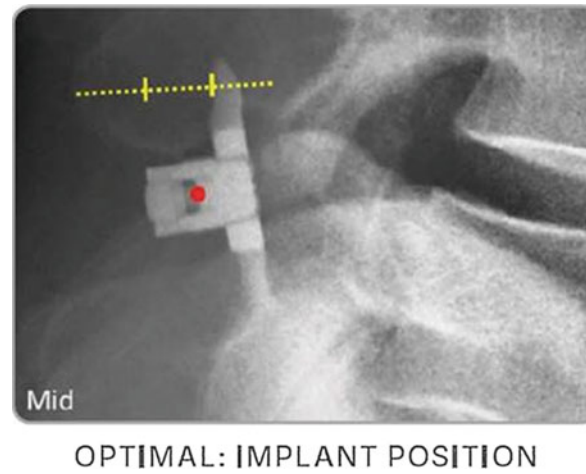

Fig. 4 Radiograph demonstrating proper placement of Superion (Vertiflex Inc., Carlsbad, CA) interspinous device (Vertiflex Inc. 2016). (Figure reprinted with permission from Vertiflex Inc.)

Table 4 Complications of interspinous device surgery (Gazzeri et al. 2015; Ravindra and Ghogawala 2017; Pintauro et al. 2017; Borg et al. 2012)

Durotomy	Device malpositioning	Instability
Hematoma	Device fracture	Nerve root distraction
Swelling	Device dislocation	New radicular deficit
Dehiscence	Spinous process fracture	Pain not improving
Infection	Spinous process erosion	Pain recurrence
		Progression of symptoms

the arthrodesis. Decortication of the superior and inferior lamina is then performed to obtain a large surface area of the bleeding bone for bony fusion. Some surgeons will elect to place pedicle screws, and some surgeons may rely only on the interspinous spacer for fusion. We recommend pedicle screw supplemental fixation, as biomechanical studies show superior fixation and increased fusion rates with pedicle screw fixation compared with interspinous spacers alone (Gonzalez-Blohm et al. 2014). Once the posterior lateral arthrodesis has been performed, the wound is copiously irrigated to obtain hemostasis. This fusion procedure does not often require a drain for postoperative management.

Closure involves approximating the fascial layer with an absorbable Vicryl suture, followed by a dermal closure, and then by skin closure, typically with an absorbable suture. For interspinous device placement, we do not feel it is indicated at this juncture to place vancomycin antibiotic powder. Once the skin is closed, a sterile dressing is applied with Steri-Strip 4 × 4's and coverall tape.

Patients are often allowed to go home the same day postoperatively. We typically recommend a lumbar corset brace for 6 weeks postoperatively to minimize patient motion and prevent implant migration. After 6 weeks, we commence a 6-week course of physical therapy involving with core strengthening and flexibility exercises. At 3 months postoperatively, patients are allowed to resume normal activity without restrictions.

Complications

Complications, Complication Rates, and Reoperation Rates

Complications (Table 4), complication rates (Table 5), and reoperation rates for interspinous devices have been reported in a large retrospective study and in review articles. In a multicenter

Table 5 Complication rates after interspinous device (ISD) surgery

	Rate	Citation and study type
Device failure (mainly spinous process fracture) or intraoperative device-related complication	4.8% mean first-generation ISDs; 2.9% mean next-generation ISDs	Pintauro et al. (2017) Review; 15 studies published 2011–2016
Postoperative complications	1.5–32.3%	Lee et al. (2015) Systematic review; 6 studies published 2004–2007
Overall complications	7%	Moojen et al. (2011) Systematic review and meta-analysis; 563 patients in 11 studies published 2004–2010
Device failures	6%	
Other (infection and postoperative leakage)	1%	
Overall complications and failures	14.81%	Gazzeri et al. (2015) Multicenter retrospective study; 1,108 patients
Recurrent pain	5.14%	
Spinous process fracture	2.44%	
Dura matter tear	2.08%	
Dislocation	1.81%	
No improvement/worsening of pain	1.81%	
Malposition (over-/underdistraction)	1.26%	
Instability	0.27%	
Infection	0%	

retrospective study of 1,108 patients (Gazzeri et al. 2015), the reoperation rate was 9.6%. The reasons for reoperation were recurrence of symptoms after an initial good outcome (3.8%), acute worsening of low-back pain secondary to spinous fracture or overdistraction of the supraspinous ligament (2.4%), implant dislocation (1.8%), and total lack of improvement (1.6%). All reoperations involved interspinous device removal. Of those reoperations, 12.15% occurred within 3 months postoperatively, and the remaining 87.85% occurred after a minimum of 24 months postoperatively. In a review of 15 studies published 2011–2016, Pintauro et al. (2017) reported interspinous device reoperation rates at a mean 24 months' follow-up as 11.1% and 3.7% for first-generation and next-generation devices, respectively. In a systematic review and meta-analysis involving 563 patients in 11 studies published 2004–2010, Moojen et al. (2011) reported a reoperation rate of 6% (follow-up period not reported).

Sources of Complications

Some complications of interspinous device implantation are related to the design or intrinsic purpose of the device. A too-stiff device can cause spinous process fracture, while a too-flexible device can lead to new radiculopathy (Serhan et al. 2011). The removal or disruption of posterior ligamentous process components during insertion of the device can cause instability (Bono and Vaccaro 2007; Kim and Albert 2007). An interspinous device with insufficient means of fixation could dislocate (Serhan et al. 2011). The V-shape of the posterior interspinous space could lead to device dislocation upon rupture of the supraspinous ligament (Gazzeri et al. 2015). (A fall can also cause device dislocation (Gazzeri et al. 2015).) The induction of segmental kyphosis with interspinous device implantation could theoretically cause adjacent segment disease (Bono and Vaccaro 2007; Kim and Albert 2007).

Incorrect surgical indications or patient selection for interspinous devices can lead to complications (Pintauro et al. 2017; Gazzeri et al. 2015). In particular, osteoporosis or osteopenia can lead to spinous process fracture (Gazzeri et al. 2015; Ravindra and Ghogawala 2017; Pintauro et al. 2017; Borg et al. 2012) and are considered as reasons for caution or as contraindications for interspinous device implantation (Bonaldi et al. 2015; Siewe et al. 2015; Pintauro et al. 2017; Gazzeri et al. 2015). The chance of spinous process fracture in patients with osteoporosis or osteopenia could be reduced by choosing a device size that results in less distraction (Gazzeri et al. 2015) or by augmenting an osteoporotic posterior vertebral arch with bone cement injection (spinoplasty) (Bonaldi et al. 2012).

Incorrect interspinous device sizing can also lead to complications. Implanting an oversized device can overdistract the supraspinous ligament, causing pain, and overcompress the spinous processes, causing spinous process fracture (Gazzeri et al. 2015). Implanting an undersized interspinous device can lessen the desired mechanism of the device to induce segmental kyphosis, leading to such results as an under-distracted ligamentum flavum being able to buckle into the spinal canal (Gazzeri et al. 2015; Gala et al. 2017).

Intraoperative durotomy is more likely at the L5–S1 level, where the dural sac is located more posteriorly than it is at higher levels. Placing the interspinous device more posteriorly (in the midportion of the level's interspinous ligament) can reduce the chance of this complication (Gazzeri et al. 2015). The spinous process of S1 is very unpredictable in size and can be small, bifid, or absent. We do not recommend interspinous device insertion at the L5–S1 level.

One study detected heterotopic ossification in 81.2% patients that had a Coflex interspinous device (Fig. 1b), at 24–57 months postoperatively (Tian et al. 2013). Although heterotopic ossification could aid in fusion and thus stabilization at the operated level (Tian et al. 2013; Gazzeri et al. 2015), there has been a case report with Coflex implantation in which heterotopic ossification caused stenosis and recurrence of neurogenic claudication (Maida et al. 2012).

Outcomes of Interspinous Devices

Interspinous Devices

Complication and reoperation rates for interspinous devices, as reported in a large retrospective study and in review articles, are discussed in section "Complications, Complication Rates, and Reoperation Rates." The large retrospective study of 1,108 patients discussed earlier (Gazzeri et al. 2015) also reported clinical outcomes for interspinous devices at a minimum 24 months' follow-up: 41.5% excellent, 34.7% good, 12.5% fair, 6.6% marginal, and 4.7% poor.

Interspinous Devices Versus Nonoperative Treatment

In their systematic review and meta-analysis, Li et al. (2017) identified 3 randomized controlled trials in 5 articles, with a total of 564 patients in the interspinous device group and 244 patients in the nonoperative group. They calculated that the interspinous device group had a lower incidence of additional surgery and a better clinical outcome than did the nonoperative group.

Interspinous Devices Versus Bony (Direct) Decompression

Two recent systematic reviews and meta-analyses have compared the outcomes of interspinous devices versus bony decompression (Zhao et al. 2017; Phan et al. 2016). Zhao et al. (2017) identified 4 randomized controlled trials in 7 articles, with a total of 200 patients in each treatment group. They concluded that both techniques were acceptable for treating lumbar spinal stenosis, but they did not have enough evidence to recommend one technique over the other. Additionally, the interspinous device group had higher reoperation rates, higher postoperative visual analog scale (VAS) back pain scores, and lower cost-effectiveness. The authors expressed a need for interspinous device studies with larger sample sizes and longer follow-up. Phan et al. (2016)

identified 7 studies with a total of 404 interspinous device patients and 424 bony decompression patients. They calculated that interspinous device implantation had significantly lower surgical complications but significantly higher long-term reoperation rates than did bony decompression. Additionally, interspinous device implantation had significantly higher postoperative VAS back pain scores than did bony decompression, but no significant difference in postoperative VAS leg pain scores or in Oswestry Disability Index (ODI) scores (for the two studies that reported ODI) was detected between the groups.

Combined Interspinous Device Plus Bony Decompression Versus Bony Decompression Alone

In their systematic review and meta-analysis, Phan et al. (2016) identified 4 articles with a total of 139 interspinous device plus bony decompression patients and 137 bony decompression alone patients. They calculated that an interspinous device plus bony decompression resulted in significantly higher surgical complications than did bony decompression alone. No significant difference was detected between the groups in reoperation rates or in postoperative VAS back or VAS leg pain scores.

Interspinous Device Versus Laminectomy plus Instrumented Fusion

In their systematic review, Li et al. (2017) identified 2 randomized controlled trials in 3 articles, with a total of 245 patients in the interspinous device group (30 with an interspinous device alone and 215 with an interspinous device plus laminectomy) and 137 patients in the laminectomy plus instrumented fusion group. One trial concluded that the interspinous device group had a lower complication rate and more improvement in VAS and in ODI than did the laminectomy plus instrumented fusion group. The other trial concluded that the two groups had comparable complication and reoperation rates and that the interspinous device group had better Zurich Claudication Questionnaire (ZCQ) scores.

Conclusions

Interspinous devices can be used in a well-selected subset of patients suffering from neurogenic claudication. The procedure can be done minimally invasive and performed in patients who have comorbidities that may preclude them from more invasive surgical procedures or in patients who want to maintain motion and avoid a fusion. Interspinous devices can also be used to supplement interbody fusion. As with any device, proper patient selection and setting realistic expectations can help achieve good results. More long-term randomized studies are necessary to help better clarify best surgical practices.

Cross-References

- ▶ Design Rationale for Posterior Dynamic Stabilization Relevant for Spine Surgery
- ▶ Lessons Learned from Positive Biomechanics and Poor Clinical Outcomes
- ▶ Lessons Learned from Positive Biomechanics and Positive Clinical Outcomes
- ▶ Posterior Dynamic Stabilization
- ▶ Thoracic and Lumbar Spinal Anatomy

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Kyphoplasty Techniques

28

Scott A. Vincent, Emmett J. Gannon, and Don K. Moore

Contents

Abstract

Galibert and Deramond performed the first percutaneous vertebral cement augmentation in 1984 for the treatment of painful vertebral hemangiomas. Over the next decade, its use became more widespread and modifications to the technique led to the development of kyphoplasty. Currently, both kyphoplasty and vertebroplasty are most commonly used in the USA for the treatment of painful osteoporotic

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vertebral compression fractures. More than 50 million people in the USA have osteoporosis or low bone density and this number is projected to only increase with the aging population. Osteoporotic vertebral compression fractures are one of the most common manifestations of the disease, with more than 1.4 million occurring worldwide each year. These vertebral compression fractures can be a source of substantial morbidity and disability. Other common uses of vertebroplasty and kyphoplasty include the treatment of vertebral body pain or fracture secondary to metastatic disease or primary bone tumors. There have been numerous studies investigating the utility of their use. Despite the large volume of research, there is still debate on the exact role and efficacy of both vertebroplasty and kyphoplasty. Prior to recommending or performing percutaneous vertebral augmentation, physicians should weigh the potential benefits andcomplications for each individual being considered for treatment.

Keywords

Kyphoplasty · Vertebroplasty · Osteoporosis · Vertebral compression fracture · Kyphoplasty technique · Percutaneous vertebral augmentation

Introduction

Percutaneous vertebral body augmentation was first performed in France by Galibert and Deramond who percutaneously injected acrylic cement into the vertebral body for treatment of painful hemangiomas in 1984 (Galibert et al. 1987). This technique was given the name vertebroplasty and was eventually used in the USA in the early 1990s where its main use has been in the treatment of osteoporotic vertebral body compression fractures (VCFs). Kyphoplasty was later developed with the added potential of deformity correction due to the addition of an inflatable bone tamp. The bone tamp is theoretically able to improve the vertebral height and decrease the amount of kyphosis that resulted from the VCF, while also creating a cavity for the cement to be injected. Since its development, the use of kyphoplasty has had widespread use for the treatment of VCFs. In 2007, 130,000 patients with VCFs were treated with either vertebroplasty or kyphoplasty (Mauro 2014). A majority of these VCFs occur in patients with osteoporosis, however, they can also occur in other patient populations including those with hemangiomas, multiple myeloma, and metastatic lesions (Wang et al. 2015). In the USA alone, the estimated number of adults in 2010 with osteoporosis and low bone mass was greater than50 million (Wright et al. 2014). By the year 2020, it was expected that the total number of patients with severe osteoporosis will exceed 14 million (National Osteoporosis Foundation 2002). Due to the aging population, it is predicted that greater than three million osteoporotic fractures will occur in 2025, with more than one-quarter of these affecting the vertebral column (Burge et al. 2007). Osteoporotic VCFs have been shown to significantly affect a patient's quality of life, both mentally and physically. The risk of mortality is also significantly increased after an osteoporotic VCF, with a mortality risk 25% higher than after hip fracture (Cauley et al. 2000). In addition to the significant long-term effect on morbidity and mortality, VCFs can also have an immediate impact on a patient's health. In many cases, narcotics are used as a primary means to attain adequate pain control. Unfortunately, these medications carry a significant risk of serious side effects. Their use for treatment among the commonly affected elderly patient is of particular concern as the geriatric population routinely experiences more severe complications with opioid use. Bed rest is another commonly used treatment modality for patients with painful VCFs. Like narcotics, bed rest can have a substantial impact on an individual in a very short period of time. Bed rest can not only lead to extensive deconditioning, but it has been shown to have an almost immediate detrimental effect on bone quality (Kortebein et al. 2008). Therefore, the risk of short- and long-term consequences can begin to increase immediately after sustaining a 9ol compression fracture

severity and complexity varies greatly, and therefore treatment decisions and management strategies should be individualized based on the clinical exam and fracture morphology. Treatment usually begins with medical and nonoperative management; however, in some cases percutaneous vertebral augmentation should be considered. Due to the significant pain some patients experience with VCFs, many physicians believe vertebral augmentation is an excellent option in the treatment pathway, as conservative treatment options fail to provide symptomatic relief. There have been numerous studies investigating the efficacy of vertebroplasty and kyphoplasty that have showed varying degrees of efficacy. Two of the more popular studies that demonstrated no benefit of vertebroplasty were published in the *New England Journal* in 2009, in which both found no difference in outcomes between vertebroplasty and a sham procedure in treatment of osteoporotic VCFs (Kallmes et al. 2009; Buchbinder et al. 2009). A significant benefit, however, was found in well-regarded articles published in the *Lancet* journal, supporting the use of vertebroplasty and kyphoplasty (Klazen et al. 2010; Wardlaw et al. 2009; Clark et al. 2016). The inconsistent findings have led to no general consensus among physicians on the role of percutaneous vertebral augmentation in the treatment of VCFs. The most recent American Academy of Orthopaedic Surgeons (AAOS) clinical guidelines for treatment of osteoporotic VCFs recommend against the use of vertebroplasty (McGuire 2011). In addition, according to the AAOS guidelines, kyphoplasty is considered an option for patients with osteoporotic VCFs with a limited strength of recommendation. Therefore, when considering using percutaneous vertebral augmentation for treatment of a VCF, a physician must consider the risks and benefits of the procedure for each individual.

Indications

The most common indication for the use of kyphoplasty is in the treatment of an unhealed vertebral compression fracture with persistent pain despite conservative therapy. Commonly accepted failures of medical therapy include inadequate relief with analgesic medications, adverse side effects with their use (namely narcotics), and hospitalization secondary to uncontrolled pain. Other medications that have been used include the initiation of osteoporotic-specific medications to prevent future fractures, namely bisphosphonates and teriparatide. Other forms of conservative care that are often used include bed rest and bracing. Much like narcotic therapy, these nonoperative methods are often poorly tolerated by the elderly population. Bed rest leads to deconditioning and has detrimental effects on bone quality, while bracing can be uncomfortable and may restrict pulmonary function. Therefore, the inherent risks and benefits of various conservative treatment modalities should be weighed based on inherent patient factors.

For those failing conservative management, kyphoplasty can be considered. The exact length of time for conservative management is still unclear. Many would consider 3–6 weeks as a reasonable time period of trialing nonoperative care and then considering cement augmentation in those that do not respond. In addition, there is advocacy for earlier utilization of vertebral augmentation in those with incapacitating pain and the inability to tolerate mobilization. The advocacy for earlier utilization of kyphoplasty in select cases is supported by the high mortality rate with VCFs and how commonly nonoperative modalities can be poorly tolerated or cause detrimental effects.

Osteoporosis is the leading cause of painful VCFs that necessitate consideration for treatment. In addition to osteoporosis, other causes of VCFs that may benefit from kyphoplasty include metastatic disease, secondary osteoporosis (i.e., steroid-induced osteoporosis), or multiple myeloma. Kyphoplasty can also be considered in patients without a vertebral fracture that exhibit a painful vertebra secondary to primary bone tumors, like a hemangioma or giant cell tumor, or in those with metastatic disease. In addition, it can be considered in patients with Kummell disease, which is the development of a vascular necrosis of the vertebral body due to a VCF

nonunion. Special consideration should be taken in those with metastatic disease and primary tumors of the spine. The timing and treatment plan is very much dependent on tumor type and stage of disease. Collaboration with medical oncologists is warranted in order to determine appropriateness of treatment. It is also important to consider timing of the treatment in regards to specific chemotherapy and radiation therapy plans. There is currently no consensus on the best timing of treatment, whether before, during, or after chemotherapy or radiation treatment. There is a theoretical risk of tumor dissemination after the injection of pressurized cement, leading some physicians to recommend its use after radiation therapy in certain circumstances. The timing of cement augmentation depends largely on the tumor tissue type and planned medical or radiation treatment. For example, multiple myeloma can be treated with cement augmentation at any time as the surgical trauma is minimal and the risk of wound complication in the setting of ongoing or prior radiation therapy is extremely low.

Contraindications

There are both relative and absolute contraindications to the use of kyphoplasty. Absolute contraindications include resultant neurologic injury secondary to the fracture, active spinal or systemic infection, bleeding diatheses, and cardiopulmonary or other health compromise that would impede undergoing the necessary general anesthesia or sedation safely. Allergy to the bone filler/cement or opacification agents is also considered an absolute contraindication. Relative contraindications include instances where the risks and difficulty of performing kyphoplasty are substantially increased. These include disruption of the posterior cortex of the vertebral body, extension of a tumor into the epidural space, significant canal stenosis, and extensive loss of the vertebral height (>70%). Most of these instances result in a significantly increased risk of spinal cord or nerve root injury due to cement leakage. With advanced vertebral collapse, placement of the cannula can become significantly more challenging. Some physicians also recommend against performing kyphoplasty on more than three levels during a single procedure due to the potential risk of developing a cardiopulmonary injury secondary to cement, fat, or marrow embolization to the lungs. The presence of radiculopathy is also considered to be a relative contraindication to the use of kyphoplasty. As a result of the increased risk of complications in patients with these relative contraindications, physicians should proceed with caution and these cases should only be performed by experienced practitioners (Herkowitz and Rothman 2011; Mauro 2014) (Fig. 1).

Initial Workup

History and Examination

Obtaining a full and detailed history is essential in the initial assessment of a patient with a known or suspected VCF. Patients with an acute VCF will typically present with new onset midline back pain that is commonly worsened with standing and motion, especially flexion. Most osteoporotic vertebral compression fractures will present without a history of a fall or trauma (Savage et al. 2014). Key elements of the history include timing of symptom onset, pain severity, individual risk factors including history of previous cancer, diagnosis of osteoporosis, or signs or symptoms concerning for infection. Attempted treatments and their efficacy, including any improvement in symptoms or adverse side effects, are also very important to document. In addition, patients should be inquired on whether they have had any radicular-type symptoms or perceived neurologic changes in sensation, strength, coordination, or bowel and bladder control. Physicians should also inquire about the patient's functional status, past medical history, and use of anticoagulation therapy. Assessing the patient's overall state of health is vital in determining appropriate treatment options and strategy.

The physical examination is another essential piece in the evaluation of a patient with a VCF. Typically, patients will have tenderness to

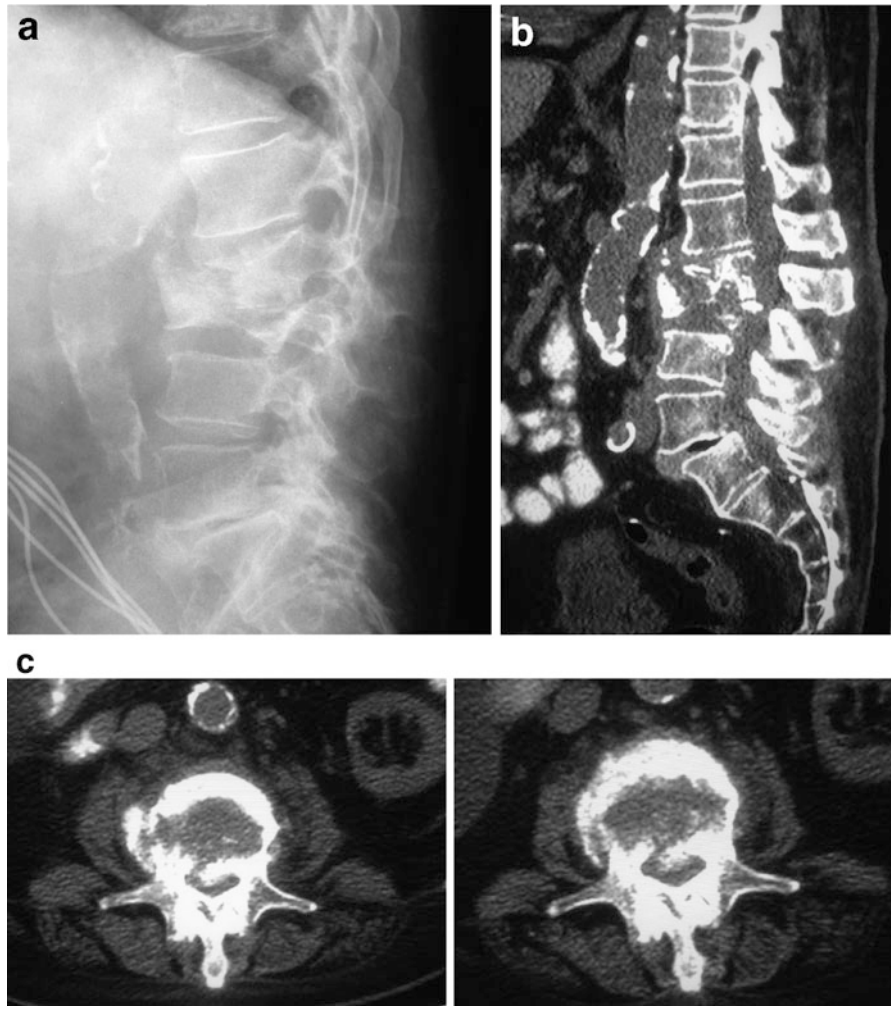

Fig. 1 Sagittal fluoroscopic (**a**) and sagittal (**b**) and axial (**c**) computed tomography images of a burst fracture. There is retropulsion of fracture fragments into the spinal canal and the posterior cortex is also noted to be compromised. These findings would be contraindications to the use of vertebral cement augmentation

palpation over the affected level's spinous process. It is critical to ascertain the level at which the patient is having symptoms, which is especially true in patients with multiple VCFs. The clinical exam and its correlation with imaging findings will then assist in determining which level(s) may benefit from intervention. It is also important to note that tenderness to palpation may not always be present in a patient with an unhealed VCF. Therefore, a lack of localizable pain with palpation should not preclude treatment. In these cases, the patient's history and imaging correlation is imperative in identifying a symptomatic VCF. In addition, a thorough neurologic assessment is the cornerstone of a complete examination and should be done in all patients. This preoperative neurologic assessment will not only identify patients that can potentially worsen with vertebral augmentation, and should be excluded from consideration, but will also aid in detecting any postoperative changes or complications.

Imaging

For every case, imaging of the spine is obtained in order to establish a diagnosis by correlating imaging results with a patient's clinical symptoms and examination findings. Imaging will not only identify potential candidates for intervention, but will also identify those in which cement augmentation would be contraindicated. Comparison to previous imaging is very beneficial in detecting new fractures and lesions or progression of those that had been previously identified. The diagnosis of a new VCF can be confirmed through either magnetic resonance imaging (MRI), serial radiographs, or bone scintigraphy.

Plain radiographs of the spine should be the first imaging modality obtained when evaluating a patient with a suspected VCF. It is an easily attainable assessment of the spine and also an excellent resource for comparison to previous or future radiographs. In addition to the wide accessibility, plain radiographs are a considerably more cost-effective source of initial evaluation when compared to more advanced imaging modalities. Furthermore, standing radiographs of the spine supply an excellent assessment of a patient's coronal and sagittal alignment and stability. This is of special importance when assessing the common kyphotic deformity that can result from a VCF, as well as any potential instability of the vertebral column.

Magnetic resonance imaging (MRI) is another useful adjunct when imaging a patient with known or suspected VCF. An important role of MRI is determining the acuity of VCFs. This can be helpful in patients without previous radiographs or in patients with a history of multiple fractures and equivocal exam findings. In these situations, having the ability to distinguish between new, symptomatic fractures and chronic fractures is essential to guide appropriate treatment when considering kyphoplasty. Findings consistent with an acute fracture include an increased signal on the short tau inversion recovery (STIR) and T2-weighted sequences, and decreased intensity on the T1-weighted sequence. Chronic fractures, which typically are not responsive to kyphoplasty, will not have an increased signal on STIR or T2-weighted sequences. For cases in which the cause of a pathologic fracture is unknown, a MRI is very useful in establishing a differential diagnosis and identifying patients that may require further diagnostic workup. Visualization of cord or nerve root compression from retropulsed fracture fragments, tumors, or other pathology is also best accomplished with a MRI.

Computed tomography (CT) can also be a beneficial resource in the preoperative evaluation of a patient with VCF or pathologic compromise of the vertebral body. A CT is most useful in assessing the integrity of the posterior cortex of the vertebral bodies. When the posterior cortex is compromised, injection of cement can lead to cement leakage or further displacement of the compromised bone posteriorly into the spinal canal. Therefore, a CT is especially valuable in patients in which the integrity of the posterior cortex is in question. It is also the imaging modality of choice for identifying other osseous injuries, and evaluation of the spine in patients involved in high-energy trauma. A CT is also useful in patients that cannot undergo a MRI safely, such as those with a pacemaker.

Bone scintigraphy is another imaging modality that can be used to differentiate between healed and unhealed fractures in patients that cannot undergo MRI. In patients with acute or unhealed fractures, a higher metabolic activity will lead to an increased uptake of technetium-99m. Although bone scintigraphy has a high sensitivity, it has a low specificity as it can continue to show increased uptake for greater than 1 year after a significant amount of healing has occurred (Savage et al. 2014). Another disadvantage of bone scintigraphy is the inability to directly visualize the spinal cord and nerve roots and the lack of spatial resolution. Single photon emission computed tomography (SPECT) is a form of bone scintigraphy that allows for improved fracture localization and characterization due to the improved spatial resolution. A MRI is still preferred over bone scintigraphy, as it is more reliable in assessing the chronicity of a fracture and provides improved visualization of the spinal cord, nerve roots, and surrounding soft tissues (Figs. 2 and 3).

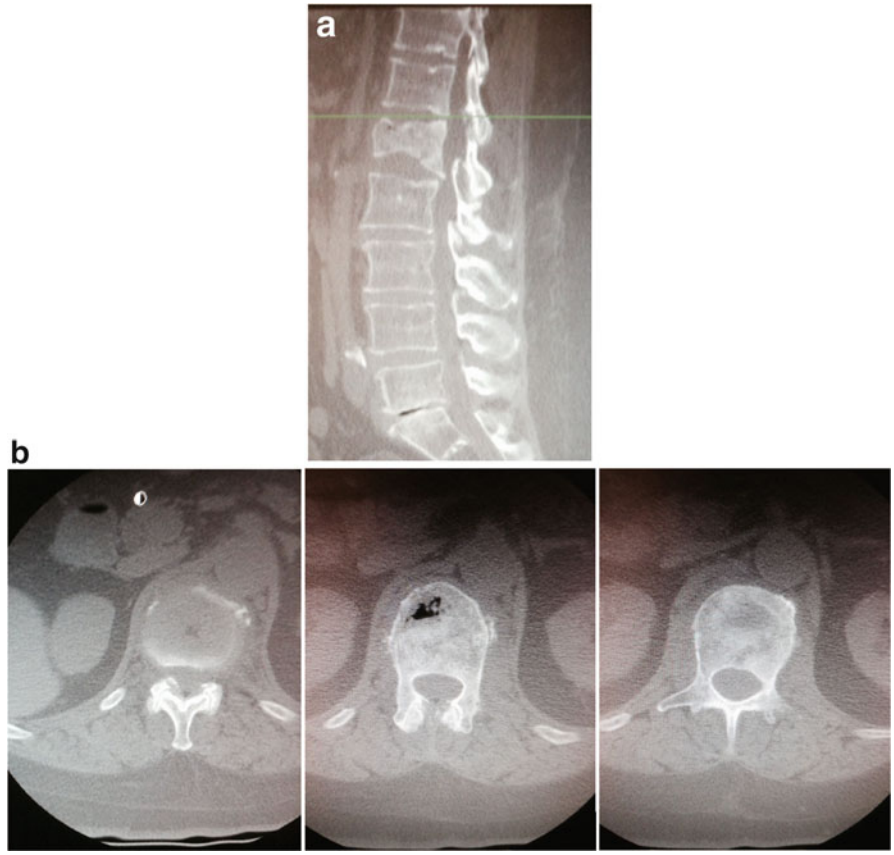

Fig. 2 Sagittal (**a**) and axial (**b**) computed tomography images of a L1 compression fracture secondary to metastatic colon cancer. No retropulsion of fracture fragments into the spinal canal noted. The integrity of the posterior cortex of the vertebral body is noted to be intact

Preoperative Testing

If a patient is considered a candidate for kyphoplasty, there are several laboratory tests that should be routinely obtained prior to proceeding. These include coagulation studies, a basic metabolic panel, and a complete blood cell count. In some instances, further testing may be warranted, such as inflammatory markers, an electrocardiogram, or a chest radiograph. Determining the necessary preoperative testing should be done on a case-by-case basis and should be based on specific patient risk factors. Ideally, this should be accomplished through a team approach that involves the physician performing the procedure, anesthesiologist, hospitalist, and in some circumstances, other medical subspecialists. It is critical to ensure a patient is medically optimized prior to the procedure in order minimize the risk of intraoperative or postoperative complications. Early involvement with referral and establishment of care with a specialist in metabolic bone disease in order to help formulate a postoperative treatment plan to prevent future osteoporotic fractures is also beneficial. Recently, the American Orthopaedic Association developed the Own the Bone program to address the need for comprehensive care of patients with metabolic bone disease. This national postfracture, system-based, multidisciplinary fragility fracture prevention initiative is designed to address physician and patient behavior in an effort to reduce the incidence of further fragility fractures.

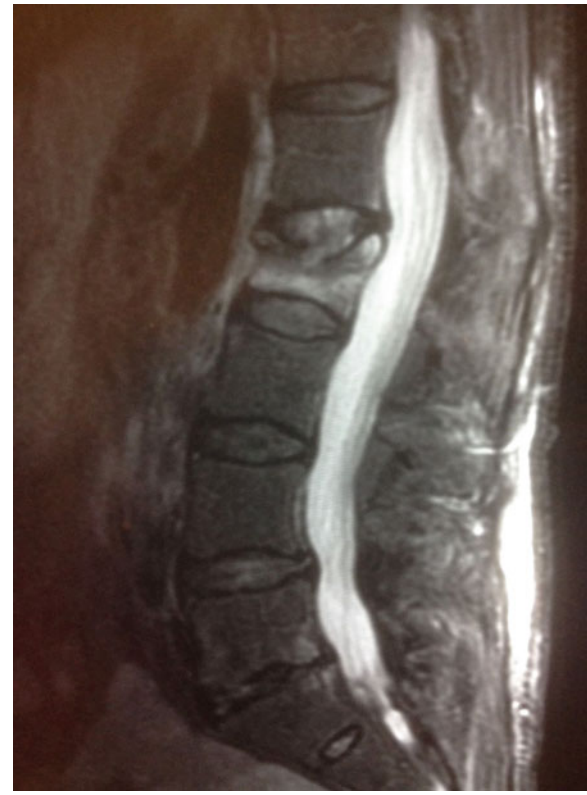

Fig. 3 Sagittal magnetic resonance image demonstrating a L2 compression fracture with accompanying increased signal within the vertebral body, indicating it is most likely an acute fracture

Technique

Before a definitive decision is made on the treatment plan and utilization of the vertebral cement augmentation, a well-informed discussion with the patient regarding the risks and benefits and alternative treatments should occur. Once a patient is determined optimized, they are brought to the operating room or radiology suite and general anesthesia or sedation is initiated. In contrast to vertebroplasty, which is generally performed under local anesthesia, kyphoplasty is usually performed under general anesthesia at most institutions. In patients with a significantly increased risk of medical complications with general anesthesia, the procedure can be performed with intravenous (IV) analgesia and sedation only, as demonstrated by Mohr et al. (2011). The decision between general anesthesia or intravenous sedation should be made in conjunction with the anesthesia provider. Adequate anesthesia should routinely be attained prior to positioning, as required movement and maneuvering can be exceedingly painful for patients with VCFs. The patient is then placed in the prone position and cushion support or chest and pelvic boosters are properly positioned to allow for spine extension. Proper positioning with adequate spine extension will facilitate reduction of the typical kyphotic deformity. The arms should also be placed toward the head of the bed to facilitate fluoroscopic visualization during the procedure. In patients with suspected limited shoulder motion, a preoperative exam testing the range of motion of both shoulders can be beneficial in anticipating lack of abduction and externals needed for positioning. In these cases, the arms may need to be placed in line with the spine. A significant portion of the patient's undergoing kyphoplasty will have underlying osteoporosis, therefore care should be taken during the transferring and positioning of the patient to prevent additional fragility fractures such as rib or sternal fractures.

After attaining adequate anesthesia and positioning of the patient, the next step is identifying the affected level(s) with fluoroscopy. Fluoroscopy is used throughout the procedure and some physicians find the use of simultaneous biplanar fluoroscopy to be beneficial. It is imperative for the correct vertebral level to be treated and close attention to preoperative and intraoperative imaging is critical in ensuring this is accomplished. For both thoracic and lumbar levels, it is helpful to count from sacrum up to the vertebral body to be addressed. Identifying transitional vertebra or anatomic variations preoperatively is very useful in order to correctly correlate with intraoperative fluoroscopic images. Obtaining both thoracic and lumbar X-rays preoperatively is imperative whenever treating thoracic level pathology in order to ensure consistency when counting from the sacrum up to the thoracic level to be treated. It can be helpful to have a discussion with the radiologist preoperatively in advance so in order to ensure the correct levels are labelled and identified prior to surgery. These steps are especially useful in cases in which the thoracic vertebral fractures reduce with positioning, which can lead to increased difficulty in identifying the correct level intraoperatively. Obtaining repetitive fluoroscopic images with a radio-opaque metallic instrument used as reference point while the counting is being done can also be extremely helpful. Placing a sterile marker such as a spinal needle adjacent to the spinous process of the vertebral body can provisionally identify the correct level. If using local anesthesia or IV sedation, a local anesthetic can be delivered via a 22-gauge needle into the skin and periosteum prior to the insertion of the larger needle and cannula. An additional benefit of this step is the ability to make adjustments to the insertion site and trajectory prior to insertion of the larger-gauge needle. A size of 11- or 13-gauge needle is sheathed in a cannula and a Jamshidi needle is then inserted. Prior to this step, a small incision can be made to allow for easier insertion and trajectory adjustments. There are two specific approaches to the vertebral body that can be utilized. These include a transpedicular approach or an extrapedicular approach. The transpedicular approach begins with needle insertion at the posterior aspect of the pedicle, followed by subsequent cannulation through the length of the pedicle and into vertebral body. The extrapedicular approach entails the needle traveling along the lateral aspect of the pedicle and then inserting into the vertebral body at the junction of the pedicle and vertebral body. One benefit of the extrapedicular approach is that it allows for a more medial tip placement of the needle in the vertebral body which may allow more centralized cement placement. This can be difficult to attain with the transpedicular approach as the path is limited by the anatomic configuration of the pedicle. An advantage of using the transpedicular approach is the utilization of an intraosseous path that protects against soft tissue structure penetration and potential neurologic injury. A general guideline for both approaches, to decrease the risk of accidental spinal canal or neural foramen penetration, is to keep the needle superior to the inferior cortex of the pedicle on the lateral fluoroscopic image and lateral to the medial cortex of the pedicle on the AP view. Advancement of the needle is done under fluoroscopic guidance, ensuring proper trajectory. A mallet or orthopedic hammer can be used to assist in needle advancement. Once the needle is advanced into the vertebral body, just anterior to the junction of the pedicle and the body, the stylet is removed and a working channel through the cannula is utilized for advancement of the balloon tamp. If necessary, biopsy needles can be used at this point to obtain samples prior to balloon tamp and cement insertion. The cannula is then brought back posteriorly to the junction of the pedicle and the vertebral body. Kyphoplasty can be performed through either a bipedicular or unipedicular approach. If the bipedicular approach is used, the Jamshidi needle or needle and cannula placement on the contralateral side is done at this time. The balloon bone tamp is then inserted and advanced within the vertebral body. The balloon tamp is then inflated under intermittent fluoroscopic visualization and pressure monitoring via a digital manometer. When inflating the balloon, inflation is stopped once the fracture has been adequately reduced; the balloon tamp reaches maximal pressure or volume, or cortical contact occurs. After one of these objectives is

Fig. 4 Example of an operating room setup used for performing a kyphoplasty procedure. In this example, utilization of simultaneous biplanar fluoroscopy is accomplished with the use of two C-arms

attained, the balloon is then deflated and removed. The cement, most commonly polymethyl methacrylate (PMMA), is then injected through the cannula until the cavity created by the balloon tamp is filled. A radio pacifier is required to appropriately visualize cement administration fluoroscopically. Most commercially available PMMA formulations contain either barium sulfate ($BaSO_4$) or ziroconium dioxide (ZrO_2) as a radiopacifier. Radiopaque cement is necessary to monitor for extravasation and ensure adequate filling of the cavity formed by the balloon tamp. In addition to the inclusion of a radiopacifier attaining an appropriate level of viscosity prior to its injection is critical. This will assist in preventing extravasation and also facilitate cement travel through the cannula. According to Lieberman et al., cement with a low viscosity or longer liquid phase is preferred for vertebroplasty, while cement with high viscosity or longer working phase is more ideal for kyphoplasty (Lieberman et al. 2005). The patient is then left in the supine position until the cement has cured. The cement plungers are inserted into the working cannula after the delivery of the cement as close as possible to the end of the cement filler. This prevents leaving a cement column that may harden inside the cannula and thus remain in the soft tissue after the cannulas are removed. Once it has cured, the cannulas are removed, dressings are applied, and the patient is transported back to their hospital bed. (Herkowitz and Rothman 2011; Mauro 2014) (Fig. 4).

Postoperative Care

After the patient is safely transported back to the hospital bed, the patient is brought to the post-anesthesia care unit for routing postoperative monitoring. Some physicians recommend obtaining a routine postoperative chest X-ray in patients undergoing thoracic kyphoplasty to rule out iatrogenic pneumothorax. Select patients may benefit from an overnight observational stay, while most patients are safe for discharge later the same day. Most of the care postoperatively focuses on assessing for any neurologic changes

and attaining adequate pain control. For the same reason kyphoplasty may be indicated, avoidance or minimized use of narcotics should be a priority when formulating a sufficient analgesic regimen in order to avoid their deleterious side effects. If the patient develops neurologic deficits, or other concerns for cement extravasation, CT imaging should be obtained urgently. Physicians must also be cognizant of the potential for pulmonary embolism, particularly if multiple levels were addressed. A chest X-ray to rule out pulmonary edema should be considered for patients with postoperative dyspnea.

Establishing appropriate follow-up is necessary for these patients as many will require treatment for their underlying cause of fracture. Most frequently, patients will require management of their underlying osteoporosis and it is important to make the appropriate referrals for necessary testing and treatment of underlying metabolic bone disease. Furthermore, many patients will be at high risk of subsequent fractures, and education regarding future risk of fracture is essential. In follow-up, if signs or symptoms of subsequent fractures occur, providers should obtain new imaging as appropriate. Routine follow-up radiographs should also be obtained and can be useful for comparison if further fracture or deformity occurred (Fig. 5).

Complications

Complications following percutaneous vertebral augmentation are generally rare; however, they can be a cause of significant morbidity. Complications that do occur are commonly a result of cement extravasation, subsequent fracture, or embolization. Other potential complications include infection, pneumothorax, nerve or spinal cord injury, pain exacerbation, hematoma formation, and intraoperative fractures (pedicle, vertebral body, and rib). The type of fracture being treated also plays an important role in risk of complications as malignancy-related fractures result in a higher complication rate compared to osteoporotic VCFs (Mathis et al. 2001; Barragan-Campos et al. 2006). When comparing kyphoplasty and vertebroplasty, the rate of procedure-related complications is significantly lower with kyphoplasty (Lee et al. 2009). Cement extravasation is a common occurrence for both kyphoplasty and vertebroplasty, but it is rarely symptomatic. In some circumstances, however, cement extravasation can lead to neurologic deficits, which may necessitate decompression and reconstruction (Savage et al. 2014). Lee et al. reported the rate of symptomatic cement extravasation is significantly lower in kyphoplasty compared to vertebroplasty (Lee et al. 2009). The study found the rate of symptomatic cement extravasation was 1.48% after vertebroplasty and 0.04% following kyphoplasty. If there is concern for complications related to cement extravasation, a CT scan is the imaging modality of choice to best visualize cement leakages. Embolization is another potential complication that is commonly asymptomatic; however, it may have severe cardiopulmonary consequences. The rate of cement embolization following percutaneous vertebral augmentation varies between 2.1% and 26% (Wang et al. 2012). The incidence appears to be lower following kyphoplasty compared to vertebroplasty. This is likely a result of the creation of a cavity that leads to the cement being injected under lower pressure. The emboli can either be from the bone marrow fat or the cement as a small fragment or as monomer that is later polymerized at a distant location. Regardless of cause, this may lead to cardiopulmonary embolism, which can be fatal in very rare cases. Clinical manifestations of cardiopulmonary embolization include patient complaints of chest pain or tightness, palpitations, and shortness of breath. Examination of the patient may reveal tachypnea, hypotension, oxygen desaturation, cyanosis, or cardiac arrhythmias with the potential development of acute respiratory distress syndrome or cardiac arrest. Physicians should be cognizant of the early signs and symptoms of cardiopulmonary embolization, as early diagnosis and treatment is critical. The development of subsequent fracture is common following vertebral augmentation. Most patients being treated will commonly have an underlying condition that already carries an increased risk of future fractures. Treatment with

vertebral augmentation, however, does not appear to be an individual risk factor. A meta-analysis done by Anderson et al. demonstrated no significant difference in secondary fractures between those treated with vertebroplasty and those treated with conservative management. In this analysis, both groups had approximately 20% of patients developing a new fracture between 6 and 12 months after the procedure (Anderson et al. 2013). Because of this high rate of subsequent

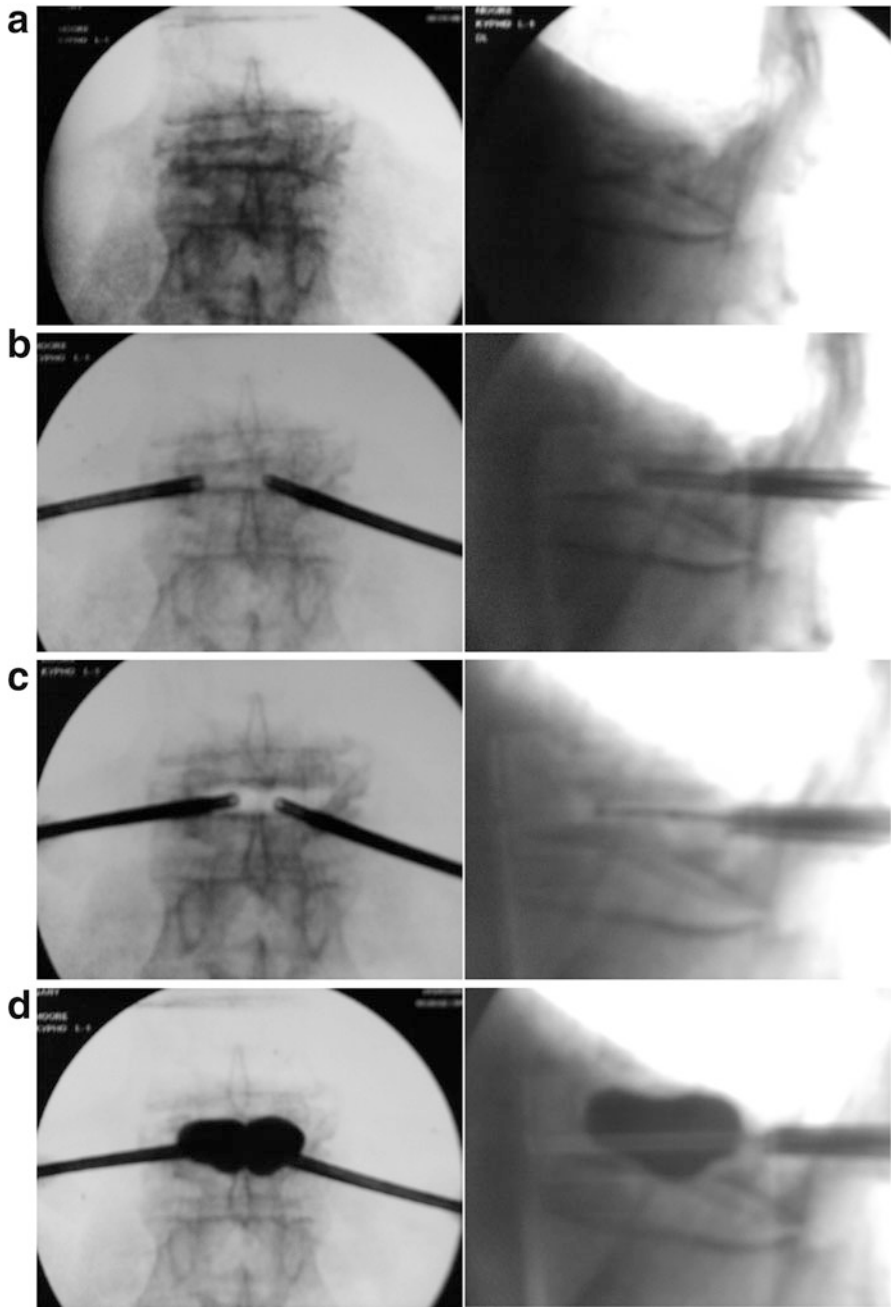

Fig. 5 (continued)

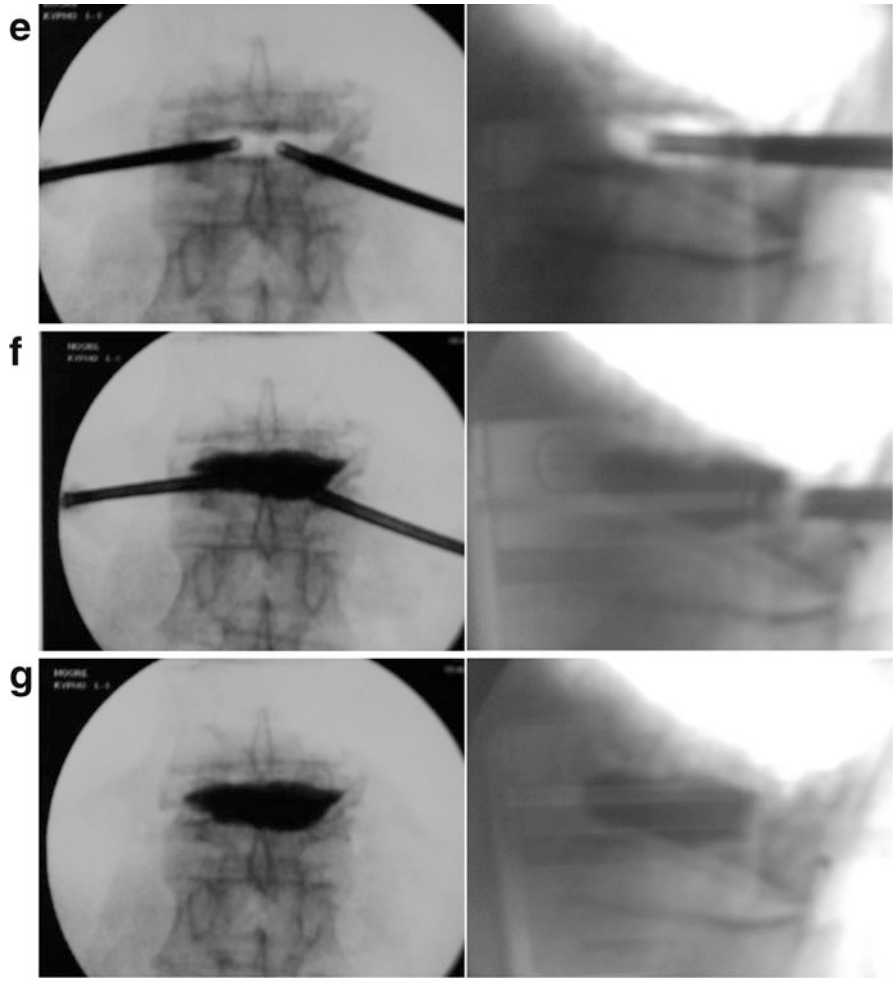

Fig. 5 Biplanar fluoroscopic images of a kyphoplasty being performed using a bilateral approach for treatment of vertebral compression fracture. (**a**) Vertebral compression fracture. (**b**), Insertion of the starting needles into the vertebral body. (**c**) Insertion of the balloon bone tamps. (**d**) Inflation of the balloon bone tamps. (**e**) Residual cavity formation noted after deflation of the balloons. (**f**), Injection of PMMA cement into the cavity. (**g**) Final AP and lateral fluoroscopic images following cement augmentation with mildly improved sagittal alignment and vertebral height

fracture, physicians should be weary of future fractures and attempt to decrease the risk by establishing appropriate treatment for underlying diseases. Although the development of an adjacent or new spinal level vertebral fracture is more common, it is also possible for patients to have a re-fracture or progression at a previously treated level. This should be of concern in patients that have no improvement, increasing pain, or worsening pain after an initial improvement period after treatment. Patients at an increased risk of re-fracture or progression include those with inadequately filled fractures or with fluid-filled vertebral fracture clefts (Jacobson et al. 2017). For these patients, a MRI or fine cut CT can assist in determining the cause for lack of improvement or early deterioration. Treatment with either observation or revision should be formulated based upon the patient's clinical status and imaging findings. Overall, complications are rare following vertebral augmentation. Treating physicians, however, should be aware of the signs and

symptoms of the potential complications as late recognition may lead to significant morbidity and poor outcomes.

Outcomes

There have been numerous studies investigating the efficacy of vertebral augmentation. Despite the extensive volume of data, debate still exists regarding its effectiveness. Since the late 2000s, a number of prospective randomized controlled trials (RCTs) have been published investigating the efficacy of vertebral augmentation for treatment of osteoporotic VCFs. Wardlaw et al. published a prospective RCT in which kyphoplasty was compared to nonoperative management of VCFs (Wardlaw et al. 2009). In this study a significant improvement in the Short-Form-36 (SF-36) physical component summary scores were found in the kyphoplasty group compared to the nonoperative group at 1 month. Another prospective RCT done by Klazen et al. found beneficial results when comparing vertebroplasty to medical management of VCFs (Klazen et al. 2010). In this study there was a significant improvement found in pain scores and in secondary outcome measures in those that underwent vertebroplasty. Similar to other prospective RCTs that demonstrated beneficial results with vertebral augmentation, both studies by Klazen et al. and Wardlaw et al. did not blind the treatment and control groups. The absence of blinding has been considered a major limitation of these and similar studies as the efficacy of vertebral augmentation may be overestimated secondary to a placebo effect. In 2009, two articles, by Kallmes et al. and Buchbinder et al., were published in the *New England Journal of Medicine* in which both the treatment and control group were blinded (Kallmes et al. 2009; Buchbinder et al. 2009). In both of these prospective RCTs, vertebroplasty was found to have no beneficial effect compared to a sham procedure in the treatment of osteoporotic VCFs. Although these studies addressed a major limitation of similar RCTs, there has been concern regarding the selection criteria for patients involved in these studies. One concern entails the inclusion of patients with fractures that were up to 12 months old. The involvement of a sham procedure instead of traditional medical management has also led many to question the impact these articles should have on practice management. The RCTs by Kallmes et al., Buchbinder et al., Klazen et al., and Wardlaw et al. were subsequently utilized in a meta-analysis performed by Anderson et al. (2013). In addition to these four RCTs, two additional studies met inclusion criteria and were used to compare vertebral augmentation with conservative management in patients with osteoporotic VCFs. The study revealed a significant improvement in pain relief, functional recovery, and health-related quality of life with vertebral augmentation compared to nonoperative management or sham procedures. This significant difference was noted at early (less than 12 weeks) and long-term follow-up (6–12 months). In 2016, Clark et al. published results on a multicenter, double-blinded, prospective RCT in which 44% of patients that underwent vertebroplasty had a numeric rated pain score below 4 out of 10–14 days compared to only 21% in the control group (Clark et al. 2016). In this study, the control group underwent a process to simulate vertebroplasty in order to control for the placebo effect. Unlike the sham procedures performed in the studies done by Kallmes et al. and Buchbinder et al., there was no local anesthetic or needle infiltration of the periosteum as lidocaine use was limited to subcutaneous administration only. Following the procedure, patients were then treated by their primary physicians with standard medical care. Inclusion criteria for this study also required that the patient's painful vertebral fractures were less than 6 weeks old. This article, in addition to the meta-analysis done by Anderson et al., support the use of vertebral cement augmentation in carefully selected patients with painful VCFs (Clark et al. 2016; Anderson et al. 2013). There have also been studies comparing the results of kyphoplasty with vertebroplasty. In a systematic review done by Han et al., the authors concluded that vertebroplasty had improved short-term pain relief while kyphoplasty demonstrated better intermediate-term functional improvement (Han et al. 2011). There was found

to be no difference, however, between the two in long-term pain relief or functional status. In a study done by Omidi-Kashani et al., both kyphoplasty and vertebroplasty demonstrated significant improvement in pain scores and outcome measures (Omidi-Kashani et al. 2013). Those that underwent kyphoplasty showed improved kyphosis with an average of 3.1° of correction. This study did not find a significant difference between the two in regards to pain and functional outcomes. As mentioned previously, complications have been shown to be more commonly seen with vertebroplasty, especially cement extravasation. The most recent AAOS guidelines recommend against the use of vertebroplasty and kyphoplasty carried a limited recommendation in the treatment of painful osteoporotic VCFs. Since this recommendation, there have been multiple articles published supporting the use of both vertebroplasty and kyphoplasty. With the substantial amount of data investigating the use of vertebral augmentation, physicians should make an effort to understand the strengths and limitations of the current literature in order to formulate the optimal treatment plan for each patient.

Special Considerations and Topics

Antibiotic Prophylaxis

For percutaneous vertebral augmentation, antibiotic prophylaxis can be accomplished one of two ways, via IV administration or by mixing with the PMMA during cement preparation. Although there is no data to support its use in this procedure, most practicing providers use at least one type of antibiotic prophylaxis due to the potential morbidity associated with infection (Moon et al. 2010). As with many other procedures, the most common infection-causing bacteria are *Staphylococci* and *Streptococci*species. For that reason, the most frequently used IV antibiotics include cefazolin, cefuroxime, and clindamycin. When using antibiotic impregnated cement, 1.2 g of tobramycin is ordinarily used and mixed with the PMMA cement. Both impregnated cement and IV administered antibiotics are considered appropriate as no evidence demonstrates superiority of one technique over the other. Theoretical disadvantages include increasing antibiotic resistance and the individual side effects that accompany their use. Based on the Surgical Care Improvement Project (SCIP) guidelines, the authors recommend intravenous antibiotics given within 1 h prior to surgical incision (Rosenberger et al. 2011).

Bilateral Transpedicular Versus Unilateral Transpedicular Approach

Kyphoplasty has been traditionally been performed using a bilateral transpedicular approach. This requires bilateral insertion of the balloon bone tamp and simultaneous inflation to create the cavity. Some studies, however, have shown that it can be done using a unilateral approach without negatively affecting outcomes. Chen et al. and Yılmaz et al. both demonstrated no significant difference in pain relief, kyphotic angle, and vertebral height restoration between the unilateral and bilateral approaches (Chen et al. 2014; Yılmaz et al. 2017). Both studies also found that the unilateral approach required a significantly shorter operative time and less cement. Hu et al. reported similar success with the use of a unilateral approach and, like many other authors, recommended a more medial trajectory to attain a midline position within the vertebral body (Hu et al. 2005). Yılmaz et al., however, questioned the necessity of a midline position when using the unilateral approach (Yılmaz et al. 2017). In their study, the needle trajectory was not altered from their typical trajectory and placement with the bilateral approach and, therefore, no additional effort was made to obtain a more medial start point or final midline position. This approach led to no difference in outcomes or decreased deformity correction when compared to other studies. The baseline position of needle placement in this study, however, was not reported, and therefore it is difficult to assess the significance of these findings. It does appear, however, that the unilateral approach can be used safely in kyphoplasty without negatively

affecting outcomes. A recent analysis of registry data evaluated the effect of cement volume on pain relief in balloon kyphoplasty. In their analysis, they found that cement volumes greater than 4.5 ml independently predicted pain relief in patients with vertebral compression fractures (Röder et al. 2013). This data may explain why a unilateral approach may be as successful as a bilateral approach, simply by restoring the mechanical property of the cemented vertebral body. Advantages of the bilateral approach include the ability to more easily access the contralateral portion of the vertebral body for cavity formation and the facilitation of cement injection using bilateral cannulas. The shorter operative time and the avoidance of the risks associated with placing an additional needle are both benefits of the unilateral approach. Some physicians also believe attaining a more midline position when utilizing the unilateral method, which is easier to obtain using an extrapedicular approach to the vertebral body. An insertion needle with a flexible tip to allow for a modifiable curve is also currently available and may aid in obtaining a more midline position within the vertebral body. Overall, the outcomes of both the bilateral and unilateral approach appear to be similar and the decision on which approach is utilized should be based on the performing physician's experience and comfort (Fig. 6).

Metastatic or Primary Bone Tumor Cases

There are a few special considerations when pathologic fractures involve metastatic or primary bone tumors. An essential part of ensuring improvement following vertebral augmentation with these types of cases is differentiating pain related to the fracture versus the tumor. This is critical, as pain originating from the tumor is typically not improved with vertebral augmentation (Savage et al. 2014). Clinical features that would be more consistent with a painful fracture include pain that increases with load-bearing activities, such as walking, sitting, or standing. Whereas pain that is secondary to the tumor will typically be present at rest and when lying supine, patients may also experience the classic worsening of symptoms at night. If a patient is having tumor-related pain, this is most often treated more successfully with radiation therapy. Patients with pain secondary to fractures with metastatic disease or primary bone tumors, such as giant cell tumors, may benefit from vertebral augmentation. First line treatment for these types of fractures, much like that for osteoporotic VCFs, consists of medical management and appropriate analgesia. The goal for treatment of painful metastatic or primary bone tumors of the vertebral body is to attain pain control and preserve function. Radiation, chemotherapy, and bisphosphonate therapy are all options that should be discussed and considered as reasonable treatment options (Gralow and Tripathy 2007). As previously discussed with VCFs, goals of treatment and timing of intervention should be addressed utilizing a team approach and individualized based on fracture pattern and underlying pathology. If vertebral cement augmentation is indicated, special care should be taken to ensure the risk of potential complication is minimized. Careful review of pertinent imaging is important for minimizing the potential risk of complication. Important aspects of the imaging include visualization of the integrity of the posterior cortex of the vertebral body, and any potential spinal cord or nerve root compression as a result of the tumor. In addition, a biopsy may be necessary in some cases and this should be known prior to proceeding. Outcomes in the treatment of cancer-related VCFs with kyphoplasty have been promising. In a randomized-control study, Berenson et al. found a significant improvement in pain relief and overall function at 1 month postoperatively compared to the control group (Berenson et al. 2011). Dudeney et al. also showed favorable results with the use of kyphoplasty in patients with osteolytic VCFs secondary to multiple myeloma (Dudeney et al. 2002). In their study, patients experienced a significant improvement in SF-36 scores, pain, and in physical and social function compared to preoperatively. With the main goals in treatment being pain relief and maintaining function, kyphoplasty is a viable option for certain patients with primary bone tumors or metastatic disease.

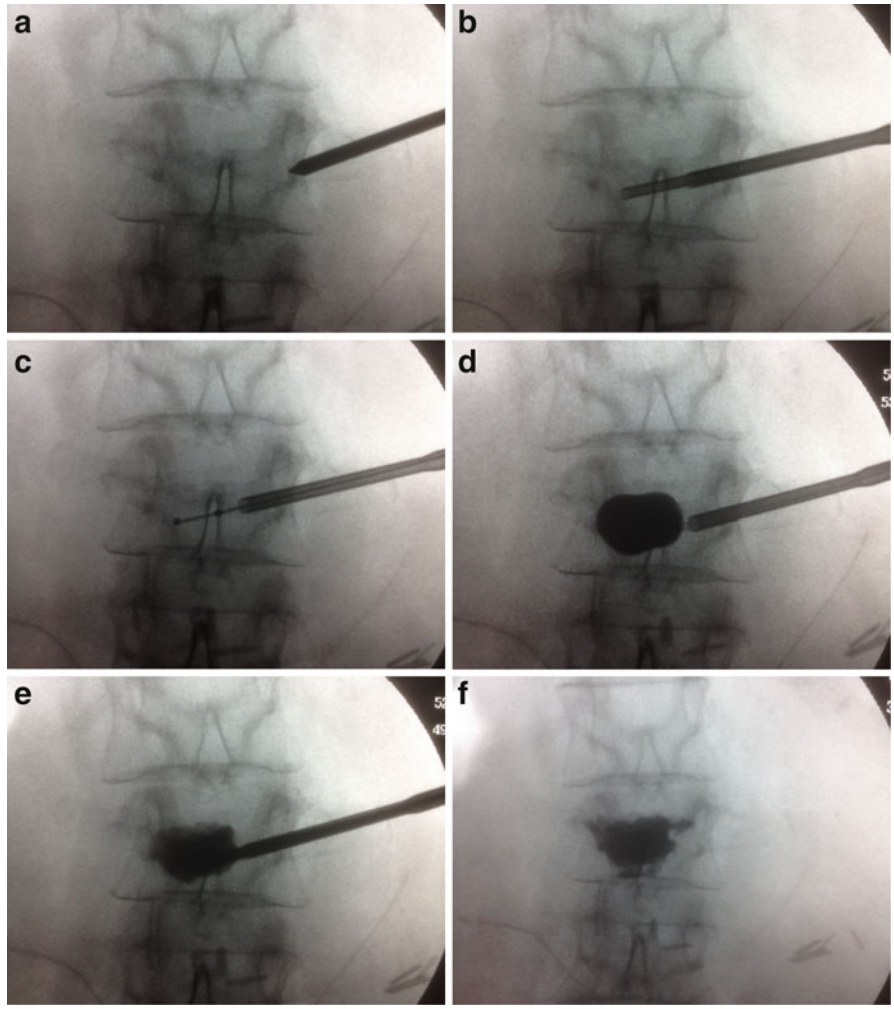

Fig. 6 Sequential intraoperative fluoroscopic images of a kyphoplasty being performed using a unilateral approach. (**a**) Initial insertion of the starting needle into the vertebral body. (**b**) Advancement of the needle utilizing a medial trajectory in order to attain a more midline final position. (**c**) Insertion of the balloon bone tamp. (**d**) Inflation of the balloon bone tamp. (**e**) Injection of PMMA cement into the cavity created by the balloon tamp. (**f**) Final AP fluoroscopic image following kyphoplasty performed via an unilateral approach

Conclusions

Despite the large volume of literature, there is still no consensus on the role of vertebral cement augmentation. Furthermore, the ideal timing of performing kyphoplasty or vertebroplasty remains controversial. Based upon the current available literature, cement augmentation should be considered for patients that meet a general set of criteria. The ideal patients being those that fail conservative management with persistent, debilitating pain, limited mobility, and an acute VCF. The length of time dedicated to conservative treatment is of debate, but generally 3–6 weeks is a commonly used time frame. Earlier consideration for patients that poorly tolerate nonoperative care, particularly narcotics and bed rest, seems to be appropriate. The use of vertebral augmentation for treatment of chronic symptomatic VCFs, metastatic disease, and primary bone tumors has also

shown promise and can be considered in certain situations. Physicians should be cognizant of the potential benefits and complications of kyphoplasty and vertebroplasty when considering treatment with vertebral augmentation. In addition, it is vital for practitioners to have a solid grasp on the current literature in order to hold well-informed discussions with patients when making an individualized treatment plan.

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Anterior Spinal Plates: Cervical

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Contents

Abstract

Anterior cervical diskectomy and fusion (ACDF) is one of the most common and effective spine procedures performed, indicated for the treatment of cervical degenerative disk disease. Patients frequently present with neck pain, radiculopathy, or myelopathy secondary to compression of the neural elements. A thorough patient evaluation is performed, consisting of clinical examination, imaging, and possibly nerve conduction studies. This chapter outlines the diagnostic evaluation, indications, operative details, considerations, and complications of the ACDF procedure.

Keywords

Anterior cervical diskectomy and fusion · Anterior cervical fusion · Diskectomy · Corpectomy · Subaxial cervical spine · Cervical radiculopathy · Cervical myelopathy

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Introduction

The anterior approach to the subaxial cervical spine was first reported by Smith and Robinson, in The Bulletin of the Johns Hopkins Hospital in 1955, where it was described for the treatment of cervical disk herniation (Robinson and Smith 1955); this reported was followed shortly thereafter by Cloward in 1958 (Cloward 1958). In contrast with posterior decompression, anterior approaches to the subaxial cervical spine provide direct decompression for compressive pathologies involving the vertebrae and/or intervertebral disks. Posterior decompressive laminectomy alone may carry a risk of progressive kyphotic deformity, especially when spanning multiple levels or when applied to patients with noted ligamentous laxity (i.e. younger patients and those with select inherited connective tissue diseases) (Song and Choi 2014; Kani and Chew 2018).

Anterior cervical diskectomy (ACDF) is one of the most common neurosurgical procedures performed, with high rates of efficacy and a relatively short recovery period. The utilization of fascial planes minimizes soft tissue disruption, and the limited range of motion in the subaxial spine does not substantially impact post-operative mobility (Robinson and Smith 1955; Cloward 1958; Song and Choi 2014; Kani and Chew 2018).

Anatomic and Biomechanical Considerations

The subaxial spine describes cervical vertebrae caudal to the axis, C2 (C3–C7). The occiput meets the cervical spine at the level of C1 (atlas), with the occipital condyles articulating with the lateral masses of the atlas. The resulting atlanto-occipital junction facilitates the majority of flexion-extension mmotion within the cervical spine. The bilateral anterior and posterior arches of C1 form the ring of the atlas and are secured to the occipital bone by the anterior and posterior atlanto-occipital membranes which help to prevent hyperextension and hyper-flexion at the O-C1 joint, respectively. The adjacent atlantoaxial junction (C1–C2) - the articulation of the atlas with the axis - allows for most of the rotational motion of the head.

The borders of the central canal are defined by the vertebral body anteriorly, the pedicles and lateral masses anterolaterally, and the laminae posteriorly. Unique to the cervical vertebrae are the foramina transversaria, which encase the V2 segment of the vertebral arteries from the level of C6 to C2, and lie within the transverse processes, located anterolateral to the lateral masses. The vertebral arteries originate from the subclavian artery and are divided into four segments: (V1) pre-foraminal, stretching from the subclavian artery to C6 foramen; (V2) foraminal, running cranially through the foramina transversaria from C6 to C2; (V3) extradural, arching laterally from the superior surface of C2, around the posterior C1 arch, through the sulcus arteriosus to the point of dural entry above C1; and (V4) intradural, running from the dural surface to the juncture of the basilar artery.

Load to the atlantoaxial junction is transmitted through the lateral masses, unlike the subaxial spine where intervertebral disks are the major shock absorbers. In the subaxial spine, the greatest degree of degeneration occurs at the C5–C6 level. In the cervical spine, each nerve root exits above the pedicle of the respectively numbered pedicle, with the exception of the C8 root which exits below the C7 vertebrae (Lang 1993; Tubbs et al. 2011; Hai-bin et al. 2012).

Motor innervation from the cervical spine is essential for upper extremity mobility and breathing. The phrenic nerve, from C3 to C5, supplies the diaphragm, with the brachial plexus supplied from C5 to T1. The musculocutaneous (C5–C7), axillary (C5, C6), radial (C5–T1), median (C6–T1), and ulnar (C8, T1) are the major terminal nerves. Patients with nerve root compression will commonly present with radiculopathy corresponding to the myotome supplied, including abduction of the arm (C5), elbow flexion (C6), elbow extension (C7), flexion of the digits (C8), and abduction of the digits (T1) (Song and Choi 2014; Kani and Chew 2018; Lang 1993; Tubbs et al. 2011; Hai-bin et al. 2012; Payne and Spillane 1957).

The combination of degenerative forces over time, and canal diameter, is important to understand the common levels of breakdown. As previously stated, disk degeneration most commonly occurs at the C5–C6 level. The canal diameter, however, is most narrow at the C4 level (13.33–17.50 mm) and widest at C1 (18.47–21.60 mm), with a mean cord diameter of 10 mm and mean overall canal diameter of 17 mm (Hai-bin et al. 2012; Payne and Spillane 1957; Gupta et al. 1982; Hashimoto and Tak 1977).

Patient Evaluation

Patients with degenerative conditions of the cervical spine frequently present with neck pain, arm pain, and/or neurologic deficits. Mechanical neck pain, exacerbated by motion, suggests instability between adjacent vertebrae. Upper extremity pain/weakness/paresthesias, however, suggest a radiculopathy due to nerve root compression. Myelopathy occurs due to spinal cord compression and may present as difficulty with fine motor skills, progressive upper and/or lower extremity weakness, gait instability, and/or bowel/bladder incontinence (Song and Choi 2014; Kani and Chew 2018; Lang 1993).

Intervertebral disk disease at C5–C6 is the most common underlying indication for patients undergoing anterior cervical diskectomy and fusion. Other indications for surgery may include fractures, neoplastic conditions, or infection (i.e., osteomyelitis) (Song and Choi 2014; Kani and Chew 2018; Angevine et al. 2003).

Diagnostic Work-Up

Plain X-ray is often the first imaging modality employed. Both dynamic radiographs (e.g. flexion/extension films) and alignment films (i.e., scoliosis imaging) are critical to assess adjacent segment motion and global balance, respectively. On dynamic films, disruption of the anterior vertebral line, posterior vertebral line, spinolaminar line, and/or posterior spinous line may suggest adjacent segment instability – manifest clinically as mechanical neck pain. Magnetic resonance imaging (MRI) is ideal for soft tissue and neural structures, critical in identifying spinal cord/nerve root compression (Kani and Chew 2018; Horne et al. 2016). Computed tomography (CT), however, is the gold standard for imaging of bony structures; the major disadvantage to this modality is the limited ability to identify compression of neural structures (Horne et al. 2016; Stanley et al. 1986). This compression, most commonly caused by disk degeneration and posterior ligamentous hypertrophy, may be readily visualized on MRI; CT is invaluable for surgical planning however, both for the aforementioned evaluation of the bony anatomy, and for the ability to identify calcification of the intervertebral disk or ossification of the posterior longitudinal ligament (OPLL) (Horne et al. 2016; Stanley et al. 1986). As such, these imaging modalities complement one another and both should be considered essential to the complete radiographic evaluation of a patient with cervical spine pain/radiculopathy/myelopathy.

Electromyogram/nerve conduction studies (EMG/NCS) are helpful diagnostic adjuvants, especially in cases of long-standing radiculopathy or where the level of symptomatic compression cannot be clearly identified by clinical exam. These may also help elucidate concomitant spinal cord, nerve root, and peripheral nerve pathology, giving a better assessment of which clinical features may be improved by surgical intervention. In addition, such studies can be beneficial in counseling patients on expected outcomes after an ACDF, offering insight into an acute or chronic radiculopathy (Alrawi et al. 2007; Carette and Fehlings 2005; Ellenberg et al. 1994).

Special Populations to Consider

Special attention should be paid to patients with connective tissue diseases and chronic inflammatory conditions known to affect the occipitocervical junction and/or subaxial spine, as these may alter the biomechanics, range of motion, and/or ligamentous structures. Conditions known to

produce these changes include Down syndrome, mucopolysaccharidoses (i.e., Morquio syndrome), Klippel-Feil syndrome, rheumatoid arthritis, skeletal dysplasias, and others like Chiari malformation type I (Frost et al. 1999; Samartzis et al. 2016; Prusick et al. 1985; Ricchetti et al. 2008; Hamidi et al. 2014).

Down syndrome, trisomy 21, is the most common chromosomal disorder and often results in ligament laxity at the craniovertebral junction. In addition to progressive atlantoaxial instability and atlanto-occipital hypermobility, patients with Down syndrome are predisposed to os odontoideum, odontoid hypoplasia, and cervical canal stenosis (Frost et al. 1999).

Patients with Morquio syndrome (mucopolysaccharidosis type IV) are predisposed to atlantoaxial instability, from dens hypoplasia, similar to a subset of patients with Down syndrome. These patients may also have aberrant retrodental soft tissue masses resulting in cervical canal stenosis and myelopathy (Samartzis et al. 2016).

Klippel-Feil syndrome involves the classic triad of short neck (Cloward 1958), low hairline (Song and Choi 2014), and limited neck mobility; the full triad of which is in 50% of patients. Klippel-Feil syndrome involves vertebral autofusion and accelerated spondylosis. Abnormal fusion of adjacent cervical vertebrae restricts motion and may lead to premature instability. This population is at high risk for atlanto-occipital and vertebral artery injury. Among patients with DiGeorge syndrome, 58% have a dysmorphic dens, and 34% have an autofusion of C2–C3 (Prusick et al. 1985; Ricchetti et al. 2008; Hamidi et al. 2014).

Recent estimates suggest that up to 80% of patients with rheumatoid arthritis, a chronic inflammatory condition, have radiographic cervical spine involvement – present within 2 years of initial diagnosis in many. Fibrovascular tissue proliferation, pannus formation, and bony erosion lead to the cascade observed: atlantoaxial instability (AAI), cranial settling (CS), and subaxial subluxation (SAS) (Nguyen et al. 2004; Wasserman et al. 2011; Krauss et al. 2010).

Surgery

Positioning and Monitoring

Patients are positioned in the supine position, with the upper extremities fully adducted and secured at the side. General anesthesia with an endotracheal tube is administered. Shoulders should be pulled down to allow for imaging, but excessive shoulder depression has been proposed as a contributing factor for post-operative C5 palsies (Alonso et al. 2018). Cervical traction (5–15 lbs) may be appropriate, especially in cases of intervertebral disk degeneration. Intraoperative monitoring, including somatosensory and transcranial motor evoked potentials, is recommended as it may help to prevent iatrogenic injury to the spinal cord or roots (Davis et al. 2013; Legatt et al. 2016).

Operative Details

Anatomic landmarks should be identified prior to skin incision, including the inferior border of the mandible, hyoid bone, thyroid cartilage, and cricoid cartilage, overlying C2/C3, C3, C4/C5, and C6, respectively (Rao et al. 2011; Moran and Bolger 2012). Due to the shorter course of the right laryngeal nerve, some surgeons opt for a left-sided approach to minimize permanent nerve injury. However, surgeon comfort and hand preference may dictate a right-sided approach which has been demonstrated to have no greater risk of permanent dysphonia (Kilburg et al. 2006).

A horizontal incision, located in the skin crease, is fashioned from the midline to the sternocleidomastoid muscle. Incisions along the skin crease are aesthetically preferred. The sternal notch can be used to approximate the midline. Dissection continues along the subcutaneous tissue, to expose the platysma. The platysma is divided with electrocautery, exposing the deep cervical fascia. The strap muscles are retracted medially, and the sternocleidomastoid laterally. The pre-tracheal fascia is bluntly dissected, with careful attention to avoid damage to the superior,

middle, and inferior thyroid arteries therein. It is necessary to develop an avascular plane, medial to the carotid sheath and lateral to the esophagus and trachea, to minimize unwanted vascular injury. The carotid sheath may be palpated to confirm the position of the carotid artery within. After lateral retraction of the carotid sheath, the location of the vertebral column can be confirmed with palpation, which reveals clearly identifiable "hills" and "troughs" representing disk spaces and vertebral bodies, respectively.

A lateral radiograph is taken to determine the appropriate level. Dissection of the thin prevertebral fascia exposes the disk space and vertebral bodies. The bilateral longus colli muscles, identified at the anterior surface of the cervical spine and originating at the transverse processes, may be reflected laterally. The placement of Caspar pins facilitates distraction across the intervertebral disk space, for ease of removal.

Diskectomy is performed by an incision into the outer annulus fibrosis and complete removal with curettes and pituitary rongeurs. Disk forceps may also be employed to ensure complete resection of the disk and adequate decompression of the neural elements. Our practice is to decompression until the posterior longitudinal ligament can be visualized, but the extent of decompression is up to individual surgeon preference. Osteophytes arising from the anterior adjacent endplates can then be removed with a high-speed drill and curettes; forward-angled curettes can be used to resect osteophytes projecting into the canal and to widen the foramina, to relieve pre-surgical complaints of radiculopathy referable to nerve root compression. A Kerrison punch may also be useful to decompress posterior osteophytes extending into the spinal canal. Throughout the exposure and decompression, meticulous hemostasis should be maintained, facilitated by bipolar cautery, cottonoid, and hemostatic agents, with particular attention to epidural venous bleeding (Rao et al. 2011; Moran and Bolger 2012). After decompression of the disk space, a high speed drill is used to decorticate and prepare the superior and inferior endplates for graft placement. Allograft has been the standard graft material for years; however, titanium and polyetherether ketone (PEEK) interbodies are both widely used and acceptable options.

Cervical vertebrectomy may be indicated in cases requiring greater anterior decompression, such as metastatic spine disease, burst fracture, or multilevel degenerative conditions (i.e., posterior osteophyte and degenerative disk disease at two adjacent levels). In cases of metastatic disease, tumor invasion typically spares the intervertebral disks allowing for safe diskectomies, but diseased bone should not be used for subsequent autograft. The uncinate process limits the lateral extent of the vertebrectomy, allowing for a ~3 mm safe zone in the central third of the vertebral body which can be corpectomized without risking injury to the vertebral arteries. Leksell rongeurs may be useful for bone removal. Additional posterior instrumentation may be required for additional support and iatrogenic instability (Kilburg et al. 2006; Buckingham and Chen 2018; Xu et al. 2014; Rhee 2015).

Interbody or cage placement, following diskectomy or vertebrectomy, should maintain normal alignment and serve as anterior column structural support. Decortication and the placement of healthy autologous bone graft, or allograft (i.e., cadaveric tricortical graft), maximize the odds of fusion. An anterior plate is securing with obliquely oriented locking screws – to minimize screw pullout, screws diverge in the sagittal plane and converge in the axial plane. Watertight closure of the fascia and skin is performed in the typical fashion (Buckingham and Chen 2018; Xu et al. 2014; Rhee 2015; Chong et al. 2015; Lee et al. 2014).

Complications

Permanent complications following ACDF are exceptionally rare, and many short-term complications can be avoided with sufficient evaluation and surgical technique (Quintana 2014). The rate of post-operative complications following anterior cervical fusion increases with the number of levels operated on (Quintana 2014; Nanda et al. 2014; Bazaz et al. 2002; Park and Jho 2012; Odate

et al. 2017; Zhong et al. 2013; Gaudinez et al. 2000; Hershman et al. 2017). Complications include post-operative hematoma, transient dysphagia, recurrent laryngeal nerve (RLN) palsy, Horner's syndrome (characterized by anhidrosis, miosis, and ptosis ipsilateral to the lesion), esophageal perforation, wound infection, vascular injury, and cerebrospinal fluid (CSF) leak (Quintana 2014; Nanda et al. 2014; Bazaz et al. 2002; Park and Jho 2012; Odate et al. 2017; Zhong et al. 2013; Gaudinez et al. 2000; Hershman et al. 2017). Complication rates are further eleveted in patients with ossification of the posterior longitudinal ligament (OPLL) (Odate et al. 2017). RLN palsy is one of the most feared complication as bilateraly injury can lead to airway compromise. Despite fears of injury, the rate of clinically symptomatic RLN palsy is 8.3%, decreasing to 2.5% at 3 months after surgery (Jung et al. 2005). Additionally, most lesions are unilateral. Other well-known cause of post-operative airway compromise is surgical site hematoma, which has been documented in up to 6.1% of cases. This requires immediate evacuation to prevent permanent sequelae). Other complications requiring surgical revision include CSF leak (0.2–1%) and esophageal perforation (0.25%) (Quintana 2014; Nanda et al. 2014; Bazaz et al. 2002; Park and Jho 2012; Odate et al. 2017; Zhong et al. 2013; Gaudinez et al. 2000; Hershman et al. 2017; Jung et al. 2005).

Case Illustration

This 37-year-old male presented with left-sided spastic hemiparesis that progressed after sustaining a fall 2 years prior. Imaging demonstrated a broad disk bulge at C3–C4 compressing the spinal cord, with signal change present in the parenchyma from C2 to C4 (Fig. 1). An ACDF was determined to be the most appropriate treatment.

The patient was placed supine, and an inflated bag was placed between his shoulders for neck extension, given the high location of the exposure in the cervical spine. The patient's head was then placed in a Mayfield horseshoe adaptor with roughly 15° of extension and 15° of rotation away from the surgeon to facilitate the conventional Smith-Robinson approach. Using the Mayfield adaptor, 10lbs of chin strap traction was applied to facilitate access to the C3/C4 disk space. At this time, intraoperative neuromonitoring leads were also placed for measurement of somatosensory evoked potentials (SEPs), transcranial motor evoked potentials (TcMEPs), and free-run electromyography (EMG) throughout the case. Leads for

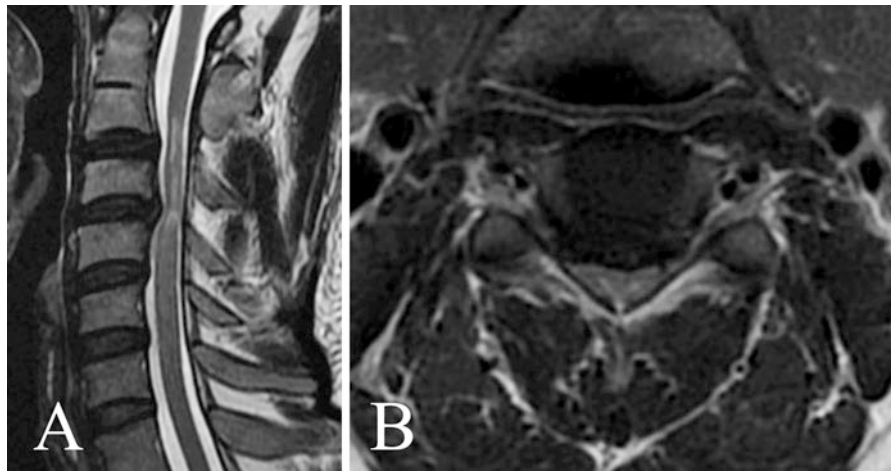

Fig. 1 Pre-operative imaging. (**a**) Sagittal T2-weighted MRI demonstrating a disk bulge at C3–C4 and cord signal change. (**b**) Axial T2-weighted MRI

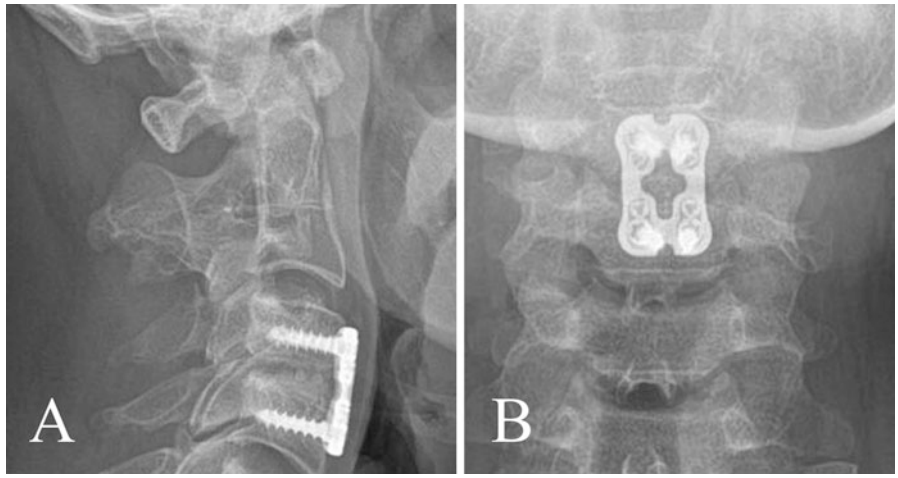

Fig. 2 Post-operative imaging. (**a**) Lateral X-ray following C3–C4 ACDF. (**b**) AP X-ray

TcMEPs were placed at the bilateral tibialis anterior, abductor hallucis, deltoid, and pollicis brevis; EMG leads were placed bilaterally at the deltoid and abductor pollicis brevis. His arms were secured and shoulders taped down; a lateral X-ray was then taken for localization and marking of the skin incision. A transverse skin incision was placed along the crease of the neck, and electrocautery was utilized to dissect the platysma. Blunt dissection proceeded medial to the carotid sheath, lateral to the esophagus and trachea. Upon encountering the spine, a repeat X-ray was taken to confirm the correct level. Caspar pins were placed in C3 and C4 for distraction. An operating microscope was brought in for the decompression. The anterior longitudinal ligament was incised with a 15-blade, and diskectomy was performed using a high-speed burr, rongeurs, and a Kerrison punch. The degenerated posterior uncovertebral joints were subsequently removed, with attention to preserve the traversing nerve. Following adequate decompression of the central canal and bilateral foramen, the endplates were decorticated. A structural allograft was sized and placed in the diskectomy defect. Distraction was released from the Caspar pins to reduce the C3 and C4 vertebrae onto the graft, and an angled curette was used to determine secure positioning. An anterior plate was placed from C3 to C4 with four locking screws. A lateral X-ray was taken showing good placement of the hardware (Fig. 2). Somatosensory and motor evoked potentials were monitored throughout the case and were stable. The wound was closed in a layered watertight fashion. The platysma was closed using 0 Vicryl, with 4–0 Biosyn sutures in the subcuticular layer. The skin surface was closed with glue and adhesive strips. The patient did well postoperatively and gradually regained function and the ability to independently ambulate over the next 2 years, working with rehabilitation.

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Spinal Plates and the Anterior Lumbar Interbody Arthrodesis

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Abstract

Each year over 200,000 lumbar spine fusions are performed. Fusion can be accomplished through an anterior, retroperitoneal approach, posterior or posterolateral approach, or more recently, through the lateral or transpsoas approach as pioneered by Pimenta and colleagues. Traditionally though, anterior interbody fusion (ALIF) has been a workhorse for discogenic pain and sagittal deformity of the lower lumbosacral spine. Most commonly this procedure involves placement of an interbody device followed by anterior tension band plating. But over the past decade and a half, new implants and new fusion devices have become available, which increase the robustness of this procedure. Here we discuss the basic indications of the ALIF procedure, provide a description of the classical ALIF procedure, and discuss current technologies.

Keywords

Lumbar fusion · Interbody fusion · Spinal fusion · Lumbar spondylosis · ALIF · Spinal implants

Introduction

The use of anterior lumbar interbody fusion (ALIF) to address degenerative spine pathologies was first described in 1933 by Burns, who described its use for the treatment of spondylolisthesis secondary to bilaminar fracture in a 14-year-old boy (Burns and Camb 1933). Since that time, it has become an increasingly popular option for addressing pathologies of the lumbosacral spine, including spondylolisthesis and intervertebral disc herniation, as well as lumbosacral kyphoscoliosis, in which it most commonly complements posterior instrumentation (Loguidice et al. 1988). At its basest level, the procedure involves an anterior retroperitoneal approach to the lower lumbar or lumbosacral spine with partial or complete discectomy followed by placement of an interbody with or without supplemental anterior plating. Over its years of use though, new technologies have been developed for both improved surgical access and spinal reconstruction, including the introduction of integrated fixation cages. Here we provide an overview of the ALIF procedure and describe the various pieces of instrumentation employed for spinal column reconstruction.

A Brief History of Lumbar Fusion

The first description of instrumented lumbar fusion in print is made by Berthold Hadra, who reported the treatment of a C6/7 dislocation using internal reduction and fixation with silver wire connecting the adjacent spinous processes (de Kunder et al. 2018). Hadra himself attributed this technique of interspinous fusion to the thoracolumbar fusions performed by Dr. W. Wilkins, though the former never published his results (Keller and Holland 1997; Peek and Wiltse 1990). Despite multiple interventions, de Kunder's wiring technique proved to have insufficient strength to maintain reduction of the patient's fracture dislocation, and the patient's symptoms recurred within weeks of surgery (de Kunder et al. 2018). As a result, it was evident that alternative methods were needed. The well-known alternative to emerge was a technique described roughly two decades later in 1909 by Fritz Lange. Lange utilized rigid rods made of celluloid – a precursor to modern plastics – along with 5-mm-thick steel and silk wire to correct scoliosis in pediatric patients, a technique far not too dissimilar to modern posterior fusion techniques (Tarpada et al. 2017). Then in 1933, Burns and Camb described the first anterior fusion in a 14-year-old boy being treated for spondylolisthesis secondary to a bilaminar fracture (Burns and

Camb 1933), using a technique first proposed by Capener 1 year earlier (Capener 1932). Over the subsequent decades, progress in anterior fusion technologies lagged behind that of posterior fusion technologies, including progress in interbody device implementation (de Kunder et al. 2018). This culminated in the development of the Harrington rod in 1962 by American orthopedist Dr. Paul R. Harrington, which was the workhorse of spinal instrumentation for several decades. Around this same time though, Melvin Watkins published his findings on far lateral fusion (M. B. Watkins 1953), paving the way for the modern oblique lateral (OLIF) and extreme lateral interbody fusion (XLIF) used today.

Part of the reason that anterior fusion advancement may have lagged behind those of posterior fusion may stem from the struggle of early spine surgeons attempting to identify a strong material capable of maintaining correction and providing long-term stabilization. The early celluloid implants of Lange were reasonably tolerated within the body; however, their flexural modulus, like that of the steel wires also employed by Lange and his predecessors, was insufficient to maintain correction over their long intended service life (Peek and Wiltse 1990). Conversely, carbon steel implants had high flexural modulus but were susceptible to degradation within the electrolytic solutions of native human tissue. This necessitated the invention of new implants with electrolytic resistance similar to the noble metals (e.g., gold) but with the relatively high flexural modulus of steel. The solution was concomitantly reached through the invention of Vitallium – a cobalt-chrome alloy – and stainless steel, both of which were developed in the late 1930s (de Kunder et al. 2018; Peek and Wiltse 1990). Despite these advances in posterior fusion, the implementation of metal instrumentation for anterior fusion did not occur until the middle of the century. Leading up to this point, anterior approaches to lumbar fusion had relied solely upon external bracing for reinforcement during the immediate postoperative period. Surgeons had also championed the use of fitted interbody devices, chief among them, Paul Harmon, who in the late 1950s and early 1960s used tibial peg grafts and iliac crest grafts as fitted interbody devices (Harmon 1960). The latter of were also employed by Freebody and Crock (Harmon 1960; Peek and Wiltse 1990). At this time though, the first description of instrumentation for anterior lumbar fusion was made by Humphries et al. in 1958, who reported the use of an intervertebral clamp in a series of 25 dogs (Humphries et al. 1958). In their abstract, Humphries et al. also described a matched control series fused without the anterior vertebral clamp; unlike the instrumented group, the non-instrumented group had a 100% pseudarthrosis rate, demonstrating the potential utility of instrumentation in anterior lumbar fusion. Humphries and colleagues further elaborated on this technique in their 1961 paper, where they reported the results in a small series of human patients (Humphries et al. 1961). This clamp served as the precursor to the modern anterior and lateral plates that maintain compression on the placed interbody to facilitate successful fusion. Finally, in the mid-1980s, Louis published his series of over 400 patients including several that had undergone anterior-only fusion using lag screen placement across the interbody device – a technique mechanically similar to the increasingly popular integrated fusion cages (Louis 1986).

Anterior Versus Posterior Approaches to the Lumbar Spine

Despite the greater cumulative experience of spine surgery with posterior instrumentation, there is no clearly superior option across all cases. As with any surgical procedure, it is imperative to first identify the indication for surgery and the goals for surgery. Based upon these goals, a surgical plan can then be developed, which includes the decision of whether they treat the pathology from an anterior-only approach (ALIF), lateral/anterolateral approach (XLIF, DLIF, OLIF), posterior-only (TLIF, PLIF), or combined anterior-posterior approach.

Determining the surgical goals begins by identifying the pathologies responsible for the patient's clinical picture, whether that is a mobile spondylolisthesis generating mechanical, low back pain or an eccentric disc producing unilateral radicular pain. For degenerative cases, this

includes assessing the patient's spine for the presence of any pathologic curvature (i.e., scoliosis, flat-back syndrome, or focal kyphosis), the presence and grade of spondylolistheses within the spine, the presence of fragility (e.g., vertebral body compression fracture) or iatrogenic fractures (e.g., pars fracture), the presence and extent of cord and nerve root compression, and the overall sagittal (normal <5 cm) and coronal imbalance (normal <2 cm). Having done so, it is then necessary to identify which of these structural lesions should be addressed by surgery. Many patients have clinically appreciable spinal deformity that is asymptomatic (Kebaish et al. 2011; Schwab et al. 2005). The basis for this decision is ultimately up to both the surgeon and patient but should be based upon the patient's clinical complaints/presentation and overall health. Patients presenting with chief complaints of radicular pain or functional radiculopathy may be adequately treated with a discectomy or two-level decompression without fusion, whereas those with significant kyphoscoliotic deformity and back pain as a chief complaint will likely require a larger operation to realize clinical benefit from the procedure. Extra caution must be exercised when considering the latter option though, as not all patients have enough physical reserve to successfully recover from large, multilevel reconstructions. The International Spine Study Group has recently published on this, suggesting that frail patients may benefit most from nonsurgical management given their high risk for complications (Miller et al. 2017).

The next step after having deemed a patient to be a surgical candidate and having localized the pathology is to formulate an approach. In some cases, either posterior or anterior fusion is superior to the other, as in the cases of long-construct fusion operations for deformity, which are optimally achieved through a posterior-only approach (Geck et al. 2009; S. S. Lee et al. 2006). But in other cases, such as one- or two-level pathologies of the lumbar spine, both anterior and posterior approaches are available, and the decision should be made on the exact pathology (e.g., disc herniation), patient body habitus, and surgeon familiarity with each approach.

For the lower lumbar spine and lumbosacral spine, there are several anatomic considerations that must be made when selecting an approach. At the L5/S1 level – the most common site of lumbar intervertebral disc herniation – lateral approaches are largely precluded, as the iliac crests make access essentially impossible in most patients. This is also a concern at the L4/5 level, though less commonly so, and is based upon the actual height of the patient's ilia. At higher levels, lateral approaches become a more robust option, and they may preferable for pathologies above the bifurcation of the iliac arteries, due to the decreased risk of vascular damage relative to the anterior approach and decreased blood loss relative to the posterior approach. Furthermore, above the level of the renal vessels (L1–2), the anterior approach largely ceases to be a consideration due to its requirement for diaphragm mobilization. As a result, the main indication for an anterior approach is one- or two-level disease between the L2 and S1 vertebrae. Here the anterior fusion can be used as either a stand-alone procedure or as a supplement to a posterior procedure in cases requiring significant correction of coronal Cobb or lumbar kyphosis. Of note though, we recommend against an anterior approach in cases of prior retroperitoneal surgery or obesity due to increased complexity of access. We also recommend against its use in cases of an ankylosed level with full disc space collapse or solid arthrodesis at the surgical level. We do however feel it is appropriate to perform an ALIF with an indirect foraminal decompression, if the collapsed disc space has not undergone ankylosis. Additionally, when considering a one- or two-level fusion, it is still important to take into consideration the patient's sagittal imbalance, as failure to correct sagittal imbalance and loss of lumbar lordosis is a previously identified negative predictor of surgical outcome in short-construct fusions (B. H. Lee et al. 2017).

Relative Advantages and Disadvantages of the Anterior Approach

As with any surgery, there are advantages and disadvantages to employing an anterior as

opposed to a posterior approach. Relative advantages of the anterior approach include superior visualization of the disc spaces of the inferior lumbar spine and lumbosacral junction (Giang et al. 2017) and the ability to avoid dissection of the posterior musculoligamentous structures (Mobbs et al. 2015), thereby preserving the posterior tension band and reducing in the risk of nerve root injury (Jeswani et al. 2012). Additionally, and more important to the scope of this work, the anterior approach may offer several mechanical advantages relative to a posterior (PLIF) or posterolateral (TLIF) approach. One study by Hsieh and colleagues reported a cohort of 57 patients operated for discogenic back pain (Hsieh et al. 2007). Among this cohort, 32 patients were treated via the anterior approach, and 25 patients were treated via a posterolateral approach (TLIF). The authors reported superior correction among the ALIF group in terms of restoration of foraminal height, disc angle, and lumbar lordosis. Similar findings have been observed by other groups (J. Kim et al. 2010; R. G. Watkins et al. 2014), with 10° of correction per level or upward of 20° to 30° per level with some of the more recent hyperlordotic cages (Saville et al. 2016). These larger cages can only be placed via an anterior approach due to the access restrictions posed by the exiting nerve roots in posterior and posterolateral approach, and as a result, the anterior approach may be the best option in patients requiring substantial sagittal correction. Although similar levels of sagittal correction can be achieved using pedicle subtraction osteotomies (K. Cho et al. 2005), this correction is non-physiologic in that it compresses the exiting lumbar nerve roots and may lead to postoperative radicular pain if concomitant foraminotomies are not performed. Furthermore, this approach requires compromise of the posterior tension band (Udby and Bech-Azeddine 2015), which may decrease the ability of patients to maintain large corrections postoperatively, though evidence to support this is still pending.

Despite these advantages, the anterior interbody fusion has several limitations. Chief among these is the complexity of the retroperitoneal approach (Giang et al. 2017). Multiple delicate structures must be crossed during this dissection, including the aorta and inferior vena cava in the prevertebral space above the level of L4, the hypogastric plexus within the presacral and L5 prevertebral space, and the ureters in the posterolateral retroperitoneal space. Injury to these structures can lead to significant blood loss, hydronephrosis, and retrograde ejaculation (Czerwein et al. 2011; Quraishi et al. 2013). Because of these risks and the lack of familiarity that the average surgeon may have with this approach, anterior interbody fusions often require the use of an access surgeon. This is especially true for surgically complex abdomens, such as those seen in patients with substantial abdominal obesity and in individuals who have previously undergone abdominal surgery. The latter have significant adhesions and scar tissue secondary to their prior operation(s), obscuring normal landmarks, while the former have significant abdominal soft tissue requiring retraction. This results in a narrow surgical corridor, and in the morbidly obese, extensive abdominal soft tissue may make adequate retraction impossible. Even in those cases where the anterior approach is possible, patients may also require a second, posterior approach for increased structural stability in order to prophylax against pseudarthrosis, which has been reported at a higher rate in this population (Jiménez-Avila et al. 2011).

In terms of biomechanical stability, results are mixed regarding the superiority of anterior- versus posterior-alone procedures for single-level disease. A recent cadaveric study by Liu and colleagues suggested that anterior interbody fusion with plating provides superior compressive strength compared to pedicle screw supplemented constructs (L. Liu et al. 2014). However, a previous cadaveric study by Tzermiadianos and colleagues (Tzermiadianos et al. 2008) saw superior strength with respect to lateral bending and flexion-extension in the pedicle screw fixation group. Additionally, multiple studies (Dorward et al. 2013; D. Kim et al. 2009), including recent meta-analyses by Phan et al. (2015) and Teng et al. (2017), observed no difference in fusion rates between anterior and posterior interbody techniques, suggesting that there may be no significant role for biomechanical considerations when selecting an approach for the treatment of

discogenic pain. Because of this and the similar complication rates for anterior and posterior approaches (Teng et al. 2017), we recommend that the approach employed be dictated by the familiarity of the surgeon with the approach and the indication for surgery. Anterior approaches may yield superior results in patients being treated for discogenic pain conditions with only minor subluxation deformity being treated by surgeons familiar with the retroperitoneal approach. Conversely, posterior approaches are preferable for patients with high-grade spondylolisthesis, especially if the attending surgeon is uncomfortable with the retroperitoneal approach.

Anterior Lumbar Interbody Fusion

Positioning, Draping, and Mapping of the Incision Site

As with all surgical procedures, the anterior lumbar interbody fusion begins with a review of preoperative imaging. In the context of an ALIF, the goal of preoperative imaging review is to identify the angle of the target disc level (generally L4/5 or L5/S1). Patients with greater pelvic incidences will have more caudally directed anterior disc surfaces, which may require induction of additional Trendelenburg positioning. Concomitant inducement of greater lordosis is recommended to open the ventral disc space, which can be done using a roll or cushion; this may not be necessary in patients with substantial native lordosis though (Heary et al. 2017). Additionally, preoperative imaging allows for evaluation of prevertebral soft tissues and identification of potential surgical obstacles. Structures of particular concern are the iliac vessels, which generally bifurcate at the level of L3 (veins) or L4 (arteries) and consequently must be mobilized in approaches to the mid- or upper lumbar spine.

After the angle of the disc space has been identified, the surgical procedure can begin. The patient is brought to the operating room and placed under general anesthesia. The patient is then transferred to a radiolucent table, such as the Jackson table, which is placed in mild Trendelenburg position to position the target disc space perpendicular to the floor. In patients with larger body habitus, we recommend securing the feet of the patient to the table to prevent sliding during the procedure. We also recommend rotating these patients slightly, placing them in a position intermediate to supine and lateral decubitus; this helps retract intraperitoneal structures during the approach. While placing an inflatable pillow or surgical bump underneath the patient buttocks is helpful in most patients, owing to an increase in exposure of the ventral disc space, it may need to be excluded in patients with significant pelvic incidence, as it can decrease lordosis and exposure of the lower lumbar disc spaces. Similar flexibility is offered during positioning of the patient's arms. The overall goal in positioning is to remove the distal arm from the abdominal region and surgical field, which we believe can best be accomplished by abducting the right arm and securing the left arm across the patient's chest in a standard room set up. This approach allows for adequate visualization of the discs with fluoroscopy while providing access to all members of the surgical team.

After positioning, the incision line is then drawn on the patient. Several options are available including a standard midline incision (Aryan and Berta 2014), a vertical paramedian incision of the linea semilunaris (Jeswani et al. 2012), and a right-angled incision with a horizontal arm between the umbilicus and pubic symphysis (Heary et al. 2017). For L5/S1 discs, a 7-cm-horizontal incision 2–3 cm above the pubic symphysis is preferred, whereas for L4/5 pathology, a vertical incision is preferred. This latter technique offers superior exposure at all levels and superior cosmetic results and can be easily extended under circumstances, such as vascular injury, that require additional exposure. Alternatively, a Pfannenstiel incision may be used, as is commonly performed in gynecological procedures (Aryan and Berta 2014). If a paramedian incision is utilized, placement on the left side of the patient is preferred as it facilitates aortic retraction and reduces the amount of retraction that the more fragile inferior vena cava must undergo (Heary et al. 2017). After the patient is positioned and the incision is marked, a rail for retractor attachment is connected to the table, the surgical field is cleared with appropriate skin preparation, and the patient is draped in the usual fashion.

Incision and Approach

Either a transperitoneal or retroperitoneal approach may be employed. Both procedures are effective means of accessing the disc space; however, previous evidence suggests that transperitoneal approaches have a 10x higher risk of hypogastric plexus injury and retrograde ejaculation (Heary et al. 2017). As such, we prefer a retroperitoneal approach, especially in male patients. It should be noted that for either the transperitoneal or retroperitoneal approaches though, it is recommended to utilize a vascular access surgeon in order to decrease the risk of injury to the genitourinary, vascular, and prevertebral nervous system structures. This is especially true for patients with risk factors for retroperitoneal fibrosis, e.g., prior abdominal surgery.

The procedure begins by making a 4–6 cm paramedian vertical incision along the planned incision line, centered roughly 2 cm to one side of the patient (left of midline for a right-handed surgeon). Incision should be through skin and the superficial fascia (Camper's, Scarpa's) to expose the anterior rectus sheath. The sheath, comprised of the aponeuroses of the external and internal oblique, as well as the transversus abdominis below the arcuate line, is divided, exposing the fibers of the rectus abdominis. To expose the posterior rectus sheath, the rectus fibers are then either dissected away from the linea alba and the released rectus muscle is retracted laterally or the fibers are dissected away from the semilunar line and the rectus is retracted medially. Both options are acceptable, and the decision is up to the individual surgeon. Note that during this dissection, splitting, as opposed to cutting of the rectus fibers, should be used to reduce the risk of postoperative hernia at the surgical site. The posterior sheath is then divided vertically with a scalpel and blunt; finger dissection is used to develop a plane between the posterior rectus sheath and the underlying peritoneum. Below the level of the arcuate line, the plane is developed between the peritoneum and more superficial transversalis fascia. Dissection continues laterally retracting the overlying soft tissues laterally and the peritoneum and intraperitoneal contents superomedially. Once the depth of the psoas muscle is achieved, the ureter should be immediately identified and protected to prevent postoperative complications; it is usually adherent to the peritoneum and can therefore be protected within this structure (Jeswani et al. 2012). The iliac vessels are then identified. For L4/5 pathologies, the iliac vessels are retracted medially along with the aorta and inferior vena cava, exposing the disc and overlying sympathetic chain medial to the psoas. The iliolumbar and segmental vessels are ligated to facilitate mobilization. For L5/S1 pathologies, the iliac vessels are retracted bilaterally away from the midline, and the middle sacral artery and vein are ligated and divided to expose the disc space. The sympathetic chain is then identified using forceps to avoid injury to it during discectomy. In some cases though, gentle retraction may have to be applied to the sympathetic chain in order to expose the pathologic level, though this is associated with an increased risk of sympathetic syndrome. Following completion of the approach, fluoroscopy is used to confirm the spinal level. A universal retractor ring is then affixed to the table centered on the level of the affected disc; this ring will be used as a fixation point for retractors during the discectomy and reconstruction.

Addressal of the Pathology

Discectomy

A #11 blade is used to outline the target disc in rectangular fashion using a templated trial selected based upon preoperative CT or MR imaging, which are used to measure the width and height of the target disc space. During incision, care must be taken to avoid damaging the sympathetic chain located immediately lateral to the disc space, a concern that is most important at the L4/5 level. Though an en bloc resection of the disc is preferred, in cases where this is not feasible, the disc can be longitudinally sectioned in several pieces to facilitate extraction. An ALIF system, straight osteotome, Cobb elevator, or laminae spreader is then used to distract the disc space (Heary et al. 2017). Additional distraction can be

achieved using sequential dilator; care should be taken to avoid overdistraction, which has been associated with postoperative neurapraxia (Taher et al. 2013). The remaining disc attachments are cleared from the superior and inferior end plates using a curette, concomitantly decorticating the end plates in preparation for fusion. Loosened cartilage and semi-mobilized disc fragments can be resected using a pituitary rongeur. We recommend preserving the posterior annulus in most cases, as it protects the ventral dura and helps to stabilize the cage postoperatively. The vertebral end plates are then prepared using a forward-angled curette. Trial implants are tested in the discectomy level until an implant large enough to restore the original disc height has been identified. Preoperative imaging is useful at this point, as adjacent, normal disc spaces can be used for selecting the appropriate trial size. Note that the implant should not be too large, as this may increase the risk of implant subsidence or kickout. Similarly, the trial should not be too small, as this (1) may provide insufficient sagittal plane correction and (2) may decrease the stability of the construct by reducing the compressive force exerted on the implant by the annulus (Patwardhan et al. 2003). The trial spacer is then removed, and the permanent interbody is placed. Femoral allograft, titanium, and PEEK implants are all available, and graft material (discussed later) can include demineralized bone matrix, allograft, autograft, and osteoinductive materials such as rhBMP-2. After placement of the implant, positioning is confirmed on fluoroscopy. If positioning is satisfactory, additional graft material may be placed around the interbody device. This additional graft has the potential to facilitate fusion and decrease the risk of implant subsidence (Kumar et al. 2005); it is difficult to assure that said graft remains in place however, and many surgeons only place graft in the interbody. Screws are then placed to fix the cage to the bone (in the case of integrated fixation cages), or a plate is affixed to prevent anterior subluxation of the cage. With some implants, notably integrated fixation cages, it is necessary to trim the lateral surfaces of the vertebrae bracketing the implant to allow placement of the screws.

Closure

After final positioning is confirmed on fluoroscopy, closure of the surgical corridor begins. Retractors are removed sequentially, inspecting both the ureter and the iliac vessels during removal to confirm that they have not been injured during the procedure. If these structures have been injured, it is necessary to repair them prior to closure of the wound. The risk of these injuries in the anterior retroperitoneal approach is one reason that it may be beneficial to utilize an approach surgeon for the exposure. The corridor is closed in layers with 2–0 Vicryl in the posterior rectus sheath, a few loose 0 Vicryl sutures in the rectus abdominis to facilitate muscle reapproximation, and 2–0 Vicryl sutures in the subcutaneous tissue; the skin is closed with 4–0 Vicryl or staples.

Spondylolisthesis

An anterior stand-alone procedure is not recommended for significant spondylolisthesis (above grade I), as the ability to reduce the translation is inferior to that offered by a posterior procedure (Jeswani et al. 2012). If the indication for surgery is spondylolisthesis, the anterior procedure should be performed exactly as described above for discectomy, except that a tension band plate is not placed, unless the spondylolisthesis can be reduced sufficiently on the anterior approach. Instead, a kickout plate or cancellous screw and washer construct are attached to one of the vertebrae to retain the interbody. The wound is then closed in layers, and the patient is flipped for the posterior portion of the procedure. Pedicle screw fixation is applied as described elsewhere, reducing the spondylolisthesis as the rods are applied, if desired. Fluoroscopy is then used to confirm placement of the instrumentation. If it is satisfactory, Valsalva is performed to confirm that no dural perforation has occurred. Note that this is not necessary in cases where pedicle screw instrumentation is placed percutaneously. Lumbar drains are placed, and the posterior wound is closed in layers, with 0–0 Vicryl in the deep fascia and 2–0 Vicryl in the subcutaneous fascia. The skin may be closed with Nylon sutures, steristrips, glue, or staples.

Case Illustration

A 32-year-old female presented to the clinic of the senior author for chronic low back pain and radicular, right lower limb pain secondary to compression of the right L4 nerve root. The patient had managed her back pain conservatively for years but underwent an L4/5 discectomy at an outside hospital for her leg pain 4 months prior to presenting to our clinic. This intervention had been minimally beneficial, relieving her leg pain for several weeks but ultimately failing to provide robust benefit for either her leg or lower back pain. Upon presenting she was neurologically intact and was advised to try conservative management prior to another surgical intervention. After failing 6 months of conservative management, including physical therapy and several epidural nerve blocks, the patient was offered an L4–5 ALIF to stabilize her pathologic level and relieve her discogenic pain.

Surgery proceeded by placing the patient supine on a Jackson table and identifying the target level. She was then draped, and vascular surgery was called in to make the approach as the patient had a history of two prior Cesarean deliveries, and it was felt that employing an access surgeon would minimize the risk posed by the potential scar tissue. A traditional left, retroperitoneal approach was adopted, beginning with an oblique incision inferolateral to the umbilicus, intermediate to McBurney and Battle incisions. Sharp dissection and monopolar cautery were used to divide the superficial tissues and expose the anterior abdominal wall, which was then divided using the monopolar cautery. The rectus muscle and anterior rectus sheath were mobilized medially, and the retroperitoneum was entered. The retroperitoneal plane was extended posteriorly until the iliac veins were exposed; these lay above the level of the L4/5 disc, and so the veins were mobilized bilaterally to facilitate the anterior approach. A #10 blade was then used to incise the annulus of the L4/5 disc, which was removed with a combination of rongeurs, high-speed drill, and curettages. After the superior L5 end plate and inferior L4 end plate were cleaned, trial spacers were placed until sufficient correction of the anterior defect was achieved. An allograft spacer with demineralized bone matrix was then placed, and an anterior plate connecting the L4 and L5 levels was placed to reduce the risk of graft kickout postoperatively. Lateral imaging demonstrated good placement of the graft, at which point vascular surgery reentered and completed the closure. The anterior abdominal wall was closed with a #1 Maxon suture, and the skin was closed in layers using 4–0 Vicryl and a subcuticular technique for the most superficial layer. No complications occurred intraoperatively, and the patient was discharged home on postoperative day 3 after an uneventful inpatient course. The patient reported significant improvement in both her back and leg pain by the 1-month follow-up appointment. The patient demonstrated solid fusion across her construct at last follow-up – 52 months following surgery – and reported minimal pain.

Lateral Lumbar Interbody Fusion

A more recently popularized anterior approach for lumbar interbody fusion is the transpsoas approach, also known as the extreme lateral (XLIF) or direct lateral approaches (DLIF) and popularized by Luiz Pimenta over the past 15 years (Ozgur et al. 2006). This technique has the chief advantage of being minimally invasive, as it requires minimal tissue disruption – an advantage over conventional anterior approaches. Similarly, it allows for more complete removal of the target disc without disrupting either the anterior or posterior tension bands and at the same time allowing the placement of a larger interbody graft as compared to posterior approaches (Winder and Gambhir 2016); it may also allow for more complete end plate preparation as compared to ALIF techniques of similar invasiveness (Tatsumi et al. 2015). Indications for this procedure are similar to those of the above-described ALIF, including low-grade spondylolisthesis, discogenic low back or radicular leg pain, and sagittal plane deformity.

The chief advantages of the XLIF and DLIF procedures relative to the more conventional ALIF procedure are that they (1) do not require

the assistance of a vascular access surgeon; (2) do not require retraction of the great vessels or sympathetic chain, thereby minimizing risk of injury to these structures; (3) are more easily performed on patients with significant abdominal obesity, who are not candidates for conventional ALIF; and (4) reduce risk of injury to the presacral autonomic plexus (Laws et al. 2012). One of the chief disadvantages for the DLIF/XLIF approach is that it is relatively contraindicated for fusion at the L5/S1 level, as the iliac crest blocks the approach to this level. It also has an increased risk of intraoperative injury to the nerves of lumbar plexus, specifically the genitofemoral nerve, which lies in close proximity to the retractor as it is passed through the psoas muscle (Jahangiri et al. 2010; Uribe et al. 2010). This risk, which is reportedly greatest for surgery at the L4/5 level due to the anteroinferior trajectory of the nerve, can be reduced by utilizing neuromonitoring and a stimulating retractor (Benglis et al. 2009; Kepler et al. 2011; Regev et al. 2009; Riley et al. 2018; Tohmeh et al. 2011). Additionally, this technique increases radiation exposure to both the patient and the operating room staff, as it requires serial fluoroscopy to ensure that the correct approach is being utilized. Lastly, XLIF/DLIF may have a decreased ability to increase segmental lordosis as compared to the traditional approach (Winder and Gambhir 2016), though evidence exists that this drawback can be nullified by resecting the ALL intraoperatively, thereby allowing for inducement of greater lordosis at the treated segment (Akbarnia et al. 2014; Deukmedjian et al. 2012) (Figs. 1 and 2).

Description

Positioning is extremely important to XLIF/DLIF approach, as proper placement of the interbody relies on the surgeon being able to align the plane of the target disc with the fluoroscope and surgical working plane (Winder and Gambhir 2016). This begins by placing the patient on a bendable radiolucent table in a true lateral decubitus position with the iliac crest at the level of the table break and the patient's back flush with the edge of the table. In addition to providing the surgeon with the most direct approach to the pathology, this position also has the advantage of allowing gravity to retract the intraperitoneal contents away from the spine, which is of increased benefit in patients with substantial visceral obesity. Under most circumstances, either the left or right lateral decubitus position may be chosen; however regional vascular variability may preclude approach from one side or the other, and surgeons are encouraged to consult preoperative imaging. Similarly, in cases where the patient also has

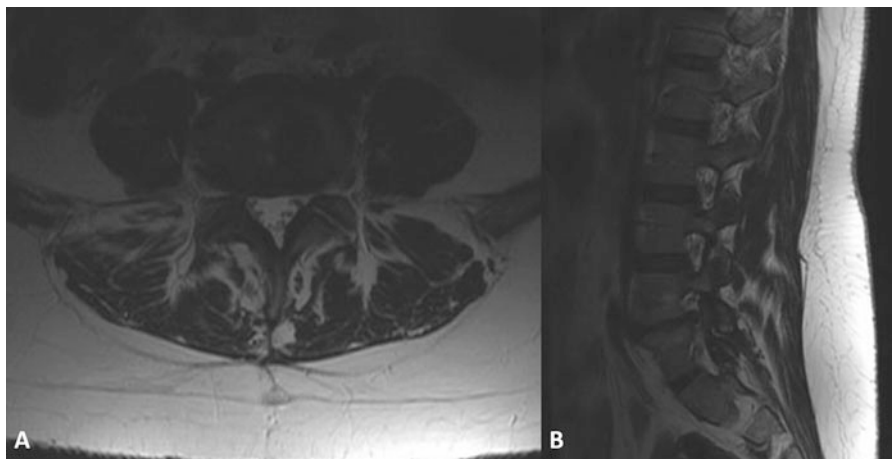

Fig. 1 Preoperative (**a**) L4/5 axial and (**b**) right parasagittal T2-weighed MR images demonstrating marked degeneration of the residual L4/5 disc leading to mild compression of the right L4 and L5 roots

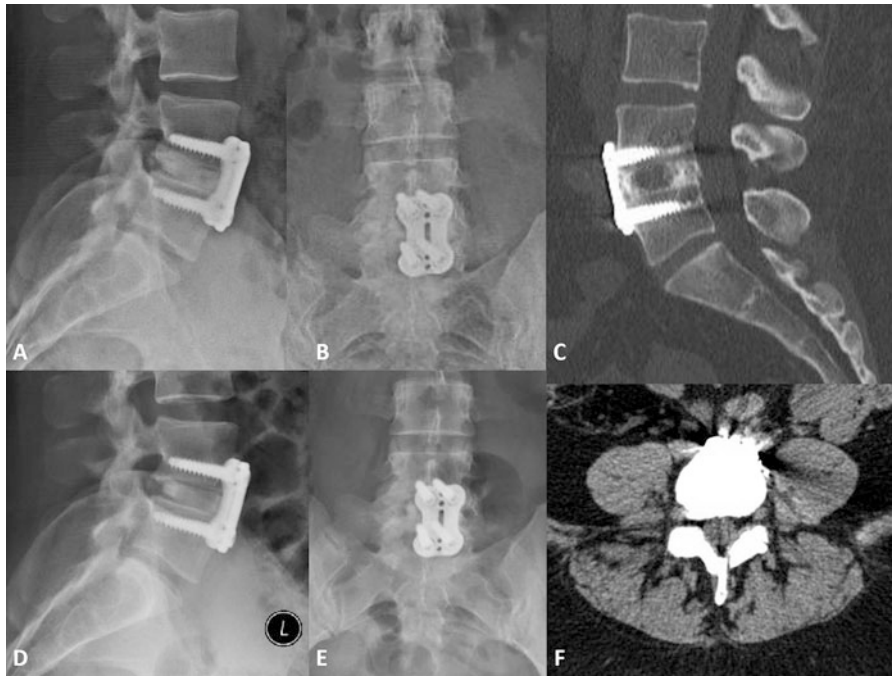

Fig. 2 (**a**) and (**b**) 3-month postoperative lateral and posterior-anterior radiographs demonstrating good alignment of the construct. (**c**) and (**f**) mid-sagittal and L4/5 axial CT views at 44-month follow-up demonstrating solid fusion with bridging of the construct by bony trabeculae. (**d**) and (**e**) Postoperative radiographs at 52-month follow-up showing successful fusion without evidence of adjacent segment disease or graft subsidence

scoliotic curvature of their lumbar spine, it is recommended that the patient be placed with the convex side facing the table (Beckman and Uribe 2017).

After the patient is placed in the lateral decubitus position on the table, their legs are flexed at the hips and knees to reduce tension in the psoas muscle, which facilitates passage of the dilators later in the procedure. Axillary and hip rolls are placed, as is a pad between the knees to reduce the risk of pressure ulcers. Positioning is then optimized using fluoroscopy to place the patient's spine in the true AP plane; the use of fluoroscopy may be most useful for patients having undergone prior lumbar surgeries, in which the native anatomy has been disturbed. It may be helpful to induce some bend at the table break to move the iliac crest out of the approach path. The patient is then secured to the table with tape at the shoulder and iliac crest, as well as at the legs, with strips parallel to the femur and tibia (Badlani and Phillips 2014). Final adjustments are then made to reestablish the true AP plane (Fig. 3a, b). Electronic monitoring leads are then placed, and preoperative signals should be acquired to establish the patient's neurologic baseline.

After skin preparation and draping, a #10 blade is used to make an incision through the dermis. As with the ALIF technique, a single 3–4 cm transverse incision can be used if only a single level is to be treated; if multiple levels are to be addressed, then a single vertical incision is planned. After passage through the dermis, monopolar cautery is used to dissect through the retroperitoneal fat until the external oblique fascia is reached. A transverse incision is formed in this fascia, and blunt dissection is used to pass through the abdominal wall musculature; examining the orientation of the fibers of the dissected muscle can be used to track that penetration of the abdominal wall has been complete. During dissection, care must be taken to remain on line with an approach to the posterior third of the disc space or middle third at the L4/5 level. Migration of the dissection

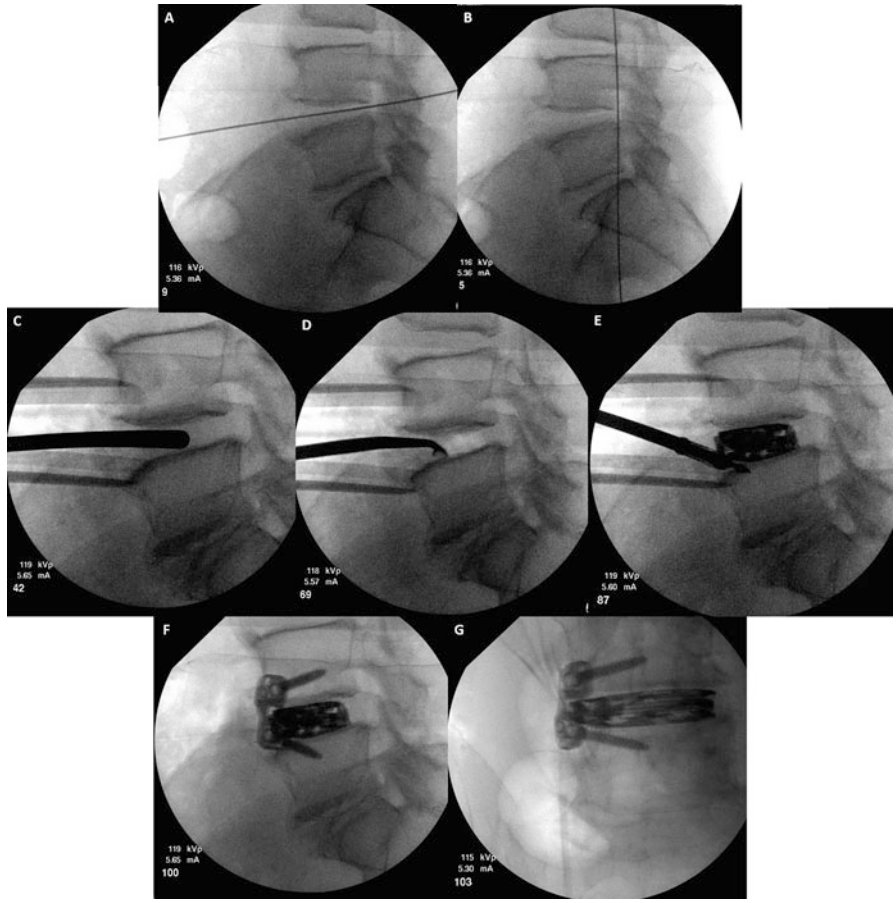

Fig. 3 (**a**) and (**b**) Fluoroscopy demonstrating effective positioning with true lateral positioning of the patient on the table. (**c**) The retractor is docked on the disc space, and a Cobb elevator is used to distract the disc space. (**d**) A forward angle curette is used to clean the superior and inferior end plates. (**e**) Titanium interbody is tamped into place, and positioning is confirmed. (**f**) and (**g**) Lateral and AP imaging demonstrating accurate positioning of the interbody and plate

path anteriorly endangers the retroperitoneal and intraperitoneal contents, whereas migration posteriorly risks damage to the nerves of the lumbar plexus.

Once the retroperitoneal space is entered, blunt finger dissection is then used to palpate the quadratus lumborum; the finger is then rotated anteriorly to palpate the psoas. The first dilator is passed along the trajectory of the finger to the top of the psoas muscle, keeping the finger anterior to the dilator to prevent injury to the retroperitoneal contents. Once the dilator has been placed, its position is confirmed on fluoroscopy, and then the dilator is passed through the psoas, docking on the intervertebral disc space; fluoroscopy is used again to confirm position. During passage of the dilator through the psoas, the target site is highly dependent upon the disc level being addressed. Previous work by Uribe et al. (2010) documenting the course of the genitofemoral nerve has established safe zones within the psoas muscle through which the retractor may be passed with minimal risk to the genitofemoral nerve. Biologic variability among patients precludes said results from eliminating nerve injury risk from the approach, but they can reduce the risk substantially. Additionally, state-of-the-art dilator models have EMG capability, which can be used during placement to prevent inadvertent

nerve injury (Tohmeh et al. 2011). For such dilators, stimulation should be performed following placement in the dilator to determine the relative position of the nerves. Low thresholds on the EMG indicate closer proximity of the nerve (threshold >11 mA are safe; <5 mA suggests direct contact); current thought is that positioning of the nerve anterior to the dilator increases the risk of nerve injury upon serial dilation. Fluoroscopy should then be performed to confirm placement. If the dilator is malpositioned on either EMG or fluoroscopy, it should be adjusted prior to serial dilation. Changes in the superoinferior plane can be accomplished without removing the dilator from the psoas muscle due to the myofiber orientation, but changes in the anteroposterior plane require removal from the psoas and reinsertion. A guidewire is then placed through the dilator, and sequential dilators are passed over the guidewire. Once the largest dilator has been placed, the retractor is passed over it and docked onto the disc space; the retractor is then fixed to the surgical bed arm, and a light source is connected to the posterior blade of the retractor. The field is inspected, and suspicious structures are stimulated with triggered EMG (tEMG) to rule out the possibility that the structure is a motor root. A protector is then placed posteriorly to prevent spinal cord injury, and retractor position is confirmed on fluoroscopy. If position is adequate, the retractor is expanded, and the anterior face of the disc is defined. Note that the goal is to minimize total retraction time (<20 min, per Beckmann (Beckman and Uribe 2017)), as extensive retraction can lead to postoperative lumbar plexopathy (Bendersky et al. 2015; Winder and Gambhir 2016).

An annulotomy is then performed using a box cutter instrument, and a pituitary rongeur is used to resect the disc; the anterior and posterior annulus are left intact to hold the interbody in place unless significant sagittal plane correction is required (C. Kim et al. 2017). A Cobb elevator is then malleted vertically along the superior and inferior end plates, making sure to continue through and disrupt the contralateral annulus (Fig. 3c). The end plates are then prepared with forward-angled curettes (Fig. 3d) and a pituitary rongeur, taking care to maintain end plate integrity. Trial interbodies are then placed until one is identified that restores adequate disc height; an equivalent interbody is then malleted into place with allograft in the central cavity (Fig. 3e). Note that some experienced centers use preoperative imaging to determine the optimal implant size and thereby spare the retraction time required for serial trial placement; this is a technique that is perhaps best left to experienced surgeons. After the interbody has been placed, hemostasis is achieved, and positioning is verified on AP and lateral fluoroscopy. It is at this point that a lateral plate can be placed to increase construct rigidity. If interbody device position is adequate (Fig. 3f, g), then the retractor is removed, and the abdominal wall musculature should return to its native position. The fascia is closed with interrupted 0 Vicryl, the subcutaneous tissue is closed with 3–0 Vicryl, and 4–0 monocryl is used to close the skin in subcuticular fashion (Beckman and Uribe 2017; Ozgur et al. 2006).

Case Illustration

A 62-year-old male presented to the neurological spine service with complaint of acute superimposed on chronic lower back pain of 7- to 8-year duration. The patient also reported minor left lower extremity radiculopathy. The patient had failed several months of conservative management, having tried epidural injections, physical therapy, and trigger point injections without robust benefit. The patient was neurologically intact on exam, and outside MR demonstrated an acute disc herniation compressing the left L5 nerve root. The patient was advised to undergo an L4–5 discectomy with pedicle screw instrumentation. The patient desired a more minimally invasive approach though. ALIF was relatively contraindicated secondary to the patient's significant abdominal obesity, and so an oblique lateral L4–5 discectomy and interbody fusion were offered.

The patient underwent a procedure as previously described in this chapter. He was placed in the left-lateral position, and sharp incision was made through the external oblique, internal oblique, and transversus abdominis in line with the muscle fibers at the level of the midaxillary line. Blunt dissection was used to navigate the retroperitoneal space and

identify the psoas muscle. The psoas was mobilized with bipolar electrocautery, and neuromonitoring was used to guide a tubular retractor to the L4/5 disc space. A subtotal discectomy was performed, leaving the anterior and posterior annulus to maintain graft position. The end plates were prepared, and a size 7 expandable cage packed with allograft was then tamped into place. Placement was confirmed on fluoroscopy, and an anterolateral plate was placed. The patient had an uneventful hospital course with near-immediate improvement of his pain. He is now 6-month postoperatively and is doing well (Fig. 4).

Indications for Plate Usage in Anterior and Lateral Lumbar Surgery

Anterior

As with surgery for degenerative conditions at other levels of the spine, the prime indication for instrumentation in anterior lumbar interbody procedures is to facilitate osseous fusion across the construct – the basis for long-term construct stability. Previous studies (Song et al. 2010) have suggested that the utilization of instrumentation in the spine construct, namely, an anterior tension band plate, can help to both improve the rate of successful arthrodesis and reduce the time to radiographic fusion, which has been reported to take up to 12 months (Blumenthal et al. 1988). Biomechanical studies, such as those of Tzermiadianos and Zhang, have suggested that the reason for these superior fusion outcomes is that the instrumentation helps to maintain positioning of and reduction onto the interbody (Tzermiadianos et al. 2008; J. Zhang et al. 2012). Said opposition is necessary to allow bony ingrowth into the interbody, the first step to osseous fusion. One recent study providing evidence to this end by Liu and colleagues (L. Liu et al. 2014) compared the biomechanical stability – axial compression, flexion, extension, lateral bending, and torsion – across three techniques for L4/5 lumbar interbody arthrodesis: ALIF without instrumentation, ALIF with an anterior fusion plate, and ALIF with posterior pedicle screw instrumentation. They observed that ALIF with anterior plate instrumentation provided superior stability relative to both the ALIF-alone and ALIF with pedicle screw instrumentation. The plate-supplemented ALIF group also had superior

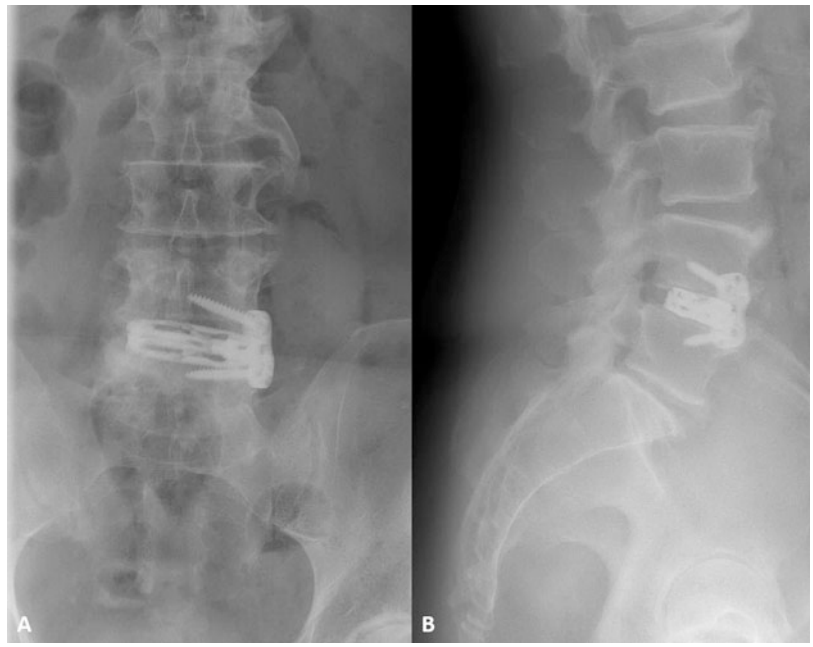

Fig. 4 (**a**) and (**b**) 6-month postoperative imaging of a patient who underwent L4–5 OLIF/XLIF with anterolateral plating for left L5 radiculopathy superimposed on chronic lower back pain

stiffness in terms of flexion, extension, lateral bending, and rotational torsion relative to the group treated with ALIF alone. Similar findings have also been reported by Gerber et al., Beaubien et al., and Tzermiadianos et al. using human cadaver models of lumbar and lumbosacral instability, though the findings of the Gerber group did not achieve the level of statistical significance (Beaubien et al. 2005; Gerber et al. 2006; Tzermiadianos et al. 2008). In all groups, supplemental stability with pedicle screw instrumentation decreased range of motion in lateral bending relative to anterior plating; Tzermiadianos also observed a significant decrease in flexion-extension range of motion relative to anterior tension band plating (Tzermiadianos et al. 2008).

In addition to facilitating long-term fusion, anterior plating can help to reduce the rate of cage migration, which is of greater concern in anterior relative to posterior procedures (Teng et al. 2017). Plating accomplishes this by having the plate function as a sort of retaining device, which traps the interbody between the plate anteriorly and the posterior longitudinal ligament posteriorly (as well as any residual portion of the annulus fibrosis). The plate also provides anterior column support, taking the role of an anterior tension band and preventing excess motion at the treated level (Yoganandan et al.). Evidence that the plate functions in this role is perhaps best supported by Bozkus et al., who compared anterolateral and lateral plating for anterior interbody fusion in a calf spine model (Bozkus et al. 2004). The authors found that while both lateral and anterolateral plates significantly decreased instability and range of motion in flexion-extension, rotation, and lateral bending relative to both sham and interbody-only constructs, the greatest decrease for each plate was in the dimension coplanar with the plate. That is to say the anterior plates provided the greatest stabilization in the flexion-extension plane, whereas lateral plates provided the greatest stabilization in the lateral bending plane, likely because the plate acts as a tension band, restricting motion that attempts to distract the anchor points of the plate.

Lateral

Indications for plating of XLIF/OLIF/DLIF constructs are similar to those of ALIF procedures. The main advantages of plating are increased construct stability (Fogel et al. 2014; Laws et al. 2012) and reduction in the risk of interbody device migration or kickout (Du et al. 2017). The latter concern is more significant in cases where the anterior longitudinal ligament has been disrupted, as such patients have lost a large portion of the annulus responsible for retaining the device. The former has received significant study in in vitro models. One series by Laws and colleagues examined stability of four constructs – stand-alone ALIF or DLIF, plated ALIF or DLIF, and DLIF with unilateral or bilateral pedicle screw fixation – under conditions of flexion-extension, lateral bending, and axial rotation (Laws et al. 2012). Plating of the DLIF construct significantly decreased range of motion in flexion-extension and axial rotation relative to unplated constructs; it also decreased range of motion in all directions relative to ALIF constructs, though these differences were not significant. These results agree with those of Heth, who also found DLIF/OLIF/XLIF to be biomechanically similar to ALIF, if not superior. Fogel et al. conducted a similar study using fresh-frozen cadaveric spines, comparing stand-alone XLIF constructs with those supplemented by either lateral plating or pedicle screw instrumentation (Fogel et al. 2014). Lateral plating provided a similar level of stability to pedicle screw fixation in lateral bending, but not flexion-extension or axial rotation (bilateral pedicle screw fixation only). All instrumentation methods provided significant reductions in axial rotation and lateral bending relative to the stand-alone construct, though the plate did not provide a significant reduction in flexion-extension range of motion. Liu et al. and Reis et al., by contrast, reported a significant reduction only in vertebral end plate stress and lateral bending with application of the plate; axial rotation and flexion-extension were not significantly decreased (X. Liu et al. 2017; Reis et al. 2016). Taken in aggregate, these results, like those of anterior plating, suggest that plates increase construct stability by functioning

as tension bands. As a result, they lead to stabilization primarily in the direction of motion that directly distracts or compresses the plate; they provide only minor stabilization when shearing forces are applied, as occurs with axial rotation and flexion-extension in lateral plates and lateral bending in anterior plates.

Anterior Plates and Other Anterior Fusion Technologies

As previously described, anterior spine fusion was developed more than seven decades ago, and dedicated instrumentation for anterior fusion has been around since at least 1953, when Wenger described the use of anterior instrumentation for the treatment of scoliosis (Dwyer et al. 1969; Ghanayem and Zdeblick 1997). These systems became increasingly popular in the late 1970s though, following the increased incidence of reports on anterior fusion techniques (Bradford and McBride 1987; Dunn 1984; Kaneda et al. 1984; Kostuik 1983; Zielke et al. 1976). Some of the earliest systems to gain mainstream acceptance were the Zielke system (Zielke et al. 1976), the Kostuik-Harrington device (Kostuik 1983), and the Kaneda system (Kaneda et al. 1984). The Zielke system was developed as a less morbid alternative to posterior Harrington instrumentation in patients being treated for scoliosis (Zielke et al. 1976). The later Kaneda system, by contrast, was developed for the treatment of thoracolumbar burst fractures, which commonly involve shorter constructs (Kaneda et al. 1984). Like the anterior Harrington device and biomechanically similar Zielke device, the Kaneda relied upon conventional screw-rod architecture, with screws placed at the superior and inferior instrumented vertebrae and rigid rods bridging the two anchor points (Kaneda et al. 1984). Contemporary in vitro biomechanical studies suggested that these devices, particularly the Kaneda, provided structural stiffness equivalent or superior to posterior Harrington rod instrumentation while requiring the instrumentation of fewer levels (Gurr et al. 1988; Zdeblick et al. 1993). And clinical work suggested that they offered superior decompression of the spinal canal (Bradford and McBride 1987; Ghanayem and Zdeblick 1997). Additionally, all three systems had the advantage of allowing for both compression and distraction. To their detriment however, all three systems were hampered by their relatively bulky nature, which had the potential to irritate prevertebral and paravertebral tissues. As a result, there was an incentive to develop new, lower-profile systems. Results of these efforts including the Z-plate, the University Plate, and the Anterior Thoracolumbar Locking Plate had the benefit of being less bulky and of creating a smaller radiograph artifact due to their titanium construction. Of these different systems, the most widely used of these was the Z-plate. The Z-plate comprised a slotted plate instrumented at the superior and inferior construct levels using two bicortical vertebral body screws at each vertebra. It was designed for short anterior fusion constructs, originally developed for the treatment of thoracolumbar burst fractures (Ghanayem and Zdeblick 1997; McDonough et al. 2004). Several in vitro studies, including those of Hitchon et al. and Dick et al., demonstrated the Z-plate to be biomechanically equivalent to the earlier Kaneda device (An et al. 1995; Dick et al. 1997; Hitchon et al. 2000; Kotani et al. 1999). Of note, Hitchon et al., Kotani et al., and Dick et al. also compared the anterolateral locking plate – the direct ancestor of modern anterolateral plating systems – to these devices. Hitchon et al. noted that the anterolateral plating system produced a less stiff construct than the earlier systems upon instrumentation, but after only 5000 cycles of flexion-extension, the Z-plate system ceased to differ significantly from the anterolateral plate (Hitchon et al. 2000). By contrast, Dick et al. and Kotani et al. found the Synthes® anterior thoracolumbar locking plate to be stiffer than the Kaneda device and Z-plate in axial compression, axial rotation, and lateral flexion (Dick et al. 1997; Kotani et al. 1999). It also had a significantly longer service life as demonstrated on fatigue testing. Since that time, this anterolateral plate and other similar designs have come to dominate the anterior fusion device market.

Currently, over a half dozen different anterior and anterolateral plate systems are commercially

available. The indications for the use of these devices are relatively uniform across manufacturers and include cases requiring anterior lumbar interbody fusion for any of the following reasons: trauma (fracture or dislocation), tumor, low-grade spondylolisthesis, spondylolysis, pseudarthrosis, deformity, and failed back syndrome. Similarly, contraindications to their use are relatively uniform, including active systemic or local infection, inadequate mechanical support (tumor infiltration, severe osteoporosis, metabolic bone disease), patient history of foreign body reaction or sensitivity to metal implants, risk factor for poor wound healing (e.g., insufficient tissue to cover implant), conditions that would place excessive load on implant during the healing period (e.g., significant obesity), and any general contraindications for surgery (e.g., concurrent drug use or psychiatric illness).

Material Selection

The majority of plates currently on the market are composed of titanium or titanium alloy. These materials are generally stronger for a given size than are stainless steel implants, which allow titanium plates to be thinner for any given combination of tensile and compressive strengths. Titanium instrumentation is also more amenable to postoperative follow-up with magnetic resonance imaging than is stainless steel or chrome-containing instrumentation. Unlike the latter, which are ferromagnetic, titanium and titanium alloy implants are paramagnetic and so produce substantially smaller artifact on MR (Do et al. 2018; Tahal et al. 2017). Additionally, the local tissues are generally thought to respond more favorably to the use of titanium implants as compared to either stainless steel or chromium-based implants (Gibon et al. 2017; Tahal et al. 2017). Chromium-based implants can be particularly irritating as they trigger cytotoxic reactions in the local tissue, which may weaken the surrounding osseoligamentous structures, though no evidence to date exists to suggest that this leads to significantly different clinical outcomes. Chromium and stainless steel-based implants are also more likely to generate delayed-type hypersensitivity reactions at the site of implantation due to the osteoclast-induced release of nickel and chromium ions from the implants (Gibon et al. 2017). Nickel and chromium ions are two of the most common causes of metal sensitivities among the general population, and so we prefer the utilization of titanium-based implants when available, unless other biomechanical considerations suggest the patient would benefit from the superior fatigue strength provided by chromium-based implants (Tahal et al. 2017).

In addition to the concern of local tissue toxicity, the propensity of an implant to serve as an infection nidus as well as implant fatigability is an important concern. The latter consideration is of biggest concern among young patients, given that the implant will undergo a substantial number of loading cycles over the course of its service life – estimated at two million cycles per year (Graham 2006). Previous research has failed to demonstrate substantial differences in the fatigue strength of titanium and titanium alloy plates relative to stainless steel implants (Pienkowski et al. 1998). However, several studies have demonstrated a lower incidence of biofilm formation and surgical site infection among those persons instrumented with pure titanium implants, as compared to either stainless steel or titanium alloy implants (Tahal et al. 2017).

Plate Design

As discussed, most commercially available anterior lumbar plates are composed of pure titanium or a titanium alloy (e.g., Ti-6Al-4 V/TC4, nitonol) due to the superior mechanical properties and greater tolerance by local tissues. The variability among implants is largely based upon implant shape, length, and screw fixation. Both straight and prelordosed plates are currently available, with the latter providing a better anatomic match to the native anatomy. This better approximation of the lumbar and lumbosacral lordosis may improve the rigidity of the construct and so reduce the rate of pseudarthrosis and need for reoperation, though no direct comparisons

currently exist. Like the more traditional straight plates, prelordosed plates are available in both one- (25–54 mm length depending upon the manufacturer) and two-level lengths (65–89 mm depending upon the manufacturer) for instrumentation at the lumbar spine or lumbosacral junction, with most manufacturers offering their plates in 3-mm size increments. Both fixed-angle and variable-angle screw systems are available, with both systems generally utilizing two 5.5–6.0 mm screws at the inferior instrumented level and one or two 5.5–6.0 mm screws at the superior instrumented level.

Variable- Versus Fixed-Angle Devices

The relative merit of a variable-angle plate, as compared to a fixed-angle plate, is rooted in the ability of the surgeon to select the screw angle when placing instrumentation. This presupposes that certain screw angles confer superior pullout strength relative to others, a conclusion that has mixed support in the current literature. Work by DiPaola et al. on cervical spine plates in a polyurethane block model has suggested that orthogonally positioned screws have superior pullout strength relative to other orientations (DiPaola et al. 2007, 2008). This is perhaps because the orthogonal angle places each thread perpendicular to the force vector, allowing it to maximally resist pullout. Regardless of the biomechanical underpinning, the said results favor the variable screw model over fixed-angle instrumentation, as the former enables the attending surgeon to place screws along optimal trajectories even in cases of suboptimal implant-bone apposition. Rodríguez-Olaverri et al. reach a similar conclusion regarding the importance of screw trajectory (Rodríguez-Olaverri et al. 2005). In their thoracolumbar calf spine model, Rodríguez-Olaverri placed bicortical polyaxial screws linked by a single 5.5 mm cobalt-chrome and then subjected the construct to 10,000 cycles of lateral bending with a 100 N load. Unlike DiPaola, they found that superior construct stabilization was provided by angled screws; however, like the former, they concluded that screw trajectory had a significant impact on construct service life. This favors instrumentation that affords the surgeon options when placing instrumentation, as is offered by a variable-angle system.

By contrast, Rios and colleagues failed to demonstrate said advantages to variable screw angle systems (Rios et al. 2012). Using a similar polyurethane block model, they investigated the relative pullout strength of anterior ALIF plates with screws fixed in one of nine different orientations, varying in both sagittal and coronal angulation (Rios et al. 2012). Though they noticed some minor but significant differences between the strongest and weakest trajectories, they failed to observe superiority of any trajectory over the neutral or "straight-in" trajectory. This suggests that the ability to select screw trajectory confers no mechanical advantages, in turn indicating the non-inferiority of fixed-angle systems. These results were replicated by Patacxil et al. and Hadley et al., the latter of whom also found no difference between variable- and fixed-angle plates in a cadaveric model (Hadley et al. 2012; Patacxil et al. 2012). Additionally, cohort studies by Oh and Hong examining radiographic outcomes in patients having undergone anterior cervical discectomy and fusion report similar findings, with the Hong group finding that fixed-angle plates may actual reduce the risk of graft subsidence (Hong et al. 2010; Oh et al. 2013). Given these mixed results, we believe that insufficient evidence exists to recommend variable-angle designs over conventional, fixed-angle designs. Rather, the plate type used should be based upon surgeon experience.

Interbody Design

Lumbar interbody devices have been used in spine surgery for more than three-quarters of a century, having been first described in 1944 by Briggs and Milligan (de Kunder et al. 2018). Their original procedures utilized a posterior approach and made use of an allograft bone peg with external fixation to facilitate fusion. Cloward published a larger series in 1953 describing a similar technique using multiple bone grafts to reduce the procedural morbidity (de Kunder et al. 2018).

From there, interbody devices remained relatively unchanged until the invention of the Bagby basket in 1986 for the treatment of Wobbler syndrome in horses – a myelopathic condition seen secondary to cervical instability in these animals (DeBowes et al. 1984; Phan and Mobbs 2016). This device was novel in that it utilized autograft-packed titanium implants, which had significant greater compressive strength than did the earlier bone graft interbody devices utilized by Briggs and Milligan (de Kunder et al. 2018). The Bagby device, or rather its successor – the BAK device – was quickly adapted by Kuslich and colleagues (Phan and Mobbs 2016), who described its use for posterior lumbar interbody fusion in 1992 (Kuslich et al. 1998). Within the decade it was approved for anterior interbody fusion, and several biosimilar devices had been presented, including the threaded cage of Ray (1997), mesh cage of Harms and Biederman, and the tapered or trapezoid-shaped cages which have become increasingly popular (Phan and Mobbs 2016). Previous in vitro analyses have suggested gross biomechanical equivalency among these different design types, though threaded cages, such as the BAK device, may provide lower intracage pressures and thereby help to protect cancellous graft placed within the cage (Kanayama et al. 2000).

PEEK and carbon fiber interbodies were also developed during the 1990s and early 2000s in order to serve as an alternative to the titanium interbodies (Brantigan and Steffee 1993; D. Cho et al. 2002; Phan and Mobbs 2016). The former had the advantage of better approximating the elastic modulus of bone and lacked the substantial radiographic artifact produced by titanium devices (Phan and Mobbs 2016). Interbody devices made from all three materials are now available, both for the traditional retroperitoneal anterior approach (ALIF) and for the lateral approaches (OLIF, XLIF). These devices offer a range of lordosis and footplate dimensions, allowing the surgeon to optimize the device to each patient. All three of these parameters – composition, lordosis, and cross section – should be considered during surgical planning.

Material

The three main materials used for anterior lumbar interbody fusion are femoral ring allograft, titanium or titanium alloy, and polyether-ether ketone (PEEK). Each material has its relative advantages and disadvantages. Ring allograft and PEEK better approximate the elastic modulus of native bone compared to titanium interbody devices (Phan and Mobbs 2016), which may reduce the risk of pistoning and implant subsidence (Niu et al. 2010; Seaman et al. 2017). Though pistoning is concern in all patients, it is most common in patients with low bone density and should be given greater consideration in osteoporotic patients, such as postmenopausal women (Melton et al. 1992).

PEEK cages and femoral ring allograft also allow for superior radiographic follow-up, as they produce no artifact on computed tomography imaging. This allows fusion across the construct to be more easily assayed than in constructs using titanium implants. Given that 11–23% of patients treated with anterior interbody fusions may experience nonunion (C. S. Lee et al. 2011), the ability to assess osseous fusion may favor the use of these materials, especially in patients at high risk of pseudarthrosis (e.g., those with current or previous history of cigarette use) (Phan et al. 2017). Despite this, studies comparing interbody fusion with PEEK vs. Ti implants have suggested that titanium interbody devices provide equal (Niu et al. 2010) or superior rates (Spruit et al. 2005) of arthrodesis. Consequently, the superior fusion monitoring available in PEEK constructs may be negated by the inferior overall fusion rates.

The reason for inferior fusion rates in PEEK implants has not been definitively established, though current evidence suggests that PEEK devices offer less bony contact per unit end plate area. This difference is most significant when comparing to the newer plasma-treated titanium interbody devices (Pelletier et al. 2016) whose porous surfaces allow for the rapid ingrowth of cancellous bone (Chang et al. 1998). Additionally, although the greater yield strength mismatch seen in constructs containing titanium interbody devices may increase the risk of implant subsidence, the high yield strength of the titanium

interbody increases the initial stability of these constructs relative to PEEK constructs (Spruit et al. 2005). As a result, such constructs are likely to better maintain graft-end plate opposition during the critical period when fusion is occurring. This may also contribute to the superior fusion rates observed in some studies. Lastly, prior in vitro studies have demonstrated PEEK to be hydrophobic and therefore biochemically inert, meaning that commercially available implants rely upon a surface coating of hydroxyapatite or biocomparable material in order to promote osseointegration (Briem et al. 2005; Dennes and Schwartz 2009; Durham et al. 2017; Noiset et al. 1999; Zhao et al. 2016).

At least some of these concerns – chemical inertness and lower contact area per end plate area – can be addressed by employing a hybrid interbody device, one comprised of a PEEK body with porous titanium face plates. The said devices have the advantage of superior osteoconduction at the titanium end plates (Han et al. 2010; X. Wu et al. 2012), while maintaining a yield modulus similar to that of natural bone. Preliminary in vivo studies by Han et al. using a rabbit model of spine fusion found that titanium-coated PEEK implants had bone-to-implant contact that was nearly twice as great as standard PEEK implants (Han et al. 2010), consistent with earlier in vitro studies demonstrating superior survival of osteoblast cell lines on titanium-coated implants (Han et al. 2010; X. Wu et al. 2012). Additionally, biomechanical analysis of an in vivo PEEK-titanium composite interbody demonstrated it to have superior strength in terms of axial rotation, flexion-extension, and lateral bending as compared to a conventional PEEK interbody device (McGilvray et al. 2017). These differences were progressively more pronounced with increasing follow-up, suggesting that their greatest advantage relative to conventional devices may be in terms of longer service life. The titanium-coated PEEK implants are not without their drawbacks though. Recently, Torstrick and colleagues reported the results of an in vitro comparison of conventional PEEK, porous PEEK, and plasma-sprayed titanium-coated PEEK interbody devices (Torstrick et al. 2018). Using a polyurethane spine model and guided weight impactor, the authors applied compressive forces to the interbody devices. While both pure PEEK devices showed minimal surface damage on SEM, the titanium-coated device showed a significant decrease in surface roughness, which may nullify the potential bone ingrowth advantages conferred by the titanium coating.

Another innovation designed to combine the advantages of PEEK and titanium interbody devices is porous titanium cages, which have only become commercially viable with the increased availability of 3D printing technologies. The first description of porous metal interbody devices for spinal fusion was by Levi et al., who described the use of porous tantalum implants in a cadaveric model of anterior cervical discectomy and fusion (Levi et al. 1998). A half-decade later, Assad and colleagues described the use of a porous titanium-nickel interbody for lumbar intervertebral fusion in a sheep model (Assad et al. 2003a, 2003b). Using standard lateral radiographs, the authors demonstrated superior bone bridging and periprosthetic radiolucency at 3 and 6 months postoperatively in animals instrumented with porous interbodies as compared to traditional titanium alloy implants (Assad et al. 2003b). Takemoto et al. reported similar findings using a porous titanium implant with 50% porosity in a canine model, which they attributed to the superior bony contact of the porous implants (Takemoto et al. 2007). Furthermore, they reported that these implants had yield compressive strengths similar to that of cortical bone – 80–120 MPa – meaning that they are theoretically less likely to suffer from implant pistoning than are traditional titanium implants. This yield strength is superior to that of porous tantalum implants, and the fact that these implants do not incorporate nickel, like those of Assad, means that they are not associated with the potential downsides of this material, namely, concerns over intraspinal metallosis and neurological deficits (del Rio et al. 2007; Takahashi et al. 2001). Fujibayashi et al. reported the first clinical series of patients treated with these implants, describing successful radiographic fusion within 6 months in five individuals who underwent TLIF with 60%

porosity implants (Fujibayashi et al. 2011). Several contemporaneous studies in animal models demonstrated that such devices had superior osseointegration as compared to PEEK implants, as well as superior mechanical stability for flexion-extension, axial rotation, and lateral bending (S. Wu et al. 2013). More recently, McGilvray and colleagues reported the result of an ovine lumbar fusion model directly comparing PEEK, porous titanium-coated PEEK, and 3D-printed porous titanium alloy interbody devices (McGilvray et al. 2018). Using micro-computed tomography and histology to evaluate fusion, and biomechanical analyses to evaluate construct stability, the authors demonstrated significant reductions in flexion-extension range of motion, increases in bony ingrowth, and increases in stiffness for the porous titanium cages relative to both the titanium-coated and convention PEEK interbody devices. The porous titanium implants are also less likely to fragment with application of compressive forces and hence may demonstrate better wear over the life of the device (Kienle et al. 2015). Further studies are required, but it appears as if the porous titanium interbodies may provide the overall best option in a cost-neutral comparison. Additionally, although some in vitro (MacBarb et al. 2017a) and in vivo animal (MacBarb et al. 2017b) evidence suggests that 3D-printed porous titanium devices are superior to conventional plasma-spray-coated implants with respect to bone infiltration, no clinical series exist to support this finding. The relative superiority of these devices is likely to depend upon the relative porosity though, with greater porosity offering greater bony ingrowth (Li et al. 2007; Taniguchi et al. 2016; de Vasconcellos et al. 2010) and lower stresses inside the implant (Z. Zhang et al. 2018) but coming at the cost of decreased construct stability (Z. Zhang et al. 2018).

Dimensions

When selecting dimensions for an anterior interbody, the goal should be to restore the native anatomy, in terms of disc height, foraminal diameter, and lumbar lordosis. To address both end points, most cage manufacturers offer their interbody devices in a variety of heights and lordosis angles, including hyperlordotic interbody devices, which may restore up to 30 degrees of lordosis per instrumented level (Saville et al. 2016). When selecting dimensions for the interbody, it is also important to consider the size of the end plates of the superior and inferior vertebral levels (Phan and Mobbs 2016). These surface areas should be determined preoperatively to select the widest interbody that can be safely placed at the discectomy level (Lowe et al. 2004). In vitro studies have shown that at bare minimum, the selected interbody should cover 30% of the end plate to prevent graft subsidence (Closkey et al. 1993). Ideally, the implant should be wide enough to engage the edges of the end plate, but not so large as to damage surrounding tissues. Doing so allows the interbody to engage cortical bone at the vertebral body in addition to cancellous bone, producing a more even distribution of stress on the adjacent vertebral levels (Kumar et al. 2005). Additionally, engaging the cortical bone, which has a significantly higher yield strength (Fyhrie and Vashishth 2000; Kutz et al. 2000), reduces the likelihood of implant subsidence – a nontrivial concern in fusions with titanium interbody devices. And there is some suggestion that the wider implants – at least for the XLIF/DLIF procedure – may provide a stiffer construct (Pimenta et al. 2012).

The risk of pistoning can be further decreased by insertion of bone graft into and around the interbody device, both of which increase the effective cross section of the implant and provide osteoconductive material to facilitate fusion (Kumar et al. 2005). Furthermore, previous research in the posterior lumbar interbody fusion literature has demonstrated fusion rates to be directly correlated to the contact area between the cage and the bony end plates. One prospective series, published by Seo et al., examined 60 patients undergoing instrumented PLIF using bilateral autograft-filled titanium cages (Seo et al. 2017). They observed that bone between the interbody devices fused in 100% of patients, whereas graft circumscribing the region bounded by the interbody devices only fused in 72.3% of patients.

Integrated Fixation Cages

Another option for interbody fusion is the use of an integrated fixation cage (IFC) or stand-alone interbody device, which first appeared on the market 15 years ago. These devices incorporate the instrumenting screws directly into the interbody and so eliminate the need for an anterior plate. This allows for a technically simpler procedure and may help to reduce operative room times.

As with any new technology, one of the questions that must be asked when considering instrumentation with an IFC is whether said device will provide similar rigidity to traditional interbody-plate constructs. A handful of publications have been presented to date directly comparing plate and IFC constructs (Beaubien et al. 2009, 2010; Kornblum et al. 2013; Palepu et al. 2017). The first of these was presented by Beaubien et al., who examined the stiffness of various interbody constructs in cadaveric spines, including traditional plate-interbody and stand-alone IFC constructs (Beaubien et al. 2009, 2010). They found that although the latter construct exhibited significantly greater motion in flexion and extension, it possessed significantly greater pullout resistances, in part, because failure required fracture of all bone surrounding the integrated screws. Similar findings were reported by Kornblum and colleagues (Kornblum et al. 2013), who noted that IFC constructs had inferior stability in flexion-extension motion relative to plate systems. More recently though, a study by Palepu and colleagues (Palepu et al. 2017) reported no difference in the flexion-extension stabilities of the two constructs. These authors compared the constructs in cadaveric human lumbar spines across 20,000 cycles of flexion-extension loading and found similar stability in flexion-extension and lateral bending motions at the time of implantation and throughout fatigue testing. Interestingly, they also found the IFC constructs to provide superior stability at implantation and throughout testing in terms of axial rotation, suggesting that newer devices may have addressed the biomechanical shortcomings of previous designs.

Of the IFC devices on the market today, the majority has similar construction – they utilize a lordosed PEEK interbody cage with an anterior titanium face plate through which 5.0 mm or 6.0 mm lag screws are placed. The interbody sizes available vary across manufacturer, but most offer interbody heights of 10–20 mm (in 2 mm increments) with anywhere between 4° and 16° degrees of lordosis and end plates between 22 × 30 mm and 28 × 40 mm. The various commercially available cages vary in the number of lag screws incorporated, using anywhere between two and four lag screws for fixation. Previous studies examining the stability of these devices (Kornblum et al. 2013) have not demonstrated significant differences between them, suggesting that cage selection should be based upon surgeon preference. Two more recent technologies include the use of variable-angle screws for fixation and the incorporation of plasma-treated titanium end plates. In a cadaveric study comparing blade-type, fixed-angle screw, and variable-angle screw devices, Freeman et al. reported that fixed-angle cages had higher pullout strengths relative to the other two technologies (Freeman et al. 2016). No confirmatory studies have been performed yet; however studies from the plate literature suggest that variable-angle and fixed-angle systems may be equivalent (Hadley et al. 2012; Patacxil et al. 2012). Similarly, no studies have been performed to compare fusion rates of the new Ti-coated PEEK IFC to those of the conventional IFC devices, but it seems likely that the former may demonstrate superior fusion rates.

BMP and Profusion Agents

As with other spine procedures, anterior interbody arthrodesis has traditionally relied on bone allograft and autograft to facilitate fusion across the construct. This bone is usually incorporated directly into the device, though as mentioned previously, it may also be packed around the implanted interbody device. Kumar et al., using a computerized model of lumbar interbody fusion, demonstrated that incorporation of cancellous graft into and around the device

decreases the load placed by the implant on the adjacent end plates, presumably by increasing the effective end plate cross section of the implant itself (Kumar et al. 2005). In so doing, this supplementation may help to decrease the risk for implant subsidence.

Other osteoinductive and osteoconductive technologies are available for use in patients who are deemed to be at higher risk for pseudarthrosis. These include demineralized bone matrix, bone graft substitutes or bone putties, hyaluronic acid, and bone morphogenic protein; in fact, the ALIF procedure is the only one for which rhBMP-2 use is currently approved by the FDA. Previous evidence has suggested that demineralized bone matrix provides similar fusion rates to traditional autograft (Fu et al. 2016), and similar findings have been reported for the other bone graft extenders, including calcium phosphate crystals and ceramic-based substitutes (Gupta et al. 2015). By contrast, numerous studies have observed superior rates of fusion in patients receiving rhBMP-2 (Boden et al. 2000; Burkus et al. 2002, 2003, 2009; Glassman et al. 2008; Gupta et al. 2015; Hustedt and Blizzard 2014), including several prospective randomized trials (Boden et al. 2000; Burkus et al. 2002), which led to its approval by the FDA in 2004. BMP use has been previously associated with higher complication rates in the cervical spine despite improving fusion rates, but evidence to support this in the lumbar spine is not conclusive. As a result, it is recommended that rhBMP-2 use be considered in all patients at high risk for nonunion, including smokers (Jackson and Devine 2016), older patients (Y. J. Kim et al. 2005, 2006), obese patients, those with low osteoblast-to-osteoclast activity (Inose et al. 2018), those with hypovitaminosis D (Ravindra et al. 2015), and those with histories of nonunion (Glassman et al. 2008). Osteoporosis, while a relative contraindication to surgery due to increased risk of implant failure, may not be a risk factor for nonunion. The evidence to support this conclusion is weak however (van Wunnik et al. 2011; Zura et al. 2016) and does not disentangle low bone density from advanced age, which has been previously associated with a decreased likelihood of nonunion (Zura et al. 2017). Obesity may similarly be a risk factor for nonunion (Zura et al. 2016) and so be an indication for the use of rhBMP-2. Evidence from the area of long bone fusion supports this (Meidinger et al. 2011), but studies on the role of obesity in spinal fusion nonunion are lacking.

Conclusion

The anterior and lateral lumbar interbody arthrodeses are robust constructs that remain an effective option for multiple pathologies of the lumbosacral spine. They allow for anatomic correction of disc height loss and for placement of larger interbody devices than can be placed through more traditional posterior interbody fusions, such as the TLIF or PLIF. Conventionally, anterior fusion has been accomplished through a combination of interbody placement and anterior plating, which reduces cage kickout and increases the stability of the construct to prevent early construct failure. In recent years, integrated fusion cages (IFC) – interbody devices with incorporated lag screws to prevent pullout – have become available. These devices allow for more expedient construct completion, and recent research suggests that they may provide stability equivalent to more traditional plate-interbody systems. Additional new technologies are being brought on the market every year, including interbody and integrated fixation cage devices with plasma-treated titanium end plates, which allow for superior osseous fusion rates relative to traditional PEEK interbody devices. Because of this continued innovation, it is apparent that the ALIF remains a valued option for select patients with pathology of the lumbosacral spine.

Cross-References

- ▶ Anterior Lumbar Spinal Reconstruction
- ▶ Bone Grafts and Bone Graft Substitutes
- ▶ Mechanical Implant Material Selection, Durability, Strength, and Stiffness

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Interbody Cages: Cervical

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John Richards, Donald R. Fredericks Jr., Sean E. Slaven, and Scott C. Wagner

Contents

Abstract

Interbody cages represent an invaluable technologic advancement in the field of spinal fusion surgery, particularly anterior cervical discectomy and fusion (ACDF). Interbody cages improve sagittal alignment, aid in fusion by allowing for containment of graft material, and restore biomechanical stability after discectomy. Various design iterations and materials have been used over the last two to three decades, and advancements in materials

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science and cage properties have provided improved functional utility of interbody cages in ACDF surgery. This chapter provides an overview of the history of cervical interbody cages, including improvements in design, material, and methods of manufacturing processes of cervical interbody cages that have yielded the designs most commonly utilized today.

Keywords

Cervical · Interbody · Cage · Spine · Fusion · Bone graft

Introduction

The first cervical interbody fusions were pioneered by neurosurgeons in the 1950s for early anterior cervical discectomy and fusion (ACDF). These procedures were developed as alternatives to posterior fusions to treat cervical radiculopathy and myelopathy. In 1958, Cloward described an anterior approach for cervical interbody fusions. This technique utilized bone dowels inserted horizontally between the adjacent vertebrae, from an anterior to posterior direction, following the decompression (Cloward et al. 1958). The vertebral bodies were prepared with a drill, and the bone dowel was cut slightly larger than the drilled defect and seated with distraction and impaction. These bone grafts were typically iliac crest autograft or, less commonly, allograft bone cut into cylindrical dowels. Robinson and Smith described a similar technique that utilized the same anterior approach and decompression, but instead used a rectangular graft in place of a cylindrical bone dowel. This technique required less augmentation and preparation of the adjacent vertebral bodies. Another advantage of this rectangular graft is that it provided a greater surface area compared to cylindrical grafts (30% more of similar size), which was theorized to provide better contact surface for revascularization and fusion (Robinson and Smith 1958).

In 1969 Simmons and Bhalla published a modification of this same technique. They utilized the same anterior approach and decompression, but instead used a "keystone"-shaped bone graft. This keystone shape was a beveled modification of the rectangular graft, making it thicker posteriorly than anteriorly. This required the adjacent vertebrae to be modified similarly. These "keystone" grafts performed superiorly in biomechanical studies demonstrating less extrusion in comparison to simple rectangular or dowel grafts with flexion and extension of the spine. In a clinical study, they also performed more superiorly than interbody fusions performed with dowel bone grafts with 3/17 symptomatic nonunions in the dowel group compared to none in the keystone group. Various original ACDF implant designs are shown in Fig. 1.

Donor site morbidity has been reported as high as 22% (McConnel et al. 1976), and is a known disadvantage to iliac crest autograft, and led to the development of alternative graft materials. Allograft was one of the most widely studied alternatives. It initially provided mixed results in clinical trials and had the downsides of significantly increased costs, slower fusion rates, and the theoretical risk of disease transmission (An et al. 1995; Bishop et al. 1996; Brown et al. 1976); however, recent studies have shown that a ACDF with autograft vs. allograft, particularly with anterior plate fixation, is nearly equivalent clinically and radiographically (Kaiser 2002 Neurosurgery). Poly(methyl methacrylate) (PMMA) was another alternative that was described. It offered a graft with immediate stability of the adjacent vertebrae, but it provided no ability to achieve fusion and was therefore abandoned (Bent et al. 1996). Biocompatible osteoconductive polymer (BOP) and coralline hydroxyapatite were two other promising bone graft substitutes, but both were ultimately found to be inferior to autograft in clinical trials. BOP was biomechanically similar to autograft, but demonstrated little ability to incorporate into host bone (Ibanez et al. 1998). Hydroxyapatite was structurally weak and demonstrated graft subsidence and fragmentation (McConnell et al. 2003). Despite a number of different alternatives studied, autograft continually demonstrated superior outcomes in both biomechanical studies and long-term clinical trials and therefore remained the gold standard.

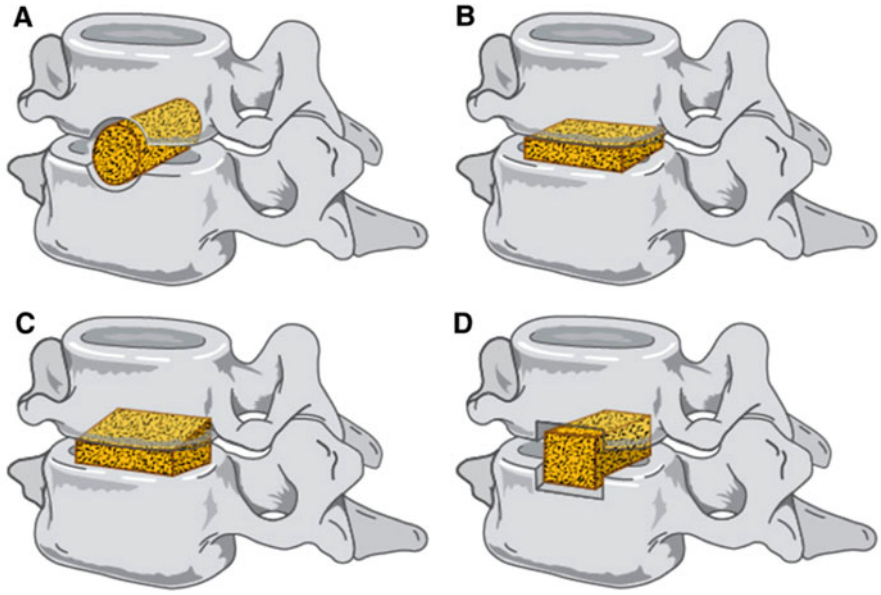

Fig. 1 Historical perspectives on ACDF implants. (**a**) Cloward dowel graft. (**b**) Smith-Robinson-based rectangular implant. (**c**) Simmons-Bhalla keystone. (**d**) Bailey-Badgley onlay strut (Reproduced from Chong et al. 2015)

The failure of graft substitutes forced a shift in the pursuit of viable alternatives. In 1988, Bagby proposed the first use of interbody cages in the human spine. He adapted a technique previously described by DeBowes to treat cervical myelopathy in horses (Bagby 1988, DeBowes et al. 1984). This device consisted of a hollow cylindrical stainless steel cage with fenestrations which was placed through an anterior approach similar to ACDF. This structure allowed bone ingrowth and provided a non-compressible scaffold (Chong et al. 2015). Interbody cage designs were developed out of necessity due to the associated morbidity of iliac crest autograft harvest. Various cage designs and materials have been since been trialed and variably adopted as the technology has advanced.

Cage Design

Cervical interbody cages may circumvent donor site morbidity associated with autograft and infection associated with allograft. For example, autologous iliac crest bone harvesting has been shown to be associated with 22% long- or short-term complications (McConnell et al. 2003). Due to their ease of use, rigid cages with internal space for local autogenous bone graft or morselized allograft with or without osteoinductive materials such as platelet-rich plasma or bone marrow aspirate fragments have become increasingly popular for cervical interbody fusions. Interbody cages have shown to be a successful means of cervical interbody body fusion with associations with less post-operative pain, shorter hospital stays, and higher rates of fusion than autologous bone graft alone (Jain et al. 2016). The ideal cage provides immediate structural supports (axial compression/anterior column distraction), adequate resistance to subsidence, and avoidance of structural allograft complications. Overall goals are to stabilize the newly operated segment to allow new boney ingrowth, maintain anatomic disc height, and avoid cage subsidence until fusion has occurred (Matgé 2002). Cage subsidence is associated with neck pain, late neurologic deterioration, and significantly lower Japanese Orthopaedic Association scores (Chen et al. 2008). Stand-alone interbody cervical cage implantation has shown to be effective with good clinical and patient-reported outcomes (93–100%) despite increased subsidence rates as compared to that with plating

or cage/bone grafting hybrid techniques (Kulkarni et al. 2007).

The basic design of cervical interbody cages encompasses a small, hollow implant with upper/lower and/or lateral windows in which autogenous bone, allograft bone, and/or osteoinductive materials may be placed (Chong et al. 2015; Wilke et al. 2000). Traditionally cage designs can be categorized into threaded (screw, horizontal cylinder) and non-threaded (open box-shaped and vertical rings/cylinders) (Chong et al. 2015; Kandziora et al. 2001). Horizontal cylinders/screws are the manufactured equivalents to allograft dowel techniques, while vertical ring cages are designed to mimic cortical ring allografts. Open boxes are the equivalent of tricortical or quadricortical graft (Weiner and Fraser 1998).

Threaded Cages

Screw Cage Designs (Horizontal Cylinder)

Examples: BAK/C (Zimmer Spine), Ray Threaded Fusion Cage (Surgical Dynamics)

A variety of cervical interbody cages exist, but the most common is the threaded titanium interbody cage. Some of the earliest available cages were described as horizontal cylinder or screw design cages. These cages were based on Cloward's original technique and functioned as dowel grafts. Screw cages, also known as horizontal cylinder cages, have a circular cross section in the coronal plane. Fenestrations along the device allow for contact between prepared endplates and non-structural bone graft or osteoinductive biologic material placed into core. Reaming is usually required to allow proper fit for cages (Pisano et al. 2016). One example of this cage design is BAK-C (Zimmer Spine, Warsaw, IN) which demonstrated device stability, accelerated fusion rates, and higher stiffness when compared to more traditional non-threaded tricortical iliac crest bone graft (Matgé 2002; Chong et al. 2015; Kandziora et al. 2002) (Banco et al. 2002). Another threaded cage design, the Ray Cervical interbody cage (Surgical Dynamics, Norwalk, CT), is shown implanted at C5-6 in the representative post-operative radiograph demonstrated in Fig. 2.

Following initial success, the failures of the threaded screw design were found to be associated with decreased maximum distractive height and increased levels of cage subsidence due to adjacent vertebral endplate weakening. Additional biomechanical studies by Kandziora et al. and others showed threaded screw designs to be less stable in flexion/extension/bending in animal models (Kettler et al. 2001; Kandziora et al. 2001; Jain et al. 2016).

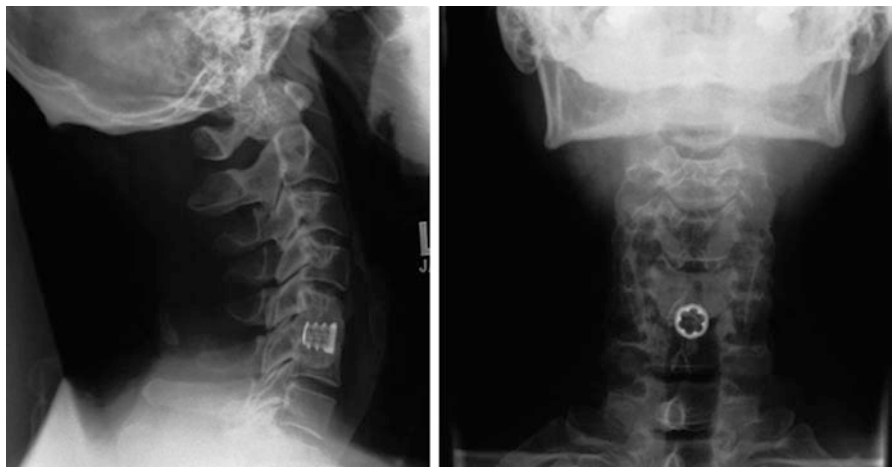

Fig. 2 (**a**) Anterior-posterior and (**b**) lateral X-rays of the cervical spine with the Ray Cervical interbody cage (Surgical Dynamics, Norwalk, CT). Used with permission from Banco et al.

By virtue of the shape of the screw cage designs, there is less space available for bone graft than obtained for either vertical ring or open box designs. The use of the BAK/C and other threaded horizontal cylinder devices has declined due to excessive endplate violation needed for insertion of device.

Non-threaded Cages

Box-Shaped Designs

Example: SynCage-C (DePuy Synthes, Raynham, MA)

Rectangular box cages initially were designed with roughened contact surfaces to improve anchorage and fusion into adjacent cervical vertebral bodies. These cages employ a design that mimics iliac crest cortical graft, with a vertically oriented box with central core allowing bone graft placement (Pisano et al. 2016). This design has demonstrated better segmental stiffness in all directions as compared to tricortical iliac crest (Kandziora et al. 2001). This design has undergone further improvements for surface fit and cage anchorage such as incorporating wedge-shaped and trapezoidal designs as well as attempting to mimic shape of vertebral endplate contours (Chong et al. 2015; Steffen et al. 2000; Kast et al. 2008). Inversely matching cervical vertebral endplate contours allows wedge-shaped box morphology to contribute to increased stability in lateral bending, axial rotation, and flexion as compared to other designs (Kast et al. 2008). Goals of wedge-like box-shaped designs are to match natural cervical lordosis by using anterior slope with 1–2 mm larger box height anteriorly than posteriorly (Gödde et al. 2003; Chong et al. 2015).

The SynCage-C (DePuy Synthes, Raynham MA) is a box form cage with both superior and inferior contact surfaces. The superior cage endplate opens to central contiguous pore (Epari et al. 2005). Within the non-threaded box-shaped design group, there is variability in manufacturer modifications. In Fig. 3, a rendition of SynCage-C is shown from the anterior view with varying superior and inferior endplate modifications.

Vertical Ring (Cylinder) Cages

Example: Harms Cage (DePuy Synthes, Raynham, MA)

Vertical ring cage design is an adaptation of cortical ring allograft interbody fusion described by Ono et al. and popularized by Kozak and O'Brien (Weiner and Fraser 1998; Kozak and O'Brien 1990; Ono et al. 1992). Vertical rings are typically cylindrical mesh cages with vertically oriented walls that have a circular cross section in the

Fig. 3 SynCage-C (DePuy Synthes) is a box-shaped design-type cage. Representative image of the cage from an anterior view, used with permission from *Epari* et al.

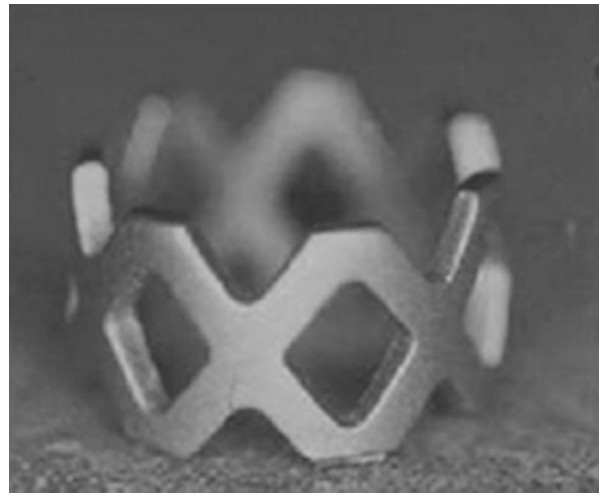

Fig. 4 An example of a Harms cage, which is a vertical cylinder of titanium mesh. Used with permission from *Epari* et al.

axial plane. With a cylindrical shape, the central portion of this graft design accepts autograft and allograft (Pisano et al. 2016). Vertical rings or cylindrical designs commonly lack superior and inferior contact surfaces in contrast to those seen in box-type non-threaded cage designs. Proponents argue that the lack of inferior and superior contact surfaces along with decreased rigidity in meshed walls results in reduced rigidity of cage and provides ingrowth path for vessels and bone (Epari et al. 2005). Cylindrical implants have been shown to subside greater than tricortical autograft, allograft, and rectangular box constructs (Wilke et al. 2000). The Harms cage is a hollow vertical cylinder design and has the largest possible pore size for its volume (Epari et al. 2005) (Fig. 4).

Due to their ability to mimic healthy cervical anatomy and confer initial stability with improvement in initial surface contact, non-threaded cages remain superior to threaded/screw design cages biomechanically (Chong et al. 2015). When comparing subsidence between a vertical ring and box design cages, Kandziora et al. showed similar amounts of endplate penetration despite having very different endplate surface area contact (Kandziora et al. 2001; Epari et al. 2005). A reduction in stiffness of interbody fusion cages in animal models has been shown to enhance interbody fusion after 6 months and up to 3 years (Epari et al. 2005; van Dijk et al. 2002). However, the clinical literature comparing cage design and shape is limited (Chong et al. 2015). Overall trends in surgeon usage had favored wedge-shaped/trapezoidal non-threaded cages, although the clinical outcome data comparing threaded versus non-threaded is sparse. These reported trends may be due to ease of implantation, restoration of cervical lordosis, and greater segmental stiffness with wedge-shaped/trapezoidal non-threaded cages (Chong et al. 2015).

Other Cage Considerations/Current Trends

Newer hybrid interbody cage devices incorporate plate and screw recesses. The cage functions as an anchored spacer with integrated screw construct allowing immediate fixation (Samandouras et al. 2001). The impetus for these new design concepts most likely is derived from increasing popularity of stand-alone cages and recognized issues of subsidence, anterior displacement, and varying results in fusion rates. In vitro studies have revealed that combined use of cage and plate is more stable biomechanically in flexion/extension than stand-alone cage constructs with bone graft (Shimamoto et al. 2001) (Keogh et al. 2008).

Expandable cages, originally used for larger oncologic en bloc resections, have become more popular for degenerative cervical conditions. Proponents of this technique tend to argue that the previously described methods for cage implantation ensure segmental endplate over-distraction

and exceedingly tight implant-endplate contact, while distraction in situ allows more precise fit (Truumees 2011).

Cages may be classified by not only design principle or geometry but also the implant material. Interbody cages may have a variety of described material properties, but more commonly the material make-up consists of titanium, polyether ether ketone (PEEK), or carbon fiber-reinforced polymers (Pisano et al. 2016; Chong et al. 2015). Design materials and designs of interbody cages have changed considerably over the last several decades. Threaded titanium alloy cages, often filled with autogenous bone graft, became popular in the 1990s due to superior fusion rates as compared to non-threaded cages and bone grafts. Non-threaded box-shaped titanium cages as well as polyether ether ketone (PEEK) cages gained popularity due to lack of flexion/extension stability and high incidence of subsidence of threaded cages (Jain et al. 2016).

Cage Materials

Cages composed of synthetic materials were originally introduced to circumvent issues with autograft, allograft, and biocomposite grafts used in ACDF. Desirable features in an interbody cage material include an elastic modulus similar to bone, biocompatibility, achievement of bony fusion, maintenance of alignment, and the ability to avoid subsidence. Bagby's initial description of ACDF in horses was using a stainless steel implant; however, the primary materials used in modern ACDF procedures have been carbon fiber-reinforced polymers (CFRP), titanium (Ti), and polyether ether ketone (PEEK). While overall results with each material have been generally favorable, differences in material properties and outcomes have been described.

Carbon Fiber

Carbon fiber-reinforced polymer implants for interbody fusion were first described by Brantigan and Steffe (1993) for use in the lumbar spine. Cages were later designed and adapted for use in arthrodesis of the cervical spine (Brooke et al. 1997), with excellent clinical results in small series with short follow-up. These initial implants were a composite material of long-fiber carbon in PEEK. The material properties of CFRP cages, such as compressive and tensile strength and isotropy, are dictated by the length, alignment, and volume of the carbon fibers. A biomechanical comparison to iliac crest bone graft by Shono et al. (1993) showed CFRP cages to be more rigid in flexion/extension testing and have higher stiffness in axial compression and rotation. CFRP cages have the benefit of being radiolucent to allow easier evaluation of the adjacent vertebral bodies and subsequent bony fusion on plain radiographs. Additionally, CT and MRI evaluation of the post-surgical spine is easier due to the lack of metal artifact. Early in their development, radiopaque tantalum beads were added in the corners of the cage to assist in visualizing the position of the cage.

Initial results of fusion with CFRP cages demonstrated reliable relief of neck and radicular pain, with authors reporting fusion rates as high as 87–98% in small series with short follow-up. Correction of cervical lordosis, another primary goal of ACDF surgery, was also reliably achieved with CFRP cages. Subsidence was noted frequently in CFRP cages, at a rate of 49% (Van der Haven et al. 2005); however, the occurrence of subsidence did not correlate with clinical outcomes. It should be noted that subsidence in the setting of cervical cages refers to the penetration of the cage through the vertebral endplate, rather than a collapse of the cage itself.

While CFRP had good initial success as a cage material, it has been largely replaced by PEEK in cage manufacturing and clinical use. Yoo et al. (2014) compared CFRP and PEEK cages and found lower fusion in CFRP cages (68.6%) than PEEK cages (82.6%), as well as a higher rate of subsidence in CFRP than PEEK (34.3% vs. 26.1%, respectively). The superior performance of PEEK in these respects is thought to be due to the difference in elastic modulus between CFRP (45 GPa) and PEEK (3.4 GPa), with PEEK more closely matching bone and therefore limiting potential stress shielding of the vertebrae (see Table 1).

Table 1 Elastic modulus of bone and cage materials

Material	*E* (GPa)
Cancellous bone	1–2
Cortical bone	12–20
PEEK	3.4
CFRP	45
Ti	106–115

Titanium

Titanium and its alloys are another material introduced early in the development of cervical cages. Like CFRP, titanium cages for vertebral arthrodesis were first described in the lumbar spine (Ray 1997) with good results and were later adapted for cervical interbody fusion, with Profeta et al. (2000) reporting favorable initial results with a threaded Ti cage compared to bone graft, noting good "immediate stability." Titanium, introduced to orthopedic practice in the 1940s, has several desirable properties for an orthopedic implant. It has a high yield strength, low density, biocompatibility, and excellent corrosion resistance due to self-passivation with titanium oxide (TiO2). With respect to cervical arthrodesis, modern Ti cages typically undergo surface modification to roughen the surface, via processes such as plasma spraying, which provides mechanical and biological advantages.

A roughened surface increases friction at the bone-implant interface, contributing to initial stability. The degree of micromotion at the bone-implant interface dictates the characteristics of bone and fibrous tissue formation; Jasty et al. (1997) demonstrated using porous-coated Ti alloy implants in an animal model that cyclic micromotion of under 40 micrometers reliably led to stable ingrowth of bone, whereas micromotion from 40 to 150 micrometers led to a proportionally increasing amount of fibrous tissue and fibrocartilage and less stable ingrowth. The use of roughened titanium cages thereby confers the potential advantage of improved stability and bone apposition at the bone-implant interface, and several authors have commented on the good perceived initial stability and handling characteristics of such cages.

Roughened Ti cages have also been shown to have potential biological advantages. When compared to PEEK (a typically smoother surface), roughened Ti surfaces have been shown in vivo to increase osteoblast maturation and the production of bone morphogenetic proteins, which may be of benefit in achieving osseointegration and ultimately bony fusion (Olivares-Navarrete et al. 2012). Due in part to this potential biological advantage, "empty" Ti cages (i.e., without bone graft material) have been trialed with good short-term outcomes reported by Krayenbuhl et al. (2008).

In contrast to CFRP and PEEK cages, Ti cages are radiopaque, rendering direct assessment of bony fusion through the cage difficult. As Profeta noted in his initial experience following patients with Ti cages, "signs of osseous consolidation can be detected around the cage," and fusion "may be deduced from the long-term stability and absence of bone rarefaction around the cage." A bigger concern with Ti cages has been early cage subsidence, which was originally reported in eight patients by Gercek et al. (2003). He described radiographic subsidence of stand-alone Ti cages in five of nine operated levels, with one patient developing recurrent radicular symptoms and foraminal stenosis after a period of initial improvement post-operatively. Other authors to follow redemonstrated the propensity of Ti cages to subside at rates of 13–62.5% with a meta-analysis showing a subsidence rate of 33/211 patients (15.6%) for Ti cages compared to 11/184 (6.0%) for PEEK cages (Li et al. 2016); however, it is important to note that this analysis failed to show a difference in functional outcomes between PEEK and Ti cages. The high elastic modulus relative to bone and the resultant potential for stress shielding has been cited as a possible contributing factor in Ti cage subsidence (see Table 1). With the advent of three-dimensional printing technology, modifications to cage surface architecture and implant porosity may improve bony ingrowth and biomechanical stability; however, long-term clinical outcomes for these new technologies are not yet readily available.

Peek

Polyether ethyl ketone was first investigated for use as an orthopedic implant in the 1980s and was used as a component of CFRP cages in early

interbody cages such as the Brantigan cage discussed previously. After CFRP cages fell out of favor, PEEK cages emerged as the primary alternative to Ti cages. PEEK is a semi-crystalline polymer, the mechanical properties of which are dependent on its molecular weight, temperature, strain rate, and crystallinity (Kurtz and Devine 2007). PEEK used in spine cages has an elastic modulus of approximately 3.4 GPa, which is similar to adjacent bone and significantly lower than its CRFP and Ti counterparts. A lower elastic modulus may lead to less stress shielding and less subsidence, as discussed above. As with CFRP cages, PEEK cages are radiolucent (with marking beads) and allow for easier, more direct visualization of bony fusion after surgery, as well as less artifact when imaging with a CT or MRI.

The structure of PEEK is very chemically stable, and as a result PEEK implants are biologically inert. While favorable in the sense that this prevents an inflammatory response or degradation, there is a concern that inertness as well as the hydrophobic nature of PEEK, which limits cellular adhesion, can lead to limited fixation to adjacent bone. An animal study on PEEK implants (Toth et al. 2006) demonstrated the development of non-osseous tissues (cartilage, fibrous tissue) at the bone-implant interface. To attempt to improve the osseointegration of PEEK implants, efforts have been made to develop PEEK cages with an altered roughened surface, which some propose accounts for differences in osseointegration between previous PEEK and Ti implants. Torstrick et al. (2017) report on the development of a PEEK cage with a porous surface microstructure, in which they showed improved histological osseointegration compared to smooth PEEK and encouraging results in early clinical application in ACDF patients.

Clinical outcomes with PEEK cages have been excellent and have led to widespread use of PEEK implants in clinical practice. PEEK has been shown to have equivalent functional and radiographic results to autograft iliac bone graft, with the expected shorter surgical time and decreased donor site morbidity expected with use of a cage (Zhou et al. 2011). PEEK has also compared favorably to Ti in several studies. Niu et al. (2010), in a prospective comparison with 12-month follow-up, showed higher fusion rates (100% for PEEK vs. 86.5% for Ti) and lower subsidence (0% for PEEK vs. 16.2% for Ti), with equivalent rates of good to excellent clinical outcomes. With a longer follow-up period of 7 years, Chen et al. (2013) demonstrated lower subsidence (5.4% compared to 34.5%), better maintenance of angular correction, and better clinical outcomes with PEEK compared to Ti while noting that fusion was achieved in all patients in both groups.

Hybrid Cages

In an effort to combine the desirable features of both PEEK and Ti cages, hybrid cages with a PEEK body and Ti coating (via plasma-spraying) have been developed. These theoretically have an elastic modulus closer to bone with a radiolucent center due to the PEEK component while incorporating the potentially better initial fixation and subsequent osseointegration of a rough Ti surface. Pre-clinical studies using this type of cage demonstrated improved bone ingrowth to the Ti-PEEK cages as opposed to PEEK alone (Walsh et al. 2015). A concern raised for this type of cage is the delamination between the Ti and PEEK layers; however, manufacturer-published biomechanical testing demonstrated no delamination at ten million cycles (Medacta 2018). Hybrid Ti-coated PEEK cages are in the early phases of clinical usage, and their long-term performance relative to other cage materials remains to be seen, though there are concerns that the coating may be susceptible to delamination during impaction (Torstrick Spine J. 2018).

Operative Technique

After standard anterior cervical spine exposure, the author's preferred surgical technique is to utilize Caspar pins for interspace distraction. Pins are placed in the midpoint of the superior and inferior vertebral bodies. Annulotomy of the intended disc space is performed with a 15-blade scalpel knife, and the interspace is then distracted. Diskectomy

is performed with a combination of pituitary rongeurs, Kerrison rongeurs, curettes, and a high-speed burr. Once a thorough diskectomy is complete, the cartilage layer on the superior and inferior endplates is removed with straight and angled curettes. Sclerotic subchondral bone is roughened with the use of a rasp. The posterior osteophytes are identified and removed with the high-speed burr, and the osseous shavings are saved as local autograft. Doing so reveals the posterior longitudinal ligament, which is then split with a nerve hook in line with the ligamentous fibers and then resected with Kerrison rongeurs. Once the posterior longitudinal ligament has been completely removed, the neural foramina are palpated and decompressed with Kerrison rongeurs. Decompression is verified using a nerve hook. Once the decompression is completed, the distracted interspace is sized for an appropriate cage. Fluoroscopic evaluation is performed to assess for alignment as well as distraction of the facet joints, to prevent "overstuffing" of the interspace. The cage is packed with local autograft, as well as osteoinductive or conductive material such as demineralized bone matrix, and distraction can be released. The cage is impacted into the interspace. The implant position is verified with intraoperative radiography. An anterior cervical locking plate is then placed in front of the cage, with screws in the cephalad and caudal vertebral bodies. Intervertebral cage devices with integrated fixation can avoid additional plating, particularly in instances such as adjacent segment degeneration above a prior fusion.

Summary

As cervical interbody fusion techniques have advanced, so too have implant designs and materials. Development of cervical interbody cages has allowed for improvements in fusion rates as well as in a reduction in the necessity of donor site morbidity for iliac crest harvest. As manufacturing processes and understanding of bone biology continue to improve, future interbody cage designs and materials will likely follow suit.

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Anterior Lumbar Interbody Fusion and Transforaminal Lumbar Interbody Fusion

32

Tristan B. Fried, Tyler M. Kreitz, and I. David Kaye

Contents

Abstract

The use of interbodies as a method for lumbar fusion has been increasing over the past decades. Increased surface area and enhanced biomechanical forces for achieving fusion have made the technique more appealing than traditional posterolateral lumbar fusion. While many interbody techniques are actually less invasive than traditional open procedures, there are unique complication profiles with different approaches. The benefits of interbody fusion must be considered with the potential

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morbidity of these approaches. This chapter focuses on the techniques of both lumbar transforaminal and anterior interbody fusion along with potential complications with special attention toward graft/interbody selection and pearls and pitfalls of the respective technique.

Keywords

Anterior lumbar interbody fusion · Transforaminal lumbar interbody fusion · Technique · Complications · Graft

Anterior Lumbar Interbody Fusion (ALIF)

Introduction

Since its description in 1932 by Capener (1932) for the treatment of spondylolisthesis, anterior lumbar interbody fusion (ALIF) has become an accepted treatment modality for many degenerative lumbar conditions. ALIF may be used as a standalone procedure or in combination with posterior instrumentation as demonstrated in Fig. 1. Anterior lumbar fusion allows for complete discectomy, indirect decompression, maximal surface area for fusion under compression, and restoration of lumbar lordosis and sagittal alignment. The benefits of anterior fusion must be considered with the potential morbidity associated with the anterior approach or combined anterior/posterior procedure. This chapter reviews the indications, perioperative considerations, and surgical technique for anterior lumbar interbody fusion (ALIF).

Indications

- Isthmic and degenerative spondylolisthesis
- Degenerative disc disease
- Discogenic back pain
- Degenerative lumbar scoliosis
- Revision transforaminal lumbar interbody fusion (TLIF)
- Pseudarthrosis after posterior fusion (Mobbs et al. 2013a)
- Sagittal malalignment
- Osteodiscitis
- Tumor
- Trauma

A thorough history and physical with review of the appropriate imaging studies is necessary prior to considering a patient for an ALIF. In the case of degenerative disc disease with associated spondylolisthesis or deformity, the patient may present with radicular symptoms. The patient should demonstrate insufficient relief of symptoms with appropriate nonoperative management including use of NSAIDs, epidural injections, and physical therapy. Surgery may be expedited in the setting of significant motor weakness or cauda equine syndrome, a constellation of findings including saddle anesthesia, urinary retention, or loss of bowel control. Discography may be selectively used to help diagnose a discogenic source in a patient with axial low back pain.

Advantages of ALIF over posterior interbody fusion techniques (PLIF, TLIF) include the potential for more thorough discectomy, maximization of surface area for fusion, the potential for greater correction of deformity, indirect nerve root decompression, preservation of posterior structures including paraspinal musculature and facet complex, and avoidance of nerve root manipulation during graft insertion (Mobbs et al. 2013a; Richter et al. 2015).

Contraindications

Spine surgery including ALIF is not indicated when other pathology is the cause of the patient's neurologic symptoms: specifically central and peripheral neuropathy (diabetes, vitamin B deficiency, multiple sclerosis, and Guillain-Barre).

Contraindications specific to ALIF include:

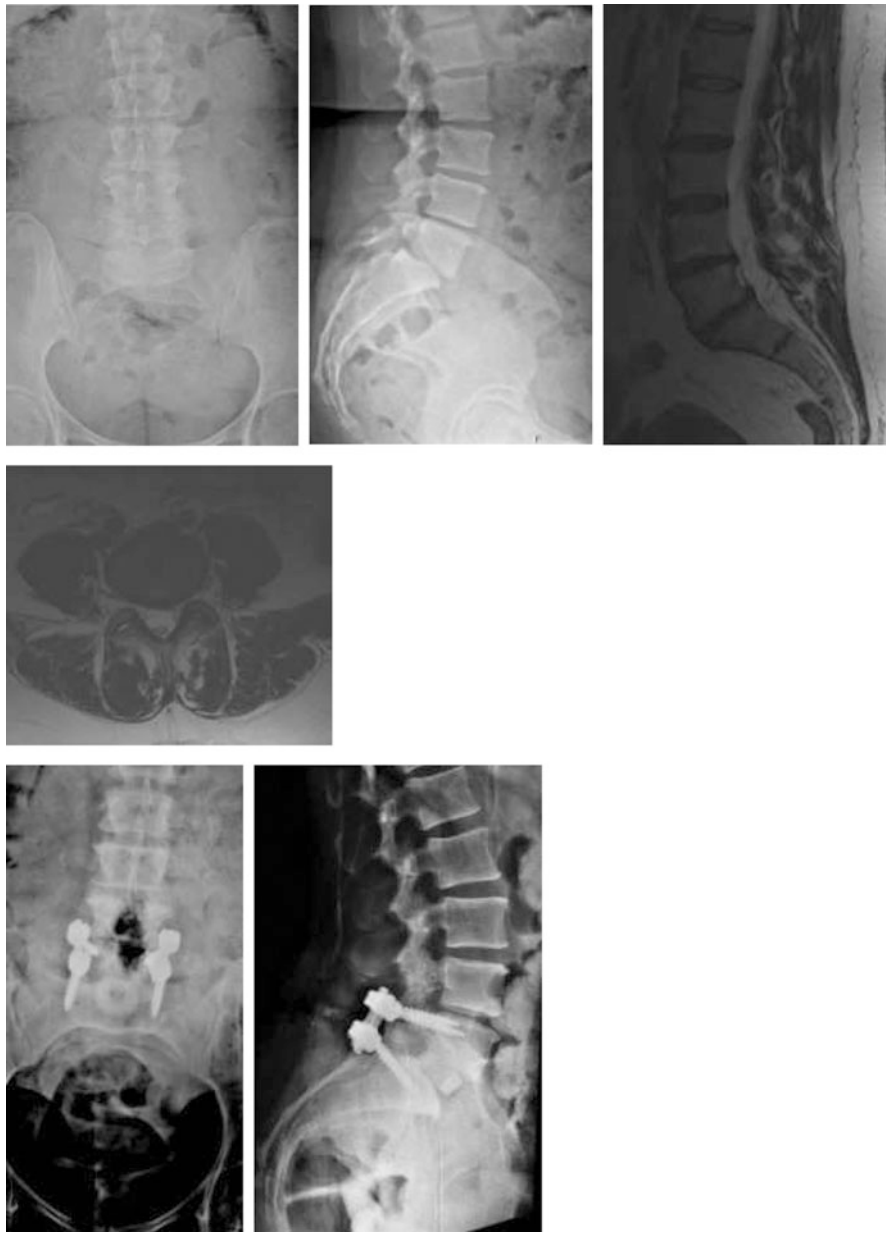

Fig. 1 Preoperative AP and lateral radiographs as well as sagittal and axial T2 MRI demonstrating stenosis and spondylolisthesis. Postoperative AP and lateral radiographs demonstrating lumbar 5 to sacral 1 anterior lumbar interbody fusion. A structural autograft was used as well as posterior instrumentation. Images courtesy of Department of Orthopaedic Surgery, Thomas Jefferson University Hospital

- Calcified great vessels (aorta, iliac vessels)
- Prior vascular reconstruction
- History of abdominal or retroperitoneal surgery
- History of pelvic inflammatory processes
- Medical comorbidities putting the patient at significant risk under general anesthesia

Operative Setup

Instruments and Materials Required

- Exposure surgeon: general or vascular
- Jackson radiolucent table
- Intraoperative radiography
- Surgical loupes or microscope
- Abdominal retractor system
- Standard spine instrument tray with curettes, Kerrison rongeurs
- Distractors and graft trials
- Interbody graft or cage

Graft Selection

Bone grafts may be used in isolation or in combination with cages, biologics (BMP-2), and anterior or posterior instrumentation. Iliac crest autograft (ICBG) is the "gold standard" for spinal fusion, but is associated with significant donor site morbidity including pain, infection, and neurovascular injury (Arrington et al. 1996). ICBG autograft may be used in combination with titanium cages or allograft material, reducing the necessary autograft quantity and associated morbidity while maintaining fusion potential (Newman and Grinstead 1992; Sasso et al. 2004). Alternatively, femoral ring allograft (FRA) or iliac crest structural allograft may be used. Allografts may lack the osteogenic and osteoinductive properties of autograft, but their versatility, availability, biologic superiority to cages, and avoidance of autograft donor morbidity make them an attractive option (Stevenson 1999; Sarwat et al. 2001; Mobbs et al. 2013a). Use of allograft in combination with posterior instrumentation demonstrates reliable rates of arthrodesis, greater than 90% among single-level procedures (Anderson et al. 2011; Mobbs et al. 2013b). Fusion rates may be enhanced with the addition of bone morphogenic protein-2 (rh-BMP2). The use of rh-BMP2 with allograft scaffold has demonstrated efficacy in ALIF procedures without the associated morbidity of ICBG autograft (Burkus et al. 2002; Anderson et al. 2011). Bone morphogenic protein-2 has been associated with ectopic bone formation, soft tissue edema, and excessive osteoclastic activity (Benglis et al. 2008; Chen et al. 2012). Titanium and composite interbody cages were developed to enhance biomechanical stability and improve fusion rates in standalone ALIF procedures, averting the risks and morbidity associated with combined anterior/posterior procedures. These interbody devices are used in combination with allo-/autograft and biologic materials (Burkus et al. 2009; Strube et al. 2012; Behrbalk et al. 2013). Titanium interbody cages in combination with BMP-2 demonstrate substantial fusion rates, greater than 90%, when used in standalone ALIF procedures without supplemental posterior instrumentation (Burkus et al. 2002, 2009; Boden et al. 2000). However, concern exists regarding titanium cage subsidence due to metal-bone modulus. Biocompatible composite material polyetheretherketone (PEEK) cages were developed as a load-bearing interbody device with similar modulus to bone to reduce rates of subsidence compared to metal cages (Galbusera et al. 2012; Behrbalk et al. 2013). Radiolucent PEEK cages also allow for easier radiographic assessment of fusion. Composite material cages carry the risk of fragmentation and extrusion over time. Ultimately, several bone graft and interbody device options have been developed for use with ALIF procedures, each with their own inherent advantages and disadvantages.

Positioning

The patient is placed supine on a flat Jackson table. Slight Trendelenburg and bump under the sacrum may remove obstructing pannus and decrease lordosis. The patient's arms are taped across the chest. Use of a Foley catheter is preferred. The patient is then prepped and draped in usual sterile fashion.

Surgical Technique

Step 1: Exposure

A left-sided retroperitoneal approach is performed with the assistance of an exposure surgeon. A low transverse incision between the umbilicus and pubic symphysis is preferred. Alternatively, a longitudinal curvilinear left-sided incision may be used for retroperitoneal approach. Dissection is carried through the dermis, and subcutaneous tissues are carried to the level of the rectus sheath. The anterior rectus sheath is divided transversely. The superior and inferior edges of the rectus fascia

are elevated off the underlying rectus abdominis muscles. The right and left rectus muscles are separated in the midline exposing the dorsal fascia and arcuate line. Underlying preperitoneal fat is separated, and the peritoneum is identified and preserved. Dissection is carried in a left lateral extraperitoneal plane. The psoas muscle with overlying genitofemoral nerve are encountered just lateral to the common iliac vessels (Spruit et al. 2005; Behrbalk et al. 2013). The left ureter may be encountered running beneath the peritoneum and should be protected. The lower lumbar spine and sacrum are identified. Overlying soft tissue is bluntly dissected exposing the spine. Middle sacral vessels may be clipped and cauterized. Exposure of the L5/S1 disc space is performed distal to the iliac vessels and cranial levels proximal to the vessels. A radiographic marker is placed in the appropriate intervertebral disc, and a plain radiograph is obtained to confirm the anatomic level.

Step 2: Discectomy

After confirmation of appropriate disc for excision, a long-handled knife is used to perform an annulotomy and define the perimeter of the identified disc. Electrocautery is avoided for risk of injury to the autonomic nervous system. A knife, high-speed burr, pituitary rongeur, and/or curette may be used sequentially to remove the identified disc posterior to the posterior longitudinal ligament (PLL). Sequential distraction can be used to allow better visualization and access to the posterior disc space. Vertebral endplates may be further defined using a cobb elevator.

Step 3: Endplate Preparation

Using a curette, the inferior endplate of the cephalic vertebrae and superior endplate of the caudal vertebrae are denuded of cartilage creating a roughened bleeding surface for fusion. Care is taken to not disrupt or compromise the integrity of the endplate resulting in stress riser and potential for implant subsidence.

Step 4: Insertion of Graft/Cage

Trial sizers may be used to determine appropriate graft size restoring intervertebral disc height. The bone graft may be asymmetrically machined to restore appropriate lordosis. The bone graft/cage complex may be augmented with a biologic to enhance bony fusion. Graft/cage positioning is confirmed using an intraoperative lateral radiograph.

Step 5: Closure

The wound is copiously irrigated. All bleeding should be controlled using hemostatic agents and electrocautery. The wound is closed in multiple (fascia, subcutaneous tissue, and skin) layers, and a sterile dressing placed.

Complications

- Sexual dysfunction, retrograde ejaculation in males
  - Due to damage to superior hypogastric (sympathetic) plexus located along the prevertebral tissues anterior to L5 vertebrae. Especially at risk when performing L5/S1 ALIF. Blunt dissection and avoidance of electrocautery are encouraged at this level.
- Iatrogenic injury to retroperitoneal structures (i.e., great vessels, ureters, bowel)
  - Care is taken during the approach and in retractor placement to identify and protect vital structures.
- Dural tear (CSF leak)
  - Rare as the epidural space is generally not encountered
- Nerve root damage
  - Rare as there is no direct nerve decompression; rather decompression occurs through distraction.
- Infection
- Pseudarthrosis
- Hardware/graft malposition or migration
- Medical complications
  - Patients are at risk of postoperative ileus and in rare instances bowel obstruction from the anterior approach to the lumbar spine.

Pearls and Pitfalls

- A bump can be used on the sacrum to retrovert the pelvis to allow for easier access to the disc space. This is particularly critical for L5–S1 isthmic spondylolistheses.

- Care should be taken during anterior exposure to identify and protect vital structures within the retroperitoneum. The use of an exposure surgeon is highly recommended to facilitate safe exposure.
- Use of electrocautery is avoided anterior to the L5 vertebrae to prevent injury to the prevertebral sympathetic plexus.
- A thorough discectomy and endplate preparation is critical for fusion.
- Bone graft/cage must be sized appropriately to restore alignment, achieve indirect decompression, and accomplish a large surface area of contact.

Postoperative Protocol

Early postoperative mobilization and physical therapy facilitate recovery and prevent the risk of medical complications associated with immobility. Due to the risk of postoperative ileus, patients are started on a clear liquid diet until they pass flatus and then advanced as tolerated. A bowel movement prior to discharge is encouraged.

Transforaminal Lumbar Interbody Fusion (TLIF)

Introduction

PLIF was first described in 1944 by Briggs and Milligan; however, it did not increase in popularity until it was described in 1953 by Cloward. Unlike the original description which used laminectomy bone chips as the interbody graft, Cloward's technique involved a graft made of iliac autograft (Briggs and Milligan 1944; Cloward 1953; Cole et al. 2009; Mura et al. 2011). A posterior approach had some advantages in that it could reduce some of the possible complications of ALIF including vascular injury and sexual dysfunction. The TLIF was then first described in 1982 by Harms and Jeszenszky as a modification of the PLIF procedure (Harms and Rolinger 1982; Cole et al. 2009; Mura et al. 2011). The TLIF approach is designed to approach the disc space unilaterally through the foraminal area (Kambin's triangle) to reduce complications associated during PLIF such as durotomy, radiculitis, and interoperative bleeding (Harms and Rolinger 1982; Craig Humphreys et al. 2001; Cole et al. 2009; Mura et al. 2011). TLIF has since evolved and can also be performed as a minimally invasive procedure that was popularized by Foley et al. in 2003 (Foley et al. 2003; Sonmez et al. 2013). This chapter reviews the indications, perioperative considerations, and surgical technique for transforaminal lumbar interbody fusion (TLIF). Figure 2 represents pre- and postoperative images from a typical TLIF procedure.

Indications

- Symptomatic spondylolisthesis
- Spinal stenosis with instability
- Degenerative lumbar scoliosis (Cloward 1953; Collis 1985; Lin 1985; Cole et al. 2009; Xiao et al. 2009)
- Discogenic low back pain
- Recurrent lumbar disc herniation (Cole et al. 2009)

Before the decision to perform a TLIF, a thorough history and physical exam must be performed. Prior to consideration of surgery, patients should have exhausted a course of nonoperative management such as NSAIDs, physical therapy, and consideration of injections. In addition, the patient's pain and symptoms should be concordant with advanced imaging.

TLIF has some distinct advantages over ALIF and PLIF procedures. In cases which require a posterior decompression, the performance of a TLIF vs. an ALIF can be significantly more time efficient. As a posteriorly based approach, performance of a TLIF can avoid complications uniquely associated with the anterior approach such as damage to the great vessels, damage to retroperitoneal structures, or sexual dysfunction. The TLIF also has advantages over the PLIF surgery in that it does not involve nerve retraction to the same degree which therefore decreased the risk of neurological damage. In addition, as TLIF can frequently be performed with unilateral facetectomy, preservation of bony structures on the contralateral side can aid in stability and ultimate fusion.

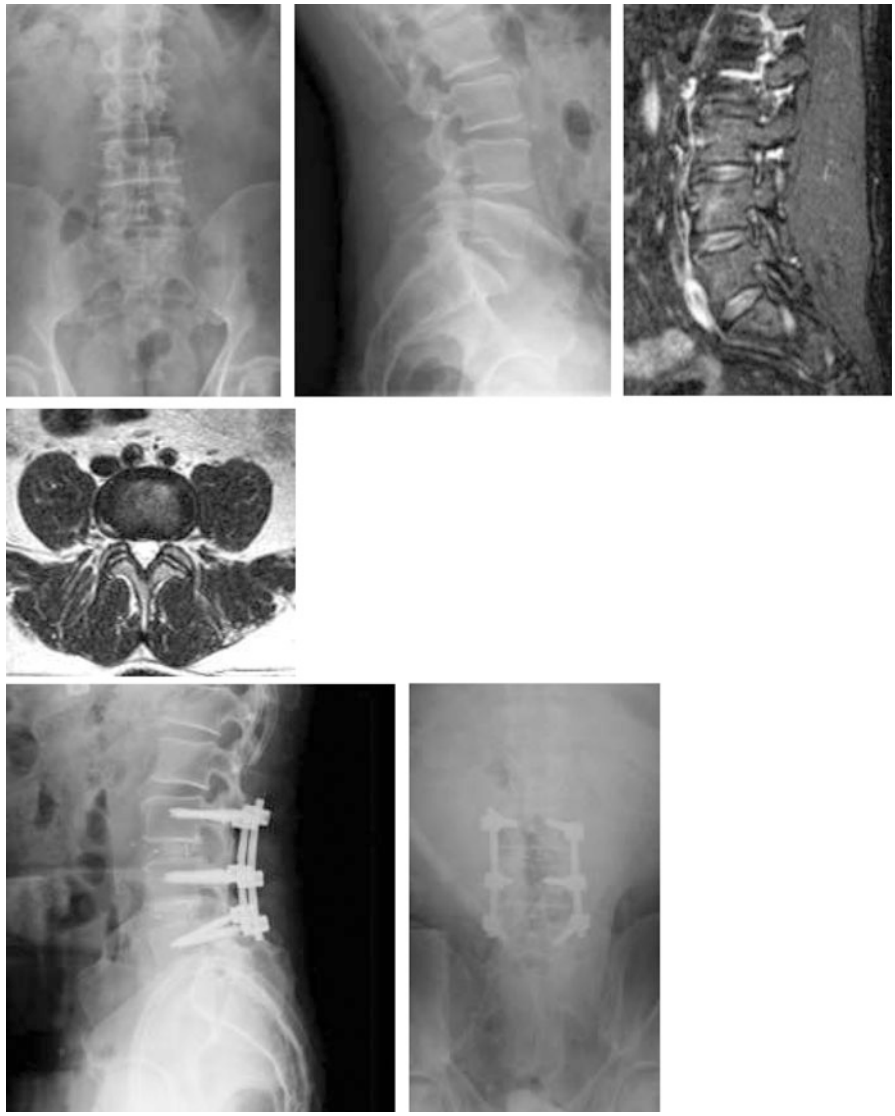

Fig. 2 Preoperative AP and lateral radiographs as well as T2 axial (L5–S1) and sagittal MRI demonstrating foraminal stenosis. Also, postoperative AP and lateral radiographs demonstrating lumbar 3–4 and 4–5 transforaminal interbody fusion. Images courtesy of Department of Orthopaedic Surgery, Thomas Jefferson University Hospital

Contraindications

Contraindications specific to TLIF include:

- Conjoined nerve root within the foramen (Holly et al. 2006)
- Previous wide posterior decompression (relative) (Ozgen et al. 1999; Lai et al. 2004; Xiao et al. 2009)
- Severe osteoporosis (Min et al. 2008; Xiao et al. 2009)
- Medical comorbidities putting the patient at significant risk under general anesthesia

Operative Setup

Instruments and Materials Required

- Exposure surgeon: general or vascular
- Jackson radiolucent table
- Intraoperative radiography
- Surgical loupes or microscope

- Abdominal retractor system
- Standard spine instrument tray with curettes, Kerrison rongeurs
- Distractors and graft trials
- Interbody graft or cage

Graft Selection

Numerous interbody and grafting options have been developed over the past decades for use in TLIF. Although generally ICBG is the gold standard for fusion, possessing osteoindicative, osteoconductive, and osteogenic potential, ICBG is rarely used for TLIF as it has been associated with significant donor site morbidity with complication rates approaching 25% (Kurz et al. 1989; Younger and Chapman 1989; Fernyhough et al. 1992; Craig Humphreys et al. 2001; Gibson et al. 2002; Lowe and Coe 2002; Coe 2004; Mummaneni et al. 2004a). An ideal substitute should be structurally capable of maintaining the reconstructed disc space's integrity (i.e., maintain disc height and neuroforaminal height) without subsidence and help create an environment conducive to lumbar fusion (Boden 2002; Mummaneni et al. 2004b; Cole et al. 2009; Xiao et al. 2009). Allograft has been used as a comparable substitute to AIBG, and while some comparative studies found increased fusion rates with AIBG, most have concluded that there is no overall difference in fusion rates between the two (Lin 1985; Rish 1989; Rompe et al. 1995; Xiao et al. 2009). Titanium interbody cages have been increasingly used over the past 5 years. Titanium cages have been reportedly more likely to subside into the endplates of the vertebral bodies due to the increased modulus of elasticity of titanium relative to bone. In addition, accurate assessment of postoperative fusion can be challenging on CT and MR imaging secondary to metallic artifact (Weiner and Fraser 1998; Lowe and Coe 2002; Cole et al. 2009). Metal artifact reducing sequencing (MARS) on MRI has made this issue less problematic. Carbon fiber and PEEK cages were developed to minimize some of the technical issues that titanium has posed. With a modulus of elasticity closer to bone, there have been theoretical reports of decreased interbody subsidence. Additionally, PEEK cages may allow more reliable assessment of fusion mass (Weiner and Fraser 1998).

There are also bone graft substitutes that have been used; however, there is limited data on these substances. The most commonly used and widely studied biological agent used as a bone graft substitute has been recombinant human bone morphogenic protein-2 (rhBMP-2) (Resnick et al. 2005; Kaiser et al. 2014). Michielsen et al. performed a level I randomized trial comparing TLIF using PEEK interbody with BMP-2 or autograft and found that for the BMP-2 cohort, there was significantly greater interbody healing on bone deniometry up to a year postoperatively ($p = 0.014$), but no difference in overall fusion rates on CT scan (all patients fused) and no clinical differences (VAS, ODI, SF-36) postoperatively (Michielsen et al. 2013). More recently, Khan et al. published their series of 191 patients undergoing TLIF with BMP-2 or autograft and demonstrated equivalent fusion rates and overall complication rates between the cohorts, but higher rates of postoperative radiculitis and postoperative seroma for the BMP-2 patients (Khan et al. 2018). Although rhBMP-2 has certainly rivaled AIBG in terms of fusion potential, the complication profile has muted more widespread enthusiasm. rhBMP-2 has been shown in multiple studies to be associated with complications including radiculitis, osteolysis, and ectopic bone formation (Wong et al. 2008; Gray and Rampersaud 2010; Helgeson et al. 2011).

Positioning

The patient is positioned prone on a Jackson table with the hip pads positioned just below the iliac crests and the chest pad positioned just below the sternal notch. The abdomen is allowed to hang freely minimizing pressure on the abdominal cavity and helping to prevent excessive epidural bleeding.

Exposure

Although the procedure can be performed via a traditional open approach or using minimally invasive techniques, this section will focus on open techniques as MIS is discussed elsewhere. An incision is made in the midline and dissection is carried through the skin and subcutaneous tissue to the level of the fascia. The fascia is then

incised on either side of the spinous processes and subperiosteal elevation of the paraspinal musculature is performed.

Surgical Technique

Distraction across the disc space can facilitate discectomy, and therefore we frequently remove the interspinous ligament at the planned level (i.e., remove the ligament between L4 and 5 for an L4–5 TLIF) but keep the spinous processes intact to serve as a buttress for placement of a laminar spreader. The laminar spreader is then expanded which allows for expansion of the interlaminar space. We performed the TLIF from the side which is more symptomatic. Partial laminectomy may be performed with the use of a high-speed burr or Kerrison rongeurs. Laminectomy is begun at the midline and proceeds in a medial to lateral direction. Once the lamina has been at least partially removed (about 50% of the height in a cranial caudal direction, which is generally above the insertion of ligamentum flavum on the undersurface of the cranial lamina and at the region where the epidural fat begins), an osteotome may be used to remove the remaining lamina and inferior articular process (IAP) of the cranial vertebrae en bloc. This bone may be used as local autograft to be placed in the disc space after discectomy. Alternatively, a burr or Kerrison rongeur can be used to remove the remaining lamina and IAP piecemeal.

During the procedure, the ligamentum flavum may be left intact until after the TLIF is performed or may be removed before the discectomy. Leaving the ligament intact may afford an extra level of protection to the dura and nerve root, and decompression may be performed after the interbody has been placed.

A woodson elevator can be used to palpate the top of the pedicle of the caudal vertebra. The woodson may be left in place, and an osteotome may then be used to remove the superior articular process of the caudal vertebrae. Any remaining bone superior to the pedicle should be removed with Kerrisons so that there is no overhanging bone above the pedicle. Similarly, the medial wall of the pedicle should be skeletonized by removing some of the lamina of the caudal vertebrae. At this point, the majority of the bony work has been completed for performance of the discectomy.

A woodson elevator is used to palpate the medial and superior borders of the pedicle and identify the disc space which is just above the caudal pedicle. Next, a Penfield 4 can be used to dissect of the overlying soft tissue above the disc, and bipolar electrocautery can be used to ligate the overlying epidural plexus at the disc level. The working zone for the discectomy is classically described as a triangle (Kambin's) bordered by the traversing nerve root medially, the pedicle/superior endplate inferiorly, and the exiting nerve root superiorly. Identification of the exiting nerve root allows for a safer working zone and more aggressive lateral disc work. Assuming the nerve has been identified and is sufficiently lateral at the level of the disc, frequently, medial retraction of the traversing nerve and thecal sac is not required. If required, gently retract the nerve and thecal sac medially with the use of a nerve root retractor. Be sure to relax the traction at frequent intervals to prevent the development of a palsy or postoperative radiculitis.

Discectomy begins with creating a box annulotomy as largely as possible with the use of a #15 blade on a long handle. We often use a Kerrison rongeur to remove the posterior lip of the caudal vertebral body as well as define the extent of the annulotomy in all directions. We begin disc removal with specially designed shavers which efficiently remove a large amount of disc material. Once bony chatter is appreciated, we no longer upsize the shavers. The size of the final shaver is generally the size of the final interbody. After shavers have removed much of the disc material, we use a combination of straight and angled curettes to remove residual adherent disc and the cartilaginous endplate. Care is taken not to violate the bony endplates. Trialing of the interbody spacers may be performed. Once a thorough discectomy and endplate preparation have been performed, the disc space is packed with a combination of locally harvested autograft and allograft. After the space has been packed, the interbody is placed and impacted into final position. A more anteriorly

placed graft may allow for better creation of lordosis, but a more posteriorly placed graft may allow better indirect neuroforaminal decompression. Once the interbody has been impacted into final position, a woodson elevator can be used to palpate the posterior disc space and ensure bone is palpated posteriorly to the interbody.

At this point, the laminar spreader can be removed to further compress the interbody. All remaining encroaching bone and ligamentum can more easily be removed at this point. The foramen must be reexplored to ensure no remaining stenosis or bone graft remains.

If necessary, a contralateral facetectomy may be performed (akin to a Ponte osteotomy) to allow for even greater creation of lordosis.

After performing the TLIF, pedicle screws are placed in a standard fashion according to the particular surgeon's preference. By compressing the pedicle screws, the interbody can be locked in place and restore even greater lordotic alignment.

The wounds are then thoroughly irrigated and closed over drains in a layered fashion per routine.

Complications

- Radiculitis (Yan et al. 2008)
- Screw loosening or hardware failure (Yan et al. 2008)
- Paraspinal iatrogenic injury (Craig Humphreys et al. 2001; McAfee et al. 2005; Cole et al. 2009; Sakeb and Ahsan 2013; Mobbs et al. 2015)
- Dural tear (CSF leak) (Holly et al. 2006)
- Deep infection (Hackenberg et al. 2005)
- Nerve root damage
  - Radiculopathy (Hackenberg et al. 2005)
- Pseudarthrosis (Hackenberg et al. 2005)

Pearls and Pitfalls

Removing the IAP and SAP en bloc with the use of an osteotome can be time efficient and serve as an excellent source of local autograft.

Use traction on the traversing nerve root and thecal sac judiciously to prevent inadvertent neurologic injury.

Biting the posterior inferior lip of the cranial vertebrae can allow better visualization for discectomy and easier placement of interbody graft.

Endplate violation during discectomy can lead to excessive bleeding from the disc space and can predispose to interbody subsidence.

Postoperative Protocol

The standard of treatment after spinal fusion procedures includes an early regimen of physical therapy to decrease postoperative complications.

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Scoliosis Instrumentation Systems

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Rajbir Singh Hundal, Mark Oppenlander, Ilyas Aleem, and Rakesh Patel

Contents

Abstract

Adult spinal deformity is a complex deformity that involves three-dimensional deformation in coronal, sagittal, and axial planes. Spinal and spinopelvic parameters such as SVA, pelvic tilt, pelvic incidence, and lumbar lordosis are important in understanding, characterizing, and treating adult spinal deformity. Treatment of adult spinal deformity needs to be tailored to each patient with respect to the nature of the curve and the patients' overall medical health. Operative techniques have changed substantially with time, from the early use of

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Harrington rods to modern pedicle screws. Multiple osteotomies (SPO, PSO, and VCR) can be applied for the desired level of spinal correction. Operative management of adult spinal deformity is wrought with complexity and severe complications. Newer techniques involving minimally invasive surgery and interbody fusions are being increasingly used for deformity correction. In this chapter, we will discuss such operative techniques for spinal deformity correction.

Keywords

Adult deformity · Scoliosis correction · Corrective osteotomy · Minimally invasive surgery (MIS) correction

Introduction

Adult spinal deformity (ASD) is an expansive term that covers a wide variety of conditions that involve deformation or malalignment of the adult spine. Among others, terms for various forms of deformity include scoliosis, sagittal imbalance, and spondylolisthesis (regional deformity). Normal anatomic variation does exist that can account for small regional curves of the spine. Adult spinal deformity, however, exceeds this normal anatomic variation and can possibly impair horizontal gaze or the neutral center of the spine over the pelvis and femoral heads. Impairment of horizontal gaze has a dramatic impact on the quality of an individual's life and has associated morbidity. Prevalence of adult deformity does appear to vary based on multiple factors. The overall prevalence in US adults aged 25–74 is about 8.3% with women having twice the rate as men (10.7% and 5.6%, respectively) (Carter and Haynes 1987). Furthermore, the prevalence appears to increase with advancing age. In a 2005 study by Schwab et al., they suggest prevalence rates of adult scoliosis (Cobb angles $>10^{\circ}$) may be as high as 68% among adults 60 and older (Schwab et al. 2005). While in some cases adult spinal deformity can be asymptomatic, severe spinal deformity can present in multiple ways including back pain, hip pain, functional decline, radiculopathy, neurogenic claudication, and other neurologic symptoms.

Spinal deformity was initially simplified to deformity in the coronal plane. In particular, scoliosis was described as a lateral curvature of the spine resulting in a deformity in the coronal plane. As knowledge of deformity has grown, we have learned that deformity consists of complex three-dimensional changes that can result in changes in coronal, sagittal, and axial (rotational) planes (Stokes 1994). As understanding of the adult spinal deformity has grown, operative management has also advanced. Various corrective osteotomies can be applied for deformity correction including Smith-Petersen/Ponte osteotomy, pedicle subtraction osteotomy, and vertebral column resection. Instrumentation techniques involving wires and hooks have given way to constructs using pedicle screws and cortical screws (Fig. 1).

In this chapter we briefly discuss adult scoliosis including etiology, presentation, clinical evaluation, radiographic assessment, spinopelvic parameters, and overview on treatment. The primary focus of the chapter, however, relates to operative correction of deformity. In particular, we will discuss the corrective osteotomies that can be employed to improve spinal deformity in adult patients.

Adult Scoliosis: Definition and Etiology

Scoliosis consists of a three-dimensional deformity involving the coronal, sagittal, and axial (rotational) planes. In the sagittal planes, this can manifest as kyphotic changes impacting sagittal imbalance (Stokes 1994; Aebi 2005). The three-dimensional nature of the deformity can substantially impact the position of the head, horizontal gaze, and general positioning of the spine in relation to the pelvis.

The etiology of adult spinal deformity can be multifactorial. Some cases of ASD relate to congenital abnormalities of the vertebrae or spinal cord such as Chiari malformations or myelomeningocele (spina bifida). Neuromuscular conditions that may involve spinal deformity include cerebral palsy, Friedreich's ataxia, Charcot-Marie-Tooth, spinal muscular atrophy, muscular dystrophy, and arthrogryposis (Berven and Bradford 2002). Adult deformity can also

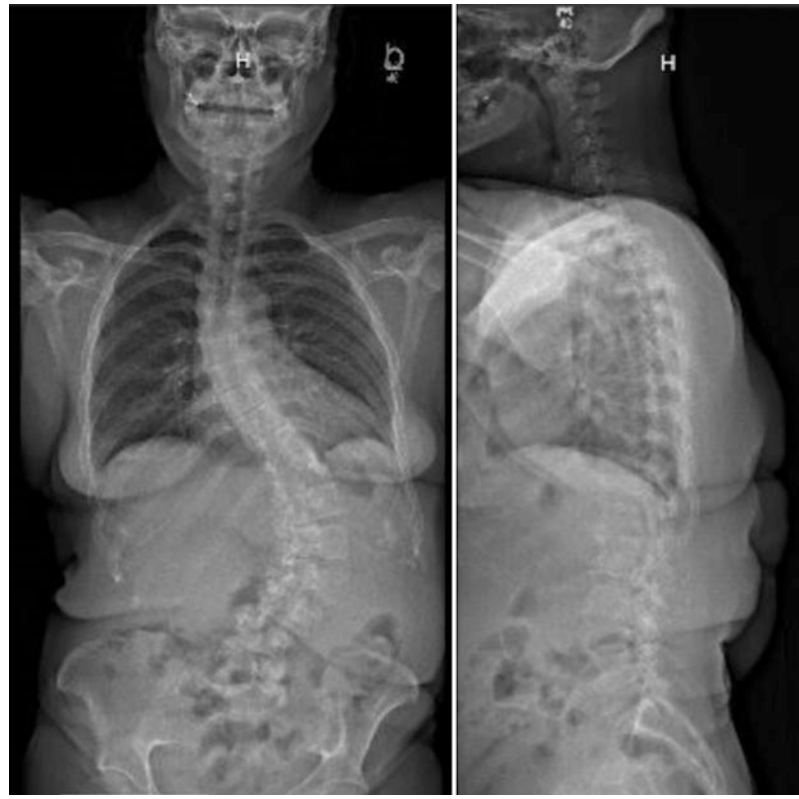

Fig. 1 Standing anteroposterior (AP) and lateral full-length spinal radiographs. AP radiograph demonstrates the deformity in the coronal plane as seen by the lateral curvature of thoracolumbar spine. Lateral radiograph demonstrates the sagittal deformity as seen by the positive sagittal imbalance

represent a progression of idiopathic scoliosis from childhood (infantile, juvenile, adolescent idiopathic scoliosis). Spinal deformity arising and developing in the adult population is often termed de novo or degenerative scoliosis. As the name suggests, this form of scoliosis is thought to relate to degenerative changes to spinal elements including the vertebral discs and zygapophyseal joints (Birknes et al. 2008). Other factors that can contribute to adult deformity include infection (poliomyelitis), spinal cord tumor, post-traumatic, and iatrogenic (post-surgical) (Berven and Bradford 2002; Birknes et al. 2008; Berven and Lowe 2007).

Clinical Evaluation

As with any complex condition of the spine, a complete history and physical examination is imperative. Pain is often a common presenting complaint that can vary from mild to severe and is often diffuse and ill-defined. The etiology of pain may be degenerative changes within the vertebral column (discs, facet joints), as well as paraspinal musculature (Birknes et al. 2008; Kostuik et al. 1973; Smith et al. 2009a, b). Given the imbalance of the spine over the pelvis and subsequently femoral heads, patients may also present with buttocks, hip, or leg pain. Patients may also present with symptoms of radiculopathy and/or stenosis (neurogenic claudication). Severe deformity may impair an individual's ability to maintain horizontal gaze. Different classification schemes, such as the Scoliosis Research Society (SRS) classifcation for adult spinal deformity, have been developed to help direct evaluation and management (Lowe et al. 2006). We will look at various spinal parameters below that can help guide evaluation and management. As part of the clinical evaluation, a full neurological exam should be performed to assess for weakness as well as additional issues such as myelopathy and cauda equina syndrome.

Imaging Evaluation

Initial imaging consists of standing full-length spinal radiographs, both PA and lateral views. Many of the spinopelvic parameters that are discussed below can be assessed on these radiographs alone. The PA view allows for evaluation of coronal alignment through measurements involving the central sacral vertical line (CSVL) and Cobb's angle. Pelvic obliquity can also be assessed on the PA radiograph. If the pelvic obliquity is related to a leg length discrepancy, repeat standing radiographs with blocks under the short leg may be needed. This is important in unmasking any perceived spinal deformity that may just relate to pelvic obliquity. The lateral radiograph allows for evaluation of the sagittal balance including any variation in lordosis and kyphosis in each spinal segment. The lateral radiographs also help to assess the sacral slope, pelvic tilt, and pelvic incidence. Additionally, the chin-brow to vertical angle, the angle formed between a line connecting the patient's chin to brow and a vertical line, can be measured in this view. Increasing chin-brow to vertebral angle suggests difficulty with maintaining horizontal gaze.

CT scans can prove useful in assessing bony morphology as part of planning for corrective osteotomies or placement of instrumentation such as pedicle screws. Being a supine study, CT scans can also be used to evaluate the flexibility of the curve in the sagittal plane when compared to upright x-rays. Given that patients may present with radicular or other neurological symptoms, an MRI can provide details regarding the location and etiology of areas of compression on the spinal cord and spinal nerves. If patient cannot undergo an MRI, a CT myelogram can be considered.

Spinal and Spinopelvic Parameters

Introduced in 1948, the Cobb method provides a quantitative measure of spinal curve on the coronal plane as seen on PA radiographs (Cobb 1948). The method consists of identifying the vertebral segment at the apex of the curve and most tilted vertebral bodies cephalad and caudal to the apex. Parallel lines are drawn along the superior end plate of the cephalad vertebral body and along the inferior end plate of the caudal vertebral. Perpendicular lines are subsequently drawn to each of the previously formed lines along the end plates. The angle formed between the intersections of the perpendicular lines is the Cobb angle. Traditionally, scoliosis is defined as a Cobb angle greater than 10° (Aebi 2005). The inter-observer error using the Cobb's method is about 5% (Mehta et al. 2009). Furthermore, studies suggest that an inherent error of up to 5° exists using the Cobb's method, meaning that only a change in the Cobb's angle of 5° or more is considered a real change (Morrissy et al. 1990). The Cobb's method can also be applied to lateral radiographs as a method of quantifying lordosis and kyphosis (Fig. 2).

While the Cobb method measures degree of curvature with respect to regional curves, the central sacral vertical line (CSVL) assesses overall coronal alignment (Lenke et al. 2001; Angevine and Kaiser 2008; O'Brien et al. 2004). A vertical line is made through the center of the sacrum. A second vertical line, C7 plumb line, is made centered on the C7 vertebral body. The difference between these two lines is the CSVL. A negative

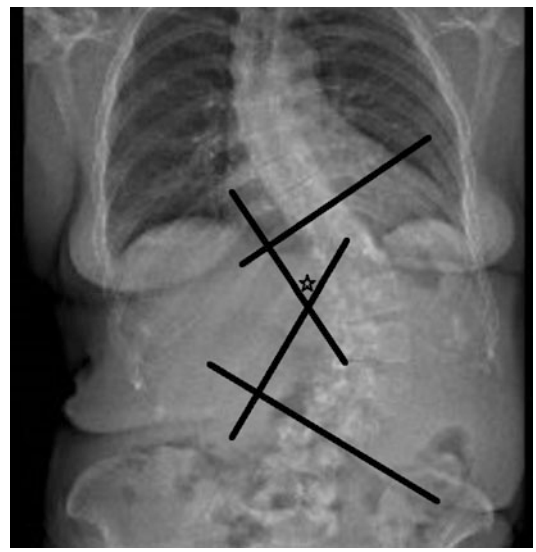

Fig. 2 Cobb's method for quantifying a curve. The star represents the Cobb's angle

value denotes that the C7 plumb line is to the left of the sacral line, while a positive value denotes that the C7 plumb line lines to the right.

The lateral radiograph provides crucial insight into the nature of the spinal deformity. Several parameters can be measured on the lateral radiographs including pelvic incidence (PI), sacral slope (SS), pelvic tilt (PT), sagittal vertical axis (SVA), and T1 pelvic angle (TPA). Pelvic incidence is the angle formed between a line perpendicular to the S1 end plate and a line between the center of the sacral end plate and the center of the femoral head (Legaye et al. 1998). Pelvic incidence also describes the sum of the sacral slope and the pelvic tilt. As a formulaic representation, PI = SS + PT. Sacral slope is the angle formed between a pure horizontal line and a line parallel to the sacral end plate. Pelvic tilt is the angle formed between a pure vertical line and a line between the center of the femoral head to the center of the sacral end plate. Of note, the pelvic tilt and sacral slope can change depending on position of the pelvis. Any movement leading to a change in pelvic inclination (i.e., increasing retroversion) will impact the pelvic tilt and sacral slope (Lafage et al. 2008; Boulay et al. 2006a; Jackson and McManus 1994; Schwab et al. 2009).

The sagittal vertical axis is also measured on the lateral radiograph. A vertical plumb line is drawn down from the center of C7 vertebral body. The distance between this plumb line and a point at the posterior-superior aspect of the sacral end plate is measured. A plumb line that lies anterior to the point on the posterior superior sacral end plate is denoted as a positive value. Normative values for the SVA are +2 to −2 cm; values outside of this range are considered positive or negative sagittal imbalance (Schwab et al. 2009; Boulay et al. 2006b; Roussouly and Nnadi 2010; Bernhardt and Bridwell 1989; Berthonnaud et al. 2005). The SVA, however, does not account for pelvic parameters and as such can be impacted by positioning and tilt of the pelvis. The T1 pelvic angle may provide more accurate insight into the overall sagittal alignment as it incorporates elements from the abovementioned pelvic parameters. The T1 pelvic angle is formed at the intersection of a line drawn from the T1 vertebral body to the center of the femoral head and a line drawn from the center of the femoral head to the center of the sacral end plate (Ryan et al. 2014). Lafage et al. introduced the TPA in 2014 as part of the International Spine Study Group. They proposed a goal/normative TPA of 10°, with a TPA greater than 20 representing a severe sagittal deformity (Ryan et al. 2014).

Scoliosis was initially viewed as a lateral curvature in the coronal plane; however, studies have not found a link between patient disability or perceived pain and degree of coronal deformity (Glassman et al. 2005a; Schwab et al. 2006a; Lazennec et al. 2009). Sagittal imbalance has been found to correlate with patient-reported pain and disability across several studies as measured by health-related quality of life measures (HRQOL). Sagittal imbalance as measured by pelvic tilt, TPA, T1 spinopelvic inclination, and SVA has been associated with worse scores on surveys such as the Oswestry Disability Index (ODI), SRS 23 Patient Questionnaire, and12-Item Short Form Health Survey (SF-12) (Glassman et al. 2005a, b; Schwab et al. 2006a; Lazennec et al. 2009; Lafage et al. 2009). In lieu of these HRQOL studies, Schwab et al. outlined ideal thresholds with regard to key spinopelvic parameters. They found severe disability with regard to ODI with SVA exceeding 47 mm, pelvic tilt greater than 25°, and pelvic incidence minus lumbar lordosis being above 11° (Schwab et al. 2006b, 2010, 2013).

Management

Non-operative management of adult spinal deformity is usually limited to patients with mild deformity, minimal to mild pain, little disability in daily functional activities, nonprogressive symptoms, and lack of worrisome symptoms such as those of cauda equina. Non-operative management can also be applied to poor surgical candidates who have high anesthetic risks given profound comorbidities. Non-operative management modalities include massage, aqua therapy, and physical therapy which can serve to strength

the surrounding paraspinal muscles and core as a whole. Additional modalities include nonsteroidal anti-inflammatory drugs, neuropathic medications (gabapentin), and epidural steroid injections (Cummins et al. 2006). The impact of non-operative modalities in improving pain and disability, however, is controversial. In 2010, Glassman et al. presented a prospective cohort study of 123 patients. Sixty-eight patients proceeded with conservative management consisting of physical therapy, bracing, bed rest, injections, and chiropractic care. Despite a mean cost of $10,815 over the course of 2 years, no significant change was found with regard to HRQOL outcomes (Glassman et al. 2010).

Indications for operative management include worsening pain, progressive deformity, declining neurological function, and failure of non-operative interventions. The spinopelvic parameters discussed earlier can help to assess the degree of deformity. Severe disability (measured with ODI) is correlated with SVA exceeding 47 mm, pelvic tilt greater than 25°, and pelvic incidence minus lumbar lordosis being above 11° (Schwab et al. 2010, 2013). In a 2009 prospective observational cohort, Bridwell et al. followed symptomatic adult scoliosis patients for 2 years. One hundred sixty patients treated either non-operatively or operatively were followed for 2 years. The non-operative cohort had no significant change in quality of life measures such as SRS and ODI. The operative cohort, however, did experience a significant improvement across all quality of life metrics (Bridwell et al. 2009). While each case of adult spinal deformity is unique, these findings do suggest that those with severe deformity and poor QOL scores may benefit from operative intervention (Bridwell et al. 2009; Smith et al. 2009c).

Operative intervention needs to be tailored to the specifics of each adult spinal deformity patient. Factors such as clinical symptoms, age, and overall medical health can help to steer direction of management. Operative modalities can include decompression, decompression with limited instrumentation, long-segment instrumentation, and corrective osteotomies. Decompression alone has a limited but important scope. Studies have shown that decompression alone may help radicular and compressive relative symptoms but risks progression of deformity (Kelleher et al. 2010). As such, decompression alone may help to address primarily compressive or radicular symptoms in an elderly individual, who may not otherwise be a candidate for extensive instrumentation or deformity correction given osteoporosis or medical comorbidities. In the following sections, we will discuss various methods of instrumentation, decision-making regarding what levels to include, and corrective osteotomies.

Early Fixation Constructs: Harrington Instrumentation, Wires, and Hooks

A key in the early development of spinal instrumentation involved the use of Harrington rods and instrumentation technique (Drummond 1988). Initially, Harrington rods were applied with the use of facet screws. However, Harrington constructs involving the use of facet screws did not prove viable in the long term as the screws were unable to accommodate the forces needed to correct spinal deformity (Harrington 1972, 1973). Subsequently, attention was directed toward new forms of spinal fixation involving sublaminar wiring and hooks. One such wiring technique, Luque wiring, was developed in Mexico. Luque wiring consisted of sublaminar wires that were twisted around rods posteriorly (Luque 1982). Since they are sublaminar, Luque wiring does place neural structures at risk during placement (Zdeblick et al. 1991). During the development of these early constructs, however, deformity was primarily understood as a problem in the coronal plane. As such, Harrington instrumentation and these early fixation models did not take into account the importance of sagittal. In the 1970s, various publications described the loss of lumbar lordosis and the development of a "flat back" resulting from Harrington distraction techniques (Doherty 1973; Grobler et al. 1978). The resultant flat back (iatrogenic fixed sagittal imbalance) made it a challenge to maintain upright posture and a horizontal gaze. To accommodate for the flat back, patient often flexes the hips and knees while extending the mobile cervical and thoracic segments (Potter et al. 2004).

Subsequent development focused on hooks as a means of providing segmental fixation that accommodated for lumbar lordosis. Examples of hooks include pedicle, laminar, supralaminar, and transverse process hooks. While adult spinal deformity is a complex malalignment involving all three vertebral columns in multiple planes, hooks primarily rely on fixation to the posterior column. Fixation through the posterior column alone may be unable to overcome the forces associated with the underlying spinal deformity required in obtaining and maintaining a correction (Rohlmann et al. 2006; Hackenberg et al. 2002). As such, these earlier techniques often involved additional anterior releases and correction to supplement the posterior fixation.

With the advent of pedicle screws, fixation could be placed across all three columns of the vertebra making it useful in deformity correction (Chang et al. 1988). Studies comparing pedicle screws versus hooks suggested that hooks had less pullout strength compared to pedicle screws (Liljenqvist et al. 2001). Clinically, pedicle screw constructs have been shown to lead to greater improvement in Cobb angles and sagittal alignment (Hamill et al. 1996). Some reports suggest increased rates of postoperative fusion with pedicle screws (Hamill et al. 1996; Gaines 2000; West et al. 1991; Thomsen et al. 1997). Multiple studies have suggested a decreased need for postoperative immobilization and bracing with the use of pedicle screws, as well as earlier process of rehabilitation (Marchesi and Aebi 1992; Suk et al. 1994, 1995). Pedicle screw placement has become safe and efficient. In particular, use of intraoperative fluoroscopy and intraoperative computed tomography and navigation has allowed for increased precision when placing pedicle screws (Miller et al. 2016; Gelalis et al. 2012).

Proximal and Distal Extent of Instrumentation

The proximal extent of the instrumentation is referred to as the upper instrumented vertebra (UIV). Generally, the UIV segment should not be at a level of segmental rotation or translation. Additionally, the UIV should not be at the apex of the curvature. Ending at a level of junctional kyphosis should be avoided. Mardjetko suggests that the UIV should be at a level within 2 cm of the coronal vertical axis and sagittal vertical axis (Shufflebarger et al. 2006). Given that spinal deformity curves may extend from the lumbar to the thoracic spine, the proximal instrumentation may need to extend to the thoracic spine. Extension to the thoracic spine, however, does raise concerns of proximal junctional kyphosis. As such, the most kyphotic range of the thoracic spine is avoided. This leaves two options for the upper instrumented vertebra: upper thoracic (T1–T6) and lower thoracic (T9–L1) (Kim et al. 2008, 2013, 2014; McCord et al. 1992). Proximal instrumentation to the upper thoracic versus the lower thoracic in adult scoliosis patients has increased operative times and blood loss but had similar levels of proximal junctional kyphosis and revision surgeries compared to UIV to the lower thoracic levels (T9–L1) (Kim et al. 2014). Mode of proximal junctional failure in the upper thoracic UIV is often ligamentous disruption compared to lower thoracic UIV in which failure is bony. While not reaching clinical significance, the total number of complications was greater with upper thoracic group, including substantial complications such as pseudoarthrosis (Kim et al. 2014).

The distal instrumented vertebra (DIV) has evolved over the years. McCord et al. defined the lumbosacral pivot point as the "intersection of the middle osteoligamentous column in the sagittal plane and the lumbosacral intervertebral disc in the transverse plane." They discuss concerns that DIV to sacrum is potentially less resistant to flexion moments and advocate for longer constructs distal to S1 and anterior to the pivot point (McCord et al. 1992). Constructs such as iliac bolts and S2-alar-iliac screws subsequently evolved to accommodate these principles. In a 2001 study, Lenke et al., they found a 95.1% fusion rate when using iliac screws for long fusions to the sacrum and severe spondylolisthesis (Kuklo et al. 2001). Another option is that of the S2-alar-iliac screws, which has a starting point at S2 with extended through the sacral

ala into the ilium (Burns et al. 2016). Biomechanical studies suggest similar load to failure in comparing iliac screws to S2AI screws with the S2AI screws having the benefit of being lower profile and lining up with the lumbosacral screws obviating the need for offset connectors. Overall, such longer constructs can potentially better resist flexion moments with lower rates of failure compared to fixation ending at L5 or S1 (Kuklo et al. 2001; Burns et al. 2016; Kebaish 2010).

Osteotomies

In cases of rigid and severe spinal deformity, instrumented fusion alone may not fully correct the deformity, and additional correction through osteotomies of the vertebral column may be needed. Several osteotomies are available to aid in deformity correction including Ponte, Smith-Petersen osteotomy (SPO), pedicle subtraction osteotomy (PSO), and vertebral column resection. These osteotomies should be viewed as a spectrum with the more complex osteotomies built on the foundation of simpler osteotomies giving a greater correction. Choice in osteotomy depends on the amount of correction that is desired. Goals for deformity correction in the sagittal plane are an SVA under 5 cm, pelvic tilt less than 25°, and pelvic incidence minus lumbar lordosis being less than 11° (Schwab et al. 2010, 2013). In 2014, Schwab et al. created the comprehensive anatomical spinal osteotomy classification, which is a system to understand vertebral osteotomies. This system classifies the osteotomies into six categories based on increasing vertebral resection and destabilization; a graphic illustration can be seen in Fig. 3 (Schwab et al. 2015). While Schwab's classification system provides a systemic framework for understanding osteotomies, we will focus the discussion on the above classically described osteotomies.

Smith-Petersen Osteotomy

Developed in 1945, the Smith-Petersen osteotomy was initially developed to address flexion deformity in patients with ankylosed spines and rheumatoid arthritis (Smith-Petersen et al. 1945). As outlined in their original paper in 1945, the SPO involves removal of elements from the posterior column. The SPO does not extend into the vertebral body itself. The overall principle behind the SPO relies on an axis of rotation through the middle column. In effect, the removal of the posterior column and subsequent closing of the posterior void lead to elongation of the anterior column through osteoclasis of the anterior disc space and anterior longitudinal ligament.

Although the terms are often used interchangeably, Ponte osteotomies are distinguished from Smith-Petersen osteotomies in patient selection. A Ponte is performed in patients with an open disc space. Although it still results in a lengthening of the anterior column, it does not involve an osteoclasis of the anterior column. It is often used in conjunction with an interbody cage which serves as a fulcrum assisting to get angular correction with posterior compression. For the purposes of this chapter, we will refer to both these techniques as SPO. A SPO consists of a standard laminectomy and resection of the inferior articular facet of cranial level and superior articular facet of caudal level. They are usually performed at multiple consecutive levels in order to achieve a gradual correction. Classically these are performed for pathology such as Scheuermann's kyphosis (Ponte et al. 2018).

SPO technique differs slightly based on location: thoracic versus lumbar spine. Overall the concept is the same, resection of posterior elements allowing for compression and angular correction of approximately 5–10°. Anatomic differences particularly in facet orientation alter the sequence of steps depending on the location.

In the thoracic spine, the first step is using an osteotome to resect the inferior articular facet of the cranial level, exposing the cartilage of the superior articular facet. Next, the spinous process of the osteotomy level is removed, exposing the interlaminar space. The amount of resection of the lamina is based on the desired angular correction. More resection will potentially lead to more correction. Ideally, after the osteotomy is performed, the lamina which is resected and the

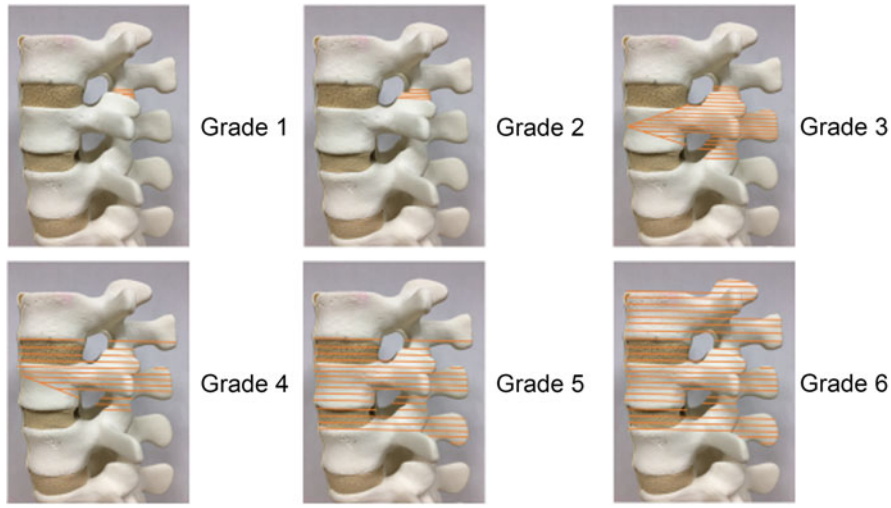

Fig. 3 Graphic illustration of Schwab et al. anatomical spinal osteotomy classification. Grade 1 involves partial resection of facet joint. Grade 2 involves complete facet joint resection. Grade 3 resects posterior elements, pedicles, and portion of vertebral body. Grade 4 resects posterior elements, pedicles, portion of vertebral body, intervertebral disc, and adjacent end plate. Grade 5 involves complete resection of vertebral segment and the adjoining intervertebral discs. Grade 6 involves complete resection of multiple vertebral segments (Schwab et al. 2015)

lamina of the caudal level should be in contact, providing a surface area for fusion. The lamina should be resected in a superiolateral direction on the midline creating a "V"-shaped bony defect. Due to the shape of the resection, these osteotomies are often referred to as chevron osteotomies. Next, the exposed ligamentum flavum is resected in the same direction exposing the spinal cord. Access to the canal can be gained through a midline defect in the ligament. After the ligament is resected, the superior articular facet of the caudal level is resected by continuing laterally with a Kerrison. Thorough excision of the ligament and superior articular facet is critical. Failure to remove these structures will lead to compression of either the spinal cord or nerve root, potentially leading to postoperative complications. If these osteotomies are performed after pedicle screws are placed, the heads of the screws may obstruct the resection of the superior articular facet. In such instances, one can either perform the osteotomy prior to placing in the screws or using a modular system where the heads are attached after the osteotomy.

In the lumbar spine, the screw heads do not interfere with the resection and therefore be inserted prior to performing the osteotomy. Additionally, due to the bony anatomy, it is not typically possible to have the resected lamina contact the caudal lamina. Therefore, a more generous laminectomy is performed. Since there is often spinal stenosis in the lumber spine which needs to be addressed as well, lamina resection at least to the origin of ligamentum flavum is recommended. Additionally, most lumbar SPOs/Ponte are performed caudal to the conus, allowing an interbody cage to be safely placed posteriorly. An appropriately placed cage can provide a pivot point to gain more angular correction. The laminectomy is performed in the usual standard fashion. Subsequently, the pars on both sides are identified and resected with a Kerrison or a drill. Our preference is to place a Woodson in the foramen, serving to protect the exiting nerve root. Subsequently, we drill away the pars in its entirety until the Woodson is visualized. The inferior articular facet is then removed as it is no longer attached to any bony or soft tissue structures. The final step is to resect the overhanging portion of the superior articular facet. Removal with a Kerrison can be challenging given overgrowth. It is our preference to use a straight osteotome and

place it in line with the superior aspect of the pedicle and remove it en bloc. There is usually venous bleeding in the foramen which can be stopped with bipolar cautery. We find this technique to be safe as the exiting nerve root typically lies in the superior third of the foramen. Therefore, even in the event of plunging with the osteotome, the exiting nerve root is safe from harm. The posterior void is subsequently closed via spinal instrumentation (Schwab et al. 2015; Bridwell 2006).

Smith-Petersen/Ponte osteotomies are best for deformities that have larger radius of curvatures as opposed to sharp curves (Cho et al. 2005). Since the anterior column is elongated, they should be avoided in cases where there is less than 5 mm of intervertebral disc present. These osteotomies allow for about 10° of correction per level performed (Cho et al. 2005).

Pedicle Subtraction Osteotomy

The pedicle subtraction osteotomy requires more resection than that for an SPO/Ponte osteotomy. While the SPO only involves the posterior column, pedicle subtraction osteotomies extend into the vertebral body at the desired level of correction, and as such is a three-column osteotomy. A PSO generally creates a triangular wedge through the vertebral body with removal of the posterior column. The osteotomy has an axis of rotation at the anterior aspect of the vertebral and shortens the posterior column without elongating the anterior column. The PSO can prove useful in patients with a rigid ALL or immobile vertebral disc, where an SPO/Ponte is usually contraindicated. Furthermore, a PSO can address sharp curves and curves that exceed 25° (Cho et al. 2005; Berjano and Aebi 2015; Chen et al. 2001). A PSO can provide 25–35° of correction (Berjano and Aebi 2015; Chen et al. 2001; Bridwell et al. 2003). Figure 4 demonstrates a case involving a PSO at L3 in conjunction with Smith-Petersen osteotomies at adjacent segments resulting in significant deformity correction.

In performing a PSO, the patient is placed prone on the operating table. When possible the PSO is below the level of the conus. There is variability as to where the conus ends; as such, it is imperative to review preoperative MRI or CT myelogram in selecting the level for the PSO. A cord-level PSO is associated with a considerably higher risk of cord injury and should be avoided when possible. The more caudal the osteotomy is performed, the greater the SVA is corrected for the same angular wedge resection. However, the more caudal the PSO is performed, the fewer fixation points will exist. For the stated reasons, L2 and L3 are commonly chosen levels. Due to significant angular correction, laminectomies are usually performed above and below the PSO site in order to prevent compression of the neural elements upon closure of the osteotomy site.

Conceptually, the building blocks of a PSO are two adjacent SPO. This will isolate a pedicle of a single level and is the first step of a PSO. The amount of angular correction is based on the angle of the wedge which is excised. This correlates to the distance between the starting points of the osteotomy along the posterior vertebral body. The limiting structures are the disc space above the pedicle and exiting nerve root below the pedicle to be excised. After two adjacent SPO are performed, these structures are identified bilaterally. The exiting nerve is followed out into the foramen. Prior to performing a PSO, all screw fixation is in place. We will routinely tap the pedicle of the osteotomy level with a large tap removing all the cancellous bone thereby making pedicle resection easier. We will also tap into the vertebral body creating a trajectory for our osteotome. The residual superior articular facet is then resected with a Leksell rongeur until flush with the transverse process. The transverse process is detached from its attachment at the lateral aspect of the pedicle. It is critical that the TP is cut flush with the lateral border of the pedicle. If it is not, when dissecting the psoas off the lateral aspect of the vertebral body, the segmental vessel is at risk. Using a large curette, the lateral wall of the pedicle and vertebral body is exposed. With the pedicle now in view circumferentially, it is removed with a rongeur. Any bony prominences need to be removed as

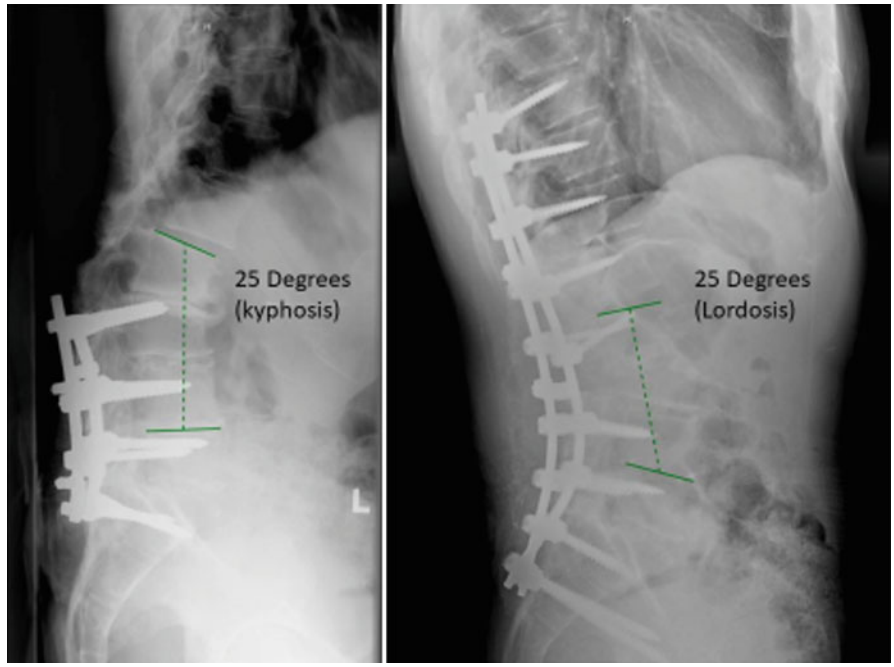

Fig. 4 A 68-year-old patient with persistent back pain status post remote L3 to S1 instrumentation and fusion. At initial evaluation, patient was found to have spinal stenosis and deformity consisting of kyphoscoliosis. Segmental Cobb angle from L2 to L4 demonstrated 25° of kyphosis. Patient underwent extension of instrumentation both proximally to T10 and distally to ilium. Additionally, a pedicle subtracting osteotomy was performed at L3 in conjunction with Smith-Petersen osteotomies at T12 to L2. Postsurgical radiographs demonstrated improvement in segmental lordosis to 25° from L2 to L4, representing an improvement in about 50°

they may cause foraminal stenosis after the osteotomy is closed. The exiting nerve root is protected with a nerve root retractor when removing the inferior wall of the pedicle. By resecting the pedicle, the two foramens have been combined making one large foramen that is housing two nerve roots. This step is performed bilaterally. A temporary stabilizing rod is now placed unilaterally, and an osteotome is used to make a wedge resection on one side. The superior cut is just caudal to the disc space above where the pedicle was, and the caudal cut is just cranial to the exiting nerve root immediately below where the pedicle was. One pass of the osteotome is directed medially and the other laterally, cutting the lateral wall of the vertebral body. The rod is moved to the opposite side, and a contralateral wedge resection is performed. The depth of the osteotome is determined by fluoroscopy or navigation. If using fluoroscopy, in the setting of a rotational deformity, the author prefers to rotate the table, so the osteotomy segment is no longer rotated. This leads to a more accurate assessment of depth of the osteotomy on fluoroscopy. After these cuts are made, a single vertical cut of the posterior vertebral body is made connecting the first two cuts. The resultant wedge is then resected and saved as autograft. Subsequently, a curette is used to remove any cancellous bone behind the remaining posterior cortex ventral to the thecal sac. A Woodson is used to develop a plane between the dura and posterior cortex. An Epstein curette or a Siefert bone tamp is used to impact the posterior wall into the defect created by removing the wedge. With the three-column osteotomy now complete, the spine should be mobile and the deformity ready to be corrected. Compression is applied on the temporary rods on either side closing the osteotomy, and wrinkling of the dura is noticed. Contact between the edges of the osteotomy marks the maximum extent of the correction obtained. If further correction is

desired, the fixation is released, and further bony resection is performed. In the osteoporotic spine, if there is concern for screw loosening with compression, the patient's hips can be extended to close the osteotomy either manually or with an axis bed (Cho et al. 2005; Chen et al. 2001; Bridwell et al. 2003; Bianco et al. 2014).

If a larger correction is needed, one can perform an extended PSO. The extended PSO involves resection of the posterior aspect of the adjoining disc space and superior end plate. This creates a larger wedge and subsequently a larger correction. In order to increase the likelihood of a fusion, this procedure is often accompanied by a TLIF with the implant placed anteriorly resting on the residual superior end plate. If a patient has a multiplanar deformity, asymmetric wedges can be resected to achieve a correction in the sagittal as well as the coronal plane.

While a pedicle subtraction osteotomy allows for substantial correction of deformity, given the complex and aggressive nature of the osteotomy, it is associated with some notable complications. Several studies have reported complications rate reaching close to 50% (Bianco et al. 2014; Kelly et al. 2014). The International Spine Study Group reported 7% rate of intraoperative complications, 39% rate of postoperative complications, and 42% rate of overall complications. Additionally, they reported an average blood loss of 55% of total blood volume. Age older than 60, a thoracic three-column osteotomy, osteotomies at two or more levels, and major blood loss were all associated with increased complications (Kelly et al. 2014).

Vertebral Column Resection

Vertebral column resection builds on a PSO and allows greater segmental correction. It entails complete removal of a vertebral segment and allows for multiplanar corrections. A VCR can also prove useful in malformed vertebral segments that are not amenable to angular osteotomies such as those encountered in congenital scoliosis. Vertebral column resection was first described in the early 1980s by Bradford as method of addressing severe and rigid spinal deformity (Bradford 1987; Lenke et al. 2010).

Setup and technique for a VCR start similar to that of a PSO. Similar to a PSO, prior to proceeding with the VCR, it is imperative to establish fixation above and below the level of correction, as the VCR will lead to destabilization of the spine. The pedicle is isolated and resected as described above. Deviating from a PSO, the authors next prepare the cranial and caudal disc spaces as one would do for a TLIF. Careful attention is paid to removing all disc material and cartilage on the inferior and superior end plates from the cranial and caudal levels, respectively. This will establish margins for resection required for a VCR and to place a cage. Subsequently, similar to a PSO, the lateral aspects of the vertebral body are accessed and protected, while the vertebral body is resected. The resection can be performed with an osteotome or a drill. Similar to a PSO, the posterior wall is resected last. Subsequently, a spacer is placed where the vertebral body was. In the lumbar spine, this can be challenging as the nerve roots block complete access to the vertebrae to be resected and to the space created during cage insertion. For this reason, we use expandable cages as they can be inserted in the interval between the nerve roots, rotated, and expanded. In the thoracic spine, the nerve roots can be resected allowing for easier access to the anterior aspect of the spine without significant neurologic repercussion. While VCRs do have the potential for significant deformity correction, they are also associated with substantial complications. In 2011 study by the Scoliosis Research Society, VCRs were associated with a complication rate of 61.1%. In contrast, they found a 28.1% complication rate in SPOs and 39.1% in PSOs (Smith et al. 2011). Suk et al. in the early to mid-2000s published several retrospective studies that detailed their preferred technique for a VCR and report outcomes. In their 2002 study, 70 patients underwent a VCR; an average correction of 61.9% in the coronal and 45.2% in the sagittal planes was achieved. Twenty-four of the 70 patients (34.2%) had a complication including 2 complete injuries to the spinal cord (Suk et al. 2002). In Suk's

2005 study, they performed 16 VCRs and achieved an average SVA correction from 4.2 to 1.6 cm. They had complications in 4 of the 16 patients (25%), including 1 involving complete paralysis (Suk et al. 2005a). These studies highlight that the potential deformity correction through a VCR comes at the cost of a technically challenging procedure with high rates of severe complications (Smith et al. 2011; Suk et al. 2002, 2005a, b).

Minimally Invasive Surgery

With technological and surgical advancements, interest has grown in minimally invasive surgery as a route to operatively address spinal deformity. Minimally invasive surgery can include use of interbody fusion through anterior and extreme lateral. A systematic review by Phan et al. in 2015 regarding direct lateral and extreme lateral interbody fusions (DLIF and XLIF) showed promise in correcting coronal deformity and regional lumbar lordosis (Phan et al. 2015). A retrospective review by Anand et al. suggests that MIS deformity correction has the potential for significant deformity correction, with less blood loss and morbidity compared to open procedures (Anand et al. 2010). Figure 5 shows correction achieved with placement of lateral retroperitoneal interbody placement in conjunction with posterior osteotomies and instrumentation.

Newer studies, however, have suggested the possibility of more substantial correction with hyperlordotic cages that can help to correct the global sagittal imbalance and improve lordosis (Gödde et al. 2003; Le et al. 2012). Additionally, the anterior longitudinal ligament resection is increasingly being appreciated as a method for additional correction. In particular, selective releases of the anterior longitudinal ligament through a minimally invasive retroperitoneal transpoas (lateral) approach can help to restore lumbar lordosis while minimizing the complex dissection and resection involved in the various posterior-based osteotomies (Deukmedjian et al. 2012a). In a 2012 cadaveric study, combination of a hyperlordotic cage and ALL releases led to an increase in 11.6° of segmental lordosis (Uribe et al. 2012). In a retrospective review of

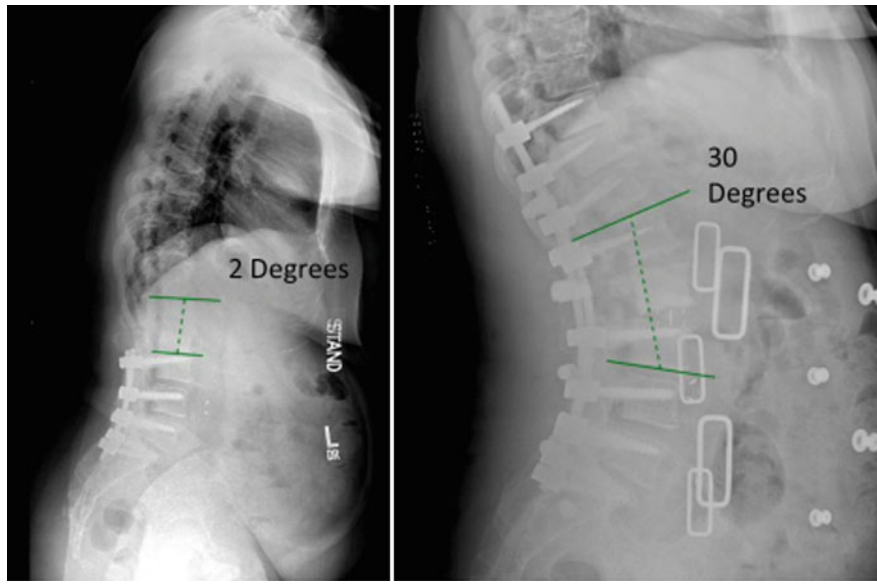

Fig. 5 A 63-year-old patient presented with global sagittal imbalance and stenosis at L2–L3. Initial radiographs on left demonstrate segmental lumbar lordosis measuring at 2° from L2 to L3. Radiographs on right demonstrate extension of fusion proximally to T10 with Smith-Petersen osteotomies at L1 and L2 with lateral retroperitoneal interbody placement at L2–L3. Segmental lumbar lordosis improved to 31°

prospectively collected data, Deukmedjian et al. assess ALL releases in patients with adult spinal deformity. In their study, they found an overall increase in lordosis of 24°, with segmental lumbar lordosis improving by 17° per level of ALL release (Deukmedjian et al. 2012b). In a cadaveric study and presentation of four clinical cases, Uribe et al. found an average increase of 10.2° per level of ALL released and 25° of overall global lumbar lordosis (Deukmedjian et al. 2012c). In a 2016 cadaveric biomechanical study by Hutton et al., they found a placement of 30° lordotic cage in addition to ALL release led to a 10.5° increase in segmental lumbar lordosis (Melikian et al. 2016). When combined with posterior facet resection and compression, one can achieve an even great degree of correction. While the individual correction values may vary in these studies, they do highlight the potential of ALL releases in deformity correction (Le et al. 2012).

Prior to performing an ALL resection, a surgeon must be comfortable performing a standard lateral interbody fusion. After prepping the disc space for the placement of an implant, soft tissue is dissected off the disc space along the anterior border of the spine. There should be a clean plane between the great vessels and the spine. If there is resistance to dissection, it is our recommendation that the ALL release should be abandoned. A retractor is then placed in front of the disc space across the anterior aspect of the spine. With a clear view of the anterior annulus and ALL, a special knife is used to cut the ALL. It is our preference to use an expanding trial to rupture any remaining fibers. We then place in a hyperlordotic implant with integrated fixation and secure it to one vertebral body in order to prevent anterior extrusion of the implant.

While MIS technology has advanced and provides a reasonable method for deformity correction in specific situations, careful patient selection and acknowledgment of MIS limitations are imperative. As in any spine case, extensive preoperative planning is critical in matching patient's diagnosis and pathology with appropriate treatment. The decision to pursue MIS, open deformity correction, or a combination of the two must match the intended degree of correction. Mummaneni et al. as part of the Minimally Invasive Section of the ISSG published an algorithm in 2014 that aimed to help in MIS and deformity decision-making (Mummaneni et al. 2014). The minimally invasive spinal deformity surgery (MISDEF) algorithm separates deformity correction into three different classes.

Class I is defined as patients with compressive symptoms relating to claudication or radiculopathy with minimal deformity. Furthermore, they use several parameters to define class I deformity: SVA less than 6 cm, PT less than 25°, LL-PI less than 10, lateral listhesis less than 6 mm, coronal Cobb angle less than 20°, and a flexible curve. They suggest that MIS techniques using decompression alone or with limited fusion are reasonable for class I deformity. Class II is defined as patients with previously mentioned compressive symptoms with a large component of back pain as well. Parameters for class II include lateral listhesis greater than 6 mm, coronal Cobb greater than 20°, and a LL-PI mismatch of 10–30°. For class II they recommend MIS surgery using decompression with multilevel interbody fusion that extends beyond just the apex of the curve (Mummaneni et al. 2014).

Class III patients are characterized by severe deformity in both coronal and sagittal imbalances. Parameters for this group include inflexible curves, SVA greater than 7 cm, LL-PI mismatch of greater than 30°, PT greater than 25°, and thoracic hyperkyphosis greater than 60. Class III patients are not readily amenable to MIS deformity correction and are better suited for traditional open deformity correction with osteotomies (as described in the previous sections). Mummaneni et al. tested the algorithm by having spine surgeons' complete surveys to classify various cases into the above classes and found MISDEF to have high intra- and inter-observer reliability (Mummaneni et al. 2014).

While algorithms like the MISDEF provide a framework to understand treatment options for deformity correction, treatment must accommodate for the unique characteristics of the patient's deformity as well as the surgeon's

comfort with various surgical techniques. Furthermore, MIS technology continues to advance, and patients that currently are treated with open corrective techniques may in the future be treated with MIS approaches.

Conclusions

Adult spinal deformity is complex deformity that involves three-dimensional deformation in coronal, sagittal, and axial planes. Spinal and spinopelvic parameters such as SVA, pelvic tilt, pelvic incidence, and lumbar lordosis are important in understanding, characterizing, and treating adult spinal deformity. Treatment of adult spinal deformity needs to be tailored to each patient with respect to the nature of the curve and the patients overall medical health. Operative techniques have changed substantially with time, from the early use of Harrington rods to modern pedicle screws. Multiple osteotomies (SPO, PSO, and VCR) can be applied for the desired level of spinal correction. Operative management of adult spinal deformity is wrought with complexity and severe complications. Newer techniques involving minimally invasive surgery and interbody fusions are being increasingly used for deformity correction.

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SI Joint Fixation

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J. Loewenstein, W. Northam, D. Bhowmick, and E. Hadar

Contents

Abstract

Surgical fixation of the sacroiliac joint (SIJ) has increased in popularity over the last few decades, especially with the recent emergence of minimally invasive techniques. The indications for this procedure are expanding and include joint dysfunction, degeneration/arthrosis, trauma, and postpartum instability, among others. With rising frequency of lumbosacral arthrodesis, interest has developed regarding the SIJ as a pain generator due to accelerated degeneration/dysfunction as an "adjacent segment" receiving more force distribution. The current body of literature suggests that a targeted history and physical examination

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specific to the SIJ, and provocative testing, are paramount for appropriate patient selection. A thorough understanding of the anatomy and biomechanics involving the SIJ is essential to forming a critical review of the various surgical approaches and hardware instrumentation options as they become available. The SIJ anatomy can be approached from several open corridors including ventral-ilioinguinal, posterolateral iliosacral, and posterior sacral-alar-iliac approach. Similarly, minimally invasive approaches have been developed using posterolateral iliosacral trans-articular and posterior intra-articular techniques. Multiple hardware options are available for SIJ fixation and continue to grow, including screw-plate and screw-rod constructs, trans-articular fusion rods, intra-articular cages, trans-articular threaded screws, and hollow modular anchoring screws. The epidemic nature of low back pain will likely lead to an expanding interest in SIJ fixation, and critical appraisal of the cost and efficacy of hardware and techniques will warrant greater study.

Keywords

Sacroiliac joint · Fixation · Instrumentation · Hardware · Techniques

Introduction

Low back pain (LBP) is a growing global problem and a common cause of disability and lost work days (Freburger et al. 2009). It is recognized as a major driver for morbidity across the economic spectrum from low- to high-income countries (Hoy et al. 2010). Although a wide range of etiologies exists, recent literature attention has focused on the sacroiliac joint (SIJ) as an important contributor to low back pain (Zaidi et al. 2015). The SIJ may be implicated as the pain generator in as many as 30% of patients with low back pain according to recent studies (Bernard and Kirkaldy-Willis 1987; Cohen et al. 2013). As such, a variety of conservative and surgical treatment modalities are being developed, with both open and minimally invasive approaches. As is the case with many spinal technologies, several different implant materials and styles have been trialed, including titanium fixation constructs and biologic materials.

As understanding of SIJ pathology grows, the clinical conditions for which surgical fixation is being utilized are also expanding. These conditions include degeneration/arthrosis, joint dysfunction, postpartum instability, trauma, pathologic fractures, and inflammatory arthropathies among others (Zaidi et al. 2015). Because imaging techniques have not demonstrated sufficient diagnostic value to determine which patients will see benefit from surgical fixation, the development of consensus over history and physical techniques, as well as provocative testing, is paramount (Elgafy et al. 2001; Dreyfuss et al. 2004). Further study of implantation techniques and materials will need to address postoperative complication profiles, rates of bony fusion, implant cost, and natural history of SIJ pathology.

Anatomy

The pelvic girdle constitutes a support structure that distributes force vectors from the spine as well as the legs. As the junction between the sacrum and the remainder of the bony pelvis, the SIJs have been conceptualized as "stress relievers" between the lower extremities and the trunk (Vleeming et al. 2012). Although there is considerable anatomic variability among individuals and sexes, the SIJ usually spans the majority of S1, S2, and S3 sacral levels. The joint can be conceptualized as diarthrodial, with hyaline and fibrocartilage, and a relatively irregular articulating surface (Forst et al. 2006). Because there are synarthrotic components, the joint has also been referred to as amphiarthrodial (Vleeming et al. 2012). However, there is a relative paucity of movement across the joint under normal circumstances, with generally less than 1 mm of transverse/sagittal translation and vertical movements usually less than 2 mm (Walheim et al. 1984). The articulating surface visualized

en face is roughly C-shaped, and the superior portion is predominately fibrous, whereas the inferior portion is mostly synovial (Cole et al. 1996). The overall joint orientation is arranged such that the vertical forces from gravity can be resisted (Vleeming et al. 2012). There does appear to be sexual dimorphism, with articular surface area ranging up to 18 sq. cm for females and 22.3 sq. cm for males (Sashin 1930; Miller et al. 1987).

The functional integrity of the SIJ is closely supported by several investing ligaments, including interosseous, ventral, and dorsal locations. The interosseous ligaments are also connected to the sacroiliac transverse ligaments. Ventrally, the ligamentous attachments of the SIJ form a connective tissue plane that is relatively thin and vulnerable to injury. Dorsally, the ligamentous anatomy supporting the SIJ is multilayered and more complex and includes dorsal sacroiliac ligaments categorized as long and short. These ligaments predominantly course from the crests of the sacrum to the posterior superior iliac spine. Stability across the SIJ is due in part to muscular action as well. These include the gluteus maximus, erector spinae, and multifidi, among others (Vleeming et al. 2012).

Innervation of the SIJ has been studied in both human and animal models, in an effort to help elucidate the origin of pain attributed to the joint itself. This supply appears to derive from both the ventral (L4 and L5) and dorsal rami (L5, S1, S2) and the superior gluteal nerve (Nakagawa 1966). However, subsequent analyses have determined that the majority of the supply may originate from the dorsal aspect (Forst et al. 2006). Murine neural tracer was applied to study this question in more detail and found dorsal root ganglion supply in the SIJ from the L1 to S2 levels primarily, with L1–3 innervating the ventral aspect and L4–S2 innervating the dorsal aspect. On the ventral aspect, there was innervation also emerging from the sympathetic trunk (Murata et al. 2001). Within the SIJ itself, nerve fibers were observed in human dissection that were both myelinated and unmyelinated (Grob et al. 1995), and this is consistent at least for the outer margins of the joint (Vleeming et al. 2012).

Biomechanics

An understanding of the biomechanical principles underlying the SIJ is critical to the design and implementation of instrumentation constructs and arthrodesis. Early twentieth-century literature had already established that there was a small amount of movement across the joint and that this tended to abate after approximately the fifth decade (Sashin 1930). Cadaveric analysis reveals that the adult SIJ orientation at the level of S1–2 is obliquely in the anterior-posterior direction with 20 degrees of offset from the vertical plane. Force testing showed that the bilateral natural joint construction most resisted medio-lateral vectors, with progressively more motion resulting from superior/inferior and then anterior-posterior vectors. When one joint was isolated, anterior shearing and torsion were seen to cause larger degrees of motion (Miller et al. 1987).

The largest degree of functional movement imparted by the SIJ was determined to occur with iliac rotation relative to the sacrum, on a transverse axis. This is called nutation in the forward direction and counternutation backward. When load is placed across the SIJs, when sitting or standing, the movement of nutation is seen. The degree of irregularity and surface characteristics of the articulating surfaces of the SIJ make it unique among similar human joints; it has a higher coefficient of friction than any other diarthrodial joint, which helps to resist shearing (Vleeming et al. 2012). The biomechanical properties of the SIJ differentiate it from nearby spinal segments; compared to the lumbar spine, the SIJ is more likely to fail under axial compression and axial torsion (Forst et al. 2006). In order to study motion about the SIJ, the radiostereometric analysis method has been validated and utilized (Kibsgård et al. 2012). Applied to human volunteers, this analysis has confirmed a very small degree of motion across the SIJs, approximately 0.5 degrees (Sturesson et al. 2000), which is compared to prior work showing mean rotation of 2.5 degrees, and no significant difference in motion between symptomatic and asymptomatic joints (Sturesson et al. 1989).

Etiology of Sacroiliac Joint Pathology

Over the lifespan, the human SIJ undergoes an expected degenerative process. Starting during adolescence, the joint surface is reported to become rougher with plaque formation. By the fifth decade, osteophyte formation was common along with corresponding articular surface irregularity. These osteophytes often were interdigitating across the joint by the seventh decade along with thinning of the articular cartilage (Bowen and Cassidy 1981). Aside from natural history of the joint through the aging process, a variety of pathologies can affect the SIJ to cause symptoms. These can include infection, arthritis, fracture and ligamentous injury, malignancy hypo−/hypermobility, chondromalacia, enthesitis, leg length or gait asymmetry, and scoliosis (Cohen et al. 2013).

Recent interest has surrounded SIJ pain that arises in the context of lumbosacral long-segment spinal fusion procedures. After a successful lumbosacral fusion, the distribution of motion across the SIJ increases, which can precipitate accelerated degeneration of the joint, as in the pathology of adjacent segment disease. In one prospective cohort study of lumbosacral fusion patients over 5 years of follow-up, the incidence of SIJ degeneration was 75% as determined by CT imaging. Patients were found to have degeneration regardless of the number of levels fused, and it was found that usage of iliac crest graft also had a deleterious effect on the SIJ (Ha et al. 2008). Possible causes of SIJ pathology after lumbosacral fusion is thought to be related to either adjacent segment disease as mentioned above, harvesting of bone graft in close proximity to the joint, or possibly misdiagnosis of a pre-existing SIJ syndrome. The study of the SIJ as a possible generator for LBP after long lumbosacral fusions bears considerable importance especially given the failure rate of these procedures and prevalence of LBP in this population of patients (Yoshihara 2012).

Diagnosis and Evaluation

Much of the difficulty associated with the treatment of pain originating from the SIJ derives from the variable clinical presentations that can arise as a result of this pathology. Regions of reported pain referral can include the lower back, buttocks, groin, lower extremities, and even the abdomen. However, provocative joint injections have indicated that the most common referral zone is the buttock, followed closely by lower lumbar, and patients with lower extremity pain usually localize to the posterior or lateral thigh (Slipman et al. 2000). Of the buttock region, the posterior superior iliac spine (PSIS) appears to be a common anatomic region identified by patients with SIJ pathology (Maigne et al. 1996). Further complicating the diagnosis of SIJ pain are the proximity of several other anatomic regions commonly implicated in pain from chronic degenerative disease in adults (the lumbar spine and hips, specifically) and the possibility for pain originating from these different entities concurrently.

Although many physical examination techniques have been developed for the purpose of evaluating the SIJ, none have shown sufficient sensitivity/specificity for standalone usage without more invasive testing (injection, etc.). Furthermore, the usage of multiple physical examination maneuvers did not augment the diagnostic power when compared to injection, including Gaenslen's Test, Patrick's Test, and tenderness of the sacral sulcus (just medial to the PSIS), among others. The highest sensitivity was seen with sacral sulcus tenderness (89%). Of note, there was also no consistent statistical validation for historical features such as relief when standing, sitting, walking, lying down, or aggravation with bowel movement or coughing (Dreyfuss et al. 1996). Because of the possibility of hip or lumbar spine pathology confounding diagnosis of SIJ-related pain, physical evaluation should include routine neurologic evaluation for weakness and radiculopathy, as well as provocative hip joint maneuvers. Of note, gait and leg length discrepancy are also important factors to address during the workup (Thawrani et al. 2018).

The usage of imaging (CT, MRI, bone scan, etc.) in the workup of SIJ pain has been shown to be largely unhelpful in determining whether the joint itself is likely to be the primary pain generator. However, imaging studies can be utilized to rule out other causes of pain such as the detection of fracture, neoplasm, infection, or spondyloarthropathy (Dreyfuss et al. 2004). In one

retrospective review of CT imaging findings relative to patients with injection-proven SIJ provocation, the sensitivity and specificity of CT imaging were found to be only 57.5% and 69%, respectively (Elgafy et al. 2001). Plain film imaging has also been difficult to apply to SIJ evaluation given the natural history that 24.5% of patients over 50 years of age show abnormalities on these studies (Dreyfuss et al. 1995). Although radionuclide bone scanning has received some attention in the literature as it relates to SIJ pain, it is not recommended as part of the basic workup due to the relatively low sensitivity (12–46%, Thawrani et al. 2018).

After sufficient clinical suspicion for SIJ-related pain has arisen, a percutaneous SIJ block is a generally agreed-upon test to establish this diagnosis. This is best performed using contrast media and fluoroscopic guidance, with an effort to avoid over-injecting the joint space and accidentally seeing false results due to anesthetizing the nearby lumbosacral nervous anatomy (especially ventrally). Additionally, >75% pain relief is the expected standard for diagnosis and is sometimes followed by a repeat injection block later due to placebo effect (Dreyfuss et al. 2004). The false positive rate from a single SIJ block injection is approximately 20% (Hansen et al. 2007). The usage of steroid injection into and around the joint and RF ablation technologies have been investigated and may be promising options for durable pain relief but require more establishment by the literature (Cohen et al. 2013).

Conservative Management Strategies

Targeted efforts to address the particular pathology affecting the SIJ are utilized first, which may include physical therapy or orthotic options for imbalances with gait mechanics or leg length discrepancy. Strength and flexibility training would fall under this category and can be beneficial. Similarly, trials of medications can be undertaken, including non-steroidal anti-inflammatory medications, non-opioid pain medications, and others, which may be especially efficacious in the case of inflammatory SIJ disease (Dreyfuss et al. 2004). Belt orthoses have also been trialed to relieve SIJ-related pain, as has been the case with SIJ dysfunction in the peripartum period. These belts, when worn above the greater trochanter, have shown approximately 30% reduction in joint motion, but should be weaned when able to reduce muscular weakening and dependence (Vleeming et al. 1992). Manual joint manipulation therapy has not yet been substantiated in the literature but has shown a potential benefit for certain patients (Kirkaldy-Willis and Cassidy 1985). Lastly, in addition to the aforementioned injection strategies for neurologic blockade, steroid use, and radiofrequency ablation, percutaneous viscosupplementation is also being explored (Dreyfuss et al. 2004).

Surgical Decision-Making

Surgical fixation of the sacroiliac joint was traditionally only considered in situations where joint instability was known such as fracture and/or severe ligamentous disruption from trauma and infection. However, in the mid-1980s, surgeons began considering fixation and arthrodesis techniques using a variety of instrumentation techniques for the treatment of refractory SI joint degeneration/dysfunction (Rand 1985; Smith et al. 2013), considered to be stable SI joint pathologies. Surgical treatment in these patients, however, is still largely thought of as a treatment option of last resort for patients whose symptoms have been unresponsive to all other non-surgical options. In addition to diagnosis with at least two positive SI joint injections, most surgeons require a course of non-surgical treatment lasting at least 6 months in duration. Discussions of risk in SI joint surgery should include explanation of all possible complications. These include neurovascular injury, hemorrhage requiring blood transfusion, superficial and/or deep infection, pulmonary embolism provoked by postoperative weight bearing status, refractory lower back and SI joint pain, non-union requiring surgical revision, etc.

The earliest reports supporting sacroiliac arthrodesis for non-traumatic SI joint dysfunction were published in the 1920s (Smith-Petersen and

Rogers 1926; Gaenslen 1927). However, the high level of complications, long periods of non-weight bearing, and unreliable rates of bony arthrodesis kept the technique from gaining widespread acceptance as a treatment for SI joint dysfunction. The emergence of SI joint arthrodesis garnered renewed interest over the past two decades as the creation of pain clinics sparked increasing numbers of diagnostic and therapeutic SI joint injections. Additionally, increased utilization of lumbar and lumbosacral arthrodesis procedures is thought to have brought greater attention to the SI joint as a generator of low back pain.

The modern era of SI joint arthrodesis began in the late 1980s with publication of a report by Waisbrod in which he reported a series of 21 surgical procedures performed for stable SI joint arthritis and lower back pain. He utilized an open posterior approach with intra-articular ceramic blocks and local autograft from the iliac crest, harvested during the approach. Postoperatively patients were maintained in short-leg spica casts for 8 weeks. The series achieved satisfactory results (defined by reduction of pain of greater than 50%) in 11 of 21 cases, all of which demonstrated bony arthrodesis on follow-up radiographs (Waisbrod et al. 1987). These early reports served as a demonstration that surgical instrumentation and fusion of the SI joint could be safely and effectively employed as a modality for treatment of the dysfunctional SI joint.

Although surgical fusion is now an accepted therapy for refractory lower back pain caused by the dysfunctional SI joint, many factors still need to be considered before surgery should be offered. CT imaging of the SI joints should be evaluated preoperatively to alert the surgeon to any bony sacroiliac anomalies that can affect the surgeon's ability to instrument across the joint or enter the joint space. Further, the presence of osteoporosis as a comorbid condition for patients with SI joint dysfunction may influence the decision as to whether surgical intervention is used and, if so, which approach will provide the chosen instrumentation with the greatest purchase to cortical bony surfaces. Similarly, patients with morbid obesity carry higher risk of complications when undergoing surgery for SI joint fusion. As such the surgeon will often benefit from choosing an approach that favors less traditional soft tissue dissection and favors fluoroscopy in the AP as opposed to lateral projection to avoid distortion from excess soft tissue. This will often be a posterior or posterolateral, minimally invasive approach, but surgeons should continue to evaluate these factors on a case-by-case basis. Finally, preoperative counseling on the postoperative course that can include non-weight bearing status and extensive physical therapy and rehabilitation will help establish expectations and can improve patient satisfaction and outcomes.

Instrumented Surgical Options

Open Surgical Approaches

Open Ventral-Ilioinguinal Approach

The ventral approach facilitates access to the iliac crest, entire iliac fossa, lateral sacral ala, and consequently the anterior and superior portions of the sacroiliac joint. The patient is positioned supine, ideally on a radiolucent OR table. An ilioinguinal incision is planned just inferior to the iliac crest and is taken deep through the subcutaneous tissues until the fascia overlying the external oblique muscle is encountered. This fascia is followed until the gluteus fascia is visualized. The border between these muscles is then identified and the interval is developed. The iliac crest is then identified and the external oblique muscle is elevated from the iliac crest in a subperiosteal fashion. The iliacus muscle is then identified and elevated from the iliac fossa in the same periosteal layer. Working anteromedially along the iliac fossa, the anterior sacroiliac joint capsule will be identified. Hohmann retractors can be utilized to maintain visualization of the joint capsule, with attention being paid to avoid injury of the traversing L5 nerve and superior gluteal artery and nerve inferomedially near the sciatic notch. The sacroiliac joint capsule is then incised sharply to visualize the joint. Joint cartilage is then resected using a combination of curettes and rongeurs. Morselized bone graft and other biomaterials are packed in the

joint, and instrumented reconstruction with screw-plate interface is most often used.

Open Posterolateral Iliosacral Approach

The posterolateral iliosacral approach facilitates access to the posteromedial portion of the iliac crest including the posterior superior iliac spine (PSIS), posterior surface of the sacral ala, and the posterior sacroiliac joint. The patient is positioned in the prone position. A longitudinal, linear, or curvilinear incision is planned just lateral to the PSIS, following the iliac crest. The soft tissues are divided, exposing the bone of the PSIS and iliac crest. The gluteal muscles are then elevated from the posteromedial ilium in the subperiosteal plane and reflected laterally to expose an adequate portion of bone, with care being taken to avoid injury to the superior gluteal neurovascular bundle. In the same subperiosteal plane, the multifidi muscles are elevated from the sacrum and reflected medially until adequate exposure of the posterior sacral surface is exposed. Retractors are placed to maintain bony exposure. Bone of the iliac crest and PSIS that overhang the posterior sacroiliac joint are resected using osteotomes or rongeurs. Bone is morselized for use as autograft. The sacroiliac joint capsule is then incised exposing the articular portion of the joint. Cartilage in the articular faces is then resected using a combination of curettes and rongeurs. Morselized bone graft and other biomaterials and/or synthetic cages are packed in the joint, and instrumented fixation is performed using screw-plate constructs, screw-rod constructs, or trans-articular screws.

Open Posterior Sacral-Alar-Iliac Approach

The posterior sacral approach facilitates access to the bilateral posterior sacral surfaces, bilateral posterior SI joints, and potentially the most medial portion of the adjacent ilium. The patient is positioned prone. A longitudinal, linear midline incision is made from the L3 spinous process down past the S2 spinous process and taken down to the deep lumbosacral fascia. Care is taken not to violate the deep layer of the fascia in the midline. This layer can be defined from the superficial layer, as the deep layer runs in a longitudinal fashion versus the oblique fibers of the superficial layer. Splitting the layers of fascia with electrocautery or a scalpel, the deep fascial layer is followed to its lateral attachment along the medial border of the ilium. Between the fascial layers, the PSIS and approximately 8–10 cm of the dorsal iliac wing can be palpated. Care should be taken to avoid damage cluneal nerves at the cephalad and lateral portions of the dissection. The deep fascial layer is then incised over the PSIS until bone is encountered and dissection occurs medially in a subperiosteal plane, exposing the posterior transverse iliosacral ligaments. These can be removed using a combination of rongeurs. The joint can then be accessed moving anterolaterally. The joint can be prepared by remove articular cartilage and bone with a combination of angled curettes, rongeurs, and a high-speed drill. An intra-articular cage and/or bone dowel is then sized and placed, often using fluoroscopy to confirm proper placement. The paraspinal musculature is then retracted medially at the cephalad portion of the exposure, and an S1 pedicle screw is placed. A trajectory into the ilium is then chosen using fluoroscopic guidance, CT-guided navigation, or freehand technique, and the hole is created using a high-speed drill or awl. An iliac "pedicle" screw of choice is then placed. The remainder of the visible sacroiliac joint can then be decorticated and residual morselized bone graft or orthobiologic material laid within the joint. A rod is then cut to size and secured with S1 and iliac screw heads, and a compression can be performed before the set screws are tightened.

An alternative method can also be utilized using the posterior midline incision. With this approach, the incision is taken to bone in the midline avascular plane exposing the L4, L5, and possibly L3 spinous process and the posterior-most portions of the sacral spinous processes. Elevation of the lumbosacral musculature from medial to lateral is performed until the sacral foramina are visualized. Continued dissection and elevation of muscles may be needed if visualization of the posterior portion of SI joint is desired. After achieving visualization of the S1 and S2 dorsal foramina, placement of sacral-alar-iliac screws can be performed. Starting point for

placement of this screw should be approximately half between the lateral edges of the S1 and S2 dorsal foramina. Trajectory of screw should be toward the anterior inferior iliac spine which can be approximated by palpating the top of the greater trochanter. Using freehand, fluoroscopy-guided, or intraoperative CT-guided techniques, fixation screws that traverse the sacral ala into the ilium can be safely placed. This technique is most commonly used in conjunction with lumbosacral arthrodesis procedures. The benefit of the sacral-alar-iliac screw is better alignment of the screw head with proximal S1 and lumbar pedicle screws for alignment of the fixation rod.

Minimally Invasive Approaches

Over the past 15 years, the popularity of minimally invasive approaches to SI joint arthrodesis has increased rapidly. These techniques aim to achieve joint fusion with decreased morbidity compared to open procedures. They emphasize smaller skin incisions, less traditional dissection using anatomic landmarks, and greater dissection using sequential dilation and tubular retractors. Additionally, these techniques have a far greater reliance on image guidance, both fluoroscopic guidance and CT-guided navigation. According to the International Society for Advancement of Spinal Surgery, by 2012, approximately 90% of all sacroiliac joint fusion were being performed using minimally invasive techniques. More than 15 distinct systems have been approved by the FDA for use in sacroiliac joint arthrodesis. The most often cited of these systems are the Rialto™ SI Joint Fusion System (Medtronic), SIJ-Fuse (SpineFrontier), iFuse® Implant System (SI-Bone), SImmetry® Sacroiliac Joint Fusion System (Zyga Technology), Silex™ Sacroiliac Joint Fusion System (Xtant Medical), SambaScrew® (Orthofix), the SI-LOK® Sacroiliac Joint Fixation System (Globus Medical), and the TriCor™ Sacroiliac Joint Fusion System (Zimmer Biomet). These systems employ delivery instruments and implants, specifically designed to fixate the ilium to the sacrum in a trans-articular fashion. To varying degrees, the technology also allows for bony decortication of the sacroiliac joint and delivery of grafting material.

Minimally Invasive Lateral and Posterolateral Iliosacral Trans-articular Approach

While the instrumentation systems each have different specifications for their technique, they follow many common themes. Although supine positioning is possible, most require prone positioning on a radiolucent table. Intraoperative fluoroscopy is used to plan the incision along the posterolateral gluteal region. Lateral imaging is the workhorse of these operations, but pelvic inlet and outlet views and to a lesser degree AP views will be utilized. Once a small skin incision is made, a guide wire is navigated to the lateral ilium until the cortical bone is encountered. Sequential dilators are then placed over the guide wire to facilitate docking of a tubular retractor. Each of the instrumentation systems then creates trajectories through the ilium into the sacral ala and body at different levels, and fixation devices are deployed across the joint. In addition, delivery of grafting material into the joint is sometimes required depending on the coating characteristics of fixation rod or screws.

Minimally Invasive Posterior Intra-articular Approach

Some minimally invasive approaches have emphasized attacking the joint along the longitudinal axis, perpendicular to the posterior joint capsule. Preoperative CT images should be utilized to measure the depth of the joint. Patients are positioned prone with either fluoroscopic guidance or CT-guided navigation. An incision is planned in the same area as the open posterolateral approach, by palpation of the PSIS or visualization of the PSIS using fluoroscopy. The incision is carried deep to the bone of the PSIS using blunt dissection or sequential dilators. Fluoroscopy is used to align the chosen instrumentation along

long axis of the joint, by shifting the axis of the C-arm cephalad and obliquely approximately 20–30° toward the contralateral side, so the images are shot posteromedial to anterolateral. From this point a variety of techniques can be utilized to implant the intra-articular graft into the joint. Hollow, threaded cages are commonly used in this technique for the ability to gain purchase on the sacral and iliac portions of the joint, while also facilitating the addition of grafting material and other orthobiologics, such as bone morphogenetic protein.

Instrumentation Options

- Screw-Plate Constructs (Fig. 1)
- Screw-Rod Constructs
- Intra-Articular (Distracting) Cage
- Trans-Articular Threaded Screw (Fig. 2)
- Trans-Articular Fusion Rod (Fig. 3)
- Hollow Modular Anchorage Screw

Evidence Supporting Different Surgical Techniques

While surgery to fixate the SI joint for patient with low back pain has been performed for approximately 100 years, until recently the literature was quite sparse regarding the safety and efficacy of SI joint fusion. Emergence of MIS techniques for these operations over the past 10 years has brought renewed attention to the problem of the dysfunctional sacroiliac joint, and the body of literature now reflects this interest. The majority of manuscripts published on the topic are derived from retrospective case series. However, during the past decade, groups have also started to study the problem and surgical interventions to treat it in a prospective, randomized fashion. Additionally, they have made efforts to measure outcomes in a more standardized, quantifiable manner using measures such as the Visual Analog Scale (VAS) for pain and Oswestry Disability Index (ODI) for functional performance.

In 2001, a single surgeon published a report of four cases in which he performed an open posterior sacroiliac joint arthrodesis using a screw-rod construct and intra-articular iliac crest autograft (Belanger and Dall 2001). The authors state that all four patients had qualitative clinical improvements with regard to lower back pain and demonstrated solid bony arthrodesis on either CT or plain radiograph. No significant complications or revisions were reported in this series, although after bony fusion was confirmed, two patient had instrumentation removed due to pain at the screw sites. This manuscript is representative of earlier reports on the topic.

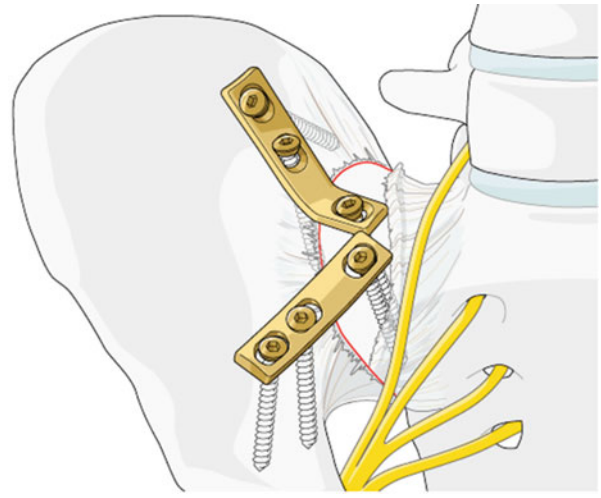

Fig. 1 Open anterior approach with use of screw-plate fixation across the SI joint (Source: AO Foundation)

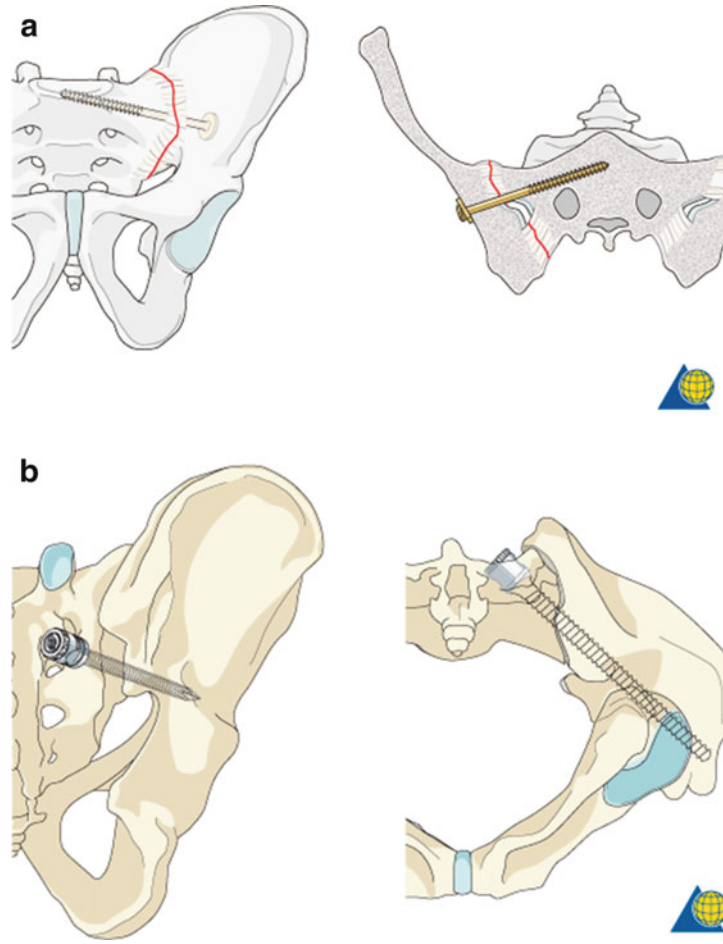

Fig. 2 (**a**) Lateral approach iliosacral fixation screw, options for open or minimally invasive placement techniques. (**b**) Sacral-alar-iliac screw (Source: AO Foundation)

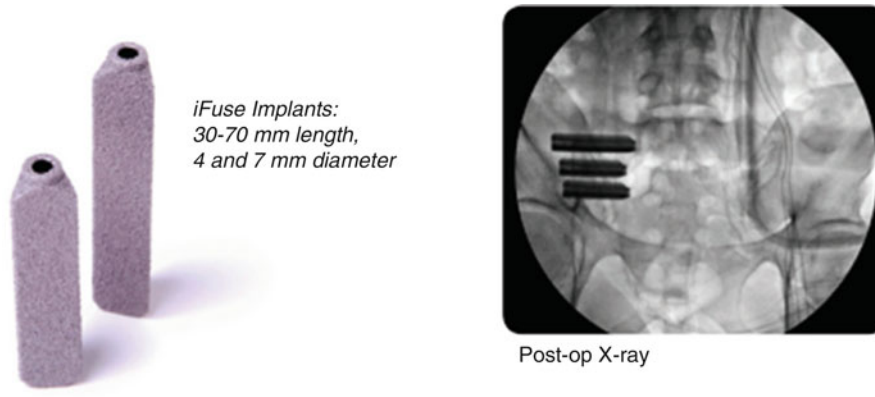

Fig. 3 Fusion rod with titanium plasma spray (TPS) coated, placed from lateral minimally invasive approach (Source: SI-Bone)

A question of whether outcomes are different between open and MIS fusion techniques has also been postulated. In 2013, a multi-centered retrospective cohort analysis of 263 patients receiving SI joint fusion was published comparing traditional, open posterior SI joint fusion to minimally invasive SI joint fusion using a series of titanium plasma spray (TPS)-coated triangular fusion rods (iFuse® system). This study found that operating room time, estimated blood loss, and length of hospitalization were all significantly lower in minimally invasive fusions than in open surgical fusions. Furthermore, the patients who had minimally invasive fusions had significantly greater reductions in their lower back pain as measured by the VAS, even when matched for age, gender, and history of lumbar spine fusion (Smith et al. 2013).

A similar retrospective cohort study was performed at single-center, comparing 27 patients who had MIS SI joint fusion to 36 patients who had open, anterior approach SI joint fusion. MIS SI fusion was accomplished using TPS-coated triangular fusion rods and CT-guided navigation, while open fusion was accomplished using anterior screw-plate constructs. Utilizing propensity score, pairwise matching of MIS, and open SI fusion patients, the study found significantly lower length of surgery, length of hospitalization, and estimated blood loss for patients in the MIS group, but no significant difference in disability score as measured by ODI. Radiographic confirmation of bony arthrodesis could not be assessed in this study.

Additionally, clinicians treating the dysfunctional SI joint have attempted to better characterize the outcomes of surgery compared to non-surgical treatment measures. A prospective, randomized trial was performed at nine European sites to explore this question. 103 patients were randomized to either MIS SI fusion (with triangular TPS-coated fusion rods) or conservative management which included medical therapy, physical therapy, and in some cases cognitive behavioral therapy, but did not include interventional procedures such as intra-articular joint injections and radiofrequency ablation. The primary endpoint was low back pain as measured using the VAS on a scale of 0–100. Patients in the SI fusion group experienced a mean improvement of 43.3 points compared to a 6.8 point mean improvement with conservative management, a statistically significant improvement. Secondary outcome measures, such as ODI, EQ-5D-3L (a quality of life assessment), and overall satisfaction, were also statistically significantly better in the SI joint fusion group at 6-month follow-up (Sturesson et al. 2017).

The INSITE, Investigation of Sacroiliac Fusion Treatment, group also performed a multicenter, prospective, randomized trial exploring outcomes of minimally invasive SI joint fusion against non-surgical management (NSM). The triangular TPS-coated fusion rod was utilized for these interventions. The NSM group received a combination of pain medications, physical therapy, SI joint steroid injections, and radiofrequency ablation, but excluded use of cognitive behavioral therapy. Cross-over was allowed after the 6-month visit, leading 102 patients to receive SI joint fusion and 46 patients to receive NSM. The SI joint fusion group had a mean improvement in VAS of pain by 55.4 at 24-month follow-up, compared to a mean improvement of 12.2 point in the NSM group, a statistically significant improvement. Furthermore, patient in the SI fusion group demonstrated statistically significant improvements on the SF-36 disability form at 6-, 12-, and 24-month follow-ups compared to NSM (Polly et al. 2016).

Given the accelerating technological advancement in instrumentation designed to fixate the SI joint, we expect the body of literature regarding sacroiliac joint fusion to continue expanding. As such, we will be able to better characterize the effects of different instrumentation techniques on outcomes when treating patient with sacroiliac joint dysfunction.

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Lateral Lumbar Interbody Fusion

35

Paul Page, Mark Kraemer, and Nathaniel P. Brooks

Contents

Abstract

Lateral lumber interbody fusion is an important technique in the continually growing field of minimally invasive spine surgery. While it had previously been utilized in the early twentieth century for the treatment of traumatic injuries and Pott's disease, the current revolution of minimally invasive surgery has seen a recurrence of this approach and expansion of its clinical applications. Though this approach was largely abandoned in the late twentieth century for anterior and posterior approaches due to a high morbidity, a combination of improved technology and understanding of lumbar plexus anatomy has allowed for

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its resurgence. Clinical applications of the retroperitoneal trans-psoas and pre-psoas approaches are continually expanding and frequently include scoliosis, neoplasms, traumatic injuries, and a variety of degenerative disorders. Here we describe the clinical utility of this approach, review the pertinent clinical anatomy, and describe the procedure in detail.

Keywords

Lateral lumbar interbody fusion · Trans-psoas · Pre-psoas · LLIF · OLIF · Minimally invasive spine surgery

Introduction

Interbody fusion in the lumbar spine is an established treatment for a wide variety of spinal disorders ranging from trauma, infection, degenerative disease, deformity correction, and neoplasms. The use of interbody fusion provides additional biomechanical advantages because of the ability to place a large interbody graft that provides support to the anterior and middle columns of the vertebral segment. Additionally, the ability to extend the graft across the thicker bone of the apophyseal ring of the vertebral body limits subsidence or fracture. Restoration of interbody height by interbody fusion allows for indirect decompression of the neural elements. The goals of treatment and surgical approaches to the spine vary based upon the spinal pathology. The options are circumferential, including the posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), lateral lumbar interbody fusion (LLIF) either pre-psoas or trans-psoas, and anterior lumbar interbody fusion (ALIF). Of these techniques, the lateral interbody approach is growing in popularity due to avoidance of the vasculature anteriorly and the thecal sac posteriorly. Additionally, there is minimal disruption of the existing ligamentous structures and surrounding musculature. The LLIF has multiple trade names depending on the company. The trans-psoas approach is called the direct lumbar interbody fusions (DLIF) or extreme lateral interbody fusion (XLIF). The pre-psoas approach is called the oblique interbody fusions (OLIF).

Compared to traditional anterior and posterior approaches to the lumbar spine, the minimally invasive lateral interbody fusion is a relatively new approach as it relates to common practice. But it is important to note that variations of this approach have been described historically. Although lateral approach to the lumbar spine was originally described and utilized in the treatment of Pott's disease in the early twentieth century by Drs. Menard and Capener, it remained infrequently used due to injury to the traversing lumbar plexus and nerve roots. Despite this neurologic morbidity, the approach became more commonplace in the treatment of Pott's disease through the twentieth century. With the emergence of the minimally invasive revolution in the late twentieth century, this approach reemerged and expanded to include a wide variety of disease pathologies. This expansion is largely attributed to recent advances in minimally invasive technologies and a better understanding of the anatomic relationships of the exiting lumbar nerve roots that form the lumbar plexus. While the traditional lateral approach accessed the vertebral column using a trans-psoas corridor, Mayer in 1997 described an oblique retroperitoneal approach in which instrumentation is performed anterior to the psoas with the benefit of fewer neural injuries (Mayer 1997). Once these anatomic limitations were identified and techniques developed to limit nerve injury, lateral approaches to the lumbar spine have proven to be versatile tool in modern spine practice.

The lateral lumbar interbody fusion has demonstrated some distinct advantages compared with the anterior or posterior approaches to the lumbar spine. Compared with traditional approaches, there is minimal disruption of the posterior elements, which may provide some benefit in the stability of the construct and postoperative pain. Additionally, lateral approaches allow for a larger access to the disc space and increase the size of interbody graft compared to posterior approaches. Research has demonstrated decreased blood loss and operative time as compared with traditional approaches. One review evaluating extreme

lateral lumbar interbody fusion (XLIF) demonstrated overall short operative times, 199 min, and relatively minimal blood loss of 155 ml (Youssef et al. 2010).

Compared to traditional ALIF approaches, lateral interbody fusion demonstrated similar degrees of foraminal height gain. However, there was less segmental lordosis correction than ALIF. In previous studies the amount of foraminal height following ALIF has demonstrated improvements in foraminal height of approximately 2.7 mm. Alimi et al. demonstrated similar foraminal height improvements, 2.5 mm on average, in their series of 145 patients who underwent interbody fusion from a lateral approach (Alimi et al. 2014). As compared to ALIF, however, segmental lordosis correction in lateral interbody fusion is generally less due to retention of the anterior longitudinal ligament. While specific degrees of improved lordosis vary, ALIF generally provides approximately 4.5° of lordosis, but only 2.5° following a lateral approach (Winder and Gambhir 2016).

Indications and Contraindications

The indications of the lateral lumbar interbody fusion are primarily to improve intervertebral height and to reduce deformity. Common indications are degenerative disease with loss of disc height and foraminal stenosis, spondylolisthesis, coronal imbalance, lateral vertebral subluxation, and revision of adjacent segment degeneration.

The contraindications of this approach are primarily related to anatomical considerations such as aberrant vascular anatomy, prior retroperitoneal approach, or prior abdominal infections or surgeries with associated adhesions in the retroperitoneal corridor. A high-riding iliac crest or low-lying rib is a relative contraindication.

Relevant Anatomy

The lateral lumbar approach traverses anatomy that is rarely encountered in traditional approaches. Given the narrow operative corridor, a detailed understanding of the relevant anatomy is crucial for safe, effective surgery. Traversing the retroperitoneal space involves significant risk to major vascular structures and vital organs. Evaluation of the preoperative imaging and understanding the location of these structures and their relationship to the disc space is a critical part of preoperative planning and intraoperative crisis management. Furthermore, if concern for major vessel injury arises preoperatively or intraoperatively, the surgeon should seek vascular surgery consultation.

When accessing the retroperitoneal space, care must be taken to first identify the external oblique fascia, external oblique, internal oblique, and transversus abdominal muscles at the beginning of the approach (Fig. 1). It is important to recognize the trajectory of the iliohypogastric and ilioinguinal nerve as they course through the psoas before innervating the internal and external oblique muscles. When unclear as to which muscular layer is being visualized, the surgeon should recognize the direction of the muscle fibers for reorientation. Once these muscular layers have been traversed, a layer of adipose tissue is identified in the retroperitoneal space. Deep to this, the peritoneum will be identified. Dissection is best performed bluntly with either finger dissection or use of cotton kittners. It is easier to dissect along the interior of the abdominal wall, palpate the iliac crest, and then identify the psoas than to try and dissect along the peritoneum. Further dissection leads to the lateral aspect of the psoas (Fig. 2). Care must be taken to expose the anterior psoas as it is easy to fall into a plane behind the psoas that leads to the spinal canal and foramen. The ureter typically will mobilize with the peritoneum and reflect anteriorly. However, if it is taking an unusual course, it can be identified by its visually identifying peristalsis with manipulation. Care should be taken to not overly compress or stretch the ureter. A keen awareness of the location of the great vessels anterior to the vertebral bodies is paramount. These can be palpated but care should be taken to avoid manipulation or retraction without adequate visualization. Segmental arteries will arise from the aorta in the midpoint, "valleys," of the vertebral bodies. Occasionally, the iliolumbar vein or veins will be

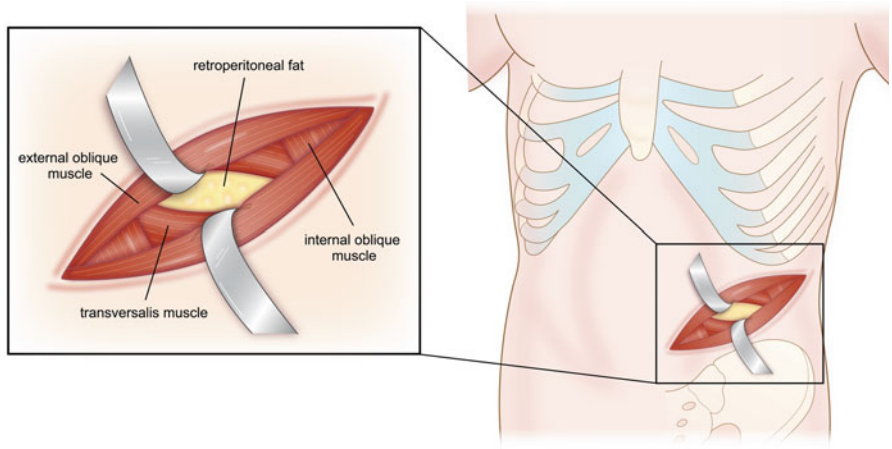

Fig. 1 This illustration shows the oblique incision, which is centered over the disc of interest and oriented along the fibers of the external oblique. Blunt dissection is performed through the external, internal, and transversalis abdominal muscles to reveal the retroperitoneal fat pad. (Reprinted with permission, University of Wisconsin © 2018. All Rights Reserved)

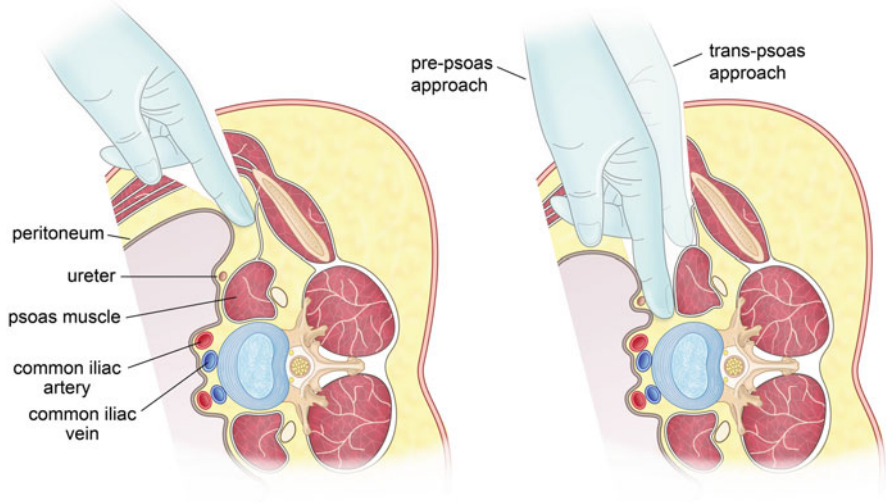

Fig. 2 Schematic demonstrating blunt dissection of the retroperitoneal fat pad from the transversalis fascia and anterior retraction of the aorta. The transverse process is first palpated before isolating the psoas muscle. If electing to perform a trans-psoas approach, instrumentation is then directed through the psoas under imaging guidance and neuromonitoring (triggered and free-running EMG). In the pre-psoas approach, the anterolateral portion of the vertebral body is identified (left) and the psoas is retracted posteriorly. Care should be taken to avoid dissection of the psoas medially, as this may irritate exiting nerve roots. (Reprinted with permission, University of Wisconsin © 2018. All Rights Reserved)

seen coursing from underneath the aorta usually at L4–L5 interval. This vein could be isolated and ligated to avoid avulsion of the vein from the inferior vena cava which can create a vascular injury that is very difficult to repair. During the course of dissection, if there is aberrant or overly large vascular anatomy, then strong consideration should be given to (1) obtaining vascular surgeon consultation, (2) aborting the procedure, and (3) operating via a posterior approach. Furthermore, a

thorough review of preoperative imaging is important to understand the relation of adrenal glands, kidneys, ureters, and renal vasculature that may be encountered when utilizing this approach.

Lumbar Plexus

The lumbar plexus is deeply integrated into the psoas muscle and contains innervation from subcostal contributions from the T12 as well as the ventral rami of the first four lumbar nerve roots. The fourth lumbar nerve root additionally supplies contributions to the sacral plexus. The lumbar plexus is ultimately divided into two divisions named the anterior and posterior division. The posterior division provides innervation to the main motor component of the posterior leg via the femoral nerve with contributions from the L2 to L4, while the anterior division provides motor innervation via the obturator nerve. Sensory innervation is chiefly accomplished by the iliohypogastric, ilioinguinal, genitofemoral, lateral femoral cutaneous, and anterior femoral cutaneous nerves.

Understanding the course of the ilioinguinal and iliohypogastric nerve is vital to avoiding complications. Both nerves run posterior to the psoas major on its proximal lateral border of the vertebral bodies and then travel along the anterior border to the quadratus lumborum. After traveling anterior to quadratus lumborum, the ilioinguinal nerve pierces the lateral abdominal wall after traveling at the level of the iliac crest to supply sensory innervation to the external ring, the area over the pubic symphysis, and the lateral area of the scrotum or labia majora. Comparatively the iliohypogastric provides motor innervation to the abdominal internal oblique and transverse abdominis until it provides a terminal cutaneous branch supplies which the skin above the inguinal ligament.

The lateral cutaneous nerve consequently pierces the psoas directly through a lateral approach most frequently in the middle location of the psoas muscle. Given its location directly through the psoas muscle, this nerve is at risk during a lateral lumbar approach. Once it emerges from the psoas, it then courses across the iliacus muscle obliquely and continues to the anterior superior iliac spine. At this point it crosses under the inguinal ligament over the sartorius muscle into the thigh.

The femoral nerve is the longest and largest nerve of the entire lumbar plexus and supplies both sensory and motor innervation to the anterior compartment of the superior leg. Contributions from the lumbar plexus arise from the L2, L3, and L4 nerve roots. After arising distal to the nerves to the psoas muscles directly, it courses through the femoral triangle lateral to femoral artery.

Vascular Anatomy Considerations

When considering a lateral retroperitoneal approach, important consideration of the major vascular structures such as the inferior vena cava, abdominal aorta, and common iliac arteries and veins must be given. In order to limit the potential injury to vascular structures, a careful review of the preoperative imaging is vital. While risk to the great vessels is highest at the L4–L5 level due to their lateral migration, major vasculature injury could occur at any level. In addition to knowledge of the great vessels, care should be taken to identify and avoid avulsion of any of the segmental vessels or iliolumbar veins crossing into the disc space during removal of the annulus that could result in avulsion of the aorta or vena cava.

Preoperative Planning and Operative Window

In considering the operative corridor during interbody fusion, it is vital to understand what constitutes a safe and effective operative window. Avoiding injury to the traversing nerve roots and lumbar plexus and great vessels is paramount. It is also important to consider that surface anatomy: a high-riding iliac crest or low-riding ribs can

make the approach more difficult. These surface limitations can be managed by removing rib or positioning the hip over a bump or table break. Care should be taken to not overextend the torso as this can cause thigh pain and weakness.

Trans-psoas

The trans-psoas approach avoids the great vessels but puts the lumbar plexus and peripheral nerves at greater risk of injury. The anatomy of the plexus cannot be well discerned on preoperative imaging. So, determination of an operative window is made intraoperatively via a combination of general knowledge of the lumbar plexus anatomy, visual and fluoroscopic inspection, and the use of neuromonitoring (triggered and free-running EMG).

Despite attempts to simplify the anatomical association of the lumbar plexus and the psoas muscle, the authors have demonstrated enormous variability. The plexus generally tends to migrate anteriorly as the psoas muscle enters the pelvis. Due to this relationship, the plexus is often at highest risk of injury at the L4–L5 disc space. A key development occurred in 2010 when Uribe et al. published a cadaveric study in which the zones of safest psoas disruption were identified (Uribe et al. 2010a). In this system four quartiles along the sagittal axis of the vertebral body were defined at each vertebral level. At the L1 and L2 disc space, the middle of this quartile was shown to have the lowest risk for injury to the nerve roots or lumbar plexus; however, at lower levels, the safest location migrates slightly anteriorly until the L4–L5 disc space. At the L4–L5 disc space, the safest location was the midpoint of the vertebral body. Additionally, the authors noted that the genitofemoral nerve was the nerve at most risk in the third quartile. This nerve must be a consideration to the surgeon as given its sensory function it will not be recognized by EMG and can be easily injured. This "safe entry zone" should not be considered universal, and as previously discussed, significant variation in patient anatomy may be present. Ultimately visual inspection and neuromonitoring are critical in minimizing risk to traversing nerves. In general, triggered EMG thresholds below 5 mA indicate direct contact, 5–10 mA indicate that the stimulation is in close proximity, and 11 mA indicates a farther distance from the lumbar plexus (Uribe et al. 2010b).

Pre-psoas

The key difference of the lateral pre-psoas approach is the intent of docking instrumentation between the psoas muscle and the great vessels. Due to the more anterior location on the vertebral body, there is a higher risk to the great vessels anteriorly, and it is frequently cited at a rate similar to the anterior approaches. Currently existing literature demonstrates a rate of vascular complication cited from 1.1% to 2.8% with damage to segmental arteries being the most common complications (Xu et al. 2018). Conversely, the risk of injury to the lumbar plexus is lower because the psoas is not blindly traversed. Determination of the operative window is made by preoperative planning and intraoperative visual and fluoroscopic inspection and dissection. Neuromonitoring is not necessary for this approach but can be considered.

Procedural Details

Surgical Positioning

Proper positioning is essential for successful lateral lumbar interbody fusion. The patient should be placed in the lateral decubitus position with the left side up. Right-sided approach may be considered, but this is generally discouraged due to increased risk of injuring the relatively thin-walled inferior vena cava during manipulation. If such an approach is undertaken, a trans-psoas corridor should be considered to decrease risk of IVC injury. Additionally, lateral jack-knife position may be used to improve access and visualization in certain cases, but this should be avoided if possible to avoid transient neurologic deficits (Molinares et al. 2016). An axillary roll is

placed to avoid brachial plexus injury. Care should be taken to position the patient perpendicular to the floor. The fluoroscope is then brought into the field, and minor table adjustments are used to obtain a perpendicular lateral view of the target disc. Similarly, the flouroscope should be easily maneuverable to obtain a clear orthogonal AP view of the disc. Alternatively, computerized stereotactic navigation may be used, in which case the registration pin is placed into the iliac crest projecting posteriorly after prepping and draping. A small amount of hip flexion may be used to relax the psoas, which also serves to position the L4 and L5 nerve roots more posteriorly. At this time neuromonitoring (EMG) may be attached. If approaching the vertebral column using a trans-psoas approach, neuromonitoring should be used to avoid the risk of nerve injury while traversing the psoas. The patient's abdomen and flank should be prepped and draped widely despite the plan for a small incision. This will allow the laparotomy incision to be enlarged in the case of difficulty with dissection or complication.

Incision and Retroperitoneal Dissection

Under fluoroscopic or navigation guidance, the intervertebral disc of interest is identified before marking its caudocranial and anteroposterior projections on the skin. For the trans-psoas approach, a 4 cm incision is centered over the disc of interested and oriented obliquely (Fig. 1). If approaching anterior to psoas, the incision should be positioned more anteriorly from the center of the disc space (approximately 5 cm) to facilitate psoas mobilization and vertebral body visualization. The external oblique fascia is then sharply divided, and splitting of the external, internal, and transversalis abdominal musculature is performed using a Kelly clamp or bluntly. The underlying transversalis fascia is identified and divided before entering the retroperitoneal fat pad. Using a gloved index finger, the fat pad is gently dissected from the transversalis fascia before advancing more medially and posteriorly and along the anterior boarder of the quadratus lumborum to palpate the transverse process of the vertebral body (Fig. 2). After palpating the transverse process, blunt dissection is used to retract the peritoneal contents anteriorly to identify the vertebral disc space. Fluoroscopy is then used to confirm the correct intervertebral disc level.

Retractor Positioning

Trans-psoas

Fluoroscopy or navigation is used to localize the planned position to dock the retractor in the disc space. This is done by placing a k-wire in the disc space and using serial dilation to split the psoas muscle fibers. Neuromonitoring (triggered and free-running EMG) is monitored as each dilator and eventually the retractor blades are advanced. The electrical contacts are different for each company and should be studied and understood prior to surgery to evaluate the direction of stimulation. Typically, one small area of each dilator will have exposed uninsulated metal, and stimulation can proceed in quadrants to look for EMG firing. This can help the surgeon determine the direction of any at-risk nerves and reposition the retractor accordingly. If the EMGs demonstrate irritation, the retractor can be repositioned away from the direction of nerve root firing. The retractor blades can be pinned into the vertebral bodies above and below the disc space firmly into position. An ideally placed retractor will be overlying the disc at about the anterior 1/2 of the disc space, parallel to the endplates and in the coronal plane (Fig. 3). Fluoroscopy should be used to verify this position.

Pre-psoas

In the pre-psoas approach, the psoas is mobilized posteriorly for exposure of the ideal operative window. This space need only be slightly wider than the planned implant. Self-retaining retractors are then placed to retract the abdominal contents and psoas. The retractors can be rotated and slid slightly above the disc space to allow the disc prep tools and implants to be positioned in the coronal plane. A second retractor is placed medially to protect the peritoneum and great

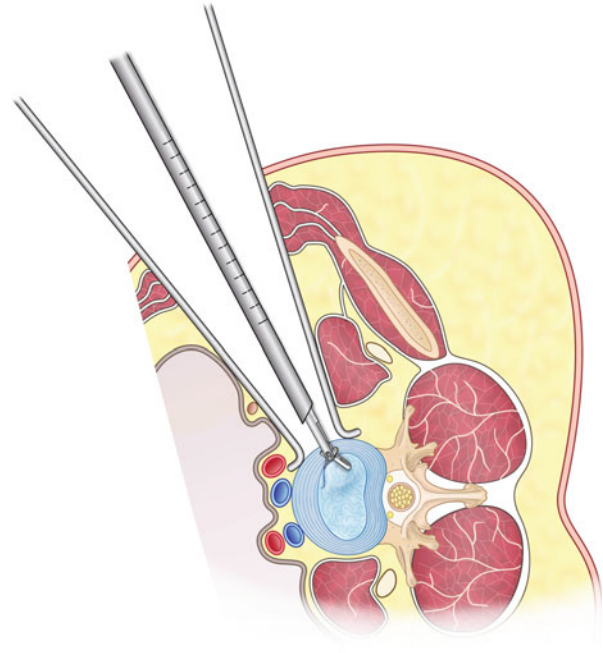

Fig. 3 In the pre-psoas approach, instrumentation is docked at the anterolateral disc space and a small annulotomy is performed followed by complete discectomy. (Reprinted with permission, University of Wisconsin © 2018. All Rights Reserved)

vessels, and if needed, a third retractor can be placed in the caudal aspect of the incision to protect peritoneal contents. Various retractor setups are available. This can also be done with handheld retractors if desired.

Disc Preparation and Implant Placement

An annulotomy is then performed followed by complete discectomy and removal of the cartilaginous endplates. This will ensure that a large surface area is available for effective fusion. Care should also be taken to bilaterally release the annulus to avoid coronal imbalances after implant placement. This may be performed by rotating a Cobb across the distal annulus of the disc space (Orita et al. 2017). Care should be taken to maintain a coronal trajectory. Failure to work in the coronal plane can lead injury to the vasculature anteriorly or neural elements posteriorly. The disc space is then sequentially distracted using spacers until the ideal height is reached. A lordotic cage filled with graft is then placed and positioned parallel to the disc space (Fig. 4) on the AP view and in line with the posterior aspect of the vertebral bodies on the lateral view. To avoid inserting the cage in a rotated alignment on the lateral view, the trials and rasps should be placed so that they are aligned with the posterior aspect of the vertebral bodies, allowing the cage to simply follow the created path.

Ideal implant placement involves adjusting the midpoint of the cage to the center of the vertebral body on AP view and between the anterior and middle-third on lateral view. Implant placement in the trans-psoas approach is directly perpendicular to the vertebral body along the planned trajectory. However, special attention needs to be used to place pre-psoas implants. The pre-psoas implant is placed obliquely from the 10 o'clock position on the disc, advanced 1/2 way into the disc space, and then the handle is rotated posteriorly perpendicular to the OR table to place it across the disc space. This is sometimes called the "orthogonal maneuver."

The surgical field is then copiously irrigated, and meticulous hemostasis is achieved before removal of the self-retaining retractor and wound closure. The surgical corridor should be inspected for any injury to the peritoneum or retroperitoneal structures.

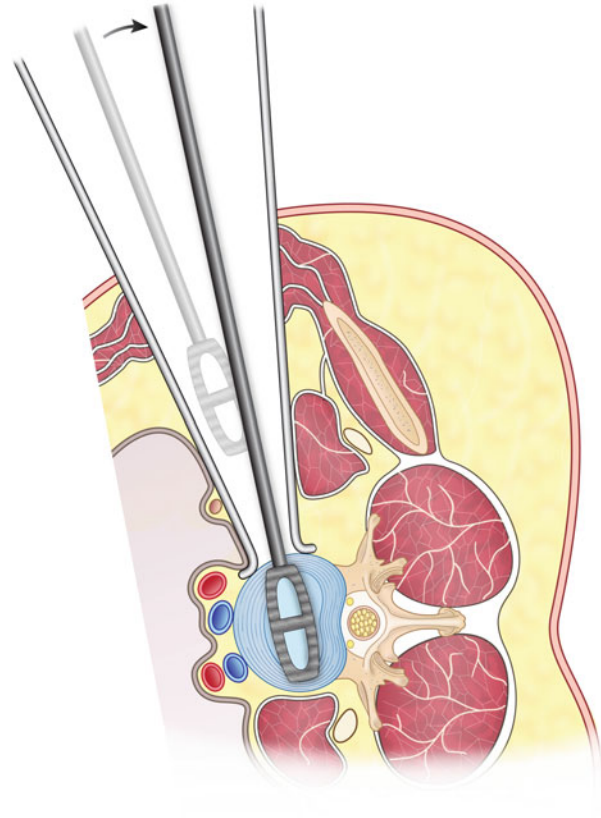

Fig. 4 Illustration demonstrating interbody graft placement using an pre-psoas approach. Ideal graft placement is midline on the lateral view and parallel to the disc space. (Reprinted with permission, University of Wisconsin © 2018. All Rights Reserved)

Posterior Instrumentation and Fusion

Posterior instrumentation can be considered to achieve a stable construct and increase the likelihood of fusion. This may be performed in multiple ways, but unless otherwise contraindicated, we prefer repositioning the patient in a prone position and performing bilateral percutaneous pedicle screw fixation using either fluoroscopic or stereotactic guidance.

Pre-psoas L5–S1

This is an advanced surgical technique but the pre-psoas approach does allow access to the L5–S1 level. This is performed by using a more anterior and medial incision and carefully docking the retractors between the bifurcation of the aorta and vena cava. An annulotomy is then performed, and discectomy and endplate preparation are completed. An anterior interbody cage is then implanted using a specially designed oblique introducer. Centering the implant can be challenging because of this oblique trajectory.

Complications and Their Management

Complications of the lateral approach are similar to those seen with ALIF with major complications related to damage of surrounding vascular, visceral, and neurologic structures. Yet, because there is generally no retraction of major vascular structures in the lateral approach, large series have reported no vascular or intraoperative injuries (Rodgers et al. 2011). If a vascular injury is identified, the first step is to obtain temporary control of the bleeding. This is often done using pressure from a kittner, suction, or sponge stick. If it is a large injury, then anesthesia should be notified to have blood products prepared to be administered. The second step will be to obtain improved access by making the incision larger. The third step will be to get adequate visualization of

the injury. Primary repair can be attempted. Typically, prolene suture is used to suture vessels. Venous injuries must be repaired with care as the thin walls of the vessel can often tear. At any point, a vascular or general surgery consultation is encouraged to be obtained.

Other major complications include injury to the exiting nerve roots, particularly the L4 root. Permanent motor deficits have been reported between 0.7% and 3.4% (Knight et al. 2009) (Rodgers et al. 2011). Yet, when compared to other approaches, there is a high rate of transient groin and thigh pain after lateral approach which ranges from 10% up to 30%. These transient injuries, often hyperalgesia in the distribution of the iliohypogastric or ilioinguinal cutaneous nerves, are likely due to a combination of stretch and compression injury during the approach and retraction during surgery. Trans-psoas approaches are generally associated with higher complications rates (32.8%) versus oblique psoas-sparing approaches (13.5%) due to a higher likelihood of encountering the lumbar plexus during muscle dissection (Abe et al. 2017). Hip flexor weakness has also been reported and relates to manipulation of the psoas.

If the peritoneum is torn or injured, this is not typically a serious complication. Inspection should be performed to verify that no intestinal injury has occurred as this can be life-threatening if not identified. The peritoneum can be stitched closed with absorbable suture to avoid herniation of intestines. The surgery can continue.

If the intestines or abdominal organs are injured, then general surgery should be consulted for repair. Strong consideration should be given to aborting the procedure as the infection risk is very high in this situation. It can be helpful to have the patients undergo a bowel preparation prior to the surgery in order to minimize spillage of visceral contents, decrease likelihood of infection in case of incidental enterotomy, and increase the rate of repair.

Ureter injury is uncommon, but if it is encountered, then a urologist should be consulted to repair the ureter. The risks and benefits of proceeding should be weighed. Urine is typically sterile so the infection risk should be lower compared to intestinal injury.

As with ALIF, there is a risk of incisional hernia. If this occurs, then a referral to general surgery for repair is warranted.

Limitation of the parallel trajectory of the cage relative to the disc space secondary to a high-riding iliac crest is not technically a complication. However, it is often encountered at the L4–L5 level. In these cases, the senior author has proceeded with a discectomy without violating the contralateral annulus and placed a shorter cage to avoid neural compression in the canal or neural foramen.

Another key consideration when comparing anterior interbody to lateral interbody fusion is the risk of subsidence, which is defined as the potential loss of height within the neural foramen following indirect decompression with an interbody graft. While the gold standard for reducing the risk of subsidence is the anterior interbody fusion with an average of 10% risk of any subsidence without any events of neurologic consequence, both LLIF and OLIF have significant risks of subsidence and are important considerations with approach. Stand-alone LLIF has been shown to have subsidence rates of up to 30% when using standard 18 mm grafts (Marchi et al. 2013).

Conclusions

The lateral lumbar interbody fusion is a useful technique for the spine surgeon to have in his/her armamentarium. The keys to performing this technique safely and effectively are appropriate patient selection, safe lateral positioning, appropriate targeting of disc space with fluoroscopy or computerized stereotactic navigation, careful dissection and retractor placement to identify and avoid injury to intraperitoneal contents or pre-vertebral vascular structures, and aligning the tools to prepare the disc space and implant the graft in the coronal plane. If performing a trans-psoas approach, then neuromonitoring (triggered and free-running EMG) should be used to limit nerve injury. The outcomes of this procedure are similar to anterior lumbar interbody fusion but with less muscular dissection because of the lateral trajectory.

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Minimally Invasive Spine Surgery

36

Bilal B. Butt, Rakesh Patel, and Ilyas Aleem

Contents

Abstract

This chapter explores the basic principles and concepts of minimally invasive spine surgery (MIS). It provides technical insight into how these procedures are performed safely. By utilizing MIS techniques, one can largely treat the same conditions, which historically have been treated in the open fashion. Both short- and long-term advantages will be discussed including but not limited to decreased blood loss, decreased postoperative pain, and faster return to baseline. The application of these methods to deformity correction surgery and interbody fusions will also be explored. The roles of navigation and robotics in this rapidly expanding field and how they

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can be utilized to improve accuracy are investigated. This chapter is targeted toward junior faculty members, residents, midlevel providers, and other individuals who wish to expand their knowledge base on MIS.

Keywords

Minimally invasive surgery · MIS · Pedicle screws · MIS TLIF

What Is Minimally Invasive Spine Surgery (MIS)?

Minimally invasive spine surgery (MIS) strives to correct surgical pathology, which is typically treated with larger incisions and greater tissue destruction, with the goal of better short- and long-term patient outcomes. Although long-term benefits are debatable, the short-term benefits, including decreased blood loss, decreased postoperative pain, decreased hospital stays, and faster return to baseline, have been well established (Lombardi et al. 2014; Tullberg et al. 1993; Obenchain 1991; Shamji et al. 2015; Terman et al. 2014; Parajon and Hartl 2017; Costanzo et al. 2014). Additionally, MIS techniques have been shown to decrease both the direct and indirect costs associated with certain surgical procedures (Shamji et al. 2015). By decreasing operative time, blood transfusions, and length of stay, the direct cost is significantly impacted. Earlier return to work and fewer postoperative hospital visits significantly decrease indirect costs. The goal of this chapter is to present the reader with current MIS techniques as well as a brief insight into the future of MIS.

Advantages and Disadvantages of MIS

There are several advantages and disadvantages of MIS techniques. A steep learning curve is associated with the safe implementation of MIS into one's practice, resulting in a lower than expected adaptation of this technique. Numerous studies have demonstrated that the first 20–30 cases of a surgeon's implementation of MIS may be associated with higher rates of complications (Sclafani and Kim 2014; Shamji et al. 2015; Fujibayashi et al. 2017). In addition to the steep learning curve, another barrier to adaption of MIS techniques is increased radiation exposure to the surgeon due to reliance on fluoroscopy. However, this risk may be minimized with the usage of intraoperative navigation.

Though introduced several decades ago, MIS techniques have made significant progress recently due to numerous technological advancements which have resulted in a numerous advantages of a less invasive approach. In utilizing an MIS approach, there is no need to detach the paraspinal muscles from their insertions on the spinous processes as compared to open techniques, thus minimizing muscle dissection and stripping (Pishnamaz and Schemmann 2018). Muscle injury in spinal surgery correlates with the length of time and force of the muscle retraction (Kawaguchi et al. 1996). With prolonged retraction, capillary perfusion is decreased and leads to accelerated rates of muscle fiber degeneration secondary to changes in cellular metabolism. The mechanism of this degeneration and necrosis are not yet fully elucidated, but most of these changes are believed to be associated with destruction of the sarcolemma and subsequent mitochondrial damage (Heffner and Barron 1978). Postoperative MRIs have demonstrated decreased cross-sectional area of paraspinal muscle, supporting the idea of muscle fiber atrophy following open surgery (Bresnahan et al. 2017) (Fig. 1). Stevens and colleagues used high-definition MRI to study the multifidus muscle postoperatively in patients undergoing MIS TLIF vs open TLIF. They observed significant intermuscular and intramuscular edema at the 6-month mark in those patients undergoing open TLIF. In patients who underwent MIS TLIF, no edema was present and overall the muscle appeared normal (Stevens et al. 2006). Levels of creatine kinase have also been used as a marker for muscle fiber injury. Open techniques have been shown to have a direct correlation with postoperative rises in creatine kinase levels, as compared to MIS, which show lower levels of CK

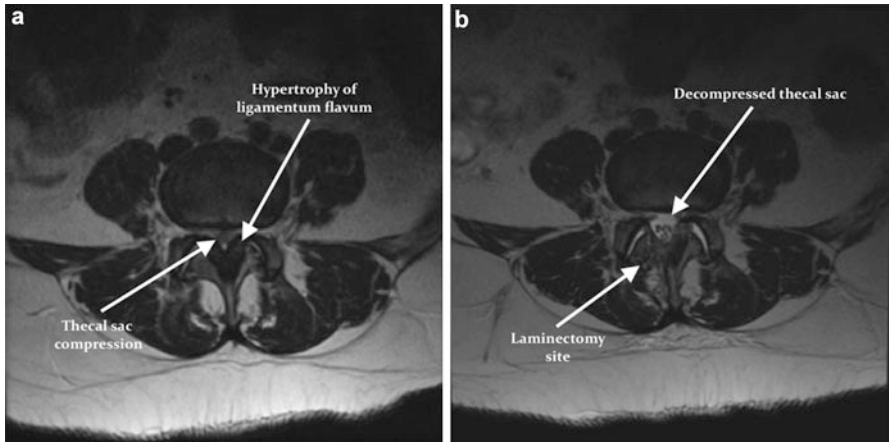

Fig. 1 (**a**–**b**) Comparison of pre-post op MIS laminectomy MRIs

(Wang et al. 2017). Cawley et al. were able to show that patients undergoing open surgery had abnormal postoperative EMG activation patterns in the lumbar multifidus as compared to those patients undergoing the same procedure via an MIS technique (Cawley et al. 2013). In evaluation of the sacrospinalis muscle using EMG, Wang et al. concluded that MIS TLIF was associated with reduced muscle damage as compared to open TLIF (Wang and FZ 2011). Newer data even suggest that with MIS techniques, the overall inflammatory state of the patient is decreased and this aids in shorter recovery periods as compared to open procedures (Lombardi et al. 2014). This is supported by lower levels of CRP, IL-6, and IL-10 following MIS procedures as compared to their conventional alternatives (Kim et al. 2006; Huang et al. 2005).

History of MIS

As a way to avoid excessive muscular retraction in spinal surgery, Wiltse et al. proposed a paraspinal sacrospinalis-splitting approach to the lumbar spine in 1968 (Wiltse 1973). The plane that Wiltse identified was an intermuscular plane between the multifidus muscle medially and the longissimus muscle laterally (Guiroy et al. 2018). Wiltse advocated that care must be taken to avoid overexposure of the vertebrae, as he had some concept of the negative consequences associated with excessive muscle stripping and damage. Because this approach utilizes an intermuscular plane, soft tissue trauma is minimized, and the posterior tension band of the spine and the supportive elements of the contralateral side are preserved (Anderson 2014). All of these taken together helped to improve patient outcomes following spinal surgery at the time.

MIS Discectomy

Disc herniations are painful and often debilitating conditions, which have a substantial impact on the function and quality of life of patients. There are also considerable social and economic impacts to society as most patients with disc herniations are of working age (Anderson et al. 2017). Given this, MIS discectomy may help mitigate some of the risks of surgery compared to open techniques and should be discussed with the patient if possible. Open surgery has been shown to be associated with longer operative times, longer incisions, increased bony resection, and increased retraction and damage to the paraspinal muscles as compared to MIS techniques (Ditsworth 1998; Rasouli et al. 2013; Alvi et al. 2018). MIS discectomy has been shown to have a shorter period of time off work, less opioid analgesia, less blood loss, and shorter hospital stays

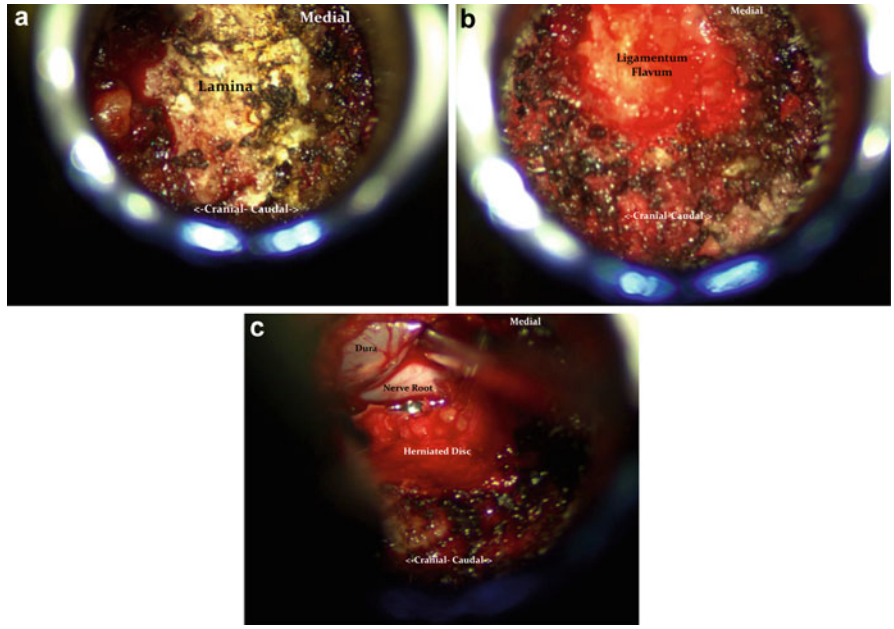

Fig. 2 (**a**–**c**) Intraoperative photos of discectomy through tubular dilator

(Tullberg et al. 1993; Kotil et al. 2007). It should be noted, however, that VAS scores both in short-term and long-term follow-up are essentially equivalent between groups of patients undergoing open procedures and those undergoing MIS procedures (Dasenbrock et al. 2012). Thus, both procedures ultimately decompress the neural elements and achieve pain relief.

As such, indications for MIS discectomy parallel those set forth for open procedures. Patients, who have failed conservative measures for a minimum of 6 weeks, have progressive motor weakness, or disabling pain can all be surgical candidates. As is standard, surgical indications should be evaluated on a case-by-case basis. The patient should always be included in the decision for surgery and appropriate informed consent should be obtained prior to surgery.

Obenchain described the first laparoscopic lumbar discectomy and was soon followed by Faubert and Caspar who published reports of lumbar percutaneous discectomy using a muscular retractor system in the early 1990s (Obenchain 1991; Faubert and Caspar 1991). This was the foundation by which Foley et al. built upon. Foley and colleagues used successive tubular dilators to achieve a desired diameter portal to which an endoscope was attached (Foley and Smith 1997). Foley's techniques were termed microendoscopic discectomy (MED) (Fig. 2).

Present day, usage of tubular retraction systems are common and are very much similar to Foley's initial description (Foley 2015). The patient should be positioned prone on a radiolucent spinal frame and prepped and draped in the usual fashion. Initially a 22-gauge spinal needle is introduced directed toward the facet joint. Careful attention is made to ensure that the needle does not aim midline, as this trajectory could puncture the dural sac and lead to a spinal fluid leak (Phillips et al. 2014). The location of the needle is confirmed using C-arm after obtaining orthogonal x-rays. Once the location is confirmed, the needle is removed, and a small, paraspinal incision is made, generally 2–2.5 cm lateral to midline. In cases where decompression of the contralateral is desired, the incision should be 3–4 cm lateral of the midline. If only an ipsilateral decompression is warranted, then the standard 2 cm from midline incision is sufficient. The incision should roughly be the same size as the

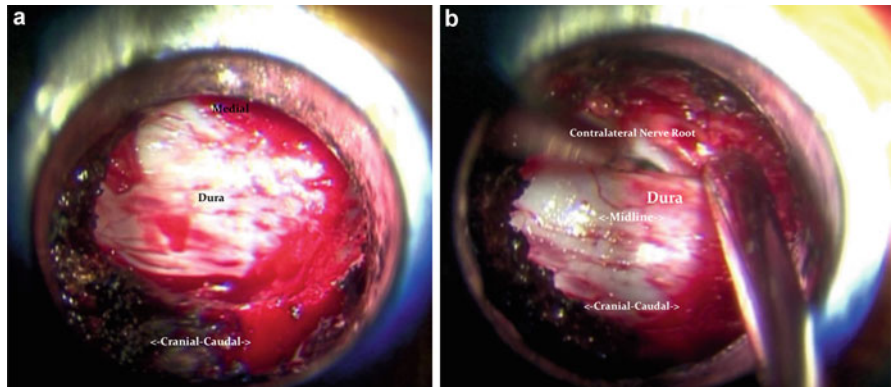

Fig. 3 (**a**–**b**) Intraoperative photos of Ipsilateral and contralateral laminectomy through tubular dilator

diameter of the intended tubular dilator (Phillips et al. 2014) (Fig. 3). Of note, in obese patients (BMIs >30), a more lateral incision may be necessary to obtain adequate visualization. There will be two distinct fascial layers present deep to skin incision. The superficial fascia represents that thoracodorsal fascial, and the deeper, thinner fascia represents that of the multifidus muscle (Schwender 2018). Both fascial incisions should extend slightly beyond that of the skin incision to allow for small adjustments by the surgeon. Once through the fascia of the multifidus, sequential tubular dilators are then used. The initial and smallest dilator is placed (docked) at the caudal edge of the lamina. Larger dilators are then placed over the initial dilator until an appropriately sized surgical window is created. Different procedures call for different diameter retractors. In the case of a microdiscectomy, 16–18 mm retractors are usually large enough for the procedure. The dilators are then removed and the retractor is placed in the muscular window. The retractor is then secured to the surgical table using a bracket mounted to the bed frame. Its location is then confirmed once again using fluoroscopy. Using a high-speed drill, a laminotomy is performed until the level of the ligamentum flavum. The flavum is then excised in a medial to lateral fashion using a Kerrison. The exposed nerve root is identified and protected and is gently retracted medially using a nerve root retractor. Using a bayonetted disc blade, an incision is made through the annulus fibrosis (Kimball and Yew 2013). Careful attention is paid to confirm the adequate decompression of the neural elements: thecal sac, nerve roots, and neural foramen. The surgical portal is then irrigated with saline, hemostasis is ensured, and the retractors are removed. The incision is closed in a layered, watertight fashion (Kulkarni et al. 2014).

MIS Laminectomy

A laminectomy in an appropriate selected patient can lead to significant reduction in neurogenic pain and its associated disability. It also has been shown to significantly improve patient-reported health-related quality of life (Shamji et al. 2015). Laminectomies are most often used to treat multilevel spinal stenosis, which is common in the aging population.

When evaluating the literature surrounding MIS laminectomy compared to open laminectomy, evidence supports that MIS procedures may be associated with less operative blood loss and shorter hospital stays (Terman et al. 2014). In a meta-analysis, Phan and Mobbs (2016) demonstrated that patients undergoing MIS laminectomies reported lower VAS scores as compared to the open approach, high rates of satisfaction, lower rates of blood loss, and thus lower rates of transfusions. They did note that reoperation rates were similar between both groups.

Much like the MIS discectomy, the MIS laminectomy utilizes the same overall approach.

The main differences that should be noted are the size of the tubular retractor is larger and there is more extensive bone and ligamentum flavum resection in order to obtain adequate neural decompression. Also it should be noted that the level of intended decompression will largely determine the necessary position for the tubular retractor. If the intended decompression is L1–L4, then the tubular retractor will be oriented more vertical and closer to the midline as compared to a decompression of L4–L5 or L5–S1 (Parajon and Hartl 2017). This is based on the anatomical bony structure of the vertebral bodies at those levels. Once the retractor is placed appropriately, a laminectomy is performed. The ligamentum flavum is then identified and removed. In cases where contralateral decompression is needed, the tube is repositioned medially; careful attention is needed as to not entrap soft tissue into the tube (Parajon and Hartl 2017). The table is then tilted away from the surgeon. The base of the spinous process is then drilled and undercut. The contralateral lamina is now removed using a high-speed drill and a Kerrison. Attention is now taken to the ligamentum flavum of the contralateral side and is removed. Some surgeons may benefit from utilization of a 90° Kerrison to aid them at this point. Once all of the flavum is removed, the table is then returned to its original position, hemostasis is ensured, and retractors are removed (Phillips et al. 2014; Watkins III and Watkins IV 2015).

MIS Transforaminal Lumbar Interbody Fusion (TLIF)

First described in early the 2000s, the TLIF provided an alternative to the standard posterior lumbar interbody fusion (PLIF) (Moskowitz 2002). A standard PLIF requires a midline incision through which exposure of the entire spinous process, bilateral lamina, and disc space is needed. This approach also places a fair amount of stress on the nerve roots as they are retracted out of the surgical field in order to garner access to the disc space. In the TILF a more lateral approach is made over the paraspinal muscles and directed toward the midline. This approach also allows for preservation of the contralateral side and requires less mobilization of the thecal sac and less risk of injury to a nerve root. There are also minimal retraction of the spinal nerves and decreased approach-related complications and morbidity as compared to the PLIF (Rosenberg and Mummaneni 2001). As a way to minimize the soft tissue trauma associated with open fusion procedures, Isaacs and colleagues described the minimally invasive transforaminal lumbar interbody fusion (MIS TLIF) (Hartl and Gelb 2017). In his original study, Issacs et al. compared their novel MIS TLIF techniques to standard single-level posterior interbody fusions at the same institutions. The authors concluded that patients undergoing the MIS TLIF had decreased hospital length of stay, decreased intraoperative blood loss, and received approximately 50% less postoperative narcotics as compared to the standard PLIF group (Isaacs et al. 2005). These outcomes were directly related the surgical approach in which normal tissue destruction was minimized. Common indications for a TLIF are foraminal stenosis, sagittal deformity, and central stenosis in patients with instability.

Following the same principles of tubular surgery described above, the MIS TLIF can be accomplished (Ozgur et al. 2006). Certain initial differences that should be highlighted are for one, the start point. The incision is initially made 4–5 cm lateral to the midline. This allows for an oblique entry into the spinal canal. As previously mentioned, the start point may have to be adjusted for larger patients. The desired visualized field for a TLIF is the inferior articulating facet joint of the level to be fused. In this, the capsule of the facet complex is entered and removed, and then the superior facet is resected down to the superior aspect of the pedicle (Hartl and Gelb 2017). The pedicle is then skeletonized. The ligamentum flavum is now exposed and can be removed in a piecemeal fashion using a Kerrison. The disc should now be visualized, and a discectomy is performed. Once the desired portion of disc is removed, the space is inspected to ensure adequate decompression. Bone graft and a structural implant are inserted to help preserve height and fuse the level. A MIS posterior fusion can

sometimes be indicated. Because transverse processes are not exposed in the approach, the only surface area exposed following the decompression is the interbody space.

Lateral Interbody Fusion

First described by Pimenta at the Brazilian Spine Society Meeting in 2001 and via publication by Ozgur in the early 2000s, the lateral interbody fusion was a way to gain access into the lumbar spine via a minimally invasive far lateral approach. The procedure is performed via incisions that dissect down through the retroperitoneal fat and psoas muscle on to the vertebral body. The procedure provides good access of the anterior portion of the spine and accomplishes this without having to approach the spine via an anterior trans-peritoneal route (Ozgur et al. 2006). The use of a general surgeon is also avoided, as a spine surgeon can accomplish this minimally invasive method safely. In his report Ogzur notes that possible advantages of this procedure as compared to a standard anterior approach to the spine include no need for a general surgeon, no need to retract the aorta and IVC, simple operative technique as compared to laparoscopic methods, and avoidance complications of laparoscopic and open approaches. The entire procedure is performed under direct vision, and there is little to no impairment of the surgeon's depth perception. Serious complications of the standard anterior approach, damage to great vessels and superior hypogastric nerve plexus, are avoided because of the lateral entry. Some the most common complications associated with the lateral approach are sensory nerve injury and psoas muscle weakness (Fujibayashi et al. 2017).

Some of the main indications for patients to undergo a lateral interbody fusion are lumbar scoliosis, spondylolisthesis, foraminal or central stenosis, and according to newer reports corpectomy and stabilization in trauma patients (Isaacs et al. 2010). In this procedure, the patient is placed in the lateral decubitus position on a table that is able to flex. Attention is made to pad all bony prominences. The greater trochanter of the patient is located at the apex of the bend in the table. Of note, in choosing the entry side, a few considerations should be made. If the patient lacks a coronal plane deformity, then the preferred entry site is the left side of the patient, as the great vessels are located more anterior as compared to the right side (Pawar et al. 2015). If the patient has a coronal plane deformity, then the spine should be approached from the concavity of the lumbar curve. This allows for access to multiple levels of the spine, with a single skin incision. Once the desired side is chosen and the patient is positioned appropriately, the patient is secured to the table using tape or straps. Using fluoroscopy, true AP and lateral x-rays are taken, and the anterior and posterior borders of the vertebral body are identified. The patient is then prepped and draped in the usual sterile fashion (Fig. 4).

A skin incision is made in an oblique fashion from the anterior inferior caudal vertebral body to the posterior superior portion of the next adjacent vertebral body. The deep dissection continues through the subcutaneous fat and abdominal muscles to the retroperitoneal space. When dissecting through the abdominal muscles, attention is made to split muscles in line with the fibers. Between the internal oblique and the transverse abdominal muscle lie the iliohypogastric and ilioinguinal nerves, so care is made as to not cause excessive trauma to this region. Once at the retroperitoneal level, the surgeon can gently sweep the peritoneum anteriorly, lifting it off of the psoas muscle. Using intraoperative neuro-monitoring the fibers of the psoas muscle are splint in the anterior to middle third of the muscle (Ozgur et al. 2006). This location, coupled with neuro-monitoring, ensures that lumbar plexus nerve roots are not harmed. Once the level of disc space is reached, the location is confirmed with fluoroscopy. Now using tubular dilators, the surgical portal is enlarged until a self-retaining retractor is then introduced and secured. A discectomy is then performed in a standard fashion, and a structural implant is placed. Posteriorly, percutaneous pedicle screws can then be inserted as required.

Fig. 4 Image demonstrating patient positioning for lateral interbody fusion

Sacroiliac (SI) Joint Fusion

The SI joint is a complex synovial joint that connects the spine to the pelvis via many ligamentous and muscular attachments. Imbalance between any of these can lead to altered biomechanics, which often lead to pain and disability (Hungerford et al. 2003). Often this pain is overlooked as a pain generator as patients may report many non-focal symptoms such as back, groin, or gluteal pain. Prior trauma to the pelvic region, prior lumbar fusion, and large body habitus are all risk factors for SI joint dysfunction. Once the SI joint is isolated as the source of the pain, non-operative treatments are initially recommended. Treatments such as physical therapy, exercise, steroid injections, NSAIDs, and in some cases nerve ablation are all recommended prior to surgery. If these measures fail and the patient reports persistent pain lasting greater than 6 months or a sudden worsening of nerve function, then surgery would be indicated. Historically the SI fusion initially was performed without any screws via an incision made over the posterior superior iliac spine, articular cartilage was removed, and bone graft was placed (Smith-Petersen 1921). This method called for long periods of external stabilization by either bracing or casting, to ensure that fusion occurred. Internal fixation for SI fusions began to appear in the literature in the 1980s. This eliminated postoperative bracing, but due to the morbidity of the approach, extent of bone grafting, and lengthy hospital stays, this was not favored among patients (Moore 1997). With the advent of MIS approaches to the SI joint, the open procedure fell out of favor. A 2012 survey of spine surgeons globally noted that 85% of SI joint fusions were occurring via MIS techniques (Smith et al. 2013). In comparing open fusions to MIS SI joint fusions, MIS has shown to have shorter surgical times, less blood loss, shorter duration of hospital stays, and larger decreases in postoperative VAS scores (Smith et al. 2013).

For a MIS SI fusion, the patient is positioned prone on radiolucent spine operating room table. The patient is then prepped and draped in the usual sterile fashion. Using fluoroscopy, the affected joint is localized. Using a lateral view in which the sacral slopes are super-imposed, the appropriate trajectory is identified (Miller and Block 2014). Next a 2 cm lateral incision is made. The tissue is dissected and a dilator is advanced through the incision until it contacts

bone. Its location can be confirmed with fluoroscopy. Next the dilator is removed and guide pin is drilled, first into the outer cortex of the ilium. Once this location is confirmed and the pin is perpendicular to the SI joint, it is advanced until it abuts the sacral cortex. The guide pin remains in place, and a 9 mm dilator is placed over it. Attention is paid to ensure that no soft tissue becomes entrapped in the dilator. Next a cannulated drill is passed over the guidewire and only the ilium is drilled. These shavings of cortex are saved on the back table for use later in grafting. Attention is now turned to preparing the SI joint for fusion. This is accomplished via insertion of a flexible decorticator (Kube). The cartilage is removed and the joint space is partially decorticated. The joint is then irrigated with saline, and dilators are reinserted. Bone graft is inserted into the cavity. A guidewire is then replaced and passed into the sacral cortex; its location is confirmed with C-arm. A cannulated screw is then placed over the guidewire and into the sacrum. Wound closure occurs in a watertight fashion.

Application of MIS to Deformity Correction

The previous sections discussed both the origins and the applications of MIS techniques to common spinal procedures: discectomy, laminectomies, and single-level fusions. In this section we will explore the literature surrounding the usage and benefits of MIS application to the field of adult deformity surgery (ADS). Historically deformity correction surgery in adults was associated with a major complication rate around 7.6% (Glassman et al. 2007) and an overall complication rate as high as 70% (Anand et al. 2014a). Major patient risk factors for complications are a sagittal vertical axis (SVA) great than 4 cm, age greater than 60 years old, and more than three medical comorbidities (Auerbach et al. 2016). As is the case with other procedures in spinal surgery, the overall goals of deformity surgery are to decompress the neural elements that are being impinged and establish/restore the global sagittal alignment. It has been demonstrated in great detail that kyphosis is poorly tolerated in lumbar region of the spine and has a direct correlation with the severity of patient-reported symptoms (Glassman et al. 2004). In attempting to measure outcomes following major ADS, Lafage et al. (2009) noted that both SVA and pelvic tilt as a measure of pelvic position have the highest correlation with health-related quality of life. Failure to restore a SVA <50 mm and a pelvic tilt less than 20° has been show to be associated with poor clinical outcomes. These goals can now be accomplished using the MIS techniques previously described and in some instances have better patient outcomes than conventional open procedures. Each clinical scenario is unique and requires a thoughtful and methodical process in planning for surgery. While MIS techniques are often sufficient to accomplish the goal, at times, there is a mix of MIS procedures and open surgery, termed hybrid surgery.

Percutaneous pedicle screw fixation's (PPSF) role in spinal deformity and spine trauma has been shown to be a safe and efficacious alternative to open surgery. Briefly, in this application, the patient is positioned prone on a radiolucent spine table, with bony prominences padded. The type of intraoperative imaging used is at the discretion of the surgeon as both navigation and fluoroscopy have been shown to be safe for pedicle screw placement (Park et al. 2010). This overview details usage of intraoperative biplanar fluoroscopy. X-rays are taken in the AP plane prior to any incisions to ensure that the superior endplate is flat (Anderson et al. 2007) and the pedicle-spinous process interface form an imaginary inverted "V." In the lateral view, careful attention is made to ensure that a single flat superior endplate and only a single pedicle shadow are identified. In obtaining orthogonal views, the relative positions of landmarks are identified (Fig. 5) (Aleem et al. 2017). An incision is then made approximately 4.5 cm lateral to the pedicle border. The fascia is incised and blunt dissection is used to obtain access to the junction between the transverse process and facet. A Jamshidi needle is then used to violate the dorsal pedicle in a lateral to medial fashion. Using AP and lateral imaging, the Jamshidi is advanced to the posterior cortex of the

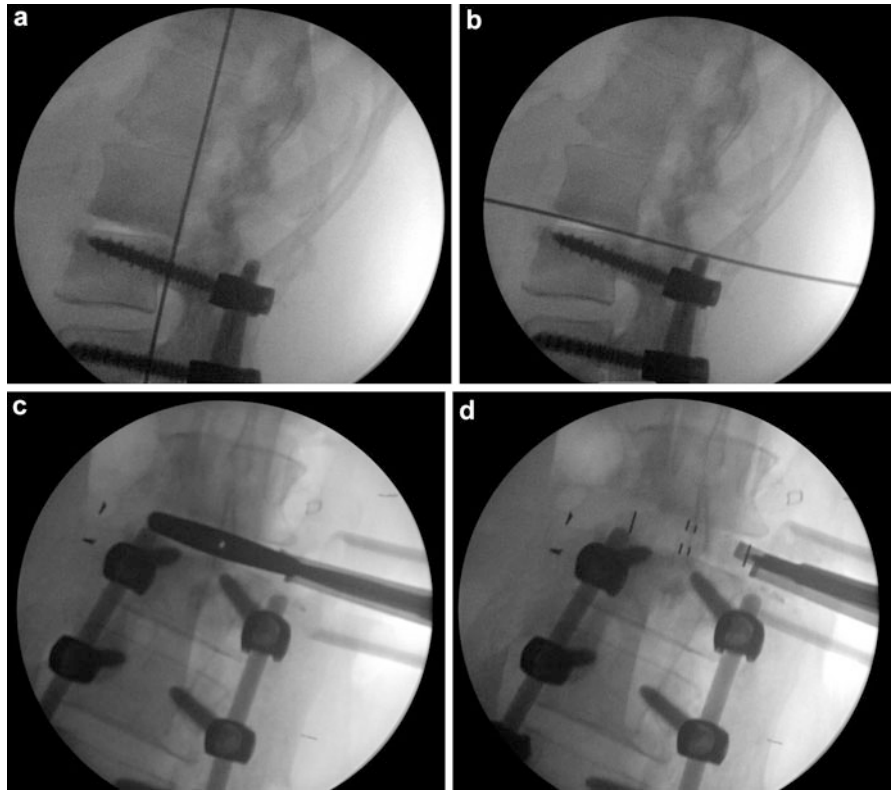

Fig. 5 (**a**–**d**) Intraoperative fluoroscopic images demonstrating level confirmation, endplate preparation, and implant plantation

pedicle (Figs. 6 and 7). The needle should be located in the center of the pedicle on lateral imaging, and it should never cross the medial border of the pedicle on AP imaging. Once in a satisfactory location, the needle is removed and replaced with a guidewire. A tap is used over the guidewire to expand the cortical opening. The guidewire should not be advanced beyond its initial placement, as this could potentially injure the great vessels located deep to it. Once tapping is completed, the tap is removed and replaced with a cannulated pedicle screw (Fig. 8). This process is then repeated, as indicated by the pathology. Once all screws have been placed, a rod is introduced usually from the most proximal screw's incision, and the desired reduction is performed. Aleem et al. described the technique of MIS screw fixation in detail (Fig. 9).

In his study Tinelli et al. demonstrated that using a MIS system in the setting of spinal trauma, his group was able to accurately place almost 98% of 682 pedicle screws in 131 fractures. The remaining 2% of screws were suboptimally placed, but not to the extent where revision surgery was necessary (Tinelli et al. 2014). Anand et al. were able to show that correction of adult lumbar degenerative scoliosis could be corrected with PPSF. He reported that multi-segment spinal corrections could be performed with less blood loss and less morbidity than open corrections (Anand et al. 2008).

Intraoperative fluoroscopy is a necessity in most cases when attempting PPSF in patients with deformity. For proper screw placement, it is imperative that both tilting view and wig-wag views are obtained if the case calls for it. As a technical note, one must ensure that one is orthogonal to the targeted pedicle to ensure proper location. If the operative case is not technically demanding and the surgeon is

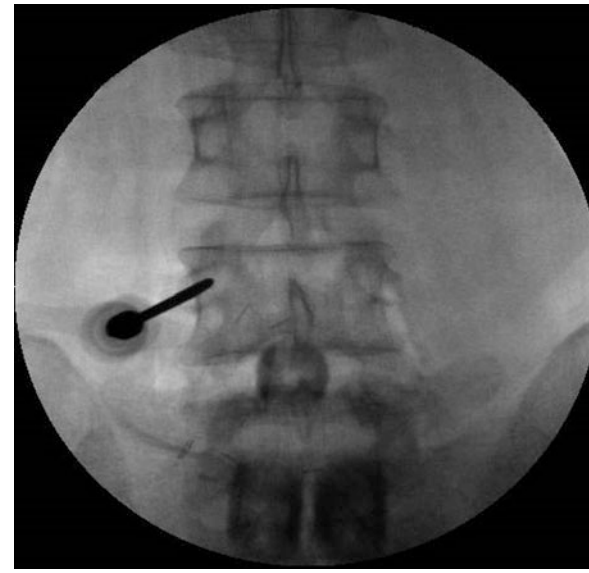

Fig. 6 AP image showing Jamshidi needle docked at start point on lateral edge of the pedicle at roughly the 9 o'clock position

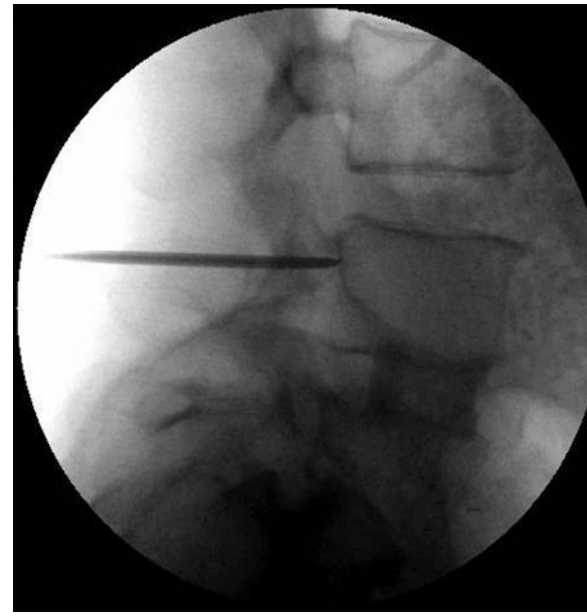

Fig. 7 Lateral fluoroscopic image showing Jamshidi needled in center of pedicle

experienced enough, use of a single anteroposterior C-arm can be sufficient for proper screw placement. Ahmad and Wang (2014) demonstrated this, when 410 pedicle screws were placed in patients with at least 10° of axial rotation. He noted that he had 15 grade 1 violations, 6 grade 2 violations, and 8 grade 3 violations and only 2 screws were required to be revised. Of note the Gertzbein classification is most often used when discussing pedicle screw placement and location relative its medial or lateral wall. There are four grades in the classification ranging from 0 to 3. Grade 0 indicates that there is no breech of pedicle; grade 1, <2 mm breech; grade 2, 2–4 mm breech; and grade 3, >4 mm breech of the pedicle.

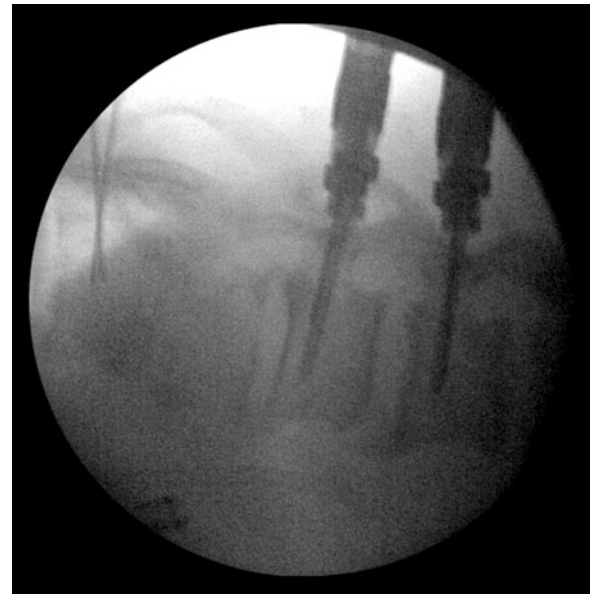

Fig. 8 Lateral fluoroscopic image showing pedicle screws with attachments

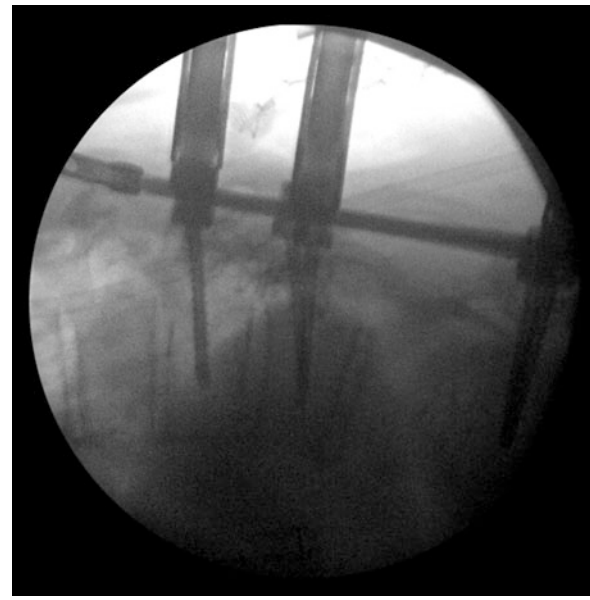

Fig. 9 Lateral fluoroscopic image showing rod capture in all screw heads

Role of Lateral Interbody Fusions

Lateral MIS approaches to the spine have numerous advantages compared to anterior approaches and however may be limited in their ability to sufficiently correct sagittal deformities in adults in isolation (Costanzo et al. 2014). In his systematic review, Costanzo et al. looked at the role of MIS lateral lumbar interbody fusions in sagittal balance and spinal deformity. He concluded that there is no clear answer with regard to how well MIS can correct sagittal balance and noted that open posterior osteotomies would continue to be the gold standard in sagittal balance

correction (Costanzo et al. 2014). Acosta et al. performed a retrospective radiographic study looking at changes in coronal and sagittal plane alignments following lateral interbody fusions. Statistical improvements in the visual analog scale (VAS), the Oswestry Disability Indices (ODI), and the coronal Cobb angle were noted; however, no statistically significant change in the overall sagittal alignment was identified by a postoperative SVA measurements. They concluded that direct lateral interbody fusions alone are insufficient to correct for sagittal imbalance (Acosta et al. 2011). Deukmedjian et al. evaluated a novel technique for attempting to restore a normal SVA. In their study, they utilized a MIS lateral approach to first release the anterior longitudinal ligament and place a 30° hyperlordotic cage. Following this, percutaneous pedicle screws were placed posteriorly to help stabilize the construct. This resulted in a 17° segmental lordosis increase per level as well as an overall SVA decrease of 49 mm and a 7° pelvic tilt (Deukmedjian et al. 2012). Manwaring noted that a two-stage MIS procedure was comparable to Smith-Peterson osteotomies (SPO), because of its ability of providing disc height and correcting coronal imbalance (Manwaring et al. 2014). The first stage of the procedure involved lateral interbody fusions with or without anterior column releases (ACR). The second stage involved PPSF. A 12° improcvement in segmental lordosis and a 31 mm improvement in SVA per ACR level released were noted. Anand et al. have since adopted these principles of staged MIS procedures and proposed a protocol for MIS correction of adult spinal deformity (Anand et al. 2017). Much like Manwaring, Anand proposed that a lateral interbody fusion should occur in the first stage, with or without an ACR. He reports that avoiding an open surgery can avoid potentially serious postoperative complications.

Wang et al. (2014) described the ceiling effects for deformity correction of three different spinal surgery techniques: stand-alone (lateral MIS procedure), circumferential MIS (combined lateral with posterior), and hybrid procedures. The authors note that the ceiling effect in the coronal plane for all three procedures were as follows: 23° for stand-alone, 34 for cMIS, and 55° for the hybrid procedure. A statically significant alteration in the SVA occurred only in the hybrid procedure group, but this was overshadowed by high rates of complications in the hybrid group. Anand et al. (2014b) previously reported that the max SVA correction obtainable is 10 mm utilizing MIS techniques without osteotomies.

Limitations of MIS in ADS

As already noted, not all patients can or should undergo a MIS procedure. The decision to undergo a MIS procedure is ultimately left up to the shared decision-making of the surgeon as well as the patient. The goal should be to safely address surgical pathology and provide the best clinical outcome for the patient. In cases where the decision to proceed with a MIS procedure for ADS is made, some important patient factors should be considered, such as presenting symptoms, physical exam findings, and radiographic findings. Utilizing MIS in deformity surgery presents some unique limitations such as limited sagittal correction, decreased ability for in situ bending and compression, concern for sub-optimal correction, and pseudoarthrosis if interbody fusions are not performed. Since MIS procedures contain some level of a learning curve, inexperienced surgeons are likely to have increased operative times and increased cost of service as well as potentially increased radiation exposure to the patient and surgical team.

As a way to help surgeons select patients that can possibly benefit from MIS, the International Spine Study Group (ISSG) published a rational framework for decision-making in 2014. In this algorithm radiographic parameters are used to guide decision-making. The parameters used in the decision-making tree are SVA, PT, LL-PI mismatch, coronal Cobb angle, curve flexibility, and amount of listhesis. At its core the algorithm is based upon the idea that MIS is limited in its ability to treat sagittal plane deformities (Mummaneni et al. 2014).

Role of Navigation in MIS

As surgical technologies continue to advance, their contributions to surgical procedures are continually investigated. In the last 20 years, image guidance and navigation have come a long way in assisting the surgeon in accurate and safe positioning of hardware. Tajsic et al. (2018) evaluated and compared C-arm navigated, O-arm navigated, and conventional 2D fluoroscopy-assisted MIS techniques. Outcomes that were analyzed included operating time, radiation exposure, and the accuracy of pedicle screw placements. They concluded that pedicle screws placed with the assistance of the O-arm had the lowest rate of malpositioning (1.23%) and screws placed with 2D fluoroscopy were misplaced 5.16% of the time. However, O-arm usage was associated with highest rate of single image radiation exposure as compared to the other two modalities. Among all three modalities, operating room time was comparable. They concluded that given increased accuracy of pedicle screw placement, acceptable doses of overall radiation exposure, and comparable operating room time, the O-arm is the best form of intra-op navigation. Other studies have validated the usage of O-arm in MIS surgeries (Kleck et al. 2018; Chachan et al. 2018).

Robotics in MIS

As surgeons attempt to tackle more complex cases in the aging population, the indications for surgical fixation continue to evolve. As such, methods of attempting to reduce overall radiation to the patient and surgical team also evolve. The use of robotic-assisted pedicle screw placements has been discussed in the literature as a way to circumvent excessive intra-op radiation exposure. To our knowledge there has been only one randomized controlled trial comparing MIS robotics to open fluoroscopic-guided posterior lumbar interbody fusion (Hyun et al. 2017). The average per-screw radiation in the robotic-assisted surgeries was 37.5% of the per-screw exposure in the fluoroscopic group. Over all there was a mean reduction in radiation of 62.5% in the group undergoing robotic-assisted surgery. The results of the study are promising, but further data is needed to validate the routine use of robotics in MIS spinal surgeries.

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Cervical Spine Anatomy

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Contents

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Abstract

An in depth understanding of cervical spine anatomy is essential to the diagnosis and management of cervical spine pathology. From the osseous anatomy down to the soft tissues structures that function to stabilize, maintain, and protect the spinal cord clinicians must be able to appreciate the biomechanics and the complex anatomy. For patients managed operatively, appropriate surgical planning and operative technique rely heavily upon a sound understanding of the intricate anatomy in this region. In this chapter we detail the cervical spine anatomy with particular emphasis on the osseous, muscular, ligamentous, and neurovascular tissues with the goal of providing clinicians a comprehensive review that they can depend on and refer to when treating patients with cervical spine disease.

Keywords

Anatomy · Cervical spine · Vertebrae · Review

Introduction

The cervical spine consists of seven vertebrae. Each is named according to its corresponding order from C1 cranially to C7 caudally. After completion of embryonic development first two vertebrae are unique in that they do not contain a typical vertebral body and are referred to as the "atlas" (C1) and "axis" (C2), respectively (Fig. 1). These two vertebrae form the atlantoaxial complex of the upper cervical spine. The remaining vertebra (C3–C7) is referred to as the subaxial cervical spine. The overall sagittal plane alignment is concave posteriorly, resulting in an overall lordotic curvature to a normal cervical spine. Each vertebra has an associated nerve root exiting bilaterally above the pedicle and through the foramina, which are referred to as C1–C7. The C8 nerve root exits below the pedicle of C7.

Atlantoaxial Complex

C1

The C1 vertebra (*atlas*) is a ring-shaped structure that is unique from C3 to C7 in that it lacks a robust vertebral body. It instead has an anterior tubercle, which is the attachment site for the longus colli muscle. On the posterior aspect of the ring is the posterior tubercle, which provides attachment points for the rectus capitis posterior minor muscle and the suboccipital membrane. Both the lateral aspects of the anterior and posterior tubercles create semicircular structures called the anterior and posterior arches. The junction of these arches on the lateral-most aspect of the rings

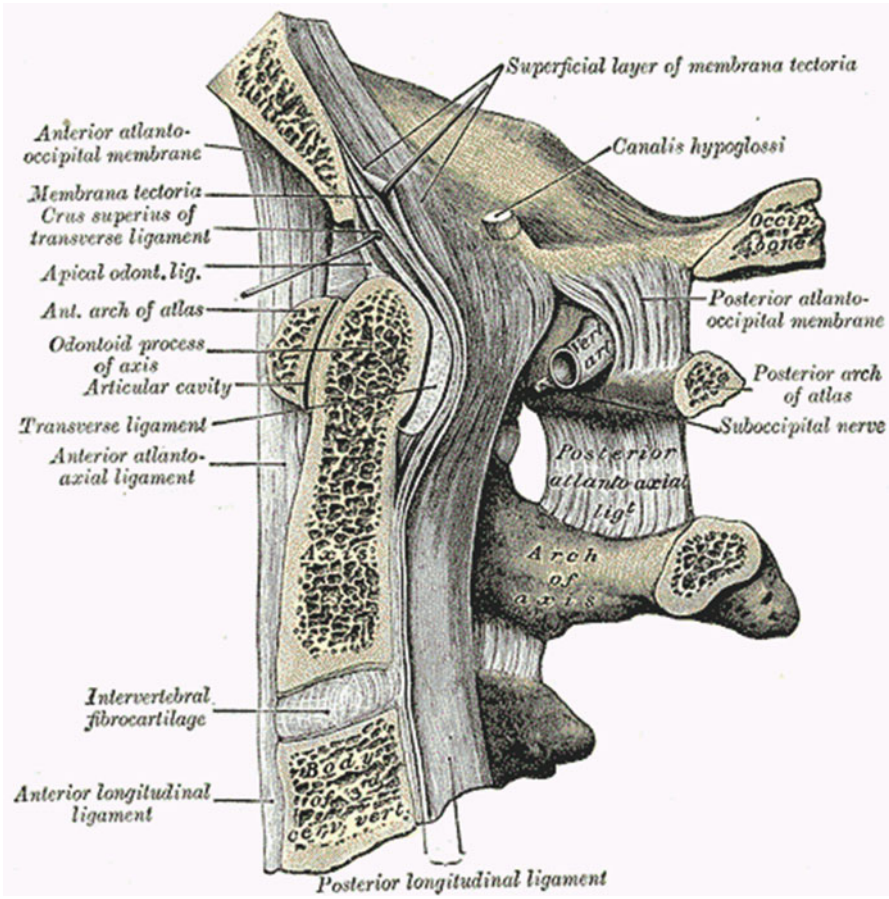

Fig. 1 Midsagittal graphical representation of the upper cervical spine. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 308, Public Domain)

form the lateral masses. Each lateral mass is composed of an articular process on both the superior and inferior aspects of the lateral mass. The superior articular process is concave and oriented inferiorly and medially, allowing for a congruent articulation with the occiput bilaterally. Inferiorly, the processes are oriented with a sloped angle inferiorly and laterally, allowing for an articulation with the superior articular processes of C2 (*axis*) (Daniels et al. 1983; Parke and Sherk 1989). Just posterior to the lateral mass is a subtle groove, in which the vertebral artery courses. The atlas' superior and inferior articulations allow for primarily flexion and extension, as well as lateral bending (Panjabi et al. 1991a). On the posterior aspect of the anterior tubercle, on the inner aspect of the anterior arch at the midline, is a subtle indention that allows for an articulation with the dens of the axis (Fig. 2). Additionally, there are insertion sites just anterior and medial to the lateral masses on the inner aspect of the ring for the transverse ligaments, which also attach to the posterior aspect of the dens of the axis. Extending laterally from each lateral mass is the transverse process. The transverse process at this level houses the vertebral arteries before they exit the vertebral column and enter the foramen magnum in order to become an intracranial structure. A subset of the population has an anatomic variation consisting of an osseous bridge that covers the ridge containing the vertebral artery; this variation is termed an arcuate foramen or ponticulus posticus and is estimated to have a 3–15% prevalence in the population.

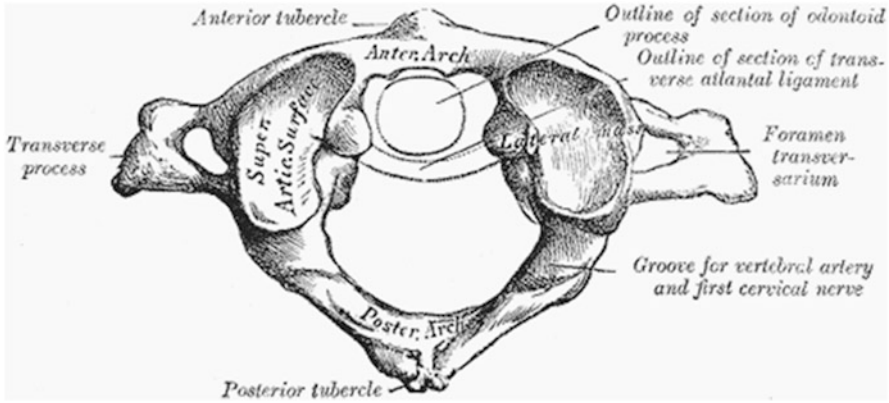

Fig. 2 Axial representation of the C1 vertebra, or atlas. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 86, Public Domain)

C2

Like C1, the C2 vertebra (*axis*) is unique in that has a bony prominence that projects cranially termed the odontoid process or dens. Anteriorly, the odontoid has a synovial articulation with the posterior aspect of the anterior tubercle of the atlas. This articulation allows for nearly half of the rotatory movement of the head and cervical spine. The posterior aspect of the odontoid has two subtle prominences that are the attachment sites of the alar ligaments, which span the atlas and attach medial to the posterior occipital condyles. These ligaments insert laterally at the base of the skull and provide stabilization of the atlantoaxial complex. The apical ligament attaches at the apex of the odontoid, which subsequently attaches to the anterior aspect of the foramen magnum at the midline. The primary stabilizer of the odontoid to the atlas is the transverse ligament, which is a structure that spans the anterior arch of the atlas and is a restraint to lateral displacement of the odontoid. The transverse ligament also has cephalad and caudal projections at the midline termed the cruciform ligaments which provide additional stability to the atlantoaxial complex. Posteriorly, the axis contains a bifid spinous process that serves as the attachment site for the rectus capitis posterior major and obliquus capitis inferior muscles attach. On the lateral aspects of the axis, there are both superior and inferior articular processes which articulate with the analogous structures on the adjacent vertebrae. The superior facet is sloped inferior laterally, congruent with the inferior facets of the lateral masses of the atlas. It is important to note that the sagittal diameter of the spinal canal in the upper cervical spine is greater than that of the lower cervical spine, allowing for adequate space for both the odontoid and the spinal cord. Steel's rule of thirds classically states that one-third of the canal diameter is occupied by the odontoid, one-third by the spinal cord, and the remaining one-third as free space preventing compression of the cord (Ebraheim et al. 1998). The transverse processes of the axis are directed caudally, containing the foramen transversaria that houses the vertebral arteries (Fig. 3).

Subaxial Cervical Spine

Unlike C1 and C2, the osteology of the five subaxial vertebrae share much in common. Each consists of a vertebral body anteriorly, which are separated by an intervertebral disc, bilateral transverse processes containing a foramen, pedicles, as well as two facet joints and a spinous process posteriorly. The subaxial spine, much like the entirety of the vertebral column, is to resist the compressive loads that are placed upon it. Additionally, the bony structures of the cervical spine act to protect important neurovascular structures and provide stability while allowing for functional flexion, extension, and lateral bending (Fig. 4a, b).

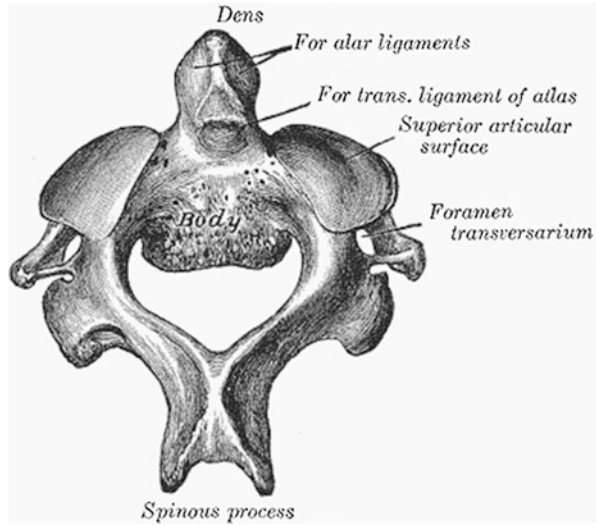

Fig. 3 Axial representation of the C2 vertebra, or atlas. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 87, Public Domain)

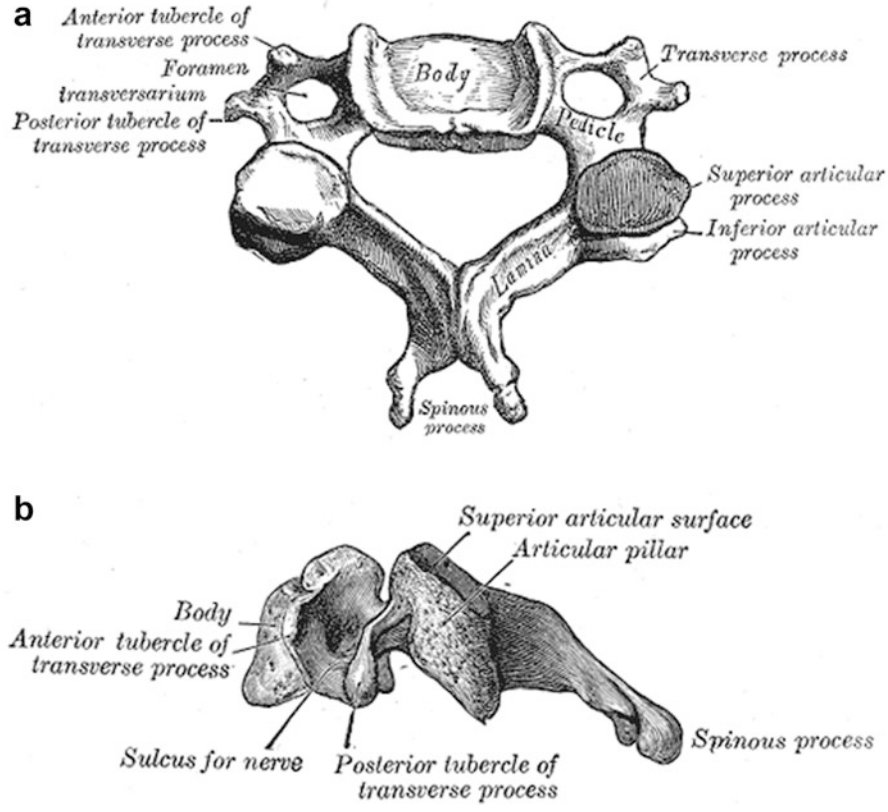

Fig. 4 (**a**, **b**) Axial and lateral representations of a subaxial cervical vertebra. (From: Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body*, Plate 84–85, Public Domain)

Vertebral Body

The anterior aspect of the vertebra is a relatively cylindrical structure called the vertebral body. The body withstands the majority of the compressive loads placed on the vertebral column, and each is separated by an intervertebral disc that functions as a shock absorber. With descending levels down the spinal column, the height of the body slightly increases in height, with the occasional exception of C6, which can be shorter than C7. Each level is larger in the coronal plan than in the sagittal plane. The diameter of each body in the coronal plane is larger than that in the sagittal plane. The superior aspect is concave, and the inferior aspect is convex. Both the superior and inferior aspects contain a shell of cortical bone called the end plate, which eventually transitions into the fibrocartilaginous intervertebral disc. In the coronal plane, the lateral superior aspects of the body demonstrate a lip of bone that projects cranially is congruent with the inferior and lateral aspects of the adjacent cranial body and make up the uncovertebral joint, or joint of Luschka. The uncovertebral joint is important in resisting lateral translation of the vertebra and helps limit lateral bending. Intraoperatively, the uncovertebral joints are important anatomical landmarks that aid in identifying the lateral extent of the body and can act as a reference point for identifying the midline when placing implants during anterior-based procedures.

Pedicles

Projecting dorsolaterally each side of the body is the pedicle, which connects the body to the posterior arch. Unlike the pedicles of the thoracic and lumbar regions, those in the subaxial spine are located midway between inferior and superior end plates of the body on the coronal plane. Descending down the subaxial spine from C3 to C7, the pedicle height increases from an average 5.1 to 9.5 mm, and width increases from 3 to 7.5 mm. Average width and height increase from 5 to 7 mm, respectively (An et al. 1999; Ebraheim et al. 1997; Panjabi et al. 1991b). Additionally, the pedicle angle transitions from 45° to 30° as it descends down the subaxial spine.

Transverse Process

Projecting laterally off of the posterior aspect of the body, anterior to the pedicle, are the bilateral transverse processes. Each transverse process contains both an anterior and posterior tubercle. The anterior tubercle is the origin of the longus colli cervicalis, anterior scalene, ventral intertransverse, and longus colli muscles. The posterior tubercle is the origin of the longissimus, levator scapulae, middle scalene, posterior scalene, splenius cervicalis, and iliocostalis muscles. The anterior tubercle of the C6 transverse process is also referred to as the carotid tubercle and is an important anatomical landmark, as it marks the transverse proves that separates the carotid artery from the vertebral artery. The transverse processes of C1 through C7 each contain a transverse foramen. The vertebral artery and vein travel through the transverse foramen of C1 through C6, and in the majority of cases, not through C7. The transverse foramen is bound by the lateral aspect of the pedicle, the posterior aspect of the anterior tubercle, and the anterior aspect of the posterior tubercle. Additionally, each transverse process contains a groove on its superior surface that runs posterior to the transverse foramen. This groove carries the exiting nerve at the corresponding level after it exits the neural foramen. For example, the groove on the C3 transverse process contains the exiting C3 nerve root.

Facet Joint

Projecting from both the superior and inferior aspects of the lateral mass is an articular process that is congruent with the adjacent articular process of the neighboring vertebra, which together comprises the facet joint. The superior articular process of the vertebra articulates with the inferior articular process of the cephalad vertebra, and the inferior facet of the vertebra articulates with the

facet of the superior articular process of the caudal vertebra. The facet joint is a diarthrodial joint with a relatively lax capsule that allows for appropriate motion to occur. In the sagittal plane, these joints are oriented obliquely from anterior-superior to posterior-inferior at approximately 45° (Fletcher et al. 1990). This orientation differs from the relatively vertically oriented facet joints in the coronal plane of the lumbar spine, and in conjunction with the relatively lax capsule, allows for a broad range of motion in flexion, extension, lateral bending, and rotation (Bland 1987). Just as in other diarthrodial joints throughout the body, the facet joint is susceptible to degenerative changes such as joint swelling, cartilage thinning, and osteophyte formation. Given its close proximity to the neural foramina and spinal canal, these changes can have significant clinical implications.

Spinal Canal

The cervical spinal canal is bordered ventrally by the posterior aspect of the vertebral body, ventrolaterally by the pedicles transverse near the location of the neural foramina, laterally by the lateral masses, and posteriorly by the lamina and spinous process. The lateral diameter of the spinal canal is larger than the anterior-posterior (AP) diameter at all levels of the subaxial spine. The AP diameter is approximately 17 mm at the C3 level and decreases to 15 mm at C7, which has the lowest cross-sectional area.

Lateral Mass

Located dorsolateral to the pedicle is a cylindrical piece of bone termed the lateral mass. The lateral mass is analogous to the pars interarticularis of the thoracic and lumbar spinal regions, as it is the structure that connects the superior and inferior articular surfaces that make up the cephalad and caudal facet joints. It is directly dorsal to the midportion of the transverse process, and as such it is in very close proximity to the exiting nerve root. It has a bony projection dorsomedially, which becomes confluent with the lamina. The lateral masses of the subaxial cervical spine have an average depth and width of approximately 13 mm and 12 mm, respectively, and slightly decrease at each descending level to C7 where it is thinnest (Mohamed et al. 2012). Given the relatively small pedicle size in this region of the spine, screw fixation within the lateral mass is sometimes a desired treatment option, and thus a proper understanding of the lateral mass size is crucial in avoiding complications.

Lamina and Spinous Process

The dorsomedial projection from the lateral masses is termed the lamina. As they continue posteriorly bilaterally, they merge to form the posterior-most bony prominence called the spinous process. The C2 through C6 vertebra are normally bifid, but the C7 spinous process is not. The lamina and the spinous process make up the posterior aspect of the spinal canal. An important anatomic landmark is the junction of the lamina and spinous process posteriorly.

Ligaments

The subaxial cervical spine contains an array of ligaments. The ligaments contribute significantly to the stability and alignment of the bony structures in the region and allow for motion in various planes while restricting extremes of motion that could compromise proper anatomic alignment and integrity of the local structures.

The anterior and posterior aspects of the vertebral bodies and intervertebral discs are bound by both the anterior and posterior longitudinal ligaments. The anterior longitudinal ligament (ALL) is composed of longitudinal fibers that run in a cranial and caudal direction spanning the base of the skull to the sacrum. The ALL attaches to the anterior surfaces of the vertebral bodies and intervertebral discs and acts as a restraint to hyperextension of the mobile segments of the vertebral column. The ALL is narrow and thick over the concave surface of the vertebral

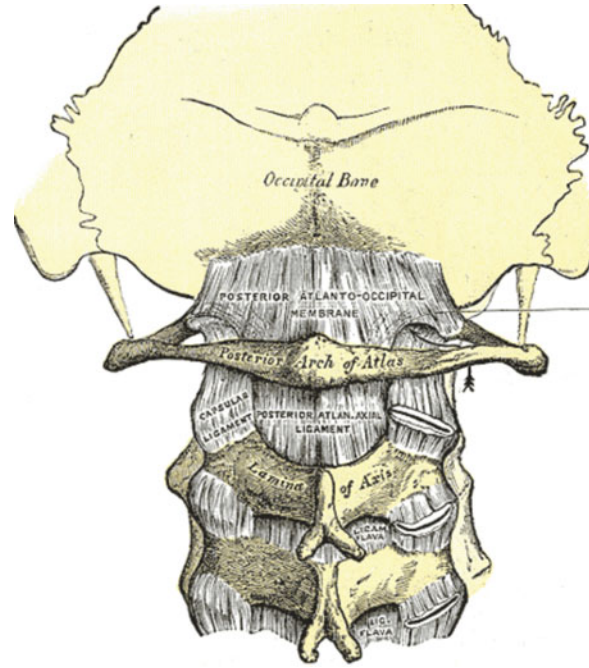

Fig. 5 Posterior representation of the upper cervical vertebra. (From: Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body*, Plate 305, Public Domain)

bodies but becomes more wide and thin over the discs. The posterior longitudinal ligament (PLL) also spans the length of the vertebral column, fanning out to form the tectorial membrane at its most cranial aspect, and attaches to the sacrum caudally. Just like the ALL, the PLL is more narrow over the bodies and wide over the discs (Parke and Sherk 1989) (Fig. 1).

The ligamentum flavum is a grouping of sequential ligaments located in the posterior segment of the vertebra, with the name arising from the relatively yellow appearance (Fig. 5). Each ligament traverses adjacent lamina, attaching anteriorly near the midportion of the cephalad lamina and running obliquely to attach to the superior most margin of the caudal lamina. These ligaments have a high elastin content that have the propensity to lose their elasticity along with the aging process. In such situations, anterior buckling of the ligaments may occur during extension which may in turn produce a mass effect in the spinal canal and contribute to spinal cord compression.

The ligamentum nuchae is composed of the interspinous and supraspinous ligaments. The interspinous ligament is a relatively thin structure that connects the spinous processes of adjacent vertebra. It runs obliquely from the anteroinferior aspect of the cephalad spinous to the posterosuperior aspect of the caudal spinous process. It is bound by the ligamentum flavum anteriorly and the supraspinous ligament posteriorly. The supraspinous ligament connects the posterior tips of the spinous processes along the length of the vertebral column. However, in the subaxial spine, these two ligaments are less distinct as individual structures until the level of C7 but rather form a complex of thick ligamentous elastic tissue that is referred to the ligamentum nuchae. The ligamentum nuchae runs from the inion of the occiput to the spinous process of C7 and acts as an attachment point for the nuchal musculature in the region.

Intervertebral Disc

The cervical spine contains six intervertebral fibrocartilaginous discs which separate the vertebral bodies (Fig. 1). There is no disc between the occiput and the atlas or between the atlas and the axis. The first disc is located between C2 and

the C3 body. The junction of the disc with the adjacent bodies is lined by a cartilaginous layer termed the end plates. The disc itself is composed of two primary components – the nucleus pulposus and the annulus fibrosus. The nucleus pulposus is the centrally located portion of the disc that is the remnant of the primitive notochord and is comprised with primarily type II collagen, proteoglycans, and water. This makeup of the nucleus pulposus results in a gelatinous type substance that allows for force dissipation to the annulus fibrosis and both end plates when compression is applied to the vertebral column. The annulus fibrosus is the component of the disc that surrounds the nucleus pulposus circumferentially and composed of type I collagen, proteoglycans, and water. It is characterized by multiple circumferential layers of fibers that run in an oblique pattern from the cephalad to caudal vertebral bodies. The annulus fibrosus has a high tensile strength that contributes to the stability within a pair of vertebra, which is assisted in the lateral direction by the uncovertebral joint. As the aging process progresses, the margin between the nucleus pulposus and annulus fibrosus becomes more difficult to distinguish (Bland and Boushey 1990). In the coronal view, the superior aspect of the disc is concave, and the inferior aspect is convex as to contour its respective adjacent end plates. The height of the intervertebral disc is slightly larger anteriorly than posteriorly, which contributes to the lordotic curvature of the cervical spine.

Fascia

Investing

The deep cervical layer of the neck is separated into compartments that can be used as landmarks during dissection. The investing layer is the most superficial layer and provides broad coverage to the trapezius posteriorly and wraps around anteriorly to enclose the sternocleidomastoid (SCM) as well. Superiorly, it reaches the hyoid bone and the caudal extent of the mandible and then dives inferiorly to capture both the suprasternal space and form the ceiling of both the ventral and dorsal cervical triangles (Fig. 6).

Pre-tracheal

The next layer is the pre-tracheal layer, which houses many structures and likewise is referred to by multiple names including the middle cervical fascia or the visceral layer. This multifaceted aponeurosis envelops the infrahyoid muscles as well at the omohyoid muscles which lie just superficial to the visceral space. This space is residence to important soft tissue structures such as the thyroid gland, larynx, trachea, and esophagus and deep to this layer run the thyroid vessels. Its superior attachments are the hyoid and thyroid cartilage and inferiorly to the clavicles and sternum. The carotid sheath makes up its lateral margin (Fig. 6).

Prevertebral

The prevertebral layer is a thick fascial plane that surrounds the vertebral column and its muscles. This layer includes the longus and the scalene muscles. The longus colli is a notable structure that aids in establishing midline during an anterior cervical approach. Identifying this structure also helps protect the cervical portion of the sympathetic chain during anterior dissection by retracting laterally. The alar layer is also included as part of the prevertebral layer and encloses the carotid sheath, which houses the vagus nerve, carotid artery, and internal jugular vein (Fig. 6).

Muscles

Ventral

The anterior cervical muscles can be divided into superficial and deep. The platysma is the most superficial layer and is a thin wispy muscle that begins from the mandible spreading inferiorly and laterally to the second rib and acromion process. It has neurovascular bundles that integrate into

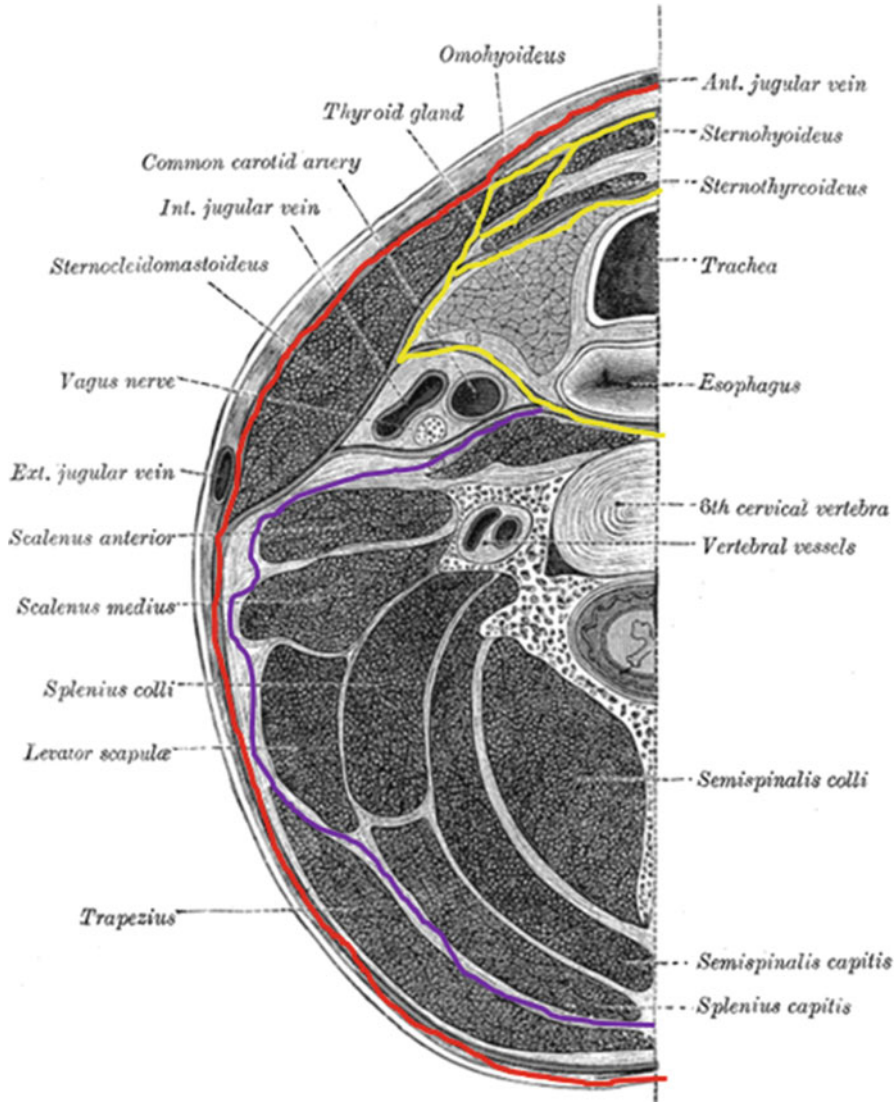

Fig. 6 Axial cuts of the neck at the level of the sixth cervical vertebrae demonstrating fascial arrangements: investing fascia (red), prevertebral fascia (purple), pretracheal fascia (yellow). (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 384, Public Domain)

the skin with its main function aiding in facial expression. Just below this lies the sternocleidomastoid (SCM) which has two heads of origin: the medical clavicle and the sternum that attach to the mastoid and occipital bones. It runs obliquely and functions to turn the head the contralateral side as well as flexion to the ipsilateral side (Fig. 7). It also separates the neck into different triangles, its contents which will be discussed later.

The next layer of muscles is the infrahyoid, scalene, and longus group. The infrahyoid muscles are a group of muscles, as the name implies, that attach to the hyoid bone. These include the mylohyoid, stylohyoid, geniohyoid, digastric, and omohyoid. The strap muscles of the larynx are the sternothyroid and sternohyoid which are important structures to landmark during an anterior approach because they have no direct

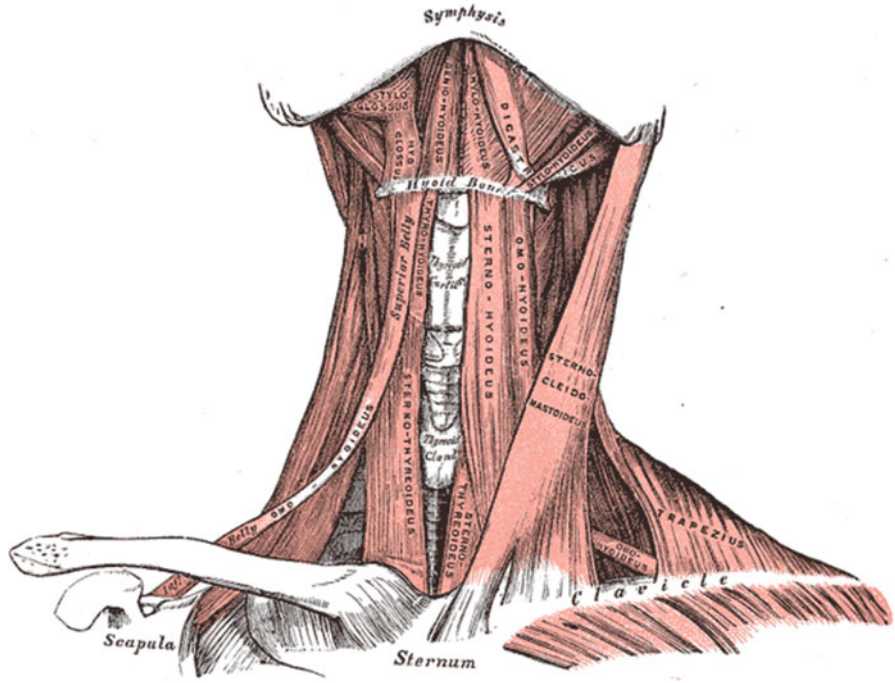

Fig. 7 Superficial ventral muscles of the neck. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 386, Public Domain)

involvement in cervical motion. The scalene group is made up of the anterior, medial, and posterior scalene muscles. The anterior muscle originates from the transverse process of the C3 to C6 vertebrae and inserts into the first rib. The medial arises from the posterior transverse process of C2 to C7 and also inserts on the first rib. The posterior scalene muscle has more variable course but originates from the posterior transverse process of C4 to C6 and inserts onto the second rib. This muscle group is well-known for its contribution to thoracic outlet syndrome, which results from neurovascular compression of either the subclavian artery or brachial plexus. The longus muscle group is composed of the longus colli, capitis, and rectus lateralis and as previously discussed are found within the prevertebral fascia. The longus colli originates from the anterior aspect of C3 to C6 and extends obliquely from C1 to T3 to attach onto the anterior atlas. The longus capitis arises from the anterior transverse process of C3 to C6 and attaches on the basilar aspect of the occiput. The rectus has two heads, an anterior and lateral head which originate from the lateral mass of the atlas and transverse process of the atlas, respectively. The anterior head will insert into the base of the occipital bone, while the lateral head will attach to the jugular process of the occiput (Fig. 8).

Dorsal

The dorsal muscle groups provide tension to the vertebrae to keep them in an upright position and deliver balance as well. These muscles are innervated by the dorsal rami. The erector muscles take advantage of the tension band principle to provide sagittal support and symmetric balance in an effort to preserve lordosis of the cervical region. Loss of strength, often attributed to pain, can lead to progressive loss of lordosis and a relative kyphotic deformity. In the coronal plane, the lateral tension bands provide support. Imbalance in any of these

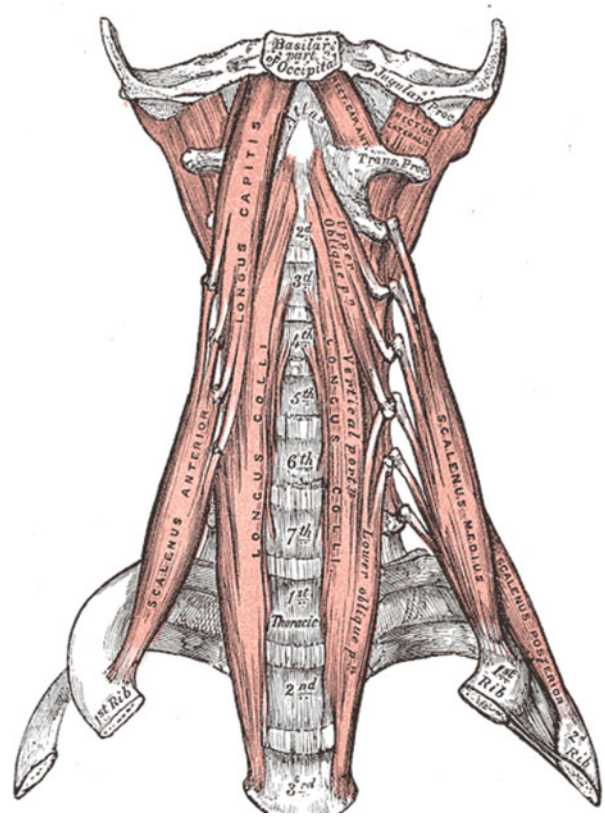

Fig. 8 Deep ventral muscles of the neck. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 387, Public Domain)

planes can lead to deformity seen in abnormal cervical spine curves. All the muscles in the dorsal compartment spread out into three layers discussed below.

Superficial Layer

From superficial to deep, this layer includes trapezius, splenius, and levator scapulae. These muscles work synergistically to rotate the head, extend, and laterally bend. The trapezius has a broad origin that extends along the cervical and thoracic spine. Its upper division begins at the occipital protuberance and attaches at the medial 1/3 of the clavicle. The splenius group consists of the capitis and the cervicis. The capitis begins from the ligamentum nuchae and the spinous process of C6 and inserts along the lateral 1/3 of the superior nuchal line and mastoid. The cervicis inserts along the posterior aspects of the transverse process of C1–C4. The levator scapulae originates along the same posterior tubercles of C1–C4 transverse process and insert along the medial border of the scapula between the superior medial angle and scapular spine (Fig. 9).

Intermediate Layer

This layer includes the erector spinae group which has a common original at the iliac crest, sacrum, and lumbar spinous process. These muscles consist of the iliocostalis, the longissimus, and the semispinalis from lateral to medial. They work together to extend and bend the neck in the coronal plane. The iliocostalis group inserts into the posterior tubercles of the C4–C6 transverse process; the longissimus group inserts on the mastoid process. The semispinalis group inserts along the spinous process of the cervical spine (Fig. 10).

Deep Layer

The transversospinalis group makes up the deepest layer and lies along the spinous process and lamina of the cervical spine. They consist of the multifidus and rotator muscles. They are

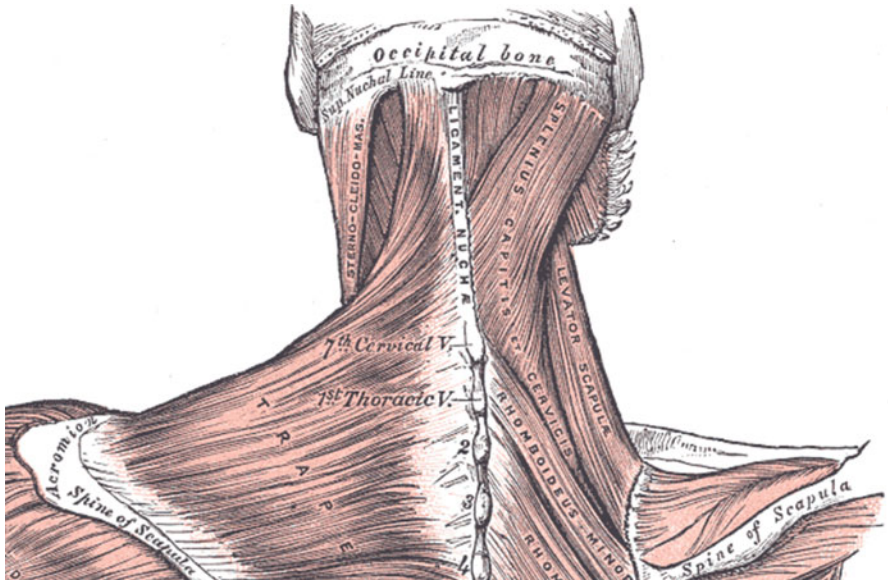

Fig. 9 Superficial dorsal muscles of the neck. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 409, Public Domain)

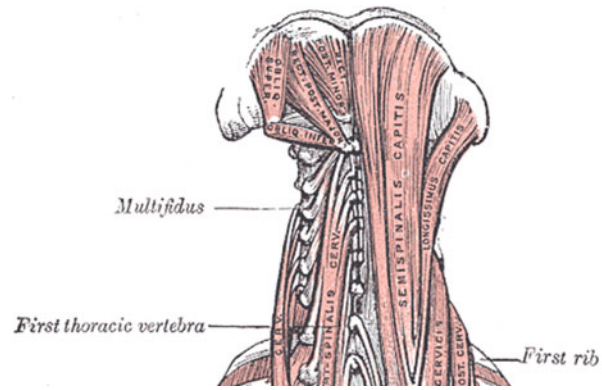

Fig. 10 Intermediate and deep dorsal muscles of the neck. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 389, Public Domain)

innervated by the dorsal rami of the spinal nerves of the cervical spine (Fig. 10).

Neurovascular Structures

Spinal Cord

Though a detailed description of spinal cord neuroanatomy is beyond the scope of this chapter, basic anatomic understanding is necessary. The spinal cord exits the intracranial space through the foramen magnum and terminates at approximately L2 as the conus medullaris. The spinal cord is widest at C6, measuring an average of 38 mm in circumference, which provides enough space for the increased density in neurologic structures such as the brachial plexus (Parke and Sherk 1989). The inner cord is made up gray matter which houses the nerve cell bodies and branching dendrites. It is separated into anterior, lateral, and posterior segments (horns). The anterior horn contains motor neurons controlling the skeletal muscles and is the column where the cell bodies of the alpha motor neurons are located. The posterior horn contains sensory neurons that

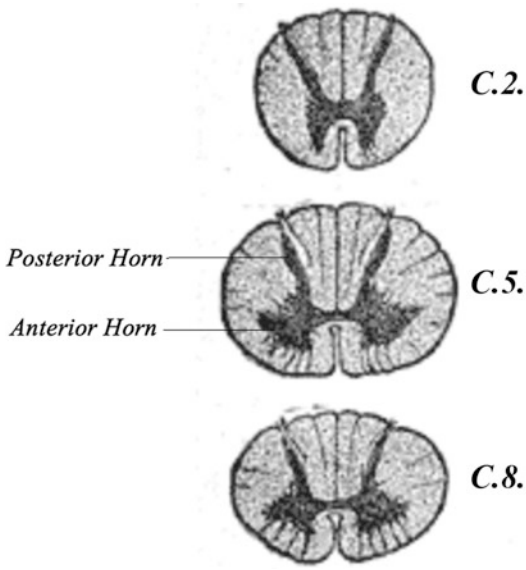

Fig. 11 Transverse section through cervical spinal cord with labeled anterior and posterior horns of the inner gray matter. (From: Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body*, Plate 666, Public Domain)

transmit sensory information from the body that includes fine touch, proprioception, and vibration (Fig. 11). The lateral segment is located only within the thoracic and upper lumbar regions and contains components of the sympathetic nervous system.

The outer circumferential layer is the white matter and is composed of myelinated axons. In a similar manner to the gray matter, it is separated into posterior, lateral, and anterior columns. The lateral column houses the lateral corticospinal tract which provides efferent motor innervation control ipsilateral extremity motion. Also within the lateral column is the lateral spinothalamic tract which is sensory pathway that transmits contralateral pain and temperature. This tract decussates to the other side of the spinal cord at the anterior white commissure, usually 1–2 spinal nerve segments above the entry point. The posterior column, composed of the fasciculus gracilis and cuneatus, is the structure responsible for ascending sensory signals transmitting proprioception, vibration, and fine touch. Sensory information from this pathway is also from the contralateral extremity although its crossover is much higher, located in the brain stem. The anterior column houses both sensory and motor systems, as well as the anterior spinothalamic tract which is responsible for crude touch.

Meninges and Dura

The meninges enclose the spinal cord and are composed of three layers: the pia, arachnoid, and dura matter. The innermost layer is the pia, followed by the arachnoid and then the dura mater. The pia has lateral projections between exiting nerves that attach to the arachnoid and dura. These projections are known as the denticulate ligaments and with the aid of CSF act as a bolster for the spinal cord. The space between the pia and arachnoid is known as the subarachnoid space and contains CSF and nerve rootlets. The space between the dura and vertebral canal is the epidural space and has a rich venous plexus and adipose tissue (Fig. 12).

Nerve Roots

In the cervical spine, there are eight rootlets that exit the spinal cord that unite and form the dorsal and ventral roots. These form nerve roots at each corresponding level and pass through the dura to the intervertebral foramina. In the cervical spine, the nerve roots pass above the corresponding pedicle, except for the C8 nerve root which travels underneath the C7 pedicle. These nerves also leave the spinal cord at an angle that approximates a right angle and explains why foraminal and central herniations will affect the same nerve root. In the foramen, the nerve root takes up one-third of the space, medially it is located at the caudal portion of the superior articular process and as it travels laterally adopts a more inferior position above the pedicle (Daniels et al. 1986). When the neck is extended, the foramen size decreases in overall volume, and the nerve takes up a more superior position within the foramen; when flexed, the foramen size increases, and the nerve root assumes a position in the caudal half of the foramen (Rauschning 1991). The remaining space is filled with fat, which provides cushion to the nerve (Flannigan et al. 1987).

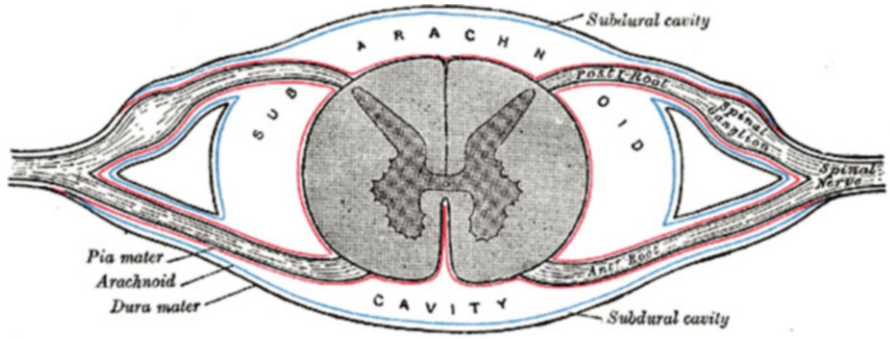

Fig. 12 Transverse section through cervical spine with labeled membranes and spinal nerve roots. (From: Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body*, Plate 770, Public Domain)

Spinal Cord Blood Supply

The vertebral arteries are the primary blood supply to the cervical spine which branch of the subclavian arteries and ultimately form the basilar artery. In general, each vertebral artery enters the transverse foramen at C6 and courses rostrally until C1 (Rickenbacher et al. 1982). It is important to note, during an anterior approach that the vertebral artery is located in the middle one-third of the vertebral body, just lateral to the uncinated process. At the atlas, the vertebral arteries curve around and enter the foramen magnum to unite with the contralateral artery to become the basilar artery. Throughout their course, they give off feeding branches to the spinal cord known as the anterior and posterior spinal arteries. The anterior spinal artery supplies the anterior two-thirds of the spinal cord, while the posterior spinal artery assumes the remaining one-third.

Venous outflow of the spinal cord consists of three anterior and three posterior veins. The most prominent are the anterior venous structures and are located medial to the pedicles. The posterior venous plexus surrounds the spinal cord.

Important Ventral Structures

Carotid Sheath

The carotid sheath contains the internal jugular vein, the vagus nerve, and the common carotid artery from lateral to medial. A small branch of the hypoglossal nerve can sometimes be seen crossing anteriorly. The common carotid artery branches approximately 1 cm above the superior border of the thyroid cartilage within this triangle. The carotid sinus lies just inferior to the bifurcation and is prominent baroreceptor regulating blood pressure. The vagus nerve, lying just dorsal, gives off two important branches to the neck: the superior and inferior laryngeal nerves (Fig. 13).

Vertebral Artery

The vertebral artery is divided into four segments and has an average diameter of 4.5 mm. It travels medial to the anterior scalene muscles and enters the C6 foramen in roughly 90% of the population. After entering cranially through the foramen transversarium of C2 and C1, it then changes course and heads medially along the superior arch of C1 at which point it goes further cranially into the foramen magnum. During a posterior approach to C1, it is critical to avoid dissection greater than 1.5 cm lateral to the midline as injury to the vertebral artery is greatest in this region (Fig. 14).

Superior Laryngeal Nerve

A branch off the vagus nerve, the superior laryngeal nerve runs medial to the carotid sheath and bifurcates at the level of the hyoid to provide motor function the inferior pharyngeal

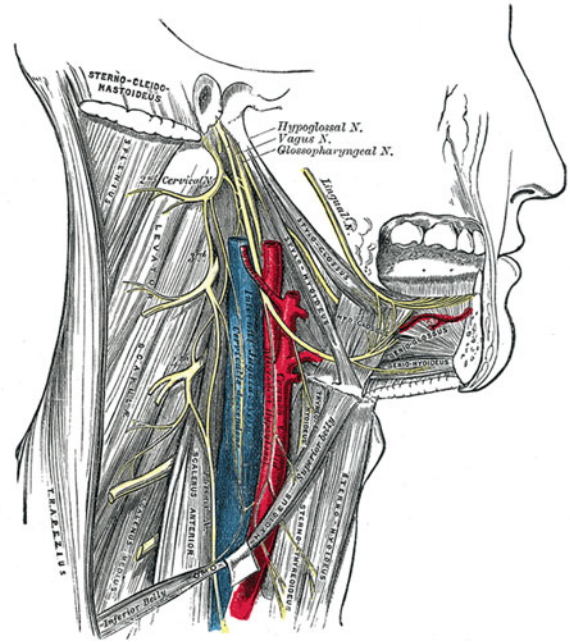

Fig. 13 Relevant ventral structures of the neck. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 794, Public Domain)

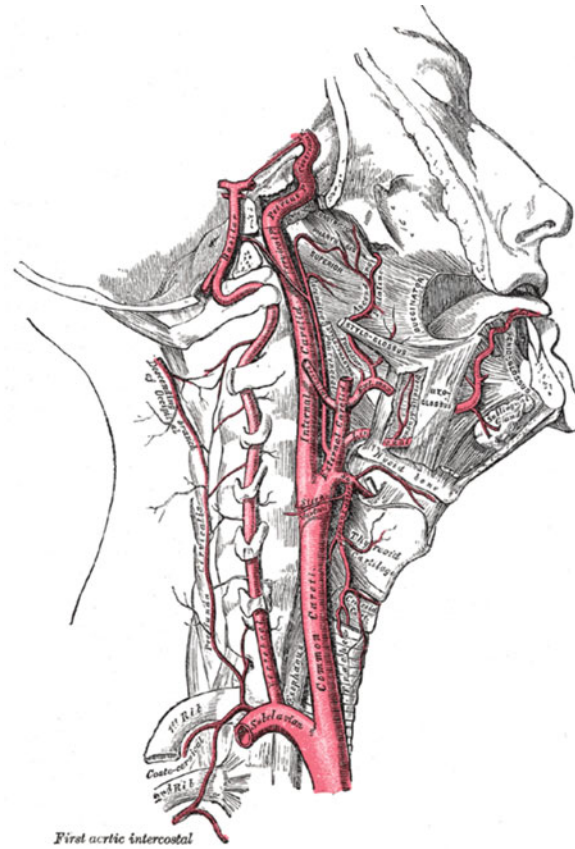

Fig. 14 Internal carotid and vertebral arteries. (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 513, Public Domain)

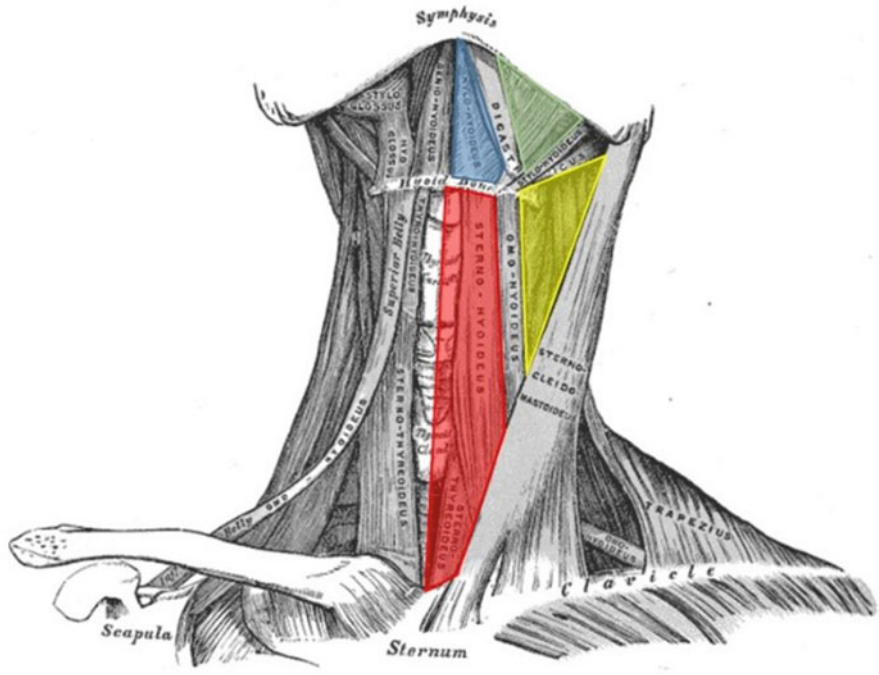

Fig. 15 Ventral cervical triangles: submental triangle (blue), muscular triangle (red), submandibular triangle (green), carotid triangle (yellow). (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 386, Public Domain)

constrictors. It also has sensory branch that provides sensation to the base of the tongue and the larynx. Injury to this nerve can be manifested with poor gag reflex and voice control especially with high pitches. Loss of the gag reflex can be most debilitating as these patients are often at increased risk for aspiration.

Inferior (Recurrent) Laryngeal Nerve

The inferior laryngeal nerve, commonly known as the recurrent laryngeal nerve, has a U-shaped course in the thorax, specifically in the tracheoesophageal groove. As it pierces the inferior pharyngeal constrictor, it provides motor function to the intrinsic laryngeal muscles. Its course in the neck is not symmetric. On the left, it loops under the aortic arch, and on the right, it loops under the right subclavian artery.

Hypoglossal Nerve

The hypoglossal can be located in the carotid triangle, deep to the belly of the digastric muscle, and as previously discussed, in between the carotid artery and internal jugular vein. Before heading toward the oral cavity to innervate the tongue, it gives off a branch to innervate the strap muscles, which is termed the *ansa cervicalis*.

Sympathetic Chain

The sympathetic chain resides in the prevertebral fascia, just ventral to the longus colli muscles. It surrounds the vertebral artery during its ascension toward the cranial vault. Injury to this structure during an anterior approach can cause ipsilateral Horner syndrome, which is characterized by ptosis, miosis, and anhidrosis.

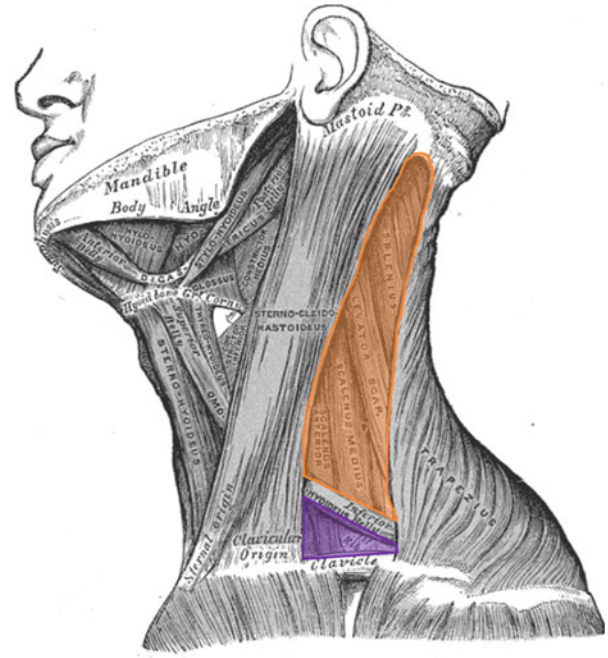

Fig. 16 Dorsal cervical triangles: occipital triangle (orange), subclavian triangle (purple). (By Henry Vandyke Carter – Henry Gray (1918) *Anatomy of the Human Body: Gray's Anatomy*, Plate 385, Public Domain)

Surgical Anatomy: The Cervical Triangles

Ventral (4 Types)

The borders of the anterior cervical triangle are the medial edge of the SCM, the inferior mandibular border, and midline of the neck. Within this triangle reside four subtriangles. The submental triangle is formed by the hyoid and the two anterior bellies of the digastric muscles; the floor of which is made up the two mylohyoid muscles. Next is the submandibular triangle, its margins being the ventral and dorsal bellies of the digastric muscle, the inferior mandibular border with the floor consisting of the hyoglossus, mylohyoid, and middle pharyngeal constrictors muscles. Important to note, is the hypoglossal nerve which passes through this triangle. The carotid triangle is bordered by the anterior margin of the SCM, the superior border of the omohyoid and inferior border of the digastric muscle. This triangle is particularly important as the common carotid artery, internal jugular vein, and the vagus nerve are found within this structure. Last, is the muscular triangle which is formed by the medial margin of the SCM, the superior belly of the omohyoid and median plane of the neck (Fig. 15).

Dorsal (2 Types)

The dorsal triangle is bordered by the lateral edge of the SCM, ventral trapezius border, and middle third of the clavicle. The floor is made up the scalene muscle group and prevertebral fascia, and the ceiling is made up of the deep cervical fascia. This triangle is divided into two smaller triangles, the occipital and subclavian triangle. The external jugular vein runs caudally through this triangle at the angle of the mandible (Fig. 16).

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Thoracic and Lumbar Spinal Anatomy

38

Patricia Zadnik Sullivan, Michael Spadola, Ali K. Ozturk, and William C. Welch

Contents

Abstract

Degenerative arthropathy, trauma and congenital anomalies, as well as focal abnormalities such as facet overgrowth and disk herniations render each patient unique, and these abnormalities can impact surgical approach. The goal of this chapter is to discuss anatomic considerations that impact surgical planning and to provide a framework for thinking about patient-specific anatomy when approaching the thoracic and lumbar spines.

Keywords

Thoracic spine · Lumbar spine · Degenerative arthropathy · Intraoperative localization

Thoracic Spine

The thoracic spine is composed of 12 rib-bearing vertebrae, separated by intervertebral disks and connected posteriorly by the interspinous ligament (Fig. 1). Each thoracic vertebra has a body, a spinous process, and superior and inferior articulating facets in addition to inferior, superior, and transverse costal facets to articulate with the head of the rib. The pedicles of thoracic spinal vertebrae vary in size, with T1 pedicles being narrow and subsequent pedicles increasing in width approaching the thoracolumbar junction (Fig. 2).

The angulation of the thoracic pedicles further changes, with more caudally oriented trajectories

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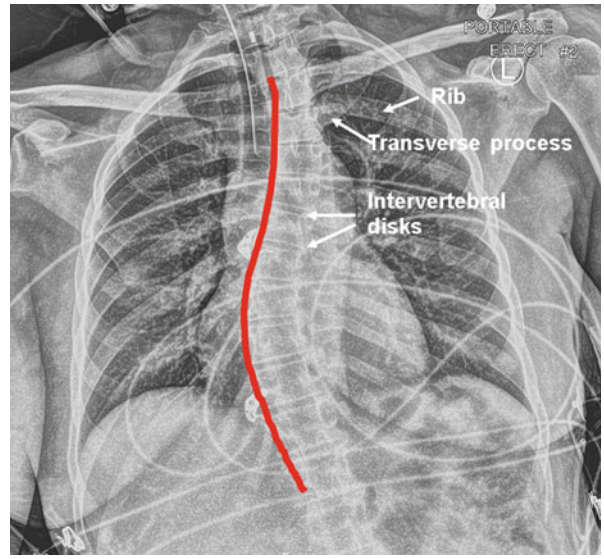

Fig. 1 Anterior-posterior x-ray of the thoracic spine demonstrating coronal scoliosis in the thoracic spine. Ribs, intervertebral disks, and bodies are shown. The red line indicates the lateral aspect of the vertebral bodies

in the upper thoracic spine. Thoracic instrumentation can be challenging due to this variability, and navigation or fluoroscopy-based techniques can assist in planning thoracic pedicle screw trajectories.

The thoracic spine is more rigid than the cervical or lumbar spine, as it is fixed to the sternum via the ribs, limiting the range of motion in the thoracic spine. The cervicothoracic junction and thoracolumbar junctions are more mobile points of transition and are thus more likely to succumb to traumatic pathology. Degenerative pathologies of thoracic spine include sagittal kyphotic deformity, typically secondary to progressive compression fractures, and coronal scoliosis (Fig. 1). Adolescent scoliosis is a common childhood disorder affecting thoracic spine alignment, and in adult patients, iatrogenic or degenerative scoliosis with coronal curvature may affect thoracic spine alignment.

Common traumatic thoracic pathologies include disk herniations and fractures. Thoracic disk herniations may occur with minimal trauma, and over time these disk herniations may become calcified (Oppenlander et al. 2016). If a thoracic disk herniation is noted on magnetic resonance imaging (MRI), computed tomography (CT) can be useful to identify the degree of calcification prior to surgical planning. If a thoracic disk is calcified and causing cord compression and neurological deficit, a transpedicular approach may be required to safely access and drill down the calcified component (Fig. 3).

In older patients with osteoporosis, falls are a common cause of compression fractures in the thoracic spine. Thoracic compression fractures may also be seen in patients with metastatic cancer involving the vertebral bodies. Pain with axial loading (i.e., standing) is a common symptom in thoracic compression fractures. Patients may develop myelopathy from cord compression following fracture or severe, radicular chest pain along the chest wall from neuroforaminal narrowing. Due to the overall stability of the thoracic spine, severe thoracic spine fractures require high velocities such as motor vehicle accidents. If the thoracic spinal column is fractured and displaced, there will likely be associated rib and sternal fractures. Spinal cord transection, although rare, can happen with these types of injures. Patients with diffuse idiopathic skeletal hyperostosis (DISH) or ankylosing spondylitis (Rustagi et al. 2017) are more likely to experience thoracic spine fractures with low velocity accidents (Fig. 4).

Intraoperative localization in the thoracic spine can be challenging if the lesion is not readily identifiable on standard radiographic studies or

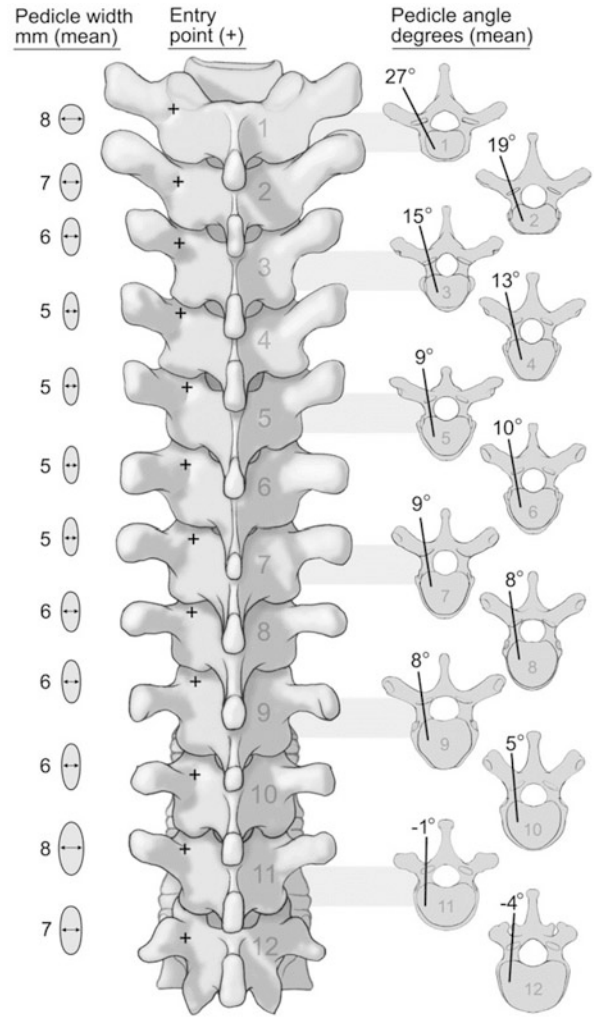

Fig. 2 Illustration showing some morphometric characteristics of the thoracic vertebrae from T1 to T12. The widths of the isthmus of the transverse pedicle are listed on the left. The pedicle entry points (+) and their relationship to the transverse process, laminae, and facets are shown in the center. The transverse pedicle angles are listed on the right. (Reprinted with permission from Hartl et al. 2004, Technique of thoracic pedicle screw fixation for trauma, *Operative Techniques in Neurosurgery*)

fluoroscopy. Unlike cervical and lumbar spine localization, there is no distinct body (i.e., sacral endplate or dens) available as a reference for counting. Preoperative thoracic and lumbar x-rays may be helpful to determine the true number of ribbed and non-ribbed vertebrae. This may help to correlate with the MRI if the patient has a transitional S1 that may be lumbarized or hypoplastic or an abnormal number of ribbed vertebrae.

Preoperative CT or MRI scans for localization may be obtained prior to surgery incorporating a reference body (i.e., sacral endplate, dens, or other identifiable structure). A radiologist can provide labeling of the localization scan to confirm the precise thoracic body affected. This allows congenital anomalies, such as sacralized lumbar vertebrae, or an abnormal number of rib-bearing vertebrae to be identified. These studies can be correlated with preoperative plain films to reduce the likelihood of wrong-level surgery.

Intraoperative anterior-posterior and lateral fluoroscopic images may be taken to localize the surgical level. Live intraoperative fluoroscopy may also be used for level confirmation, typically by counting up from the sacrum. Intraoperative 3-D imaging, if available, may also help to provide more definitive surgical localization. Prior instrumentation, kyphoplasty cement, or unique fractures may further help to confirm the target level.

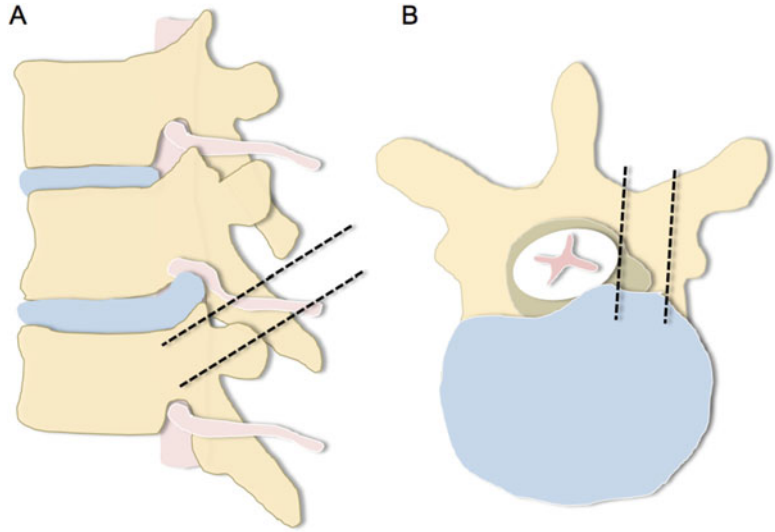

Fig. 3 Transpedicular approach for resection of calcified thoracic disk. (**a**) Lateral view of herniated thoracic disk causing deformation of exiting nerve root. Black lines indicate transpedicular approach to the calcified thoracic disk. (**b**) Axial diagram depicting approach to calcified thoracic disk

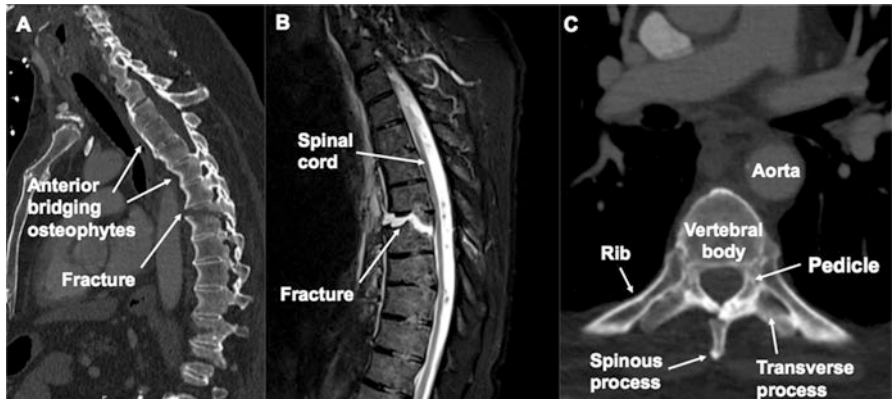

Fig. 4 T8 fracture extending though vertebral body, pedicle, and spinous process in a patient with ankylosing spondylitis. (**a**) Sagittal CT scan demonstrating anterior bridging osteophytes consistent with ankylosing spondylitis and fracture line extending through the T8 vertebral body, pedicle, and spinous process. (**b**) Sagittal T2-weighted fat-suppressed MRI demonstrating T2 hyperintensity along fracture line. The spinal cord can be seen draped ventrally along the posterior aspect of the vertebral bodies. (**c**) Axial CT scan through mid-thoracic vertebra demonstrating relationship of the rib, spinous process, transverse process, and pedicle

It is important to note that technical and patient factors (obesity, surgical position, non-radiolucent OR tables, and others) may interfere with the correct interpretation of these studies. In these instances, consultation with a radiologist should be undertaken.

Direct anterior approaches to the thoracic spine are uncommon, as the aorta and vena cava abut the ventral aspect of the thoracic vertebrae and the lungs and other key structures obstruct direct access (Fig. 5). En bloc resection of thoracic spinal tumors or metastatic pathology may merit anterior approaches (Xu et al. 2009), and these surgeries are often conducted with a cardiothoracic access surgeon. Anterolateral approaches to the thoracic spine include costotransversectomy with removal of the transverse costal facet and rib head for access to the lateral vertebral body and the lateral extracavitary approach, which removes portions of the rib head lateral to the transverse process for greater access to the vertebral body. Careful coordination is necessary when planning

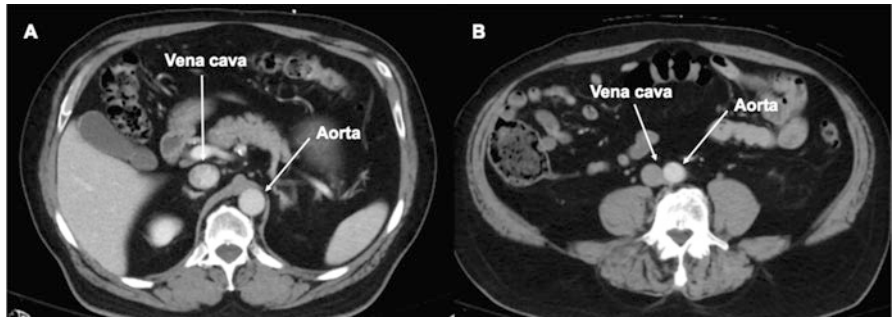

Fig. 5 Sagittal CT scan through (**a**) T12 and (**b**) L3 levels illustrating the relationship of the aorta to the thoracic and lumbar spines

an anterior thoracic approach, as the patient may be intubated with a dual-lumen endotracheal tube. This allows the anesthesiologist to selectively hold respirations in the lung adjacent to the surgical field, facilitating access to the vertebral body. Injury to the lung pleura puts patients at an increased risk of pulmonary complications in some studies, and a chest tube may be electively placed to reflate the lung and prevent pneumothorax or large pleural effusions after anterior thoracic spine approaches. Other treatments such as the application of talc powder or mechanical abrasion of the pleural surfaces to promote pleural adhesion may also be considered. Minimally invasive and endoscopic techniques have also been described to reduce complications for anterior spinal surgeries (Borm et al. 2004).

Posterior and posterolateral approaches to the thoracic spine provide limited access to the posterior vertebral body for debulking of metastatic tumors and decompression of fracture fragments. Following laminectomy, unilateral or bilateral pedicles can be resected via careful drilling to access the ventral vertebral body. In the thoracic spine below T2, nerve roots do not provide significant motor contributions, and these roots may be sacrificed lateral to the dorsal root ganglion to further expand the exposure and improve access to the ventral disk space. Nerve root avulsion or compression should be avoided as this may result in postoperative radicular pain.

For calcified disk herniations, pedicle resection can be an effective way to access the disk space. If the pedicle is sacrificed for access, unilateral or bilateral posterior fusion may be required to limit segmental motion and collapse. Posterior fusion of the thoracic spine typically involves placement of pedicle screws, and preoperative evaluation should take into account pedicle length and width. Medialized screws in the thoracic spine result in cord compression, while lateralized screw trajectories can incorporate rib or injure thoracic viscera. Intraoperative navigation is a useful tool to decide optimal screw trajectory.

Bullet Points

- Ventral disk herniations in the thoracic spine may be calcified.
- Thoracic spine localization requires careful preoperative planning.
- Unilateral nerve roots T2-12 can be sacrificed to improve surgical exposure in posterior and posterolateral approaches.

Lumbar Spine

The lumbar spine is composed of five vertebrae in lordotic alignment, joined by intervertebral disks and posteriorly via facet joints (Fig. 6). Lumbar vertebrae are composed of a body, two pedicles, two transverse processes, and a superior and inferior articulating facet. The transverse processes project laterally and may become fractured during an assault or trauma, leading to musculoskeletal discomfort. There is no load-bearing function of

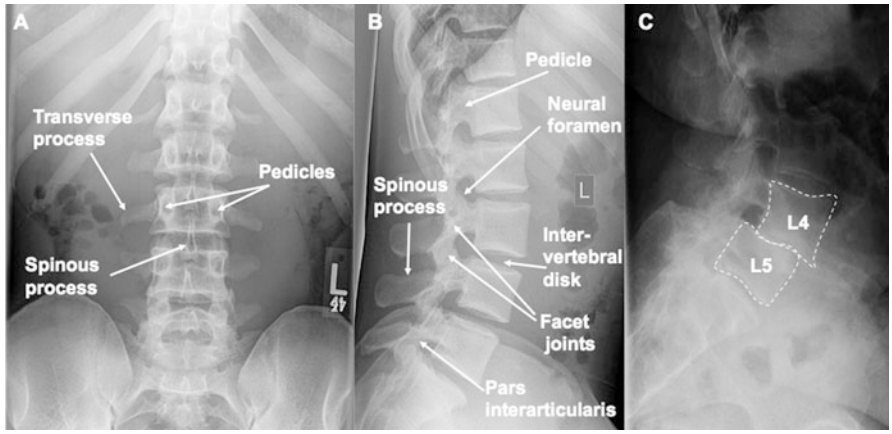

Fig. 6 (**a**) AP and (**b**) lateral x-rays of the lumbar spine illustrating the transverse process, pedicles, spinous process, facet joints, and neural foramen of the lumbar spine. (**c**) Lateral x-ray of the lumbar spine of a different patient, illustrating spondylolisthesis of L4 on L5. The vertebral bodies are outlined with dotted white lines

the transverse processes, and these do not need to be repaired in the case of fracture. The iliopsoas muscle attaches at the transverse processes along the lumbar spine and inserts on the trochanter of the femur. During posterior instrumented fusion, the transverse processes may serve as a surface to encourage fusion. The midportion of the transverse process, as determined in a superior-inferior direction, generally correlates with the midpoint of the lumbar pedicle (again as determined in the superior-inferior axial plane). This landmark can be used to help localize the starting point for pedicle probe or drill insertion.

Intraoperative localization for lumbar spine surgery is typically achieved with lateral radiographs, and the levels are identified by counting from the L5 to S1 disk space. In some patients the fifth lumbar vertebrae may be sacralized, meaning its orientation mimics a typical S1 caudal orientation. This anatomic variant should be identified prior to surgery, as it affects intraoperative localization. Spina bifida occulta may be recognized in patients undergoing evaluation for other spinal issues, and laminar defects may be identified prior to surgery. Another congenital anomaly in the lumbar spine is a pars defect. In this variant, the pars interarticularis (the bony bridge between the superior and inferior articulating facets) fails to develop. The pars interarticularis resists the vector of anterolisthesis, and when the pars is compromised, patients may be at increased risk of developing progressive spondylolisthesis (Fig. 6).

Many patients with lumbar stenosis experience worsening of symptoms with axial loading and ambulation. In contrast, MRI and CT images are traditionally acquired in a supine position. Standing, 36-in. x-rays with neutral leg position (i.e., no compensatory knee bend) provide a more accurate illustration of a patient's global alignment. Spinopelvic parameters can help surgeons to establish how much correction is needed if a lumbar fusion surgery is planned (Celestre et al. 2018). Among these measurements, pelvic incidence and lumbar lordosis are particularly relevant to lumbar spinal anatomy. Lumbar lordosis is measured by the angle between the lower T12 endplate and S1 endplates (Fig. 7).

The pelvic incidence is measured as the angle between a line drawn perpendicular to the center of the S1 endplate and a second line from the center of the S1 endplate to the center of the femoral heads. A patient's lumbar lordosis should be comparable (within 10°) to their pelvic incidence; otherwise an iatrogenic "flat-back" deformity of the lumbar spine may occur.

Common lumbar pathologies include lumbar stenosis, facet arthropathy, spondylolisthesis, and disk herniations (Issack et al. 2012). The posterior facets are prone to degenerative arthritis from

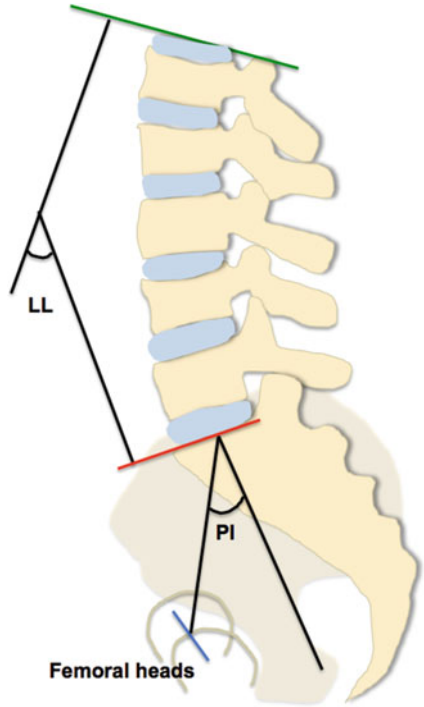

Fig. 7 Pelvic incidence (PI) and lumbar lordosis (LL). The green line indicates the interior endplate of T12 and the superior endplate of S1 (red line). Pelvic incidence is depicted as the angle subtended from the perpendicular line to the S1 endplate and the midpoint of a line drawn (blue) between the femoral heads

repeated abnormal motion, leading to facet overgrowth and synovial cyst formation (Fig. 8). These arthritic changes can compress the spinal canal and contribute to lumbar stenosis. Patients will manifest with radicular symptoms or lumbar claudication in cases of severe stenosis. In cases of spondylolisthesis (Fig. 8), subadjacent vertebral bodies may angle away from the surgeon, complicating the initial dissection. If facet overgrowth is suspected, removal of facet osteophytes may be necessary to identify the anatomic laminar edge.

Posterior approaches to the lumbar spine include laminectomy, hemilaminectomy with discectomy, and instrumented lumbar fusion. Hemilaminectomy is appropriate for patients with unilateral symptoms and a focal disk herniation; however, if the disk herniation is large or central (Fig. 9), a full laminectomy may be completed. If decompression without fusion is planned, the surgeon should avoid manipulation of the facet joint, as removal of the bone may disrupt facet integrity and lead to progressive instability. When fusion is planned, removal of facet overgrowth via rongeur or drilling can improve the surgical exposure and help to identify the laminar edge.

Anterior approaches to the lumbar spine are typically achieved with the help of an access general surgeon or vascular surgeon. The anterior lumbar interbody fusion (ALIF) involves removal of the intervertebral disk, placement of a disk replacement, and securing the disk replacement with an anterior plate and screws (Phan et al. 2017). This approach is complicated by the presence of the lumbosacral plexus (L5-S1) and the iliac bifurcation (L4-5). Anterior approaches may be utilized for patients with failed posterior fusion or in patients with severe deformity requiring anterior and posterior instrumentation to facilitate strength and reduce the risk of failure. Anterior lumbar approaches can be challenging in obese patients if the abdominal girth exceeds the length of surgical instruments. Further, retrograde ejaculation is a reported complication in men at a rate of 7.4–9.8% following manipulation of the lumbosacral plexus in ALIFs, thus compromising male fertility (Lindley et al. 2012).

Bullet Points

- Lumbar degenerative arthropathy can obscure the laminar edge on initial dissection.
- Sacralized lumbar vertebra can complicate intraoperative localization.
- Anterior lumbar fusions may be challenging in obese patients and carry the risk of retrograde ejaculation in male patients.

Conclusion

Careful patient examination and review of available preoperative imaging is crucial for success in spine surgery. CT scans provide key information regarding calcifications, and MRI scans are necessary to identify disk herniations. Prior to

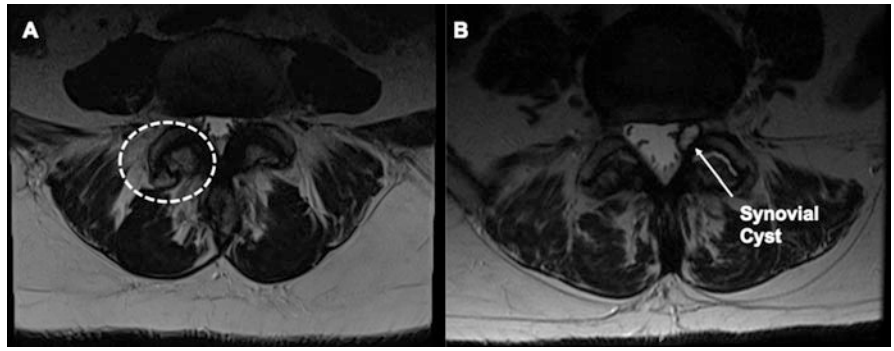

Fig. 8 Axial T2-weighted MRIs of the lumbar spine demonstrating (**a**) spine facet arthropathy with osteophytes noted at the superior and inferior articulating facets. (**b**) Synovial cyst with impingement of spinal canal

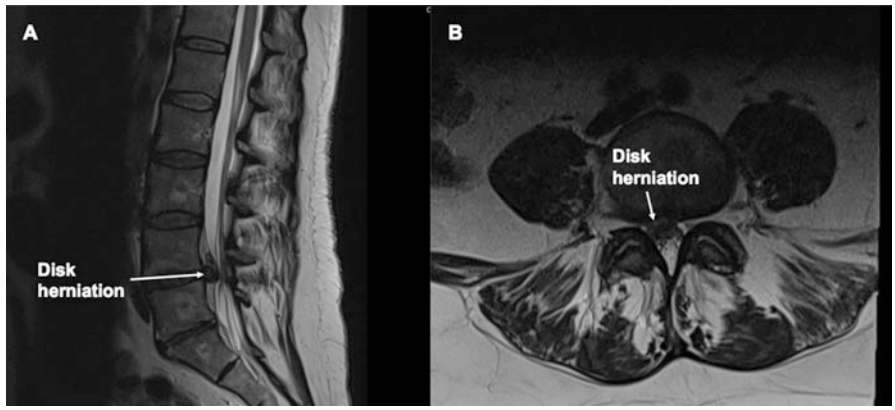

Fig. 9 Right-sided disk herniation causing compression of spinal canal and cauda equina nerve roots. (**a**) Sagittal T2-weighted MRI demonstrating compression of spinal canal and nerve roots. Swelling of nerve roots is noted caudal to the disk herniation. Heterogeneous T2 signal abnormality can be seen within the vertebral bodies of adjacent spinal levels

entering the operating suite, technical aspects of the surgery should be decided, including the type of surgical instrumentation if indication. Patient anatomical anomalies, such as sacralized vertebrae, abnormal rib-bearing vertebrae, osteophytes, and overgrown facets, should also be reviewed in detail. Upright or standing radiographs can complete the picture, as they may highlight loss of lordosis or spondylolisthesis. While knowledge of general spinal anatomy is crucial to form the foundation of spine surgery, patient-specific details must be considered to ensure the optimal outcome.

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Part V

Technology: Motion Preservation

Cervical Total Disc Replacement: FDA-Approved Devices

39

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Abstract

Cervical total disc replacement is a routinely used treatment for radiculopathy due to degenerative disease of the cervical spine. The procedure originated to avoid some of the complications seen with the traditional anterior cervical discectomy and fusion. Appropriate patient selection is paramount to obtain acceptable patient outcomes, with particular indications and contraindications for these procedures. As the procedure gained more acceptance, several cervical artificial discs have been developed and, subsequently, approved by the US Food and Drug Administration (FDA). Each of the eight FDA-approved devices is briefly reviewed in this chapter including outcomes from device-specific studies.

Keywords

Artificial disc · Cervical · Disc replacement · FDA-approved · Outcomes

Introduction

Anterior cervical decompression and fusion (ACDF) is one of the most common surgeries done worldwide to decompress the cervical canal, provide stabilization, and restore the normal lordosis of the cervical spine (Cloward 2007; Smith and Robinson 1958). It has been utilized in the treatment of degenerative disc disease, cervical radiculopathy, myelopathy, instability, and segmental deformity. Fusion rates for ACDFs are reported above 95%, and this fusion has been shown to cause a change in motion characteristics of the adjacent segments (DiAngelo et al. 2003; Eck et al. 2002). The change in the kinematics of adjacent levels may be responsible for increased risk of adjacent segment degeneration (Hilibrand et al. 1999; Dohler et al. 1985).

Cervical total disc replacement was developed to avoid some of these complications seen with ACDF. Preservation of the motion segments after total disc replacement surgery may reduce or delay the progression of adjacent segment disease by maintaining motion as well as normal segmental lordosis and anatomic disc space height (Fuller et al. 1998). Indications and contraindications are reviewed in this chapter as not all patients who are candidates for ACDF are candidates for total disc replacement.

Acceptance of this procedure has led to the development of numerous artificial disc designs. Eight devices have been approved by the US Food and Drug Administration (FDA) after thorough investigation through investigation device exemption (IDE) studies. Each of the eight FDA-approved devices (Prestige ST, Bryan, ProDisc-C, Secure-C, PCM, Mobi-C, Prestige LP, M6-C) and their outcomes are briefly discussed in this chapter. All eight artificial discs are FDA-approved for one-level use from C3-7. Only two artificial discs, Mobi-C and Prestige LP, are FDA-approved for two-level use. Most of the artificial disc designs have either uni- or biarticulating surfaces, although the newest FDA-approved device, M6-C, has a non-articulating, compressible core. Most of these discs are metal-on-polymer (M-o-P), although the Prestige ST and Prestige LP represent metal-on-metal (M-o-M) designs. Despite the controversy surrounding M-o-M total hip arthroplasty implants, there have been no widespread reports of M-o-M cervical artificial discs causing complications such as elevated serum metal ion levels, osteolysis or pseudotumor formation (Coric et al. 2011).

Rationale for Total Disc Replacement

As mentioned, despite long-term clinical success of ACDF, it has been associated with the development of adjacent segment degeneration. This

degeneration can be associated with symptoms such as radiculopathy, myelopathy, or neck pain and may necessitate additional interventions. Due to loss of motion at the fused segment, the kinematics are changed at the levels above and below the fused segment. This has been shown in biomechanical studies to cause increase in intradiscal pressure and motion at the adjacent levels (Eck et al. 2002). It is still unclear whether this degeneration is a result of the natural progression seen with aging or a result of the change in biomechanical stresses seen with ACDF.

In contrast, biomechanical studies have reported that total disc replacement does not disrupt the kinematics at adjacent levels and allow for restoration of more normal load transfer (DiAngelo et al. 2003). Additional studies report that there are reduced stresses at adjacent levels in total disc replacement when compared to levels adjacent to a fusion (Pickett et al. 2005).

Indications/Contraindications

Cervical spondylosis is a common condition and can result in radiculopathy and myelopathy. Patients presenting with these symptoms should undergo appropriate work-up including radiographic evaluation and nonsurgical management. Radiographic evaluation, including MRI and CT imaging, can reveal single versus multilevel disease, presence of facet arthropathy, overall cervical spine alignment, kyphotic deformity, instability, and the location of compressive pathology (anterior, posterior, or both). The results of radiographic evaluation are crucial in determining whether a patient is an appropriate candidate for a total disc replacement.

In the setting of normal cervical alignment and mobility with failure of medical management, appropriate indications for total disc replacement include:

- Radiculopathy due to paracentral or central disc pathology or foraminal stenosis
- Myelopathy due to anterior compression by herniated disc

Contraindications for total disc replacement include:

- Significant multiple level degenerative disc disease (> two levels) with baseline motion abnormalities or advanced degeneration of the facet joints
- Abnormal global spinal alignment
- Cervical Instability (translation >3 mm and/or >11° rotational difference to that or either adjacent level)
- Active or prior discitis
- Osteoporosis (T-score < −1.5)
- Traumatic instability (ligament disruption or facet injury)
- Ossified posterior longitudinal ligament (OPLL) or the presence of bridging osteophytes
- Known allergy to implant materials

FDA-Approved Devices

Starting in 2006, eight cervical artificial disc devices have become available in the United States for one-level use, two of which, Mobi-C and Prestige LP, are approved for two-level use (Table 1). These devices vary in size, shape, materials, and articulating surfaces. They can be categorized based on biomechanical design, biomaterials, and type of fixation (Fig. 1) (Mummaneni and Haid 2004; Mummaneni et al. 2007).

Bryan Cervical Disc

Device Description

The Bryan cervical disc was developed in the early 1990s by neurosurgeon Vincent Bryan. The device is made of two titanium alloy shells with a polyurethane nucleus, which makes it a biarticulating contained bearing design. This is a non-modular disc. Fixation is achieved via milled vertebral end plates, and it allows end plate bony ingrowth through a porous end plate design (Fig. 2).

Table 1 Comparison of the eight FDA-approved artificial disc devices

Name	Design	Modular	Articulating method	Implant composition	Primary fixation	Manufacturer
Bryan	Metal-on-polyurethane, Biarticulating contained bearing	No	Biarticulating	Titanium, polyurethane core	Milled vertebral end plates	Medtronic
PCM	Metal-on-polyethylene Ball-and-socket	No	Uniarticulating	Cobalt - chromium, UHMWPE	Ridged, V-tooth design	NuVasive
ProDisc-C	Metal-on-polyethylene, ball-and-socket	Yes	Uniarticulating	Cobalt-chromium, UHMWPE	Central keel	DePuy Synthes (recently sold to Paradigm Spine)
Prestige ST	Metal-on-metal Ball-and-trough	No	Uniarticulating	Stainless steel	Locked vertebral body screws	Medtronic
Prestige LP	Metal composite, ball-and-trough	No	Uniarticulating	Titanium/ ceramic composite	Dual rails	Medtronic
Mobi-C	Metal-on-polyethylene, mobile core	Yes	Biarticulating	Cobalt - chromium, UHMWPE	Lateral self-retaining teeth	LDR
Secure-C	Metal-on-polyethylene, mobile core	No	Biarticulating	Cobalt - chromium, UHMWPE	Ridged central keel	Globus Medical
M6-C	Metal on polyurethane	No	Nonarticulating Compressible	Titanium/ Polyurethane UHMWPE	Triple fins	Spinal Kinetics

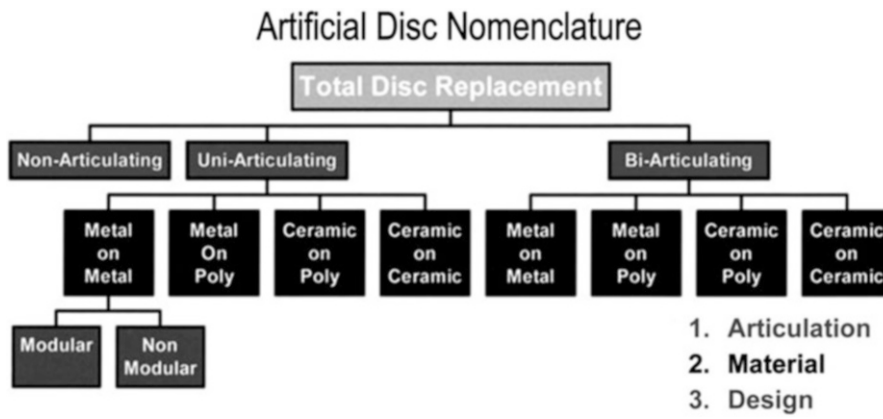

Fig. 1 Nomenclature for artificial disc implants based on design, articulation, and materials. (Permission for the reprint of figure obtained from Journal of Neurosurgery: Spine)

Outcomes

Recently, Goffin et al. reported results in 89 patients treated with the Bryan disc. Ten-year follow-up was available for 72 cases (81%). Maintenance or improvement of the neurological state was seen in 89% of patients. SF-36 patient reported scores improved significantly at all follow-up points. Mean angular motion of the

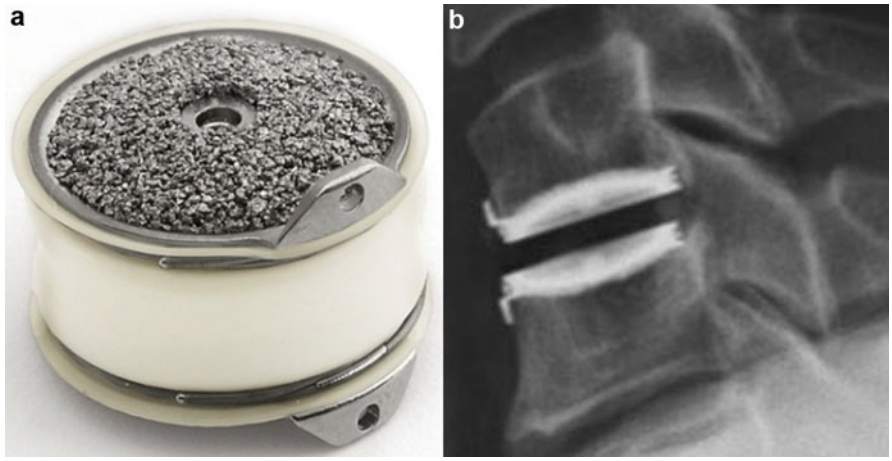

Fig. 2 Bryan artificial disc: (**a**) device; (**b**) lateral X-ray after implantation

prosthesis at 10-year follow-up was 8.6°. Mobility of the device, defined as >2° of angular motion, was reached in 81% of patients. During their study period, 21 patients (24%) developed new or recurrent radiculopathy or myelopathy; the majority of these patients were treated conservatively. Seven patients (8%) required 8 additional spine surgeries to treat persistent or recurrent symptoms. Of these, two patients (2%) were reoperated on at the index level, and five (6%) patients underwent surgery at an adjacent level (Goffin et al. 2003).

Heller et al. presented the results of a randomized controlled multicenter clinical study in 2009 with 242 patients in the investigational group (Bryan arthroplasty) and 221 patients in the control group (single-level ACDF). They showed statistically significant favorable results in the investigational group in various parameters like NDI, neck pain, and return to work and comparable results in other parameters like arm pain and SF 36 physical and mental components. At 24 months, overall success was achieved in 82.6% of the patients in the investigational group and 72.7% in the control group. This difference of 9.9% was statistically significant ($P = 0.010$), and a similar difference was noted at the 12-month follow-up interval ($P = 0.004$) (Heller et al. 2009).

Porous Coated Motion (PCM) Prosthesis

Device Description

The porous coated motion prosthesis is designed to have a metal-on-polyethylene articular surface. This device is a uniarticulating design, which is not modular. It is made up of cobalt-chromium-molybdenum alloy end plates with a TiCaP porous coating for bony ingrowth. Fixation is achieved with a central V-tooth design in a "press fit" fashion (Fig. 3).

Outcomes

In 2015, Philips et al. published the long-term outcomes of the FDA IDE prospective, randomized controlled trial, which compared the PCM prosthesis to anterior cervical discectomy and fusion. The total patient pool of 293 patients (163 PCM, 130 ACDF) was evaluated at 5-year follow-up, and 110 patients had 7-year follow-up. They reported that at 5-year follow-up, all patient-reported outcomes – neck and arm pain visual analogue scale score, neck disability index, and general health (36-Item Short Form Health Survey physical and mental component scores: physical component summary, mental component summary) – were significantly improved from baselines in both groups. Mean scores were

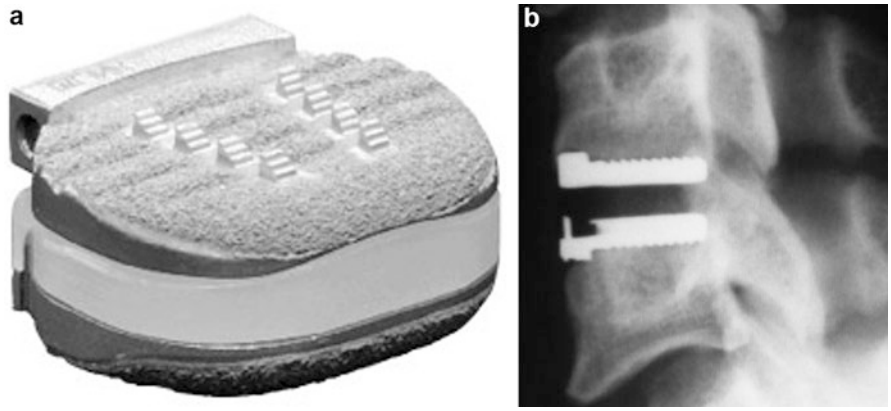

Fig. 3 Porous coated motion prosthesis: (**a**) device; (**b**) lateral X-ray after implantation

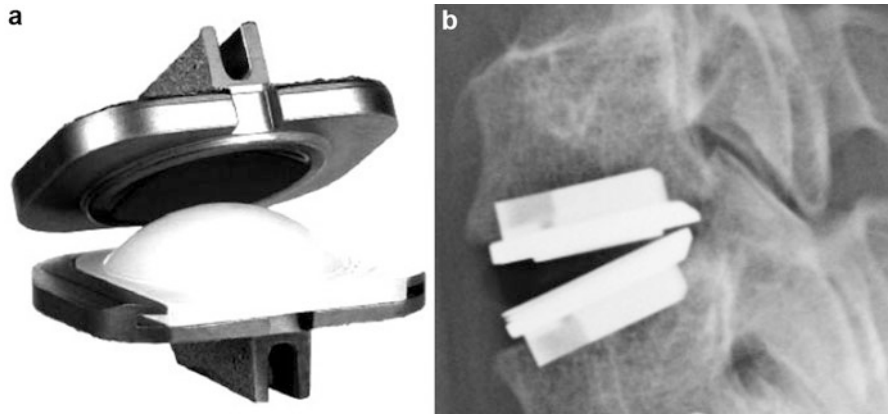

Fig. 4 ProDisc-C cervical disc: (**a**) device; (**b**) lateral X-ray after implantation

significantly better in the PCM group for neck disability index, neck pain, general health, and patient satisfaction. PCM patients trended toward fewer 2- to 7-year device-related serious adverse events and secondary surgical procedures. Adjacent-level degeneration was radiographically more frequent after ACDF and was the primary indication for the increase in late-term secondary surgical procedures after ACDF (Phillips et al. 2015).

ProDisc-C Cervical Disc

Device Description

The ProDisc-C cervical disc is similar in its design to the ProDisc lumbar disc prosthesis. It is a modular ball-and-socket type uniarticulating design. It consists of two cobalt-chromium-molybdenum end plates with an ultrahigh molecular weight polyethylene (UHMWPE) core. Fixation is achieved via a central keel (Fig. 4).

Outcomes

In 2016, Loumeau et al. published data from a randomized controlled trial comparing 7-year clinical outcomes of one-level symptomatic cervical disc disease following ProDisc-C total disc arthroplasty versus ACDF. A total of 22 patients were randomized to each arm of the trial. The authors reported that neck disability index (NDI) scores improved with the ProDisc-C greater than with ACDF. Total range of motion and neck and arm pain improved more in the ProDisc-C group

compared to the ACDF group. Patient satisfaction remained higher in the ProDisc-C group at 7 years. Six additional operations (two at the same level; four at an adjacent level) were performed in the ACDF group; however, no reoperations were performed in the ProDisc-C group. They concluded that ProDisc-C implants appear to be safe and effective for the treatment of cervical disc disease and had a lower reoperation rate than those patients treated with an ACDF (Loumeau et al. 2016).

Prestige ST Cervical Disc

Device Description

The Prestige ST was designed by Mr. Brian Cummins and was the first cervical total disc replacement to receive FDA approval in 2006. It is a stainless steel disc, which has a ball-and-trough design with biarticulating surfaces. It is secured to the vertebral body with screws. The superior and inferior surfaces, which contact the end plates, are treated to promote bone integration (Fig. 5).

Outcomes

A FDA IDE randomized controlled study reported by Mummaneni et al. compared cervical disc replacement using the Prestige ST device versus a single-level ACDF. Two-, 5-, and 7-year results have been published. Out of the 541 total patients in the study, 395 patients (212 Prestige ST, 183 ACDF) completed a 7-year follow-up. They found significantly improved NDI scores and neurological improvement scores in the investigational group as compared to the control group. Additionally, rates for subsequent surgical procedures that involved adjacent levels were significantly lower in the Prestige ST group (4.6% vs. 11.9%). They concluded that cervical disc arthroplasty using the Prestige ST cervical disc had the potential for preserving motion at the operated level while providing biomechanical stability and global neck mobility and could result in a reduction in adjacent segment degeneration (Burkus et al. 2014).

Prestige LP Artificial Disc

Device Description

The Prestige LP artificial disc has the same ball-and-trough articulation as the Prestige ST disc. However, the Prestige LP is made from a titanium ceramic composite material. It is anchored to the vertebral bodies via dual rails on the superior and inferior end plates. It also has a porous titanium spray coating to facilitate fixation and bone ingrowth (Fig. 6).

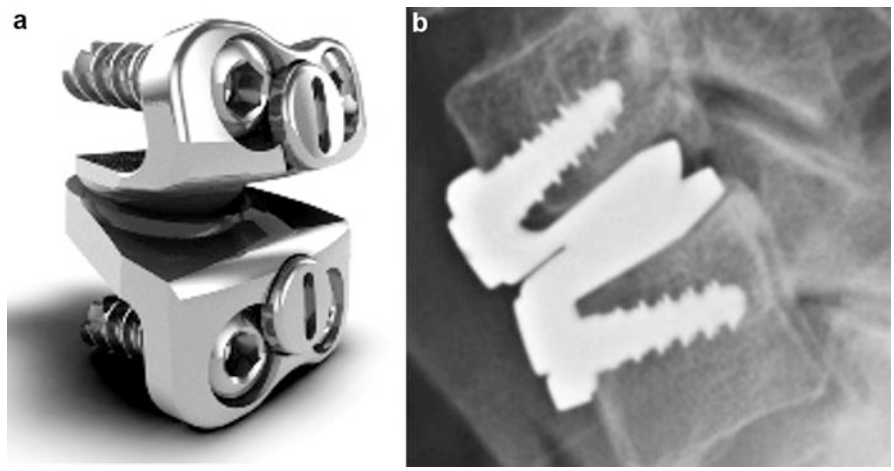

Fig. 5 Prestige ST cervical disc: (**a**) device; (**b**) lateral X-ray after implantation

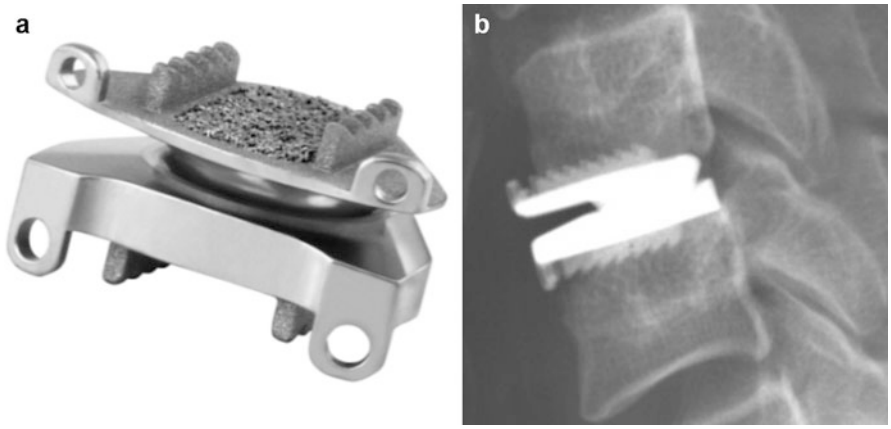

Fig. 6 Prestige LP cervical disc: (**a**) device; (**b**) lateral X-ray after implantation

Outcomes

The results of a randomized control study, investigating the Prestige LP device, were published by Gornet et al. in 2017. They assessed the long-term clinical safety and effectiveness in patients undergoing total disc replacement using the Prestige LP prosthesis to treat degenerative cervical spine disease at 2 adjacent levels compared with ACDF. The study was conducted at 30 centers in the United States with a total of 397 patients (209 Prestige LP, 188 ACDF). At 84 months, the Prestige LP demonstrated statistical superiority over fusion in overall success, NDI improvement, and neurological success. There was no statistically significant difference in the overall rate of implant-related or implant/surgical procedure-related adverse events up to 84 months. The Prestige LP group had fewer serious (Grade 3 or 4) implant- or implant/surgical procedure-related adverse events (3.2% vs. 7.2%,). Patients in the Prestige LP group also underwent statistically significantly fewer second surgical procedures at the index levels (4.2%) than the fusion group (14.7%). Angular range of motion at the superior- and inferior-treated levels on average was maintained in the Prestige LP group up to 84 months (Gornet et al. 2017).

Mobi-C Cervical Disc

Device Description

The Mobi-C cervical disc was first implanted in 2004. This device has a biarticulating design of metal plates articulating on a polyethylene modular core. It has lateral self-retaining teeth on the superior and inferior metal plates, which are pressed into the bone for fixation. The plates are coated with hydroxyapatite to enhance bone integration (Fig. 7).

Outcomes

Hisey et al. published their results in 2016 of a prospective, randomized, controlled study which was conducted as a FDA IDE trial across 23 centers with 245 patients randomized (2:1) to receive total disc replacement with Mobi-C cervical disc or ACDF. The 60-month follow-up rate was 85.5% for the Mobi-C group and 78.9% for the ACDF group. The composite overall success was 61.9% with Mobi-C vs. 52.2% with ACDF, demonstrating statistical non-inferiority. Improvements in NDI, VAS neck and arm pain, and SF-12 scores were similar between groups and were maintained from earlier follow-up through 60 months. There was no significant difference between Mobi-C and ACDF in adverse events or

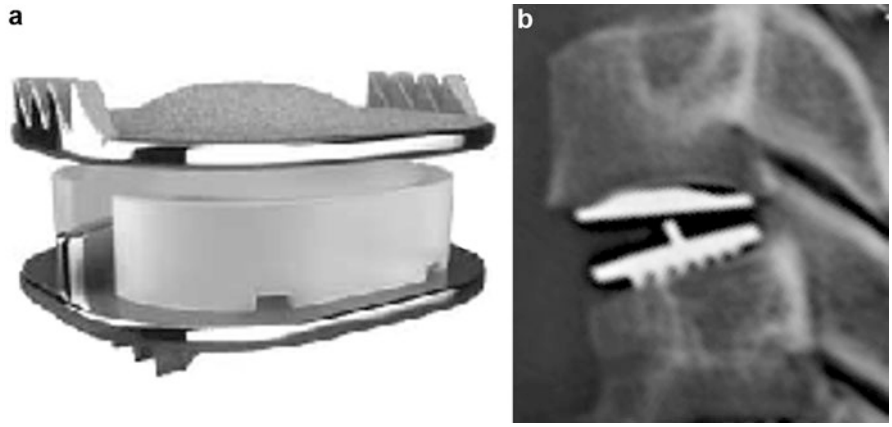

Fig. 7 Mobi-C cervical disc: (**a**) device; (**b**) lateral X-ray after implantation

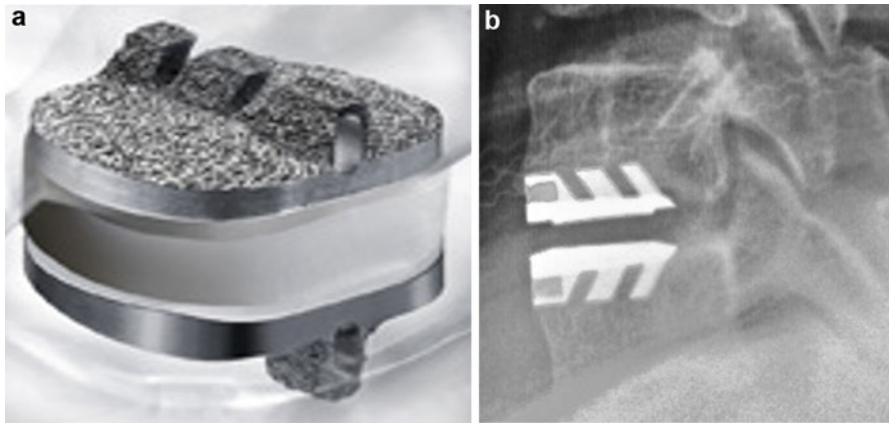

Fig. 8 Secure-C cervical disc: (**a**) device; (**b**) lateral X-ray after implantation

major complications. Range of motion was maintained with Mobi-C through 60 months. Device-related subsequent surgeries (Mobi-C 3.0%, ACDF 11.1%) and adjacent segment degeneration at the superior level (Mobi-C 37.1%, ACDF 54.7%) were significantly lower for Mobi-C cohort. They concluded that total disc replacement with Mobi-C is a viable alternative to single-level ACDF (Hisey et al. 2016).

Secure-C Cervical Disc

Device Description

The Secure-C device is a selectively constrained anterior articulating intervertebral device comprised of two end plates and a central core. The superior and inferior cobalt-chrome alloy end plates have multiple serrated keels for short-term fixation and titanium plasma spray coating on bone contacting surfaces for long-term bony ingrowth. The sliding central core is composed of ultrahigh molecular weight polyethylene, with a spherical superior interface (Fig. 8).

Outcomes

Vaccaro et al. published results of a prospective, multicenter, randomized controlled IDE trial to compare the clinical safety and effectiveness of the Secure-C device versus ACDF. A total of 380 patients from 18 investigational sites were randomized and evaluated. Overall, the study

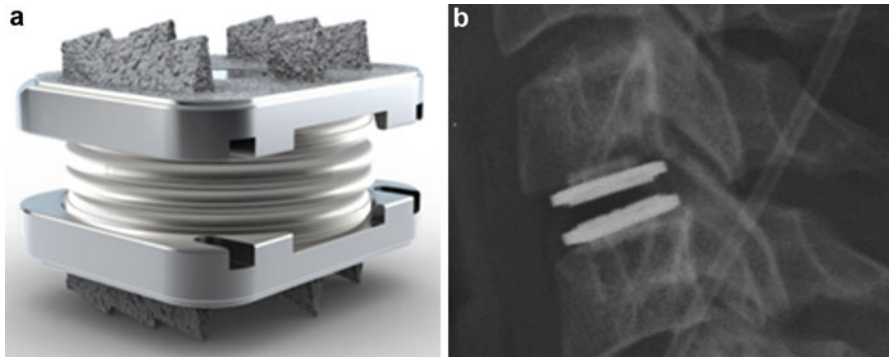

Fig. 9 M6-C artificial disc: (**a**) device; (**b**) lateral X-ray after implantation

demonstrated the statistical superiority of the Secure-C group compared with the ACDF group at 24 months. At 24 months, the Secure-C cohort demonstrated clinically significant improvement in pain and function in terms of NDI scores, VAS scores, and 36-Item Short Form Health Survey. At 24 months, the percentage of patients experiencing secondary surgical interventions at the index level was statistically lower for the Secure-C group (2.5%) than the ACDF group (9.7%). This type of disc has also proven to be a viable alternative to ACDF in appropriately selected patients (Vaccaro et al. 2013).

M6-C Artificial Cervical Disc

Device Description

The M6-C disc is an unconstrained disc with a polyethylene weave (designed to mimic the annulus fibrosus) which houses a compressible viscoelastic polyurethane core (designed to mimic the nucleus pulposus). The end plates are titanium with a plasma spray coating, and fixation is achieved with three rows of "fins" on the upper and lower end plates (Fig. 9).

Outcomes

Lauryssen et al. published results of a prospective, multicenter, non-controlled IDE pilot study to evaluate the clinical safety and effectiveness of the M6-C disc. A total of 30 patients from 3 investigational sites were evaluated and demonstrated significantly improved clinical outcomes (NDI, VAS neck and arm scores) compared to baseline at 2-year follow-up (Lauryssen et al. 2012).

Conclusion

Eight cervical artificial disc devices have been approved by the FDA dating back to 2006. These devices have a sound evidence basis as safe and viable alternatives to ACDF in properly selected patients. Patient selection is key to ensure appropriate patient outcomes as seen in these FDA IDE studies. Further long-term investigations will be necessary to ensure the longevity of these devices.

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Cervical Total Disc Replacement: Next-Generation Devices

40

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Abstract

Cervical disc arthroplasty techniques were developed as an alternative to fusion in order to preserve natural motion and reduce the risk of adjacent segment degeneration in the appropriately selected patients with cervical myeloradiculopathy. These arthroplasty implants must provide stability, preserve physiologic motion, and replicate the kinematic signature of the natural disc. There are currently eight cervical arthroplasty implants approved by the Food and Drug Administration (FDA) for use in the United States. The majority of approved

implants follow a metal on polyethylene ball-in-socket or saddle-type design. Over the past decade, there has been an explosion of cervical arthroplasty implant designs each with their own advantages and disadvantages. The purpose of this chapter is to review the biomechanics and kinematics of the natural cervical disc. We will also review available in vivo and ex vivo literature on novel elastomeric compression, hydraulic, and next-generation ball-in-socket cervical arthroplasty designs.

Keywords

Cervical spondylosis · Arthroplasty · Radiculopathy · Myelopathy · Novel implants

Introduction

Motion-preserving cervical disc arthroplasty implants were developed as an alternative to fusion in order to preserve natural motion and cervical biomechanics and reduce the risk of adjacent segment disease for patients with cervical radiculopathy or myelopathy (Hilibrand et al. 1999). The goals of cervical disc arthroplasty are to restore disc and foraminal height, preserve physiologic motion, and provide long-term stability (Cepoiu-Martin et al. 2011; McAfee 2004; Mummaneni et al. 2007). There are currently eight cervical arthroplasty implants approved by the Food and Drug Administration (FDA) for clinical use. These include the Prestige ST and LP (Medtronic), Bryan (Medtronic), ProDisc-C (Centinel Spine), SECURE-C (Globus Medical), Porous Coated Motion (PCM) (NuVasive), Mobi-C (LDR), and the recently approved M6-C Artificial Cervical Disc (Orthofix). The majority of currently approved designs involve a bi-articulating ball-in-socket type design with a polyethylene core and metal (titanium or cobalt chrome) endplate. Most endplate designs include a keel for initial stability and textured surface to promote long-term bony ingrowth (Staudt et al. 2018).

Physiologic Kinematics

A healthy cervical intervertebral disc is viscoelastic and allows for three-dimensional motion in sagittal, coronal, and axial planes. Physiologic motion of a normal cervical segment allows for 15° of flexion-extension, 4° of lateral bending, and 5° of axial rotation in each direction (Holmes et al. 1994; Iai et al. 1994; Ishii et al. 2006). Additionally, there is a linear coupling of ipsilateral lateral bending and axial rotation resulting from facet and uncinate process orientation in each cervical segment (Bogduk and Mercer 2000; Patwardhan et al. 2012; Senouci et al. 2007). The physiologic sagittal center of rotation (COR) varies by cervical segment. The flexion-extension COR at the C5–C6 segment occurs at the midpoint of the superior endplate of the C6 vertebrae. The COR occurs at a point more caudad and dorsal in upper cervical segments and more cephalad in lower segments (Bogduk and Mercer 2000; Hwang et al. 2008; Patwardhan et al. 2012). An arthroplasty device should replicate both physiologic range of motion (ROM) and maintain a natural COR. An arthroplasty device that alters segments of physiologic COR may result in abnormal translations of the adjacent vertebrae during motion, unnatural forces across the segment including the facet joints and uncinate impingement. These abnormal forces may result in limited motion, pain, or ultimately facet joint or adjacent segment degeneration (Bogduk and Mercer 2000; Patwardhan et al. 2012; Pickett et al. 2006).

The viscoelastic cervical disc demonstrates nonlinear flexion-extension load-displacement curve. This characteristic allows for motion with minimal energy expenditure around the neutral zone, termed high flexibility zone. Increasing stiffness outside this high flexibility zone prevents damaging motion beyond the physiologic range. This graded resistance to angular motion also allows for energy dissipation, thereby reducing forces across index and adjacent segments under physiologic load (Panjabi 1992; Patwardhan et al. 2012). Additionally, the viscoelastic nature of the nucleus pulposus allows the disc to conform under compressive loads and act as a shock absorber, thereby reducing force across adjacent

segments and facets (Lazennec et al. 2016). The ideal cervical arthroplasty implant allows for compressibility and graded resistance to motion. Replicating this kinematic signature will reduce shear stresses across the facet joints and adjacent segments and improve implant longevity. First-generation ball-in-socket designs do not allow for compressibility or graded resistance to motion. Elastomeric cervical disc implants were developed as an alternative with these physiologic biomechanical characteristics in mind. Elastomeric compression devices are primarily designed with a polyurethane core that theoretically allows for motion under compression and graded resistance mimicking that of the native disc. To date, there are only a few cervical disc replacement designs that claim to fit this description. These include the M6-C Artificial Cervical Disc (Orthofix), Freedom Cervical Disc (FCD, AxioMed LLC), Cadisc-C (Rainier), and CP-ESP (FH Orthopedics) (Chin et al. 2017; Staudt et al. 2018).

Design Considerations

Multiple characteristics should be considered when designing and evaluating cervical arthroplasty devices. These include articulating surface design, mono or multipiece implant, constraint, materials, and fixation methods. The majority of cervical devices contain a mono or bi-articulating surface. First-generation implants use a ball-in-socket or saddle articulation design. Next-generation implants take advantage of these traditional designs but also include elastomeric and hydraulic-type designs. Implants may exist as a single monoblock or multipiece design. Experience with hip and knee arthroplasty would suggest that monoblock designs may predispose to increase stress across the implant/bone interface leading to early failure. Modular multipiece implants may reduce stress across adjacent interfaces and provide flexibility with sizing, though multipiece implants with more articulating surfaces inherently have more methods of failure. Certain first-generation ball-in-socket designs have highly congruent articulations with a resulting fixed COR. As a result, precise implant position is necessary for restoration of physiologic COR, which varies by cervical segment (Bogduk and Mercer 2000; Hwang et al. 2008; Patwardhan et al. 2012). Other designs that allow for some translation will have a mobile COR and theoretical flexibility in implant position and may accommodate segmental differences. Constraint is defined by the amount of motion in all directions allowed by the implant. Implants may be constrained, unconstrained, or semiconstrained. Constrained designs provide greater stability but may prevent physiologic motion thereby increasing stress on the implant/bone interface, adjacent segments, and facet joints. On the other hand, unconstrained designs may be unstable under physiologic loads. The majority of cervical arthroplasty designs are semiconstrained providing stability with physiologic motion.

Most currently approved cervical arthroplasty implants are made of a metal endplate (titanium, chrome/cobalt, stainless steel) with a polyethylene or polyurethane center. This basic design was born from hip and knee arthroplasty experience, providing a low-friction bearing surface with stable bone interface. Endplate metals offer different advantages and disadvantages based on modulus, stress shielding, biocompatibility, corrosion resistance, and advanced imaging metal artifact. Newer designs are taking advantage of polyetheretherketone (PEEK) and ceramic materials thereby improving MRI compatibility. Articulating surfaces, whether they are metal on metal, metal on polyethylene, or metal on polyurethane, have different wear debris profiles. Wear debris may result in osteolysis, bone loss, loosening, and ultimate implant failure as seen in hip and knee arthroplasty. Metal on metal articulations have been largely abandoned due to concerns for metal wear debris. Overall, the long-term wear profiles of polyethylene and polyurethane devices in the cervical spine are largely unknown. Finally, the majority of devices contain metal spikes or keels for initial fixation into the adjacent vertebral endplates. Long-term fixation is achieved by bony ingrowth into porous-coated (calcium phosphate, hydroxyapatite, and plasma-sprayed titanium) surfaces (Staudt et al. 2018).

Elastomeric Implants

M6-C Artificial Cervical Disc

The M6-C Artificial Cervical Disc Implant (Orthofix) is a next-generation non-constrained viscoelastic compression-type implant. The nucleus core is made of viscoelastic polyurethane surrounded by ultrahigh-molecular weight polyethylene fiber designed to mimic the nucleus and annulus, respectively, and mimic the physiologic properties of the natural disc (Fig. 1). This physiologic core is attached to two titanium endplates and surrounded by a sheath to prevent wear debris elution and tissue ingrowth. Both titanium endplates contain three fins for provisional fixation and titanium plasma spray coating to promote bony ingrowth. Biomechanical analysis of the M6-C design has demonstrated physiologic ROM, COR, and stability in cadaveric specimens. Patwardhan et al. evaluated the biomechanics of an implanted the M6-C artificial disc at the C5–C6 segment in 12 cadaveric specimens. ROM in flexion-extension, lateral bending, axial rotation, coupled motion, stiffness, and COR was evaluated using digital video fluoroscopic images under 1.5 Nm force moments and compared to control segments. They demonstrated implantation of the M6-C prosthesis within 1 mm of the disc-space midline closely replicated control segment COR and ROM in flexion-extension. Additionally, implantation in a more posterior position did not significantly affect ROM, coupling, or stiffness, suggesting an advantage to and flexibility of implant insertion associated with this novel elastomeric implant (Patwardhan et al. 2012). An initial multicenter FDA-regulated feasibility study evaluated 24-month clinical and radiographic outcomes of 30 patients undergoing one- or two-level M6-C prosthesis implantation with 24-month follow-up. They demonstrated improvement in Neck Disability Index (NDI) and Visual Analog Scale (VAS) neck and arm scores at all time points. No patients experienced surgical or neurologic complication. Radiographic disc height increased in all patients, while global and segment ROM in flexion-extension and lateral bending was maintained (Lauryssen et al. 2012). The results of the feasibility study suggested that the M6-C produces excellent results similar to current approved implants and suggested further prospective studies are necessary to determine the motion provided by the elastomeric compression design improves long-term clinical outcomes and reduces adjacent segment disease (Lauryssen et al. 2012). A recent retrospective study by Thomas et al. in Belgium evaluated clinical outcomes of 33 patients who underwent M6-C arthroplasty for spondylotic radiculopathy or myelopathy with mean 17.1-month follow-up. All patients demonstrated improvement in NDI, VAS arm and back, and

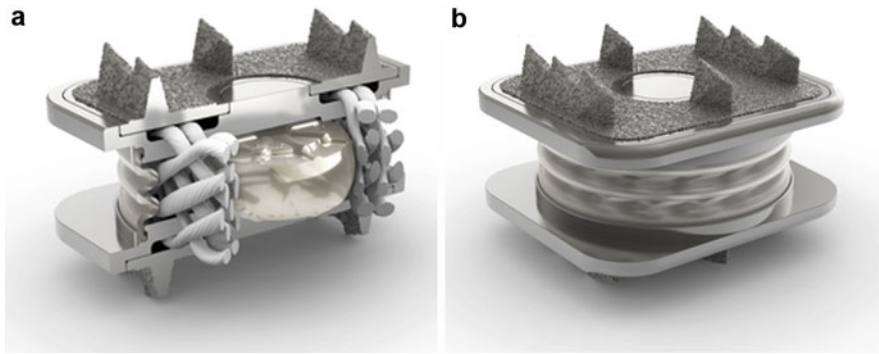

Fig. 1 (**a**) Cutaway schematic of the M6-C Artificial Cervical Disc Implant. It demonstrates viscoelastic polyurethane nucleus core surrounded by ultrahigh-molecular weight polyethylene fiber mimicking the nucleus and annulus of the natural disc. (**b**) Exterior schematic of M6-C Artificial Cervical Disc Implant demonstrating physiologic core attached to two titanium endplates. The core is surrounded by an external sheath to prevent tissue ingrowth and elution of wear debris. Each titanium endplate contains three fins for provisional fixation and titanium plasma spray coating to promote bony ingrowth

SF-36 scores. Four patients experienced device-related complications, two with endplate subsidence, one with implant loosening after motor vehicle collision, and one with immobility due to heterotopic ossification. All four of these patients had a history of previous cervical surgery. They concluded that the M6-C prosthesis is a good addition to the cervical arthroplasty options, though should be avoided in patients with history of previous cervical surgery (Thomas et al. 2016). Early reports on the FDA Investigational Device Exemption (IDE) outcomes data demonstrated favorable outcomes of 83 patients who underwent M6-C implantation at 12 (Phillips et al. 2017) and 24 months (Sasso et al. 2018) follow-up. There was significant improvement in the mean VAS neck and arm scores and index level lordosis. Mean index level ROM increased slightly from 7.8° preoperatively to 8.1 at 2 years. There was radiographic evidence of subsidence in three cases, no evidence of migration, and no revision procedures in the follow-up period (Phillips et al. 2017; Sasso et al. 2018). Further long-term studies with larger patient cohorts are needed to determine the effects on development of adjacent segment disease and long-term wear properties. The M6-C implant has recently received FDA approval for use.

Freedom Cervical Disc

The Freedom Cervical Disc (AxioMed) is a monoblock viscoelastic design consisting of an elastomeric core fixed to two titanium plates. The elastomeric polymer core consists of a silicone polycarbonate urethane copolymer. This polymer is molded and bonded to two titanium-retaining plates. Both titanium plates have a porous bead coating designed to engage and allow for bony ingrowth between the cephalad and caudad endplates. The Freedom Cervical disc is created with 8 degrees of lordosis and available in heights ranging from 5.7 to 6.9 mm. The prosthesis is designed to mimic a normal physiologic cervical disc by establishing appropriate alignment and lordosis, viscoelasticity to mimic load sharing, and stable range of motion in flexion, extension, lateral bending, and rotation. Surprisingly there are no biomechanical studies published to confirm the kinematic features claimed by the manufacturer. Specifically, there is no data regarding the stiffness of this monoblock polymer prosthesis and concerns for resultant high bone-implant forces.

The Freedom Cervical disc has undergone previous pilot studies outside the United States but is not currently approved for use within the United States (Chin et al. 2017; Staudt et al. 2018). One study by Chin et al. reported on the 2-year post market clinical outcomes of the Freedom Cervical Disc in Europe. A total of 39 patients with cervical radiculopathy at 5 institutions underwent one- or two-level cervical disc arthroplasty using the Freedom Cervical Disc. At 2 years clinical follow-up, all patients demonstrated improvement in NDI and VAS neck and arm pain scores. There were no new neurologic symptoms or device-related complications. ROM was surprisingly not evaluated in this study. They concluded that the Freedom Cervical Disc performed as expected in the appropriately selected patients with one- and two-level degenerative disc disease (Chin et al. 2017). This single study is limited by the number of patients and lack of long-term follow-up. Criticisms of this implant design include concerns regarding a single polymer of unknown compressibility matching physiologic properties of the native disc (Staudt et al. 2018).

CP-ESP Cervical Disc

A similar design, the CP-ESP cervical disc prosthesis (FH Orthopedics) is an evolution of the LP ESP lumbar prosthesis that has been implanted in Europe for over 10 years. The CP-ESP disc is a monoblock elastomeric implant with a central polycarbonate urethane (PCU) core fixed to two titanium endplates. Both endplates contain anchoring pegs, textured titanium, and hydroxyapatite layers to provide preliminary fixation and allow for bony ingrowth. The PCU core demonstrates resistance to oxidation both in vivo and ex vivo (Kurtz et al. 2007; Lazennec et al. 2016). The core is attached to the endplates via adhesion molding with peg and groove design without the

use of adhesives avoiding the risk of fluid infiltration and fatigue fractures. This design also allows the implant to replicate the anisotropy of a healthy disc, allowing for controlled compression while avoiding shear in flexion and extension. Mechanical analysis demonstrates a physiologic flexion/extension arc of 14°, lateral bending of 12°, and rotation of 8°. The CP-ESP implant is available in 5, 6, and 7 mm heights with various anterior-posterior and lateral dimensions.

A biomechanical assessment of wear debris and fatigue measured using a three-axis motion simulator over the course of ten million cycles demonstrated loss of height ranging from 0.02 to 0.12 mm and no detectable wear debris. Lazennec et al. prospectively evaluated 1- and 2-year clinical and radiographic outcomes of 62 patients who underwent one- or two-level cervical disc arthroplasty using the CP-ESP prosthesis. At both time points, all patients demonstrated improvement in NDI and VAS neck and arm scores. They also demonstrated improved radiographic range of motion at the index levels. No patients experienced implant-related complications or revision procedures during follow-up (Lazennec et al. 2016). Though this design is available for use in Europe, it is not currently under FDA review (Staudt et al. 2018).

Cadisc-C

The Cadisc-C (Ranier Technology) is an evolution of the Cadisc-L design for lumbar disc disease. This unique monoblock elastomeric design consists of polycarbonate-polyurethane nucleus with calcium phosphate coating without an associated metal endplate. The polycarbonate-polyurethane implant contains a lower modulus "nucleus" integrated into a surrounding higher modulus "annulus" allowing it to more accurately mimic the biomechanics of the natural intervertebral disc (McNally et al. 2012; Rieger 2014). The lack of metallic endplate and articulating surfaces is theorized to reduce potential for wear debris (McNally et al. 2012). Though, concern exists regarding the all polymer monoblock design lack of fixation and potential for migration. There is also no published data regarding wear debris profile of this design (Staudt et al. 2018). Currently, prospective trials are underway evaluating clinical outcomes of the Cadisc-C design in Germany (Rieger 2014).

Next-Generation Pivot/Ball Type Artificial Discs

Synergy Cervical Disc

The Synergy (Synergy Disc Replacement) Cervical Disc prosthesis is a next-generation ball-in-socket cervical disc comprised of bi-articulating titanium endplates with an ultrahigh-molecular weight polyethylene core. Bony fixation is augmented by six plasma-sprayed titanium "teels" (a combination of teeth and keels) on each articulating surface. Its three-piece design is MRI compatible and is available in 5 or 6 mm height options. The Synergy device also has a proprietary geometry which incorporates 0° or 6° of cervical lordosis (Staudt et al. 2018). Synergy was compared to two similar constrained ball and pivot arthroplasty designs (Bryan and ProDisc-C) in a retrospective study of 60 patients undergoing single-level cervical disc arthroplasty for cervical radiculopathy. Pre- and postoperative ROM along with dynamic lateral cervical spine imaging were assessed for each group. The Synergy cohort showed the least variability in change of sagittal alignment, achieving six degrees of lordosis on average with maintenance of cervical ROM achieved in all groups (Lazaro et al. 2010). A recent retrospective cohort study compared both the clinical outcomes and postoperative sagittal alignment of patients undergoing single-level surgery for cervical radiculopathy or myelopathy. Forty patients in the arthroplasty group were compared to 33 patients in the single-level fusion group with a minimum follow-up of 24 months. Both the arthroplasty and ACDF groups showed significant improvement in NDI and VAS neck and arm scores. The arthroplasty group maintained an average cervical lordosis of 6 +/− 2.7°, while the ACDF group demonstrated an

average of 4 +/− 2.4° of lordosis. The authors concluded that the Synergy system demonstrated comparable outcomes and improved sagittal alignment in comparison to cervical fusion (Yucesoy and Yuksel 2017). While it has undergone various stages of testing and pilot studies, the Synergy arthroplasty system lacks FDA approval and is not currently available in the US market.

Baguera C

The Baguera C (Spineart) is a novel ball-in-socket implant with a mobile core designed as a shock absorber. The mobile core is made of ultrahigh-molecular weight polyethylene (UHMWPE) nucleus that articulates with two titanium endplate components. The titanium endplates contain a bioceramic internal coating in contact with the UHMWPE nucleus and a porous titanium exterior intended for endplate ingrowth. Each endplate contains three fins intended to provide initial stability. The nucleus allows to 0.3 mm anterior to posterior translation, 2° rotation, and 0.15 mm elastic deformation mimicking that of the physiologic disc. One biomechanical analysis demonstrated reduced core contact pressures and liftoff throughout ROM compared to ProDisc-C (Centinel Spine) and Discocerv (Alphatec) using a cervical spine finite element model (Lee et al. 2016). Fransen et al. performed a retrospective registry analysis of 99 patients at 5 European investigational centers undergoing one- or two-level cervical arthroplasty for radiculopathy or myelopathy using the Baguera C implant. They demonstrated a decreased range of motion from 10.2° preoperatively to 8.7° for single-level procedures and from 9.8° to 9.1° for two levels at 2 years radiographic follow-up. They also demonstrated evidence of heterotopic ossification in 54% of patients. None demonstrated radiographic evidence of subsidence, kyphosis, or degeneration of the adjacent disc (Fransen 2016). While lack of radiographic evidence of adjacent segment disease is encouraging, larger long-term studies are needed to determine the efficacy of the implant. Additionally, the mobile nucleus design may theoretically predispose to long-term wear debris and potential for osteolysis as seen in hip and knee arthroplasty.

Simplify Cervical Disc

The Simplify disc has completed one- and two-level IDE study but is not yet received FDA approval. It is a semiconstrained design with titanium plasma-sprayed PEEK endplates with a retention ring housing a mobile ceramic core. Simplify is a modern generation disc with novel biomaterials (PEEK and ceramic) which provide for positive imaging characteristics.

Conclusions

The goal of motion-preserving cervical arthroplasty devices is to restore natural kinematics and motion under physiologic load and prevent degeneration of adjacent segments. Traditional, first-generation cervical arthroplasty devices contain ball-in-socket type designs and do not allow for physiologic coupled motion and compressible graded resistance. As a result, these designs may predispose to adjacent segment and facet stress predisposing to facet degeneration, pain, reduced motion, and degeneration. Early biomechanical evidence suggests that next-generation elastomeric compression devices may better replicate physiologic coupled motion and graded resistance. Further studies are necessary to determine the wear properties, durability, and long-term outcomes of these novel implants.

Cross-References

- ▶ Cervical Total Disc Replacement: Biomechanics
- ▶ Cervical Total Disc Replacement: Evidence Basis
- ▶ Cervical Total Disc Replacement: Expanded Indications
- ▶ Cervical Total Disc Replacement: Heterotopic Ossification and Complications

▶ Cervical Total Disc Replacement: Technique – Pitfalls and Pearls

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Cervical Total Disc Replacement: Evidence Basis

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Abstract

Anterior cervical decompression and fusion has long been the gold standard for cervical degenerative disc disease, but concerns about the deleterious effects of fusion on adjacent segments have led to the development of cervical total disc replacement (TDR). While many TDR designs have been evaluated, metal-on-polymer and metal-on-metal designs are the most commonly used today. Different types of metals and surface modification have been introduced in attempt to improve osseous integration and decrease failure of implant. Correct positioning, adequate exposure, and thorough decompression and end plate preparation are necessary to ensure proper disc placement. Patients benefit in the postoperative period from early mobilization, improved range of motion, and often return to work earlier, with a lower risk of reoperations than with fusion. Long-term outcomes from many of the IDE trials consistently demonstrate to be comparable and even superior to fusion with cost-effective analysis further supporting financial feasibility.

Keywords

Cervical disc replacement · Degenerative disc disease · Intervertebral disc · Cervical spine · Arthroplasty · Cervical radiculopathy · Cervical myelopathy

Introduction

Joint arthroplasty has been an evolving treatment modality for degenerative joint disease for decades. Its evolution has permitted improved prostheses, better outcomes, and the inception of arthroplasty being used in numerous areas of the body. Utilization of arthroplasty for cervical spine pathology has been a topic of recent discussion. While prior treatment has been centered on hip and knee arthrodesis, cervical total disc replacement (TDR) displays promise for the maintenance of native spine biomechanics and kinematics while minimizing the progression of adjacent segment disease seen in arthrodesis.

Currently, the most commonly used treatment of cervical spine spondylosis and disc disease centers on Smith-Robinson, who pioneered the widely known and used anterior cervical decompression and fusion (ACDF) surgery in the 1950s with multiple studies reporting remarkably good success with this procedure (Bohlman et al. 1993). However, adjacent segment degeneration, or the appearance of degenerative changes at a level above or below a fused segment, has been seen during long-term follow-up, and efforts toward artificial joint prostheses became a potential alternative. Symptomatic adjacent segment disease (ASD) affects approximately a quarter of all patients who undergo an ACDF by 10 years with more than two-thirds of patient failing nonoperative therapy and requiring addition operative interventions (Hilibrand et al. 1999).

The first attempt to create an artificial intervertebral replacement appeared in the 1960s under Ulf Fernström. The initial implant utilized was a stainless steel ball bearing prosthesis trialed in both the cervical and lumbar spine (Baaj et al. 2009). Unfortunately, little success was obtained, and nearly 90% of the cases demonstrated implant migration and subsidence of the

prosthesis (Fernström 1966). Its failure briefly dampened enthusiasm for TDR and shifted the focus back to ACDF procedures. However, B. H. Cummins developed the first modern model of the cervical disc prosthesis in 1989 at the Frenchay Hospital in Bristol. This new device was a metal-on-metal ball-and-socket design with screws anchoring anteriorly, fixing it to the vertebral body. Again, early implants demonstrated a high degree of screw cut out, dysphagia, and implant mobilization (Cummins et al. 1998). Attempting to avoid this complication, Cummins developed a second-generation device where the anterior portion of the device, articulating surface, and locking screw device were all redesigned. This device became known as the Prestige I Disc, which was continually modified to a fifth-generation product ultimately called the Prestige LP made of a titanium-ceramic composite that could be more aggressively anchored to the vertebral body (Nasto and Logroscino 2016). In July 2007, the Prestige ST disc was approved by the FDA. Since then numerous models or varying materials were to follow such as the Bryan, which consists of two titanium alloy end plates articulating with a polyurethane core. This device is fixed to the bone by a porous titanium layer that maintains a tight fit between the vertebrae. The ProDisc-C with cobalt-chrome-molybdenum end plates and a polyethylene articulating surface is a ball-and-socket constrained prosthesis that has a central keel for initial fixation to the bone (Smucker and Sasso 2011).

Over the past 30 years, there have been increased efforts toward the development of TDR. While currently not widely accepted as a substitute for ACDF, the concept of joint arthroplasty in the spine remains in clinical practice and as a topic of evolving research. In a recent international survey of spine surgeons, only 7% used TDR as a standard treatment, while 84% used ACDF (Chin-See-Chong et al. 2017). The development of TDR has the potential to not only minimize adjacent segment disease but to ultimately mimic healthy spine kinematics and biomechanics. Additional studies are required to help gain insight into the better use of these prostheses.

Biomechanics

The goal of cervical total disc replacement is to restore native cervical spine biomechanics. While ACDF remains the standard for many cervical spine pathologies, numerous studies have found that it decreases motion at fused levels and transfers increased motion and stresses to adjacent levels, creating higher intradiscal pressure and ultimately increasing the incidence of adjacent level disease when compared to arthroplasty (Smucker and Sasso 2011; Dmitriev et al. 2004).

Constraint

The different types of movements in the cervical spine can be grouped into rotational and translational. They occur in the sagittal, coronal, and axial planes, making up the six degrees of freedom. When one degree of freedom is limited, that movement is constrained, and a fully constrained device would indicate no movement at all in the six degrees of freedom. There is a lack of consistency in the literature when defining and classifying a device based on constraint, but they have been described as unconstrained, semi-constrained, and fully constrained. The degree of constraint typically refers to translational movements since rotation is unconstrained in all devices; otherwise a fully constrained device would technically be a fusion. An unconstrained prosthesis allows for more motion, but does not resist shearing forces which are shifted on to the facet joints. A more constrained prosthesis limits motion but assumes more of the shearing forces, thus relieving the facet joints.

Kinematic studies of the cervical spine after artificial disc implantation have shown promising results in retaining native biomechanics. TDR has demonstrated preserved postoperative sagittal rotation, translation, center of rotation, and disc heights when compared to preoperative measurements (Pickett et al. 2005). When comparing biomechanical data of different implants in vivo and in vitro, DiAngelo et al. reviewed the biomechanics of different devices and noted the motion of two different prostheses in cadaveric models.

The designs in question were a semiconstrained device allowing anterior-posterior translation and a constrained device with minimal to no anterior-posterior translation. The semiconstrained device, the Prestige ST disc, more closely replicated native cervical spine kinematics at all ranges of motion, whereas the constrained disc, ProDisc-C, failed to reproduce native motion (DiAngelo et al. 2003, 2004).

Anatomical Considerations

The anatomical relationships in the cervical spine are complex, and correct alignment is essential for efficient biomechanics. Relevant bony anatomy with regard to cervical biomechanics includes intervertebral disc, uncovertebral joints, and the facet joints. Each plays a role in the overall range of motion and stability of the spine through the range of motion. During flexion, the center of rotation is located in the anterior region of the inferior vertebra, and forces are relieved off the facets, where as in extension the facets and spinous process are engaged. The two uncovertebral joints aid in lateral bending by providing resistance to shear forces. The significant changes in stability after uncovertebral joint resection highlight the importance of preserving them during decompression (Kotani et al. 1998). During lateral bending, the center of rotation moves to the superior vertebral body, and the lateral uncovertebral joints are engaged like a rail to limit translation.

Sasso et al. further evaluated the biomechanical properties of the BryanTDR versus ACDF preoperatively and postoperatively. After 24 months, TDR slightly improved flexion and extension range of motion from 6.4 to 8° without implant complication. Meanwhile, ACDF only retained about 1° of flexion and extension, which gradually decreased over a 24-month period (Nasto and Logroscino 2016; Sasso et al. 2008). Janssen et al. reported significantly higher flexion-extension range of motion after disc replacement with the ProDisc-C compared to the ACDF group at 7 years follow-up (Janssen et al. 2015). Similarly, Hisey et al. reported no loss of segmental range of motion in the disc replacement group but did note an increase in overall flexion-extension range of motion at the 5-year follow-up (Hisey et al. 2016). Conversely, others have also reported no difference in cervical range of motion between ACDF and TDR at long-term follow-up, but in general range of motion is maintained or improved with TDR (Radcliff et al. 2016b).

Biomaterials

An ideal arthroplasty device is one that is biocompatible, has superior biomechanical properties, produces minimal wear debris, and can achieve strong fixation. Immediate fixation and stability are based on screw fixation or physical stops, while long-term fixation relies on osseous integration between the prosthesis and vertebral body. Another important consideration is the wear properties of the different materials since the generated particles create an inflammatory response, resulting in osteolysis and eventually failure of implant. To address several of these factors, different materials have been used for the implant design including titanium alloy, stainless steel, and cobalt-chrome (CoCr) alloy. Also, polymers such as ultrahigh molecular weight polyethylene (UHMWPE) and polyurethane (PU) are used as articular surfaces.

End Plate Materials

Titanium alloy is a biocompatible metal that contains titanium, vanadium, and aluminum. Its modulus of elasticity is closer to cortical bone than steel allowing for better osseous integration. This property has led to the use of titanium as part of a porous coating on the outer surface of cervical implants to improve fixation at the implant-bone interface. Calcium phosphate has also been added to titanium resulting in increased osseointegration (Cunningham et al. 2009). Titanium is also inert and forms an oxide film making it highly resistant to corrosion. It also produces less imaging artifact than steel or cobalt-chrome, and both the index

and adjacent levels can be easily visualized on MRI (Fayyazi et al. 2015). However, its poor wear properties and propensity to generate more wear debris make it less useful as a bearing surface.

Stainless steel is primarily an iron-carbon alloy that can be combined with other metals to alter its properties. It is a widely available and inexpensive metal that is strong, stiff, and resistant to fatigue. However, its high elasticity modulus leads to stress shielding of bone. It also tends to be more corrosive than other metals, but when used in combination with chromium, it is less susceptible to corrosion. The biggest limitation with stainless steel is the artifact produced with MRI which does not allow for visualization of either the index or adjacent levels such as with Prestige ST (stainless steel end plates) (Fayyazi et al. 2015).

Cobalt-chrome is a strong alloy that is biocompatible and resistant to corrosion. It has demonstrated superior wear characteristics making it a more reliable metal for bearing surfaces. It also produces less debris compared to titanium alloy and is relatively resistant to fatigue. All these properties together have made cobalt-chrome a popular choice for cervical arthroplasty devices. Cobalt-chrome devices are MRI compatible, but imaging artifact lies somewhere in between that of stainless and titanium where adjacent levels can be visualized but the index level is typically obscured.

Until recently, implant designs have been solely evaluated based on the mechanical properties of the materials used, but now the focus has shifted to surface topography. The three most commonly used surface modifications in TDR include titanium spray coating, hydroxyapatite (HA) coating, and porous surfaces. Titanium spray coating has been shown to improve osseous integration on Co-Cr implants through enhanced cellular attachment, proliferation, and differentiation (Pham 2014). Hydroxyapatite accounts for a majority of inorganic bone, and HA coatings provide an osteoconductive environment. Surface porosity is another technique that is often utilized in multiple orthopedic implants due to its ability to promote bony ingrowth and stable interlocking fixation while reducing stress shielding of metals by lowering the modulus of elasticity (Dabrowski et al. 2010). These techniques function in different ways but ultimately work to enhance the osseous integration at the bony-implant interface in an attempt to achieve long-term fixation.

Bearing Designs

The most commonly used bearing surfaces are metal on metal and metal on polymer. Despite ceramics superior wear and corrosion properties, its brittleness, inability to absorb shock, and potential for catastrophic implant failure have limited its use in arthroplasty.

Metal-on-metal articulations were the initial design for total hip replacements. This was in large part due to in vitro studies that showed lower wear rates compared to polymer and clinical studies which showed a low mechanical failure rate and no osteolysis at long-term follow-up (Walter 1992; Dorr et al. 2000). The wear rates in simulator testing of metal-on-metal cervical arthroplasty have lower rates than that of metal-on-metal or metal-on-polymer total hip arthroplasty (Traynelis 2004). However, studies using metal on metal begun to show elevated levels of metal ions in urine, serum, and several organs (Jacobs et al. 1996; Urban et al. 2000). Concerns about ion toxicity and metal hypersensitivity began to mount, and the design lost some of its initial traction.

The metal on polymer design is similar in principle to modern total hip replacement devices. It is composed of two metallic vertebral end plates along with a core polymer. This was introduced as an alternative to metal on metal designs, due to concerns about systemic toxicity. UHMWPE is a thermoplastic polyethylene polymer with extremely long hydrocarbon chains. The long chains allow for more efficient load transfer giving it a high-impact strength. Cobalt-chromium on UHMWPE has a long track record of success in THA, but osteolysis is a known issue with this combination.

A new alternative currently under investigation is a PEEK-on-ceramic bearing. One of the advantages of this design is the absence of artifact

produced on imagining as well as MRI compatibility. This allows for accurate postoperative radiographic monitoring and reduces the exposure to ionizing radiation from CT scans which is often utilized with metallic TDR. Also, the wear rates, particle size, and morphology produced by a PEEK-on-ceramic bearing indicate a potential alternative to the commonly utilized CoCr-on-polyethylene and metal-on-metal bearings (Siskey et al. 2016).

Surgical Procedure and Technical Pearls

Indications and Contraindications

Well-defined patient selection criteria are critical for successful outcomes. Indications for cervical total disc replacement include radiculopathy or myelopathy resulting from one- or two-level disease, primarily anterior or disk-related pathology, preserved segmental motion, preserved disc space height, minimal facet arthropathy, and maintained sagittal alignment. Contraindications to performing TDR are tumor, trauma, infection, known allergy to implant metal, segmental instability, osteoporosis, collapsed disk space, circumferential pathology, severe cervical spondylosis, and prior cervical spine surgery at targeted level. Only about 40% of patients with symptomatic single-level cervical radiculopathy will be candidates for TDR (Auerbach et al. 2008).

Positioning

First, the patient is placed under general anesthesia and positioned supine on a radiolucent table. A bolster is placed between the shoulders and the neck is placed in neutral position. In contrast, for ACDF, the neck is often hyperextended. Tape is placed across the forehead to prevent rotation of the head intraoperatively. The arms are placed along the patient's side and taped with gentle traction, allowing for better access to the lower cervical spine. All bony protuberances should be well padded. The patient is then prepped and draped in the typical sterile fashion. Fluoroscopy should be utilized for intraoperative guidance. Rotational alignment can be assessed on AP fluoroscopy by confirming that the spinous process bisects the pedicles. The use of head weights is not recommended as this will cause a false impression of disc height through distraction of adjacent levels.

Pearls

- Poor head positioning can lead to sagittal malalignment and incorrect implant placement (Buchowski et al. 2009).
- Hyperextension leads to excessive removal of the posterior end plates, resulting in kyphosis.
- Hyperflexion leads to excessive removal of the anterior end plates, resulting in excessive lordosis.

Exposure

Prior to skin incision, fluoroscopy is used to confirm the approximate level of the incision. A standard Smith-Robinson approach is performed to access the anterior cervical spine. First, a transverse incision is made on the neck, either right- or left-sided, and sharp dissection is used down to the platysma. The platysma is dissected from the underlying fascia bluntly and split with electrocautery. Then the interval between medial portion of the sternocleidomastoid muscle (SCM) and the strap muscles is bluntly dissected. The carotid pulse should be palpated to locate the artery. Blunt dissection is continued medially to the SCM and carotid sheath. This is carried down through the pretracheal fascia and into the retropharyngeal space. Overlying the spine are the prevertebral fascia, anterior longitudinal ligament, and longus colli muscle. The longus colli is elevated in a subperiosteal manner. Retractors are then inserted and exposure of the anterior cervical spine is complete. The targeted intervertebral disc is confirmed on lateral fluoroscopy. The midline is located halfway between both uncinate processes, and a mark is made both in the superior and inferior vertebral bodies for implantation.

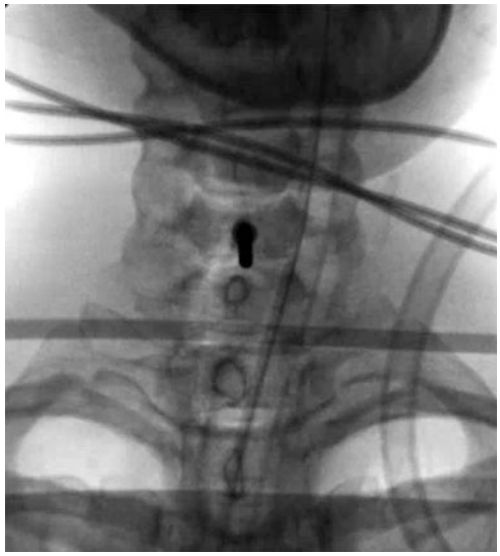

Fig. 1 AP fluoroscopy demonstrating midline placement of Caspar pin to avoid axial rotation

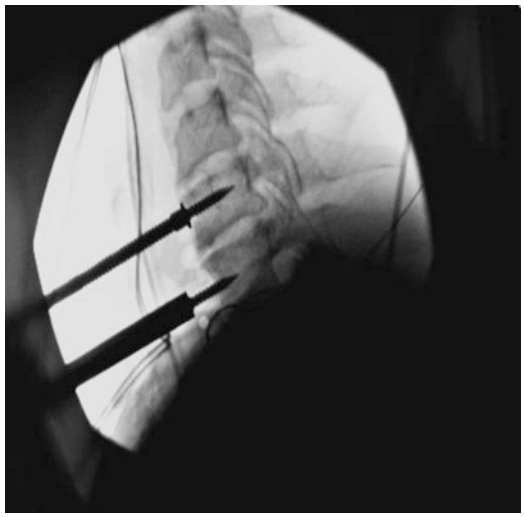

Fig. 2 Lateral fluoroscopy showing placement of Caspar pins parallel to vertebral end plates

Pearl

- Expose the lateral boundaries of the uncinate processes so they can be visually identified in order to ensure the implant is properly centered in the coronal plane.

Technique

After confirming the intervertebral disc, distraction pins are inserted midline in the superior and inferior vertebral bodies (Fig. 1).

Pearls

- Place the distractor pins parallel to the vertebral end plates so that the disc is symmetrically opened (Fig. 2).
- Ensure that the distractor pins are parallel to the true sagittal plane and do not deviate in the axial plane. Otherwise, a rotational displacement will be created once the pins are distracted.
- Use a Cobb elevator to carefully distract the disc space by levering on the end plates. Use the distractor pins to maintain the amount of distraction achieved from end plate leverage. Do not spread the vertebral bodies apart directly with the distractor pins.
- Take a preoperative X-ray to identify the facet joint height prior to distraction.

Depending on the implant used, this part of the procedure may sometimes follow the discectomy. Lateral fluoroscopy is used to confirm pin placement is parallel to the disc space. A locking distractor is attached to the pins and a Cobb elevator, and distracting forces are applied (Figs. 3 and 4). An annulotomy and discectomy are carried out using curettes and rongeurs.

Pearl

- Perform a wide, symmetric annulotomy.

This is completed between uncinate processes and from ventral to dorsal while using progressively smaller curettes. For complete decompression, meticulous removal of all osteophytes is critical. We recommend minimal use of a high-speed burr. However, if a one is used, copious amounts of irrigation and bone wax should be applied to reduce the risk of heterotopic ossification. When preparing the end plates, only the cartilaginous portion should be removed. Special attention should be paid to osteophytes located by

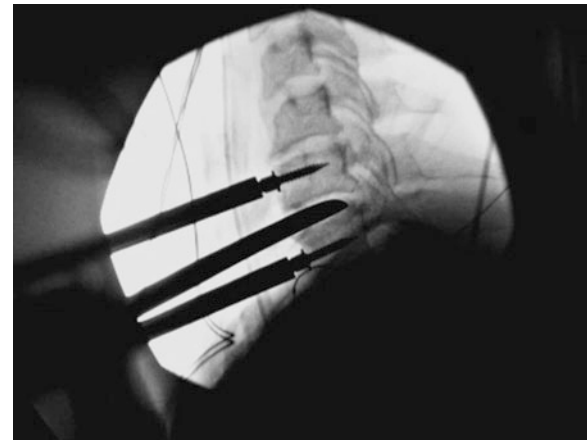

Fig. 3 Lateral image of same patient as Fig. 2 showing use of a Cobb to distract disc space

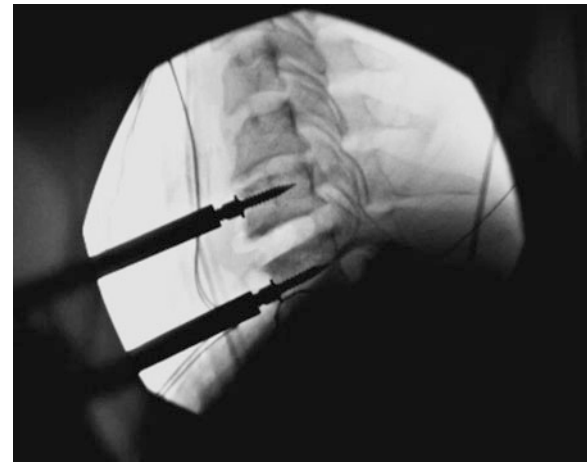

Fig. 4 Lateral image after use of Cobb and distraction forces applied to distract disc space

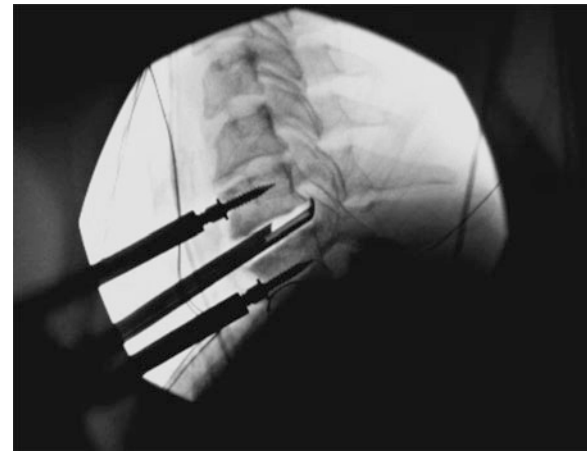

Fig. 5 Lateral fluoroscopy showing use of a Kerrison rongeur to remove posterior osteophytes for a complete decompression

the uncinate process or posterior vertebral body (Fig. 5). Partial resection of the uncinate process can be performed if necessary, but complete resection should be avoided as this could lead to cervical instability. If resection of the uncinates is necessary, try to perform bilateral symmetric

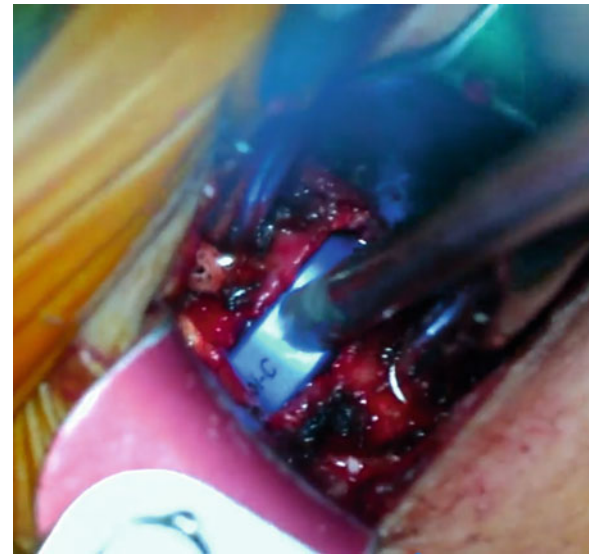

Fig. 6 Trial implant placed following decompression

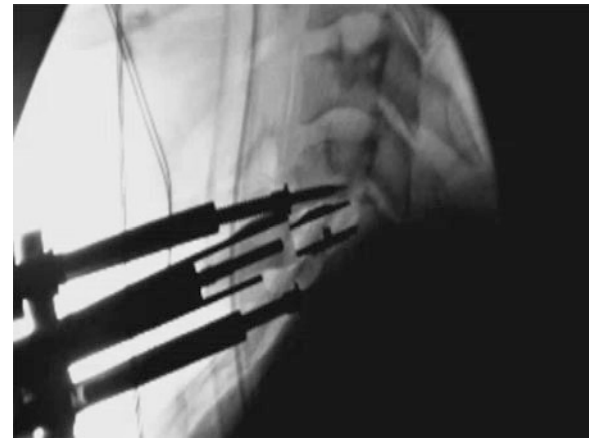

Fig. 7 Lateral image showing compression of the Caspar pins onto the disc replacement. Notice that facets are not distracted compared to other disc levels

resection. Bilateral neuroforaminal decompression is performed with rongeurs. Once the decompression has been completed, trial implants and fluoroscopy are used to determine the optimal implant size and position (Fig. 6).

Pearls

- Ensure that the trial implant is as far posterior as possible as the center of rotation of the cervical spine is near the posterior vertebral body border.
- Select as wide of a trial as possible to ensure maximal medial-lateral surface area coverage and reduce surface stresses.
- Select as deep of a trial as possible to ensure maximal anterior-posterior surface area coverage and reduce surface stresses.
- Study the adjacent level facet joints when trialing and after disc replacement is placed to ensure that you are not over distracting the segment (Fig. 7).
- Remove all distraction while trialing.
- After trialing, cover all cut bone surfaces (e.g., uncovertebral joints) with bone wax to reduce the rate of heterotopic ossification.
- The trial should fit snugly into the disc space, but ideally some cranial-caudal toggle motion

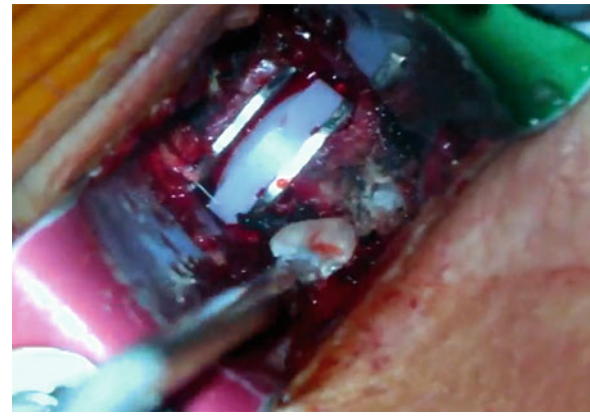

Fig. 8 Final placement of disc replacement with distractor pins removed

of the trial handle should occur to indicate that the disc is not overstuffed.
- If the surgeon is having difficulty visualizing the precise posterior vertebral body margin, then take a lateral fluoroscopy shot with a nerve hook behind the vertebral body.
- For devices with a keel, ensure that the keel cut goes as far posteriorly as the intended implant. Otherwise, the implant could fracture a piece of posterior vertebral body cortex if it is attempted to be placed more posteriorly than the extent of keel cut.

The device is then inserted according to manufacturer's standards while confirming placement visually (Fig. 8) and radiographically in the coronal and sagittal planes.

Pearls
- Occasionally, the cranial and caudal end plates will not advance uniformly. If you notice that one end plate is more anterior than the other end plate, use the single end plate tamp. Otherwise, the implant will have a kyphotic appearance.
- Performing a thorough discectomy, decompression and preparation of the end plates are critical for proper implant placement and to optimize postoperative range of motion. Care should be taken to not violate the vertebral end plates when using the high-speed burr as this could result in implant subsidence.
- Use bone wax on all cut bone surfaces (e.g., anterior osteophytes, distractor pin holes) to prevent the egress of marrow and reduce the rate of heterotopic ossification.

Postoperative Course

Patients are routinely discharged same day for single-level arthroplasty and on postoperative day 1 or 2 for multilevel disc arthroplasty. Postoperatively, a soft collar is not generally used. Instead, the patient should be mobilized out of bed on postoperative day 0 and can immediately start gentle neck range of motion, but extremes should be avoided. Follow-up radiographs are useful to assess for postoperative kyphosis, implant subsidence, and early and delayed fusion. However, imaging artifact may limit radiographic accuracy. Physical therapy should be instituted as tolerated, generally 2–6 weeks postoperative. One of the early touted benefits of TDR is the restoration of motion at the diseased segment and less strain on adjacent levels. This has clinically manifested in improved postoperative range of motion and earlier return to work (Burkus et al. 2014; Zhu et al. 2016a).

Complications

Complications associated with cervical total disc replacement is one of the main reasons cited for not offering it as an option to patients in a survey of spine surgeons (Chin-See-Chong et al. 2017) However, a recent meta-analysis comparing

the adverse events between ACDF and TDR indicated no difference in terms of dysphagia/dysphonia, hardware-related complications, heterotopic ossification, neurological deterioration, overall neurologic adverse events, or mortality. There were three types of adverse events that did show a significant difference. First, there was a small increase in minor wound-related adverse events for TDR, but none required a second procedure for deep wound infection or removal of infected implant. There was a high variation in rates of infection among the different studies, and this was attributed to inclusion of a general category of infection instead of specifying wound-related infections in some studies. Also, ACDF was associated with a higher incidence in surgical-related neurologic adverse events and secondary surgeries which generally occurred late. The definition of neurologic adverse events was not consistent and leads to variable rates from 2.8% to 73.8%. Overall, there does not appear to be a major difference in complication rates between TDR and ACDF, but future studies will need to use uniform definitions in order to make accurate comparison.

Anterior Approach

Cervical total disc replacement shares some of the same complications that are associated with an ACDF by virtue of a similar anterior approach. The anterior approach can be associated with dysphagia due to injury to the esophagus or surrounding nerve plexus. Transient dysphonia or dysarthria can result from injury to recurrent laryngeal, superior laryngeal, and hypoglossal nerve. Periodic release of retractors and a good understanding of the anatomy can reduce the risk of these injuries. Postoperative hematoma should be closely monitored for as it could compromise the airway. Kato and colleagues conducted a propensity score matching analysis of a cohort of CSM patients which showed that there is no difference in outcomes or overall complication rates between anterior and posterior cervical approaches (Kato et al. 2017). However, dysphagia and dysphonia were more common in an anterior approach, while surgical site infections and C5 palsy are more common with a posterior approach.

Heterotopic Ossification

Heterotopic ossification (Fig. 9) is an abnormal deposition of the bone in soft tissue and was first described in total joint arthroplasty procedures. One of the main advantages of a TDR over fusion is its ability to preserve motion, and HO could hamper this by restricting range of motion and potentially affect outcomes. The clinical significance of HO remains questionable. Several predisposing factors have been identified including age, gender, degree of preoperative spondylosis, and implant type. Heterotopic ossification has

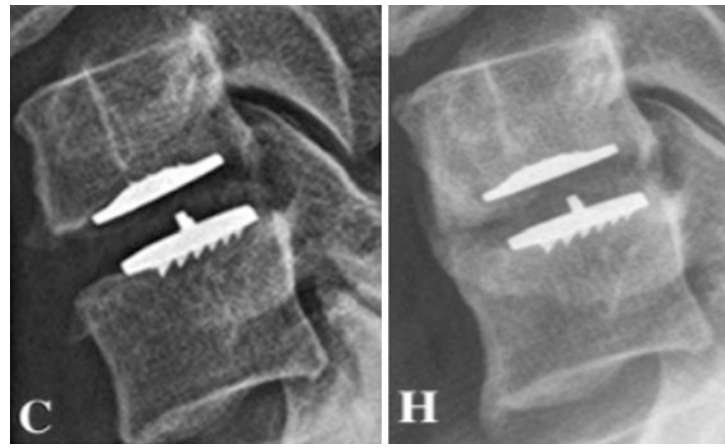

Fig. 9 Normal postoperative X-ray following cervical disc replacement (C) versus same patient after developing heterotopic ossification (H). (Lee et al. 2012)

been found to be more common in two-level TDR compared to single-level TDR (Wu et al. 2012). The incidence of HO is highly variable, ranging from 17.8% to 77.3%, and was proportional to the duration of follow-up (Leung et al. 2005; Lee et al. 2012). Although Lee et al. showed that cervical range of motion was limited by high-grade HO, it has not been found to affect clinical outcomes following TDR (Wu et al. 2012). Treatment of HO with NSAIDs is largely based on literature from total joint arthroplasty, but strong evidence to support its use is lacking. Additionally, in order to attempt to reduce the rate of HO, it is recommended to bone wax all cut bone surfaces (e.g., anterior osteophytes, distractor pin holes) to minimize the exposure of marrow.

Adjacent Segment Disease

Adjacent segment disease is a broad term that includes the degenerative changes at vertebral levels neighboring surgically treated segments (Fig. 10) and is associated with signs and symptoms such as radiculopathy, myelopathy, or instability. ASD is one of the major influences that promoted further investigations of TDR. The motion-preserving properties could theoretically reduce the risk of ASD and subsequent reoperations. A meta-analysis of 14 randomized controlled trials comparing TDR and ACDF confirmed that TDR was associated with a lower rate of ASD and fewer adjacent segment reoperations (Zhu et al. 2016b). The use of TDR for ASD following fusion is controversial with only smaller studies indicating it is potentially a safe option (Rajakumar et al. 2017) (Fig. 11).

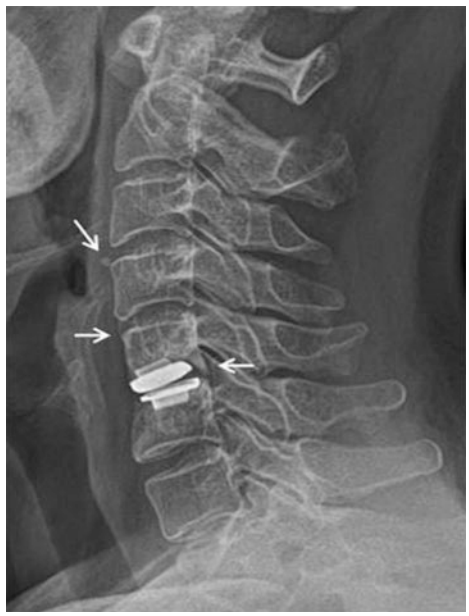

Fig. 10 Adjacent segment degeneration superior and inferior to disc replacement, as well as posterior osteophyte at index level (Kim et al. 2016)

Postoperative Sagittal Imbalance

One of the relative contraindications for TDR is the presence kyphosis or positive cervical sagittal balance (Johnson et al. 2004). Sagittal balance determines the load distribution on the device, and any imbalance could lead to abnormal wear and worsening kyphosis. The clinical significance of segmental kyphosis can be profound, resulting in segmental instability, adjacent segment degeneration, axial neck pain, early hardware failure, and poorer functional outcomes (Cao et al. 2011). However, different techniques have been developed to prevent kyphosis, but caution should be used. Some techniques can lead to overcorrection of lordosis, anterior migration of prosthesis, restricted range of motion, and neck pain (Lei et al. 2017).

Implant Migration and Subsidence

Migration and subsidence are generally uncommon. Goffin et al. reported a single case of both migration and subsidence (Goffin 2006; Goffin et al. 2003). He proposed techniques such as maintaining the integrity of the end plates, using the widest possible device to improve load distribution, and avoiding TDR in patients with poor bone quality (i.e., osteoporosis, metabolic bone disorders). Also, the addition of a keel to the arthroplasty device, which lies up against the anterior vertebral body, has been utilized by some devices to reduce the risk of posterior migration.

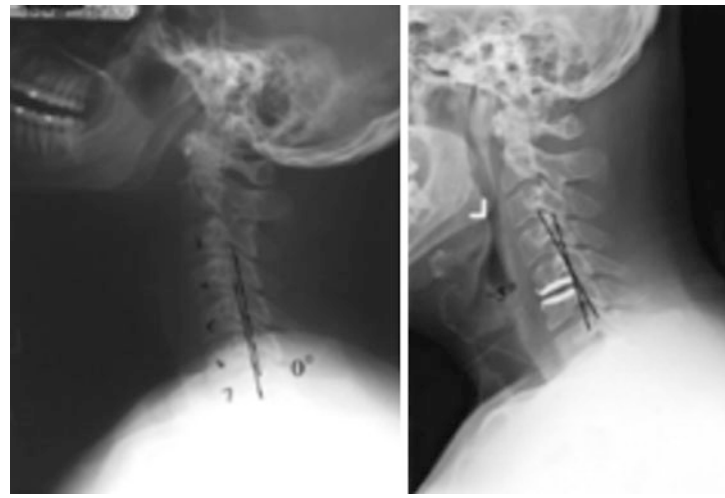

Fig. 11 Preoperative x-ray (right) showing neutral alignment. Postoperative x-ray (right) showing increase in segmental kyphosis. (Johnson et al. 2004)

Evidence

Single-Level Disc Arthroplasty Outcomes

Several long-term randomized prospective trials have been conducted to evaluate patients undergoing cervical total disc replacement. A meta-analysis comparing TDR versus fusion for single-level cervical disc disease concluded that TDR improved neck and arm pain and had a higher neurological and overall success rate (Xing et al. 2013). Later studies have continued to demonstrate comparable and even superior clinical and radiographic outcomes (Janssen et al. 2015; Rožanković et al. 2017).

In a study with longest follow-up to date, Dejaegher et al. reported a 10-year follow-up on patients undergoing disc replacement with the Bryan prosthesis (Dejaegher et al. 2017). Eighty-nine patients underwent single-level disc replacement, and patients were assessed every 2 years. Neurologic success was achieved in more than 80% of patients, and they saw significant improvement in terms of level of disability, neck and arm pain, and functional status. Twenty-four percent of patients developed new or recurrent neurologic symptoms, similar to previously published rates for ACDF.

Multilevel Disc Arthroplasty Outcomes

Similar studies have investigated outcomes for patients who underwent multilevel TDR, which have been largely limited to two and three levels. Gornet et al. investigated outcomes for those patients undergoing adjacent level disc replacement with a Prestige LP device in comparison to ACDF with cortical ring allograft and anterior plating (Gornet et al. 2017). Success for this study was defined by four criteria: Neck Disability Index (NDI) score improvement of $\geq$15 points, maintenance or improvement in neurological status, number of serious adverse events caused by the implant or surgery, and need for additional surgeries. Results showed that patients had better success with multilevel disc replacement compared to a multilevel fusion (81% vs. 69%).

Radcliff et al reported results from a 5-year study comparing two-level TDR to fusion. Patients undergoing disc replacement demonstrated significantly improved Neck Disability Index scores compared to the fusion group (Radcliff et al. 2016b). Similarly, Lanman et al. reported greater overall success of the Prestige LP TDR over fusion at 84-month follow-up (Lanman et al. 2017). Patients undergoing disc replacement also demonstrated improved NDI scores and higher neurological success when compared to fusion.

In comparison to single-level TDR, Huppert and colleagues showed that multilevel TDR had similar levels of improvement in outcomes, satisfaction, and range of motion compared to single-level TDR (Huppert et al. 2011). Although the multilevel cohort had a higher rate of dysphagia and dysphonia, all but one resolved spontaneously. In addition, there was no significant difference in the number complications or reoperations. Likewise, a meta-analysis comparing single- and multilevel TDR revealed no differences in outcomes, functional recovery, or reoperation rates (Zhao et al. 2014).

Several studies have compared multilevel ACDF and TDR, and a recent meta-analysis concluded that both groups had similar clinical outcomes (Wu et al. 2017). However, patients who underwent TDR did experience lower rates of ASD and complications while achieving greater overall range of motion. Altogether multilevel TDR appears to be as effective as single-level TDR and multilevel ACDF.

Reoperations

There are several reasons why patients have to undergo additional surgery after their index cervical total disc replacement. The most common reasons included removal of device with conversion to fusion, recurrence of symptoms, and procedures to address ASD.

Janssen et al. reported that after 7 years, 18% of ACDF patients underwent secondary procedures, while only 7% of the ProDisc-C group needed additional procedures (Janssen et al. 2015). The risk for secondary surgery was approximately 3.7 times higher for single-level ACDF. Mostly reoperations were performed at the index level for both groups; however, adjacent level procedures were more commonly done in the ACDF group. Hisey and colleagues reported similar trends, with the Mobi-C group requiring a higher number of additional procedures compared to the ACDF group (Hisey et al. 2016).

For multilevel disc replacements, Radcliff et al. found that the disc replacement cohort underwent fewer secondary surgeries and adjacent level procedures than the fusion group (Radcliff et al. 2016b). The reasons for reoperations for the Mobi-C group included neck pain and radiculopathy (most common), hematoma, poor device attachment, and inferior level end plate migration. For the Prestige LP, Lanman et al. reported a reoperation rate of 4.2% through 84 months, compared to 14.7% for the ACDF group (Lanman et al. 2017). In this study patients had their device removed mostly due to radicular arm pain, cervical kyphosis and sagittal imbalance, foraminal stenosis and other degenerative changes, "failed arthroplasty," and loosening of hardware. Likewise, Gornet et al. reported on the Prestige LP device, showing reoperation rates of 2.4% compared to 8% with ACDF (Gornet et al. 2017).

Overall, all of these studies and even a meta-analysis have demonstrated that TDR has a superior advantage in regard to reoperations rates (Gao et al. 2015). Reoperation rates for TDR have been consistently lower than 10%. This is particularly important due to the heavy burden that reoperations place on the cost-effectiveness, outcomes, and patient satisfaction.

Cost-Effectiveness

Due to the rapid expansion of spine surgery and increasing healthcare expenditure, the costs of a procedure are an important consideration. In addition, due to the similar outcomes between ACDF and TDR, a cost-effective analysis can offer an economic perspective and potentially shed light on which procedure is superior. Numerous studies have analyzed the cost-effectiveness of the two procedures with some studies indicating no difference (Overley et al. 2017) and others indicating that TDR is more cost-effective (Ament et al. 2016). Clinical outcomes are typically converted to health state utility when performing a cost-effective analysis. In general, utility scores for TDR are either similar (Qureshi et al. 2013) or superior to ACDF (Ament et al. 2015). However, cost has been more variable with some studies indicating lower cost with TDR (Radcliff et al. 2015, 2016a) and others showing

higher costs when compared to ACDF (Overley et al. 2017). In comparison to the often-cited willingness-to-pay threshold of $50,000, TDR is a cost-effective procedure in its own right and is comparable to ACDF.

Patient Satisfaction

With a growing emphasis on improving patient satisfaction and linking it to reimbursements, many of the IDE trials have incorporated it into their studies. Overall patient satisfaction is very high for TDR and is comparable to fusion with a more recent meta-analysis indicating that it is higher for TDR (Hu et al. 2016).

Murrey and colleagues asked patients whether or not they would undergo the same surgery again. Results demonstrated that 96% of ProDisc-C patients would choose to have another disc replacement, which was similar to patients who were fused (Murrey et al. 2009). Similarly, Hisey et al. reported high levels of satisfaction among the Mobi-C and ACDF groups at all time points up to a 5-year follow-up (Hisey et al. 2016). Of note, 97.1% of patients stated they would recommend the Mobi-C single-level disc replacement to a friend, compared to 91.1% for patients who had an ACDF.

For multilevel cervical disc replacement, Radcliff et al. reported 96% satisfaction rate at 5 years with the Mobi-C device versus 89.5% satisfaction for the ACDF group. Ninety-five percent of patients receiving the Mobi-C device stated that they would recommend the surgery to a friend, while only 84% of patients in the ACDF group would recommend it (Radcliff et al. 2016b). For the Prestige LP, 95% of patients receiving the disc replacement stated they were "definitely" or "mostly" satisfied, and the same percentage of patients stated they would undergo the procedure again (Lanman et al. 2017). Gornet et al. surveyed patient's responses and reported three findings: (1) patient satisfaction was greater with TDR (94.5% vs. 89%), (2) more TDR patients felt they were helped by their surgery (94% vs. 85.5%), and (3) a larger percent of TDR patients were willing to have the surgery again (93% vs. 89%) (Gornet et al. 2017).

Pain Medication Usage

Due to widespread concerns about narcotic abuse, the impact on cost of care, and the fact that pain medication acts as a surrogate for pain control, the amount of pain medication used is another factor that has been monitored. Janssen et al. reported that the use of narcotic pain medications and muscle relaxants for TDR and ACDF was similar preoperatively and postoperatively (Janssen et al. 2015). However, Murrey et al. found that at 24 months a lower percentage of TDR patients used narcotics and muscle relaxants compared to those who had an ACDF (Murrey et al. 2009).

Return to Work

The ability to return to work is a reflection on functional outcomes and influences patient satisfaction and cost-effectiveness. One of the initially proposed advantages of TDR over fusion was that early mobilization and maintenance of normal cervical kinematics could result in earlier return to work. A systematic review comparing TDR and ACDF indicated that an equivalent rate of patients ultimately returned to work at 6 months, but those who underwent TDR resumed work sooner (Traynelis et al. 2012).

In two separate studies, Gornet and colleagues evaluated return to work following single-level and two-level TDR compared to ACDF (Gornet et al. 2015, 2017). Preoperatively, 67% of single-level and 70% of two-level disc replacement were working, and after 2 years both groups had a return-to-work rate of 73%, indicating they retained their preoperative work status well. For single-level procedures, they found that TDR returned to work on average 20 days earlier than the ACDF group even after adjusting for preoperative work status and propensity scores. With regard to two-level TDR, there was a trend to earlier return, but no statistical difference was noted. Similarly, Malham et al. reported a return to work rate of 74% after 2-year follow-up for patients undergoing disc replacement, with a median return to work time of 39 days.

In general, patients who undergo a TDR maintain their preoperative work status well, have similar return-to-work rates compared to fusion, and do appear to allow for earlier return to work. Return-to-work rates also appear to be roughly similar between the different TDR devices with most returning around 40–50 days after surgery, but no direct comparisons have been made.

Conclusion

The advent of joint arthroplasty has created many avenues in the management of degenerative joint disease; in particular, TDR has challenged the most commonly used treatment modality for cervical spine disease. While ACDF has proven to be an effective and reliable procedure, long-term data demonstrates an inevitably high incidence of adjacent segment disease. In contrast, treatment with TDR aims to eliminate strain on adjacent levels through its ability to recreate cervical spine biomechanics and preserve motion. Many biomaterials including titanium, cobalt-chromium, stainless steel, and polymers have been explored, along with different surface topographic modifications, but the ideal construct has yet to be perfected.

TDR has demonstrated many attractive advantages. It permits patients the ability to initiate range of motion immediately in the postoperative period. This eliminates periods of immobilization and permits quicker recovery to baseline status. Patients who underwent TDR have consistently expressed a very high level of satisfaction. Additionally, in comparison to ACDF, TDR has similar or even superior clinical outcomes, cost-effectiveness, and time to return to work, along with a decreased need for pain medication and lower reoperations rates. However, most of the data has resulted from the initial IDE trials which raises concerns about publication bias, external validity, confirmation bias, and financial conflict of interest (Radcliff et al. 2017). Results have been promising, but future independent research efforts are needed if TDR is to gain acceptance as a reliable alternative to ACDF.

Cross-References

- ▶ Cervical Total Disc Replacement: FDA-Approved Devices
- ▶ Cervical Total Disc Replacement: Next-Generation Devices
- ▶ Cervical Total Disc Replacement: Biomechanics
- ▶ Cervical Total Disc Replacement: Technique – Pitfalls and Pearls
- ▶ Cervical Total Disc Replacement: Expanded Indications
- ▶ Cervical Total Disc Replacement: Heterotopic Ossification and Complications

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Cervical Total Disc Replacement: Biomechanics

42

Joseph D. Smucker and Rick C. Sasso

Contents

Abstract

Cervical disc arthroplasty is an evolving surgical concept designed to treat certain pathological conditions of the cervical spine. The introduction of arthroplasty devices has stimulated novel studies aimed at understanding motion in the cervical spine and has also driven investigators to examine the consequences that result from surgical alteration of pathological structures. The study of cervical "biomechanics" and "kinematics" has evolved from basic analysis of flexion/extension radiographs to complex, computer-assisted modeling that aides investigators in understanding concepts such as center of rotation (COR), functional spinal unit (FSU)

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translation, and coupled motion. In recent years kinematic studies have contributed to our understanding of adjacent level degeneration and index-level facet loading. We review the young science of cervical arthroplasty biomechanics.

Keywords

Cervical spine · Arthroplasty · Biomechanics · Kinematics · Finite Element · Motion

Introduction

The design of arthroplasty devices for the human cervical disc has brought about a renewed interest in the biomechanics of the cervical spine. Modern techniques of assessment and measurement are currently being employed parallel to traditional outcome measurements in the hope that such information may advance the collective understanding of disc arthroplasty on cervical motion.

Concepts of cervical arthroplasty have undergone a dramatic evolution since the development of the original Bristol/Cummins disc arthroplasty device. At a basic level, motion retention/preservation is a primary kinematic measure of device success in this procedure, though the current indications for the procedure are typically of neurological origin. Retention of motion or "motion sparing" in cervical arthroplasty has quickly evolved in device design over the past 20–30 years. Materials used in disc arthroplasty have also changed. The evolution of metal-on-metal implants has occurred in parallel with the development of novel bearing concepts incorporating metal alloys, polyethylene, and ceramics.

Currently the term "cervical arthroplasty" is applied to the procedure of "disc arthroplasty" or "disc replacement." A number of these devices are in the process of early use or are involved in US Food and Drug Administration (FDA) trials. While the early data from clinical trials is encouraging, there remains a need to demonstrate the biomechanical properties of these devices and techniques in the intermediate and long term. Cervical arthroplasty of the disc alone is not intended to address the posterior elements at the index surgical level – leaving open the option for future modifications of the concept of cervical arthroplasty and kinematic motion sparing.

Background

The cervical spine consists of vertebral bodies with intervening discs and soft tissue structures that support motion and protect the neural and vascular elements. From a biomechanical perspective, these discs and their corresponding facets function in load bearing and motion transfer allowing for flexion/extension, lateral bending, and rotation as well as complex coupled motions. In addition to its biomechanical functions in motion, the cervical spine serves as the protective passage for the spinal cord and vertebral arteries.

Cervical spondylosis is the process by which the cervical spine most frequently loses motion and is occasionally to blame for ensuing neurological phenomena which have been the traditional indication for surgical interventions. Disc degeneration is well documented as the transition from mild degenerative disc disease to multilevel cervical spondylosis progresses. For many years, the surgical treatment for pathology in the cervical intervertebral disc has been limited to procedures which remove pathologic disc material and address the bony and neurologic pathology in the region of the excised disc.

Anterior cervical discectomy and fusion (ACDF) is a proven intervention for patients with radiculopathy and myelopathy (Bohlman et al. 1993). It has served as the standard by which other cervical and spinal disorders may be judged as the result of its high rate of success. The success of this technique is often judged based upon its consistent ability to relieve symptoms related to neurological dysfunction. In this sense, the clinical results with regard to the patient's index complaint are outstanding. The radiographic results of this technique are also initially predictable with a high rate of fusion. Plating techniques have diminished the need for postoperative immobilization or eliminated them entirely (Campbell et al. 2009). However,

because of limitations specific to this procedure, investigators have developed surgical alternatives to fusion that attempt to address the kinematic and biomechanical issues inherent in it.

A major concern related to the treatment of cervical degenerative disc disease (DDD) and spondylosis with ACDF are the issues of adjacent segment degeneration and adjacent segment disease (ASD). Adjacent segment degeneration is manifest as the radiographic appearance of degenerative change at a level directly above or below a level treated with a surgical intervention – typically being associated with degeneration of a level adjacent to a fused level. Adjacent segment disease (ASD) is defined as adjacent segment degeneration causative of clinical symptoms (pain and/or neurological disorders) severe enough to lead to patient complaint and/or require operative intervention (Hilibrand et al. 1999). Adjacent segment degenerative change has been reported to be as high as 92% by Goffin et al. who wrote a long-term follow-up on patients after treatment with anterior interbody fusion (2004). While there remains some debate as to the causation of adjacent segment degeneration – with a mix of postsurgical (altered biomechanics) and naturally determined aging (genetics) cited as root causes – there is little debate as to the existence of this phenomenon. A number of studies have made a consistent point of distinguishing between radiographic "degeneration" and symptomatic "disease" (Goffin et al. 2004; Robertson et al. 2005).

There is clinical evidence to support the postsurgical nature of ASD with respect to kinematics. In patients previously treated with fusion, adjacent segment disease has been documented at a rate of 2.9% of patients per annum by Hilibrand et al., and 25% of patients undergoing cervical fusion will have new onset of symptoms within 10 years of that fusion (Hilibrand et al. 1999). This study has received a great deal of attention and has led to further investigations as to kinematic and biomechanical causation. Other reports have focused on the recurrence of neurological symptoms and degenerative changes adjacent to fused cervical levels (Goffin et al. 1995, 2004). The concept that adjacent levels need to kinematically compensate for loss of motion in the fused segment may also be valid. Segments adjacent to a fusion have an increased range of motion and increased intradiscal pressures (Eck et al. 2002; Fuller et al. 1998).

Total intervertebral disc replacement (TDR) is intended to preserve motion, minimize limitations of fusion, and may allow patients to quickly return to routine activities. The primary goals of the procedure in the cervical spine are to restore disc height and segmental motion after removing local pathology that is deemed to be the source of a patient's index complaint. A secondary intention is the preservation of normal kinematics at adjacent cervical levels, which may be theorized to prevent later adjacent level degeneration. Cervical TDR avoids the morbidity of bone graft harvest (Silber et al. 2003; St. John et al. 2003). It also may avoid complications such as pseudarthrosis, issues caused by anterior cervical plating, and cervical immobilization side effects.

General Cervical Spine Biomechanics

Motion in the cervical spine implies a direct interaction between two or more cervical vertebrae and their supporting structures. A motion segment of the cervical spine, often analyzed as a functional spinal unit (FSU), is complex. The cervical spine is much more than a single FSU, and investigators have found that much more complex kinematic relationships exist as they seek to understand not only the effects of various treatments on a single ("index") FSU but also the effects of that same treatment on adjacent or remote FSUs.

Each FSU consists of three compartments (the disc and two facets) and multiple supporting ligamentous and soft tissue structures. The normal cervical spine exhibits complex coupled motions in addition to the traditionally understood independent kinematic motions such as anterior-posterior translation during flexion and extension. An implant designed to replace the cervical disc should consider the effect of all three compartments and the multiple ligamentous and soft tissue structures present in this complex environment.

One of the primary goals of cervical disc replacement is to reproduce "normal kinematics" after implantation. Fortunately, numerous kinematic studies of various designs have been undertaken parallel to US FDA (IDE) studies. Collectively, these studies may be classified by device and/or study design criteria. Some investigators have taken advantage of novel finite element (FE)-based techniques, while others have used more traditional in vivo or in vitro means. Review of these studies is instructive in understanding the current state of kinematic knowledge with regard to cervical TDR. Over time, similar studies may suggest which type of implant design will provide "kinematically accurate" motion.

Early device designs made use of ball-in-socket articulations within the device. A ball-in-socket (constrained design) does not allow for natural translation. The complexity of the cervical spine requires a "balance" of all the significant structures including facets and ligaments. A ball-in-socket, by its design, dictates the kinematics of motion irrespective of traditional FSU behaviors and eliminates the normal anterior/posterior translation that the facets provide. A number of studies describe the increased forces born by these facets – a phenomenon sometimes described as "kinematic conflict."

The most significant effect of this change in facet loading is in extension. During flexion the facets "un-shingle" and reduce their involvement in constraining the motion of the functional spine unit. However, when the spine goes into extension, the facets "shingle" and become more involved in constraining the motion. Thus, with a constrained facet joint and a constrained arthroplasty device, one would expect to see binding or limited motion as one joint works against the other in the FSU. For this reason device designers have introduced less constraint in more recently designed devices.

There are a number of methods by which kinematic data may be derived. In vivo measurements in the human are often made through review of flexion and extension radiographs that are digitized and subsequently measured with software packages (Sasso and Best 2008) (Figs. 1 and 2). Alternatively, nonhuman in vivo measurements may occur in translational projects wherein the spine is tested via histological and radiographic means as well as benchtop environments with mechanical loading devices, optical tracking (Fig. 3), and pressure sensors. In vitro testing of human cadaveric specimens occurs via similar benchtop testing protocols with the obvious exclusion of histological means (Figs. 3 and 4).

Computer-assisted finite element (FE) modeling is a technique by which a computer-generated

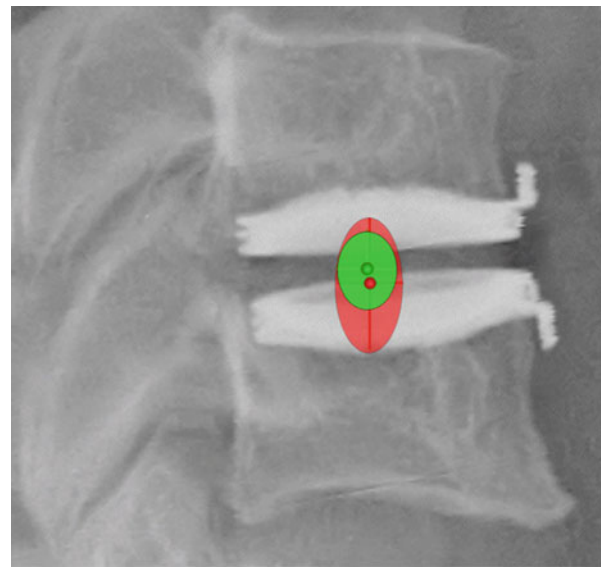

Fig. 1 The BRYAN® Cervical Disc Prosthesis is demonstrated in vivo in this lateral cervical radiograph. The center of rotation (COR) has been calculated pre- and post-placement of the arthroplasty prosthesis at the index surgical level. Software allows for in vivo analysis of kinematic changes in humans via radiographic means over time. Changes in COR may correlate to long-term kinematic outcomes, device survival, and adjacent level changes. (© Courtesy of Rick Sasso, Indianapolis, IN)

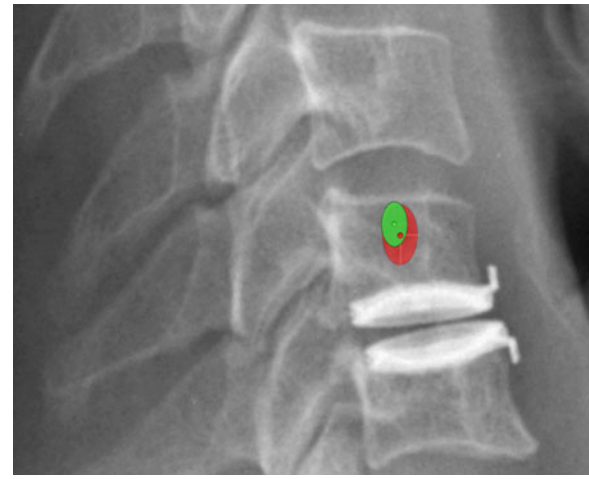

Fig. 2 The BRYAN® Cervical Disc Prosthesis is demonstrated in vivo in this lateral cervical radiograph. The center of rotation (COR) has been calculated pre- and post-placement of the arthroplasty prosthesis at the adjacent surgical level. (© Courtesy of Rick Sasso, Indianapolis, IN)

Fig. 3 Explanted spinal specimens may be tested in a number of ways. Optical tracking allows for real-time tracking of motion and is commonly used in conjunction with forces applied to the cervical spine in a controlled, monitored environment. Cameras on this OptiTrack™ Device (NaturalPoint® Inc., Corvallis, Oregon) follow the motion of rigid bodies. (© Courtesy Nicole Grosland, PhD and Joseph D. Smucker, MD – The University of Iowa and Indiana Spine Group)

model of the cervical spine is modified to include surgical procedures such as ACDF or arthroplasty techniques and principles (Ahn and DiAngelo 2008; Kallemeyn et al. 2009). Specimen-specific modeling is a more refined method of testing such principles (Kallemeyn et al. 2009) (Fig. 5). FE modeling has the potential advantage of providing investigators with a more flexible testing environment given the assumption of model-specific limitations.

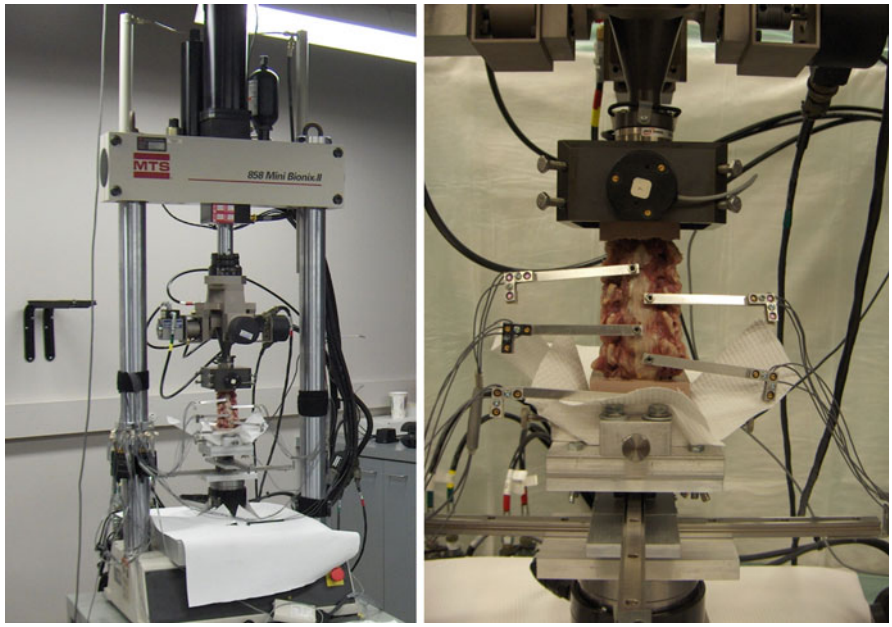

Fig. 4 Controlled application of force within the defined degrees of freedom in the cervical spine is applied to create motion in an ex vivo environment. This MTS™ 858 Mini Bionix II system (MTS Systems Corp., Eden Prairie, MN) applies precise force via computer-controlled hydraulic mechanisms. Optical tracking via the OptiTrack™ system is combined with this controlled application of force to track and analyze simple and coupled motions created in this multi-FSU spinal specimen – allowing for real-time tracking of motion. (© Courtesy Nicole Grosland, PhD and Joseph D. Smucker, MD – The University of Iowa and Indiana Spine Group)

History of Disc Arthroplasty Design Kinematics

An understanding of the evolution of cervical TDR serves as an important lesson in the concepts of kinematic device design properties and articular constraint. In the late 1980s, Cummins et al. (1998) developed a metal-on-metal ball-and-socket cervical disc replacement comprised of 316 L stainless steel. With the acquisition of this technology and the later development of new metal-on-metal devices, a rapid transition evolved to the most recent device, the PRESTIGE® LP (Medtronic Sofamor Danek, Memphis, TN). A predecessor of this device, the PRESTIGE® ST (Medtronic Sofamor Danek, Memphis, TN), is currently approved for human use by the US FDA.

A number of devices have evolved parallel to the metal-on-metal implants and include the BRYAN® Disc (Medtronic Sofamor Danek, Memphis, TN), the Porous Coated Motion Prosthesis (PCM®, NuVasive, San Diego, CA), the SECURE-C® (Globus Medical, Audobon, PA), and the MOBI-C® (Zimmer Biomet, Parsippany, NJ). To date, several such devices have obtained approval for use in the US market: the PRODISC-C® (Centinel Spine, West Chester, PA) and the BRYAN® Disc. Each of the other devices is in the process of limited human trials and/or US FDA-IDE submission and represents an alternative to metal-on-metal bearing surfaces which have the potential for metal debris and systemic concentration of metal ions.

While the ideas of bearing surfaces, wear debris, and constraint are not new to discussions with regard to arthroplasty in general, they are relatively young in the spine. In fact, a full understanding of the term "constraint" with regard to cervical kinematics post-disc arthroplasty has not been agreed upon – as constraint may arise within the device or as a result of the local anatomy

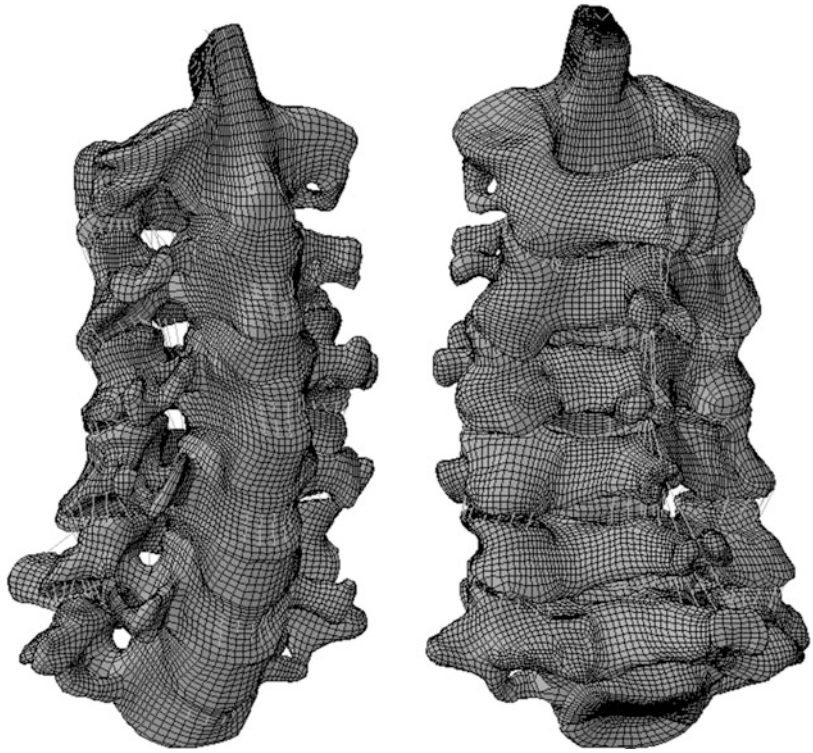

Fig. 5 Dorsal and ventral views of a finite element (FE) model of the human cervical spine (C2-C7) are presented. Multiblock analysis occurs after biomechanical properties are assigned to bony and soft tissue structures. Initial specimen-specific models are created from computed tomograpic (CT) analysis of the human cervical spine. The specimen may then be analyzed in a computer environment with simulation of motion via computer applied forces to the model. The model may be further modified via implantation of spinal devices such as disc arthroplasty devices. Facet forces, intradiscal forces, and other kinematic measurements such as COR may be calculated. (© Courtesy Nicole Grosland, PhD and Joseph D. Smucker, MD – The University of Iowa and Indiana Spine Group)

(facets, PLL, etc.). As the knowledge base in spine TDR increases, intelligent investigations and discussions will include many of these concepts and may redefine our understanding of them.

It is relevant to understand that the load born by devices in the cervical spine is dissimilar to that born in the lumbar spine. The biomechanical environment of the cervical spine has been taken into account in the design of the current generation of these devices. As intermediate- and long-term studies on individual devices become available, the design concepts of these initial devices will have the opportunity for continued examination in their in vivo environment.

Current Kinematic Studies

The BRYAN® Disc

Galbusera et al. published their review in March 2006 of the biomechanics and kinematics at the C5–C6 spinal unit both before and after placement of a BRYAN® Cervical Prosthesis (Galbusera et al. 2006). In this study, the authors produced a finite element (FE) model of the functional spinal unit at C5–C6. The model employed reconstruction of both the vertebral bodies at C5 and C6 and representations of the vertebra, ligaments, and

discs at this level. The authors applied motion through the intact FSU to assess several kinematic measures with a compression preload. The kinematic measures studied included flexion/extension moments, pure lateral bending moments, and a pure torsion moment. They reviewed their results comparing this to known data from prior publications. The FE model was then modified to include the placement of the BRYAN® Arthroplasty Device with repeat stimulations.

The authors noted that they were able to calculate the instantaneous center of rotation of C5 with respect to C6 throughout flexion/extension. In general, FSU rotation curves post-arthroplasty were comparable to those obtained from the intact FSU with the exception of a slightly greater stiffness that was noted to be "induced by the artificial disc" (Galbusera et al. 2006). Pre- and post-arthroplasty data suggested that the position of the instantaneous center of rotation was similar in both models and was stable throughout flexion and extension – being confined to a small area "corresponding to the physiological region in both models" (Galbusera et al. 2006).

Galbusera et al. later published a more detailed finite element model from C4 to C7 expanding upon their 2006 study (Galbusera et al. 2008). In this study the group produced a finite element model including functional spinal units and appropriate soft tissue structures from C4 to C7 for kinematic testing in flexion and extension. Once again, a BRYAN® Disc Prosthesis was inserted at the C5–C6 level. Pre- and post-placement motions were analyzed. Once again, in both flexion and extension, placement of the BRYAN® Disc Prosthesis showed that there was a "general preservation of the forces transmitted through the facet joints" and that "calculated segmental motion was preserved after disc arthroplasty" (Galbusera et al. 2008). Similar to the prior study, the instantaneous centers of rotation (ICR) in flexion and extension showed preservation pre- and post-placement of the BRYAN® Disc.

This study did suggest some post-placement asymmetry in flexion and extension that the authors summarized may be secondary to lack of the anterior longitudinal ligament post-prosthesis placement. However, they were able to conclude that disc arthroplasty with the BRYAN® Disc in this multi-FSU model reproduced "near physiological motion" at the C5–C6 level (Galbusera et al. 2008).

Pickett et al. have also described the kinematics of the cervical spine following implantation of the BRYAN® Cervical Disc (Pickett et al. 2005). In this prospective cohort study, the authors described a total of 20 patients who underwent single- or two-level implantation of the BRYAN® Disc. Each of these patients was treated per protocol for a degenerative condition of the cervical discs that was producing neurologic symptoms including radiculopathy and/or myelopathy. From a kinematic standpoint, this study examined pre- and postsurgical plain radiographs including neutral lateral as well as flexion and extension radiographs at prescribed intervals. Kinematic parameters including rotation, horizontal translation, change in disc height, and center of rotation at each spinal level were evaluated using quantitative motion analysis software produced by Medical Metrics Corporation (Houston, Texas).

The authors demonstrated a postsurgical preservation of range of motion at the operated spinal segment with a mean postsurgical range of motion of 7.8° at the 24-month postsurgical follow-up. They noted that disc placement "either placed at C5–6 or C6–7" seemed to change the "relative contribution of each spinal segment to overall sagittal rotation (DiAngelo et al. 2004)." They also noted that total overall cervical motion as measured from C2 to C7 was increased at late follow-up intervals. There were no significant changes in sagittal rotation, anterior-posterior disc height, translation, or center of rotation following placement of the BRYAN® Arthroplasty Device at the follow-up intervals. The authors concluded that placement of BRYAN® Artificial Disc for cervical radiculopathy and or myelopathy appears to "reproduce the preoperative kinematics of the spondylotic disc (Pickett et al. 2005)." This in vivo study tends to support the finite element studies noted earlier as published by Galbusera et al. (2006, 2008).

Rick Sasso and Natalie Best published a novel BRYAN® Disc article in February 2008 analyzing

radiographic data from patients who had undergone either ACDF with allograft and plating or placement of a single-level BRYAN® Cervical Disc (Sasso and Best 2008). In this single-level study, all patients had radiographic follow-ups immediately preoperatively as well as postoperatively at regular intervals up to a 24-month endpoint. The study represents data from a subset of patients involved in the randomized prospective BRYAN® Cervical Disc Arthroplasty study for the US FDA. The authors evaluated flexion/extension and neutral lateral radiographs at the prescribed intervals and analyzed motion using Medical Metrics software similar to that described in the prior chapter by Pickett et al. (2005). They quantified functional spinal unit motion, translation, and center of rotation.

As expected, there was significantly more motion in flexion and extension in the disc replacement group than in the fusion group at the index surgical level. In this study, the arthroplasty FSUs were able to retain an average range of motion of 6.7° at the 24-month follow-up interval. This was in contrast to the range of motion of the fusion group which was initially 2.0° at the 3-month follow-up, decreasing overtime to 0.6° at the final 24-month follow-up. The authors also noted that flexion/extension both above and below the operative level was not statistically different in those groups having undergone cervical arthroplasty versus fusion. An interesting finding, however, is that mobility overall increased for both groups over time. At levels above the fusion, there was an increase in translation in comparison to the arthroplasty device which showed no evidence of an increase in translation at the adjacent level. The finding of increased translation was only statistically significant at the 6-month follow-up interval. The authors concluded that the BRYAN® Disc appeared to preserve preoperative kinematics at adjacent levels in comparison to fusion which showed some changes overall in the kinematics (Sasso and Best 2008). This did support the postulation that arthroplasty has the potential to preserve cervical kinematics at adjacent levels postoperatively.

Sasso et al. also reported upon the motion analysis/kinematic properties of all patients enrolled in a prospective randomized multicenter trial for the BRYAN® Cervical Artificial Disc Prosthesis (Sasso et al. 2008). Their overall objective in this study was to analyze the entire set of patients in a prospective fashion similar to the subset which was previously reported (Sasso and Best 2008). In this study, all patients received either a single-level ACDF or a single-level disc arthroplasty with the BRYAN® Cervical Disc Prosthesis. A total of 221 patients received fusion, whereas 242 received a single-level arthroplasty. Operative segments could include the C3–4 disc space down to the C6–7 disc space. Similar to the previous subset, the authors analyzed flexion/extension and neutral lateral radiographs obtained at prescribed intervals postoperatively in comparison to the preoperative interval. This study examined patients up to and including the 24-month interval. Medical Metrics software was once again used to track the cervical vertebral bodies at the index FSU looking at flexion and extension range of motion as well as translation.

Similar to the prior subset, the arthroplasty group retained statistically significant increases in motion at the index FSU in comparison to the ACDF group. The arthroplasty group had an average of 7.95° of motion at the 24-month follow-up. The preoperative range of motion at the same FSUs was 6.43° with no significant evidence of degeneration of motion at the same FSU following arthroplasty at the 24-month interval. As expected, average range of motion in the fusion group slowly diminished to the point of being 0.87° at 24 months. Preoperatively this group had a range of motion of 8.39°. Also noted was no evidence of BRYAN® Disc migration or subsidence at the 24-month follow-up – suggesting that the arthroplasty device was functioning as designed at this early follow-up interval and reproducing the kinematics of the degenerative disc space at the index FSU in comparison to fusion of those same levels.

The PRODISC-C®

DiAngelo et al. have examined the in vitro biomechanics of the PRODISC-C (DiAngelo et al. 2004). Their study was designed to compare disc

arthroplasty to ACDF in cervical spine biomechanics in a multilevel human cadaveric model. This study employed three spinal conditions: intact harvested specimens alone, single-level arthroplasty specimens, and single-level fusion specimens. The study incorporated a total of six fresh human cadaveric specimens harvested from C2 to T1. All specimens were treated according to the group assigned at the C5–6 level following testing in their intact condition. This study simulated fusion in a unique way. Fusion was accomplished across the treated spinal level via custom designed fixtures similar to an external fixation system. Following surgical treatment according to protocols, kinematic principals were tested under biomechanical loading devices. This was done with a programmable testing apparatus that "replicated physiologic flexion/extension, lateral bending, and axial rotation (DiAngelo et al. 2004)." The authors then measured vertebral motion via applied load and bending moments.

As expected, the simulated fusion was successfully able to diminish motion at the treated level relative to the harvested untreated as well as disc arthroplasty conditions. The authors noted that adjacent segment motion increased in those specimens following the reduction of motion at the simulated fusion segment. This study noted that in all modes of testing, the PRODISC-C arthroplasty device "did not alter the motion patterns at either the instrumented level or adjacent segments compared with the harvested condition except in extension (DiAngelo et al. 2004)."

Puttlitz et al. have examined post-disc arthroplasty kinematics using the PRODISC-C in a human cadaveric model (Puttlitz et al. 2004). This study utilized a total of six fresh frozen human cadaveric spines to evaluate two different spinal conditions including both the intact and post-disc arthroplasty condition at the C4–C5 level. Prior to testing, compression and a follower load were applied, as well as pure moment loading to the specimens to evaluate treatment kinematics and pretreatment kinematics. Range of motion (ROM) kinematics was then measured using an optical tracking system, and data was reported.

The results of this limited cadaveric study suggest that the PRODISC-C was able to retain "approximate" intact motion in all three rotation planes "flexion/extension, rotation, and lateral bending (Puttlitz et al. 2004)." They also examined coupled rotations including lateral bending during axial rotation and axial rotation during lateral bending – noting no significant difference in these two tested conditions following arthroplasty. They concluded that ball-and-socket devices such as the PRODISC-C can "replicate physiologic motion at the affected and adjacent levels (Puttlitz et al. 2004)." This is the only study on the PRODISC-C that examines a motion coupling from a kinematic standpoint and suggests maintenance of the coupled motions following cervical arthroplasty. It is possible that a larger in vitro study could provide further insight into the coupling motions examined in this study that were novel to it.

Combined PRODISC-C®/PRESTIGE® ST/LP Studies

Chang et al. have looked at both the PRODISC-C® and PRESTIGE® Artificial Devices compared with ACDF in a cadaveric model (Chang et al. 2007a). The object of the authors' investigation was to examine cervical kinematics at surgically treated levels as well as adjacent segments in a cadaveric model – evaluating two different types of cervical artificial disc devices in comparison to the intact spine and a fusion model. For the purposes of this study, a total of 18 cadaveric human spines were tested in their intact state with kinematic modes including flexion/extension, axial rotation, and lateral bending. These three groups of specimens were then subjected to a surgical intervention including placement of a PRODISC-C®, a PRESTIGE II® Artificial Disc, or ACDF. All specimens were operated at the C6–7 level. This study simulated ACDF with placement of a 7 mm tapered cortical allograft followed by placement of a rigid anterior cervical plate and screws "to maintain lordosis at the treated level (Chang et al. 2007a)." Placement of either the PRESTIGE® or the PRODISC®

device was performed according to the manufacturers' recommended surgical technique at the C6–7 level.

Range of motion was noted to increase after arthroplasty in comparison with the intact spine in extension in both the PRODISC-C® and PRESTIGE® groups as well as in flexion in both arthroplasty groups. With respect to bending, the post-arthroplasty ROMs were greater than those of the intact spine in both arthroplasty groups; this was also similar for rotation. Adjacent level ROM was noted to decrease in all specimens that underwent implantation of a cervical arthroplasty device for all tested kinematic modes. With respect to ROM adjacent to the fusion-treated spines, it was noted to diminish in all motion modes at the treated level but increase at all adjacent levels with a reported range of 3–20%. Adjacent level range of motion diminished in all modes post-arthroplasty with the exception of extension in those patients who underwent a total disc arthroplasty.

This study lends additional credence to the idea of adjacent level disease as a result of surgery as noted by the increased range of motion kinematics at adjacent levels in those cadaveric specimens undergoing ACDF in comparison to the diminished range of motion noted in those patients undergoing cervical disc arthroplasty.

Chang et al. have also evaluated adjacent level disc pressure and facet joint forces after cervical arthroplasty with the PRODISC-C®/PRESTIGE® devices in comparison to ACDF in an in vitro human cadaveric model (Chang et al. 2007b). In this study, the authors examined intradiscal pressures at adjacent levels, as well as facet joint stress following both arthroplasty and cervical spine fusion in 24 human cadaveric spines obtained from C3 to T2. This study examined a surgical intervention at C6–7 in 18 of these specimens. Six specimens were excluded from the original 24 in the study based upon pre-procedural radiographic studies suggesting bone abnormalities. This study examined intradiscal pressures with pressure transducer needles. The forces in the facets, however, were indirectly measured.

The specimens were then divided into three groups with six specimens per group – each receiving either an artificial disc implantation (PRODISC-C® or PRESTIGE®) or in the case of the third group an ACDF. With respect to the PRODISC-C® group, a 7 mm height disc was chosen, and with respect to the PRESTIGE® group, an 8 mm height disc was chosen. These were determined to be "adequate for the cadaveric specimens (Chang et al. 2007b)." The fusion groups, as per a previous study reported by Chang et al. (Rousseau et al. 2008), underwent fusion with a 7 mm lordotic tapered allograft fixed with a rigid plate and screw.

Biomechanical testing ensued with flexion/extension, lateral bending, and axial rotation modes measured. In the arthroplasty-treated specimens, the intradiscal pressure was not significantly different in comparison to the intact spine at adjacent levels proximal and distal to the arthroplasty FSU. However, in those specimens treated with fusions, the intradiscal pressures increased at the location of the posterior annulus fibrosus in extension and at the location of anterior annulus in flexion at the cranial adjacent level. At the caudal adjacent level intradiscal pressure change was not noted to be significant. Indirect measurements of facet forces were computed in this study and were noted to be minimal in flexion, bending, and rotation modes in both arthroplasty- and fusion-treated spines. In extension the arthroplasty models exhibited an increase in facet forces at the treated FSUs in comparison to the fusion model where the facet forces decreased at the treated FSU and increased at the adjacent segments (Chang et al. 2007b).

Rousseau et al. undertook an in vivo analysis of two types of ball-and-socket cervical disc devices which they classified as "two-piece implants (Rousseau et al. 2008)." The authors of this study considered three-piece implants to be those with a mobile nucleus between two metal implants. They examined a total of 26 patients who had been implanted with the PRESTIGE® LP Device and compared them to 25 patients who had been implanted with the PRODISC-C® Device. Investigational specimens were then referenced against the measurements of 200 healthy cervical discs in vivo. Spineview™ software (Surgiview, Paris, France) was used to

calculate the intervertebral range of motion and the mean center of rotation kinematic variables. The authors also calculated the center of rotation between full flexion and extension for range of motion.

In comparison to the normal non-implanted vertebral discs, the range of motion kinematics in flexion and extension were noted to be significantly reduced with both types of arthroplasty. Comparing the two arthroplasty groups head to head, range of motion was similar, and the location of the center of rotation with full flexion and extension appeared to be "influenced by the type of intervertebral disc despite interindividual variability (Rousseau et al. 2008)." Specifically, the authors noted that there was a trend toward a "more anterior and superior" location of the center of rotation in full flexion and extension with the prosthetic devices then observed in normal nonoperated control discs (Rousseau et al. 2008). This comparison of two-piece ball-and-socket-type prosthesis was notable for the fact that neither cranial nor caudal types of device designs were able to fully restore flexion and extension kinematics to normal mobility in the kinematic measurements described in the study including range of motion and center of rotation.

The PRESTIGE® Disc

DiAngelo et al. have described an in vitro biomechanical study comparing non-fusion (intact specimen) to ACDF and cervical arthroplasty in a multilevel human cadaveric model (DiAngelo et al. 2003). The study was conducted using a programmable testing apparatus that allowed for replication of physiologic flexion/extension and lateral bending. The authors measured vertebral motion applied load and bending moments. The authors used the PRESTIGE® ST cervical joint for arthroplasty and an Orion® (Medtronic Sofamor Danek, Memphis, TN) plate to simulate fusion in this small cadaveric study. Included were a total of four fresh human cadaveric specimens harvested to include C2–T1.

Following their measurements, they reported findings. The application of an anterior cervical plate significantly decreased the motion across the fusion site relative to the native or artificial joint conditions. The placement of a PRESTIGE® artificial cervical joint "did not alter the motion patterns at either the instrumented level or the adjacent segments compared with the harvested condition (DiAngelo et al. 2003)." This study of kinematics is novel not only in the maintenance of normal range of motion at the implanted FSU but also with regard to maintenance of normal motion at all segments of the spine status post-placement of a PRESTIGE® cervical disc prosthesis. Unfortunately, this small in vitro study did not have the power ability to make large in vitro analyses.

The PCM® Disc

Several novel kinematic studies have been performed with regard to the PCM® Device. The device has undergone basic testing from a kinematic standpoint (Hu et al. 2006) in addition to studies that add to the basic kinematic studies in novel ways (McAfee et al. 2003; Dmitriev et al. 2005). These have included studies that examine the role of the posterior longitudinal ligament (PLL) and those that measure adjacent level intradiscal pressures following placement of the PCM® Device (Hu et al. 2006; McAfee et al. 2003; Dmitriev et al. 2005).

Hu et al. have examined the PCM® arthroplasty device, evaluating biomechanical as well as other factors, in a caprine animal model (Hu et al. 2006). The PCM® Disc was tested in vivo and ex vivo in 12 goats divided into 2 distinct groups. These two groups differed in their survival periods – 6 and 12 months, respectively. Each specimen underwent an anterior discectomy at the level C3–C4 followed by implantation of the PCM® Device. Outcomes of the study were based upon examination of the prosthesis by computerized tomography, multidirectional post-sacrifice flexibility testing, decalcified histology, and histomorphometric and immunochemical analyses.

With regard to postoperative survival, there was no evidence of prosthesis loosening at the

two examined survival periods. Multidirectional flexibility testing from a kinematic standpoint was performed in all standard measures. Under axial rotation and lateral bending, there was no significant difference in the range of motion of the operated FSU in comparison to nonoperative controls. The authors concluded that intervertebral range of motion was preserved under axial rotation and lateral bending at the two examined postsurgical time frames in this animal mode (Hu et al. 2006).

McAfee et al. established that the posterior longitudinal ligament (PLL) may provide a stabilizing influence to the cervical spinal segment (McAfee et al. 2003). Biomechanical testing was performed using human cadaveric spines and a six-degree-of-freedom spine simulator with additional optoelectronic motion measurement. The major finding was that biomechanical stability may be restored following complete anterior cervical discectomy with resection of the PLL via implantation of an arthroplasty device such as the PCM® Device.

Dmitriev et al. have looked at intradiscal pressure and segmental kinematics following cervical disc arthroplasty with a PCM® Device (Dmitriev et al. 2005). This in vitro human cadaveric study examined a total of ten spines. Each spine underwent intact analysis with subsequent reconstruction at C5–C6 with a total disc replacement, an allograft dowel, or an allograft dowel and an anterior cervical plate. The authors then tested the specimens in displacement control under axial rotation, flexion/extension, and lateral bending kinematic modes. They recorded intradiscal pressure at levels adjacent to the C5–6 space including C4–5 and C6–7 FSUs. Range of motion was monitored at the operative FSU (C5–C6).

The authors noted that the intradiscal pressures recorded at adjacent levels were similar to the intact (nonoperated) condition in those patients who had undergone a total disc replacement with the PCM® Device. However, the intradiscal pressures at C4–5 in flexion/extension for both types of simulated fusions were noted to be significantly higher than the mean intradiscal pressures measured at these same levels in the intact and disc replacement groups. Similar findings were noted at C6–7, where significantly increased intradiscal pressures were achieved in all three loading methods including axial rotation, flexion/extension, and lateral bending. As expected, both types of simulated fusions at C5–6 produced a significantly diminished range of motion during flexion/extension testing. The authors concluded that the PCM® Disc has the ability to maintain adjacent level intradiscal pressure in comparison to increased intradiscal adjacent level pressures noted with simulated fusions. This study lends some support to the concept of adjacent level disease as a result of the modified kinematic environment adjacent to a fusion.

Computer Simulation and Finite Element (FE) Modeling Studies

In addition to numerous disc-specific kinematic studies that have been published in recent years, several authors have contributed to the collective understanding of finite element (FE) modeling with respect to artificial cervical disc replacements. Ahn et al. published such a study, noting as background that there was a need for further simulation studies to understand common design themes for restoration of motion as the result of numerous types of cervical disc designs (Ahn and DiAngelo 2008). They cited the numerous examples of both constrained and semi-constrained devices. The study proposed to expand upon the limited number of in vitro studies previously discussed herein.

The study incorporated a three-dimensional graphics-based computer model of the subaxial cervical spine that had previously been developed. This model was used to study the kinematics and mechanics of an arthroplasty device placed at the C5–6 disc space – the validation for which had been described in a previous study by the same group (Ahn and DiAngelo 2008). The basic computer model incorporated the geometry of cervical vertebrae as established from the computer tomographic images of a 59-year-old woman, linking the adjacent vertebrae at C5 and C6 as a “triple joint complex

comprised of the intervertebral disc joints in the anterior region and 2 facet joints in the posterior region and the surrounding ligament structure (Ahn and DiAngelo 2008)."

The authors modeled intervertebral discs as nonlinear elements having a total of six degrees of freedom. With this model, they studied three different theoretical prosthetic disc devices. The first device tested was a disc with the center of rotation of a spherical joint located in the midportion of the C5–6 disc, the second device being with the center of rotation of the cervical joint located 6.5 mm below the midportion of the C5–6 disc, and the third being the center of rotation of the cervical joint in a plane located at the C5–6 disc level. The authors simulated removal of the anterior longitudinal ligament and the anterior portion of the annulus as well as the nucleus pulposus for placement of the disc prosthesis. They then tested the three disc implantation designs throughout the six degrees of freedom allowed by the computer model.

With the three types of disc devices, the authors noted that a constrained spherical joint (device design #1 with the joint placed at the midportion of the disc) significantly increased facet loads during cervical spine extension kinematics. Tested design #2 lowered the rotational axis of the spherical joint toward the subjacent body, and this was noted to kinematically cause a "marginal increase in facet loading during flexion, extension, and lateral bending (Ahn and DiAngelo 2008)." Unconstraining the device (device design #3) minimized facet loading buildup during all loading modes by placing the center of rotation of the spherical joint in a plane located at the C5–6 disc level.

The authors concluded that a finite element model was able to demonstrate simple design changes that may have effects on the kinematic behavior of cervical discs placed in human spines at the C5–6 disc space. They were able to predict facet loads calculated from their computer model but noted that the computer model still needs to have validation with regard to in vitro experimental studies. This model does add credence to kinematic principles of device design and goes one step beyond some of the in vitro research in its theoretical device design principles.

Liu et al. have described a fluoroscopic kinematic study looking at the kinematics of the anterior cervical discectomy fusion versus cervical artificial disc replacement at the C5–6 joint (Liu et al. 2007). In this novel study, the investigators used a controlled group of ten normal subjects as well as ten patients treated with ACDF in comparison to ten patients treated with cervical artificial disc replacement. Both types of surgical procedures were performed at the C5–6 level. Radiographic data was collected with the patient performing a full flexion and extension motion under fluoroscopy surveillance with kinematic data collection obtained from these fluoroscopic images. The data were derived based on the "inverse dynamic model of the entire cervical spine (Liu et al. 2007)." This custom model was created based on "KANE'S Dynamics and the Reduction Modeling Technique (Liu et al. 2007)." The authors then calculated kinematic data using software and reported the results.

The ACDF group had notable increases in intersegmental rotation at adjacent disc spaces (C6–7 and C4–5 levels) in comparison to the intact normal specimen. Also notable was the fact that the intact spine (no surgical intervention) had a greater range of motion than that observed in ACDF despite these increases of adjacent segment rotations in the ACDF population. The authors noted that the kinematic measurements in the cervical arthroplasty group were similar to those in the normal group and postulated (by their measurement principles) that cervical artificial disc arthroplasty has the potential to restore "normal dynamic motion of the cervical spine (Liu et al. 2007)."

This study provides a novel approach for analysis of in vivo contact forces and expands upon basic kinematic measurements that have been reported in disc arthroplasty studies. It also suggests that cervical arthroplasty has the potential to maintain adjacent segment kinematics, although it is difficult to make predictions with respect to adjacent segment degeneration as a result of this motion analysis study.

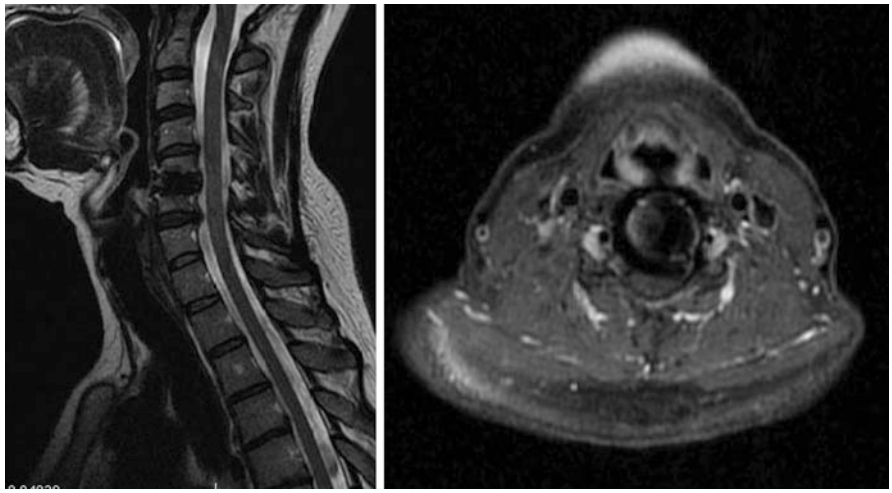

Fig. 6 The BRYAN® Cervical Disc Prosthesis is visualized on these postoperative MR sagittal and axial images. Titanium alloy devices such as the BRYAN® device may have less MRI artifact that similar devices constructed with CoCr or stainless steel. These images demonstrate the imaging characteristics of this device at the index and adjacent surgical levels. (© Courtesy of Rick Sasso, Indianapolis, IN)

Multidisc Studies

Lin et al. created a novel in vivo study to evaluate bone/implant stresses at the C5–6 disc space with placement of BRYAN®, PRESTIGE® LP, and PRODISC® Cervical Disc prostheses (Lin et al. 2009). Their image-based finite element modeling technique was designed to predict stress patterns at the interface between the prosthesis and the lower vertebral endplate – an effort to elucidate possible mechanisms of subsidence and describe load transfers of disc designs. The group built a three-dimensional finite element model of the C5–6 functional spinal unit based on computed tomographic (CT) images acquired from a patient who had previously been identified as a candidate for cervical disc arthroplasty.

The modeling process included facet joints, uncovertebral joints, and specific artificial disc designs that could be placed within the intervertebral disc space. The authors evaluated the discs and endplates in flexion/extension and lateral bending with compression applied. The authors noted that the PRODISC-C® and PRESTIGE® LP Discs caused "high stress concentrations around their central fins or teeth, which may initiate bone absorption (Lin et al. 2009)." With respect to the BRYAN® Disc, the prosthesis appeared to recover the highest range of motion secondary to what the authors described as the "high elastic nucleus" which was notable for diminishing the stresses at the superior endplate of C6 (Lin et al. 2009). The authors also noted that the PRESTIGE® LP Disc, with its rear positioned metal-metal joint, may be a concern for a mechanism of possible subsidence in the posterior aspect of this arthroplasty device.

The authors concluded that the rigidity of the nucleus/core in both the PRESTIGE® LP and the PRODISC-C® prostheses is capable of maintaining initial disc height at the consequence of high contract stresses at the bone endplate interface with either "improper placement or under sizing (Lin et al. 2009)." The BRYAN® Device differs in its core rigidity creating a much larger displacement during motion allowing for "more variation in disc height that may theoretically increase the load sharing of facet and uncovertebral joints compared to more rigid artificial disks (Lin et al. 2009)." This in vivo finite element study goes beyond typical center of rotation and flexion/extension

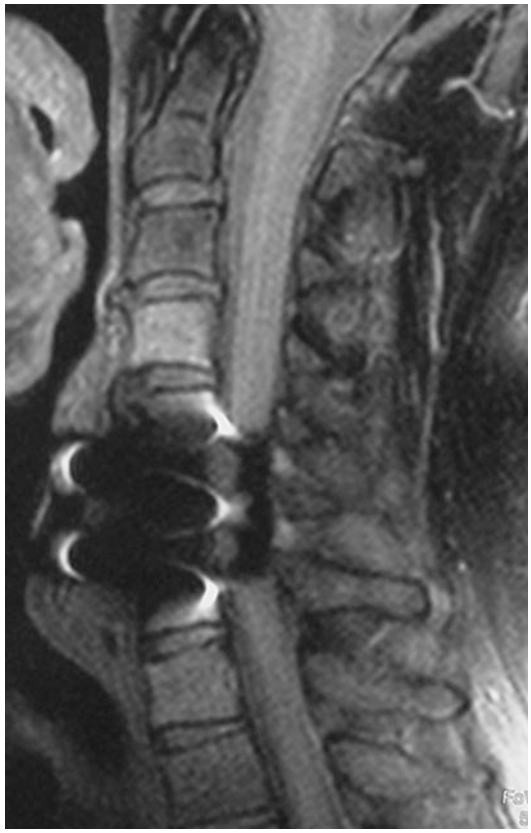

Fig. 7 The MOBI-C® is visualized on this sagittal MRI (T1/FS technique). These images demonstrate the imaging characteristics of this device at the index and adjacent surgical levels. Significant artifact is present at the index and adjacent levels making diagnostic interpretation challenging. (© Courtesy of Rick Sasso, Indianapolis, IN)

kinematics in looking at one of the major causes for implant failure, subsidence. The study is only predictive of the stresses caused by device design and does not predict ultimate subsidence mechanisms. It goes beyond prior studies in elucidating possible areas of increased device/endplate mechanical stresses that are the result of normal device kinematics.

Future Kinematic Design Principles

With respect to basic device design principles, kinematic modeling will likely have an effect on patient outcomes and adjacent segment disease in the long-term. Future design work will continue to make heavy use of preclinical modeling, FE modeling, biomechanical testing, and translational nonhuman testing. Currently implanted cohorts from US FDA trials will alter our understanding of device kinematics over the intermediate and long-term. At the time of this writing, US follow-up of these devices has been published up to 10 years (Sasso et al. 2017). Wear debris caused by device design and kinematic conflicts may play a role in device construction materials and constraint properties as we understand long-term outcomes beyond this interval. Postoperative imaging limitations will also affect future device design as in vivo human studies will continue to make heavy use of imaging techniques and measurements in lieu of biomechanical and histological techniques (Figs. 6 and 7).

Current arthroplasty designs restore only the anterior and middle columns of the cervical spine. They rely on posterior column preservation at the index surgery and over time. Future device designs may include techniques that modify not only structures at the level of the disc but also facets.

Conclusions

We sought to review the basic cervical kinematics that exist and correlate the early data reported from in vivo, in vitro, and finite element (computer-based) studies on disc arthroplasty. Device design with respect to the modified center of rotation at an FSU, device fixation to the vertebral endplates, and flexibility of the articulating nucleus all appear to play a role in reproduction of normal cervical kinematics after cervical disc arthroplasty. A number of these studies also begin to suggest kinematic means of surgical contribution to adjacent level degeneration. It is extremely encouraging to see that many kinematic studies that have been undertaken coincide with the results of US FDA-IDE trials of these devices.

Little data currently exists on how reproduction (or lack of reproduction) of normal kinematics affects intermediate- and long-term patient outcomes and adjacent segment degeneration. Abnormal kinematics may contribute to early

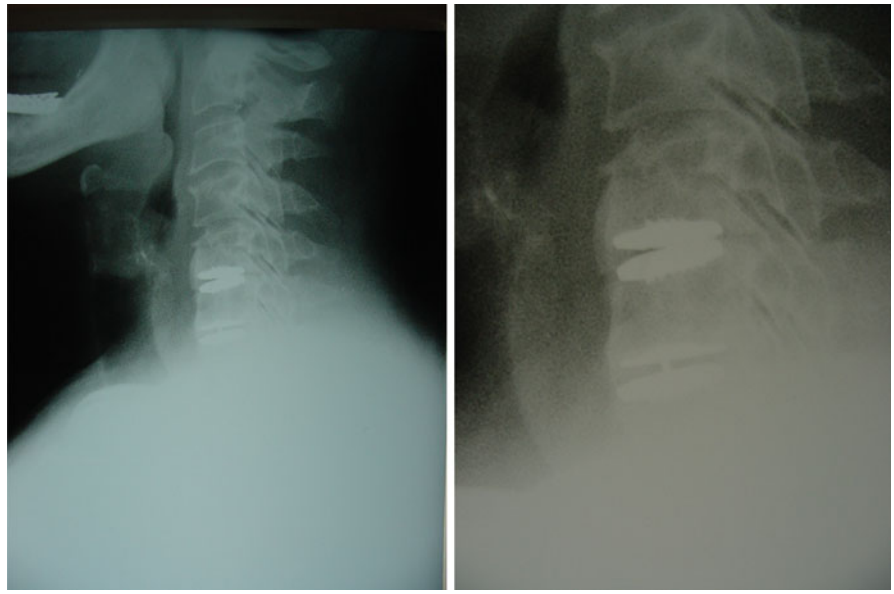

Fig. 8 The MOBI-C® is visualized on these lateral radiographic views of the cervical spine. This patient presented with loss of motion and radiographic evidence of heterotopic ossification at the index surgical levels (C5-C6 and C6-C7). These images demonstrate the imaging characteristics of this device at the index and adjacent surgical levels. Significant artifact is present at the index and adjacent levels making diagnostic interpretation challenging. (© Courtesy of Rick Sasso, Indianapolis, IN)

subsidence in some of these devices; however, other than descriptive subsidence complications in a number of clinical series, the abnormal kinematics of the devices themselves have not clearly been suggested to be at fault for such events. Several studies have suggested that cervical disc arthroplasty causes an early-term risk of heterotopic ossification (Mehren et al. 2006; Leung et al. 2005; Heidecke et al. 2008) (Fig. 8). The authors of this publication are not aware of any current kinematic studies that demonstrate or further elucidate either the biomechanical or kinematic mechanisms that may result in heterotopic ossification. Indeed, it may be that device placement/implantation techniques place patients at more risk of heterotopic ossification than properties intrinsic to the arthroplasty devices. This is supported by indirect experiential evidence of a diminished rated of heterotopic ossification in patients who have been treated with NSAIDS in some randomized prospective studies (Sasso et al. 2007a, b; Heller et al. 2009).

As cervical device design continues to proceed, it will be critical for both device designers and study investigators to understand the kinematics in the short-, intermediate-, and long-term phases of the various devices. Modified kinematics as the result of improper placement of arthroplasty devices must also be investigated. Such understanding will likely contribute to increased knowledge with respect to the long-term wear and survival of the devices and may possibly alter the patient outcomes in a positive manner.

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Cervical Total Disc Replacement: Technique – Pitfalls and Pearls

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Abstract

Anterior cervical discectomy and fusion (ACDF) is still considered the gold standard for surgical management of cervical spondylosis. The discovery of the impact of fusion on other functional spinal units in the form of adjacent segment disease has led to the development of motion-sparing techniques in cervical spine surgery, such as cervical arthroplasty. A substantial number of different cervical artificial disc implants have been approved for clinical use, some with long-term follow-up data demonstrating the safety and efficacy of the implants in maintaining motion of the index level. However, a significant number of prostheses failed to retain the desired mobility, mostly due to heterotopic ossification and unintentional fusion. Choosing the appropriate implant design, along with meticulous surgical technique, is the most important prerequisite for good surgical results and longevity of implant integrity and function. In this chapter we discuss the evolution of key characteristics of implant design crucial for successful surgery, as well as surgical tips and techniques related to cervical arthroplasty.

Keywords

Cervical arthroplasty · Total disc replacement · ACDF · History · Adjacent segment · Implant design · Implant selection · Discectomy · End plate preparation · Heterotopic ossification

Introduction

Since its introduction in the mid-1950s, anterior cervical discectomy and fusion (ACDF), as first described by Robinson and Smith (1955) and Smith and Robinson (1958), has become the gold standard for the treatment of single- and multilevel cervical disc disease and cervical spondylosis. Although many different additions and minor changes have modified the ACDF approach over time, such as by Cloward (1958), the approach itself and the basic surgical technique implied have conceptually remained the same, testimony to the rationale and technical simplicity of this approach. ACDF is still justifying its position as a straightforward technique that yields unequivocally excellent clinical results.

It was not until the late 1980s and 1990s that awareness emerged of the impact of fusion of diseased cervical segments on adjacent functional spinal units in a clinically significant proportion of patients. Although the existence of adjacent segment degeneration has been reported before, it was only after the landmark paper by Hilibrand et al. (1999) in which the authors reported on a small percentage (2.9%) of new-onset adjacent segment symptomatic radiculopathy cases per year, but a significant cumulative rate of 25% in a 10-year period after the index ACDF surgery that cervical spine motion preservation techniques have come again under focus by the spine surgical community. The purported mechanism for the non-negligible incidence of adjacent segment disease following ACDF has been speculated to be a higher, nonphysiological degree of stress imposed upon functional spinal units next to the fused segments, leading to their accelerated degeneration. Various reports have shown that intradiscal pressure in segments adjacent to those fused by surgery increased after surgical immobilization. This begs the question of whether the incidence of adjacent segment disease could be lowered by preservation of motion in the operated segment after surgical decompression.

History of Cervical Arthroplasty

The idea of arthroplasty as opposed to arthrodesis has a long history in orthopedic surgery, specifically in the field of hip and knee surgery (Wiles 1958; McKee and Watson-Farrar 1966).

While loss of function of a hip or knee joint creates a debilitating condition for the individual, the fusion and loss of function of a single functional spinal unit, or even multiple segments in the cervical spine, are surprisingly well tolerated. Nevertheless attempts to retain mobility in operated cervical levels have also a long history dating from the 1960s, with the first reported implantation of a cervical

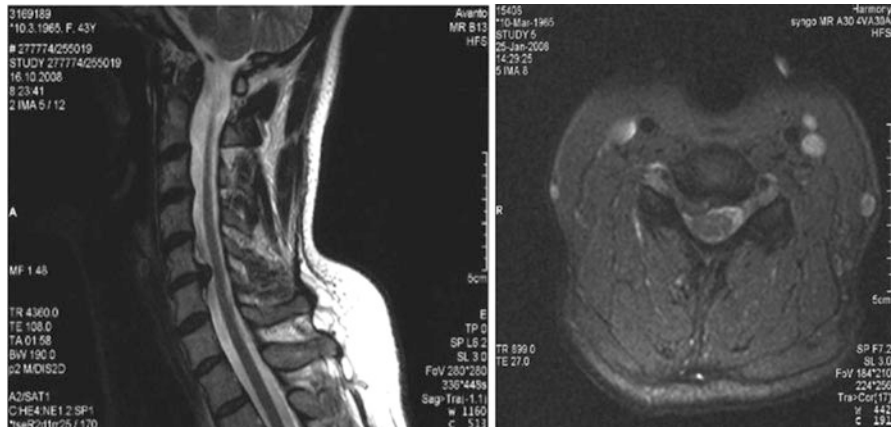

Fig. 1 MRI showing a typical indication for cervical disc arthroplasty – a single level soft disc herniation causing radiculopathy refractory to conservative treatment

arthroplasty device by Fernström (1966). These implants consisted of a stainless steel ball implanted in the intervertebral space after discectomy. Because of a high proportion of implant subsidence and implant migration, the placement of these devices was quickly abandoned.

Spinal arthroplasty for arthrodesis fell out of favor until the newly emerged success of lumbar arthroplasty in the 1980s. It was the invention of the SB Charité lumbar disc prosthesis with excellent results in trials that renewed interest in spinal arthroplasty (Cinotti et al. 1996; Lemaire et al. 1997; Zeegers et al. 1999; Guyer and Ohnmeiss 2003). Different other lumbar devices, such as the ProDisc, have been widely implanted, and all of these have survived to see different design changes and improvements. Because of this trend, renewed interest in cervical spine arthroplasty also reemerged.

Rationale for Cervical Disc Arthroplasty

With the introduction of modern cervical total disc replacement devices, the initial indications for surgery included patients with cervical degenerative disc disease confined to one level causing radiculopathy and/or myelopathy with radiological evidence of only soft disc herniation or mild spondylosis. Cervical arthroplasty was therefore considered only for a selected subgroup of patients with single-level disease between C3 and C7 with no evidence of pathological changes to facet joints and posterior elements of the spine (Fig. 1). Intuitively, this raises questions regarding possible selection bias with regard to surgical outcome. Counterintuitively, and interestingly enough, in the paper by Hilibrand et al., a negative correlation between the number of levels included in the ACDF construct and onset of adjacent segment disease was reported. Two- and three-level ACDF somehow appear to be correlated with a lower incidence of adjacent segment disease than single-level arthrodesis.

After initial reports (Cummins et al. 1998; Goffin et al. 2002), mainly case series in Europe followed by the reports of US Food and Drug Administration (FDA) investigational device exemption (IDE) studies that the spectrum of indications for cervical arthroplasty has expanded. The indications beyond radiculopathy due to soft disc herniations include axial neck pain, myelopathy and foraminal stenosis, and nerve root entrapment due to narrowed disc space.

In contrast to the initial limitation to single-level disease, the indications now are widely accepted for two-level disease (Fig. 2) and in cases where a symptomatic degenerative disc disease (DDD) is addressed in conjunction with an adjacent level to a previously fused level (Fig. 3).

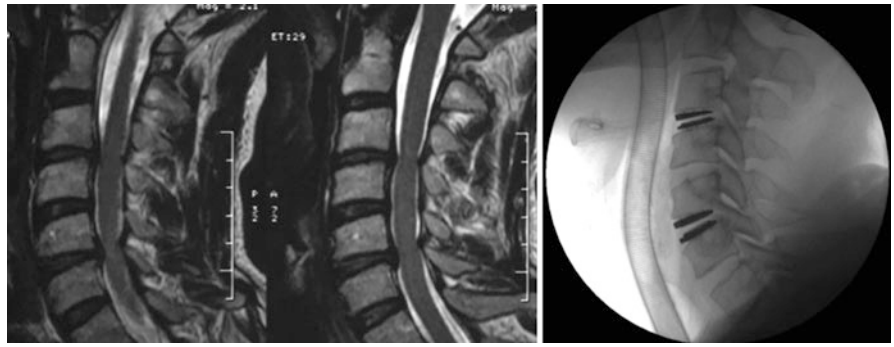

Fig. 2 Extended indication for cervical TDR – two-segment disease

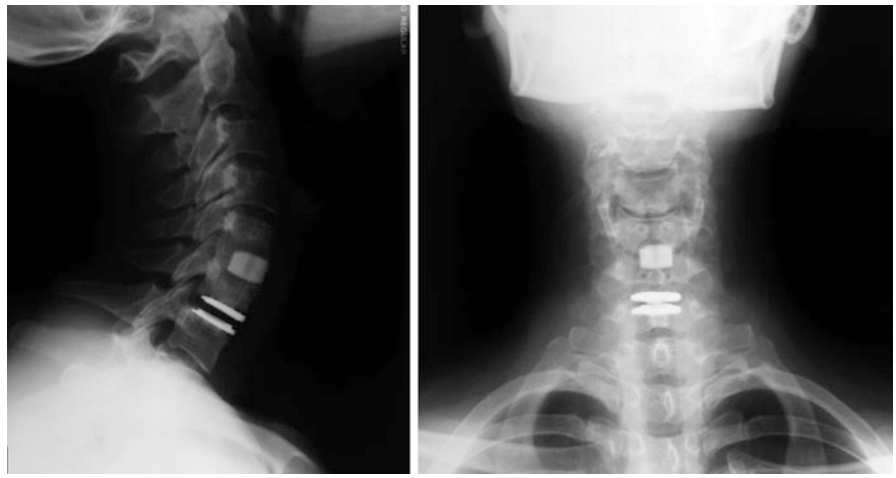

Fig. 3 Extended indication for cervical TDR – arthroplasty adjacent to previous fusion

Patients in whom a cervical arthroplasty procedure is considered must have failed a course of conservative treatment of at least 6–8 weeks.

Contraindications, Disadvantages, and Specific Complications Related to Cervical Total Disc Replacement (TDR)

A number of spinal conditions strongly preclude the use of cervical TDR devices. These include conditions with predominantly posterior compression of neural elements, such as cases with facet joint or yellow ligament hypertrophy and cases of congenitally narrow spinal canal that cannot be adequately addressed only from anteriorly. These also include cases where there is no motion preserved in the index level, such as cases of ossification of the posterior longitudinal ligament (OPLL), for instance. A vast number of metabolic conditions including osteoporosis or severe osteopenia and bone metabolic diseases (such as Paget's) are a contraindication.

When comparing the indications, surgical goals, and expectations in the long run for the two procedures (ACDF vs TDR), different factors come into play with respect to the surgical procedure undertaken. The main goal of both ADCF and TDR is the adequate surgical decompression of neural structures from an anterior approach. In the case of ACDF, the secondary goal after decompression is the solid fusion and restoration of ideal vertebral body alignment. This is achieved by proper end plate preparation and

implantation of adequate allograft material with or without an anterior plating system. After achievement of bony fusion, further formation of bony spurs toward the spinal canal in the operated segment(s) is prevented, and sometimes the resorption of previously formed ones can be detected. Basically, outpatient follow-up of these patients in the majority of cases comes to an end, or patients tend to be lost to follow up after achievement of bony fusion because they are no longer symptomatic.

The goals of arthroplasty somewhat differ in that after surgical decompression a different milieu is set up. The surgeon must take into account the need for adequate end plate preparation, which differs depending on the prosthesis to be implanted, but also be minimally disruptive to adjacent tissues. It has been shown that meticulous surgical technique is of paramount importance for the long-lasting success of cervical arthroplasty, both in optimizing clinical results and in complication avoidance. This of course also true with ACDF, but in TDR the impact of surgical technique is even more pronounced. For example, trauma to the longus colli muscle has been connected to the formation of heterotopic ossification, a new complication specific for artificial disc surgery. Unlike with the ACDF procedure, there is no termination to follow-up of these patients since there is a need to follow the functionality of the prosthesis itself.

Principles of Artificial Cervical Disc Designs

A vast number of different artificial cervical disc prostheses are available on the market worldwide. However, some crucial key points of design, biomechanical parameters, construction elements, and materials differentiate these various TDR designs. Although there may not be an ideal artificial disc implant, and due to the variability of individual anatomy and pathology, a single ideal implant likely cannot exist, and the history of implant development has brought to light some features that are clear improvements. An artificial disc has to be easy to implant, available in different sizes in terms both of height and footprint size (endplate coverage), and to have an incorporated lordotic angle of approximately 7°. Ideally, it should be MRI compatible with as few MRI-related artifacts as possible and has to have radiopaque markers for safe implantation. It also needs to be able to resist the stress imposed by millions of cycles of movement without mechanical failure and at the same time produce virtually no shear material debris. A key function is to have an adequate instantaneous axis of rotation, unrestrained near-to-physiological range of motion in all directions coupled with a small but crucial amount of translation while at the same time allowing for some degree of motion present in the facet joints. Ideally, the prosthesis must be confined to the intervertebral space to minimize dysphagia, while at the same time precluding prosthesis migration and subsidence. And lastly, revision surgery, if required, must not be complicated.

As one can see from the list of characteristics, these implants are subjected to a very rigorous group of requirements. From the history of the evolution of their design, one can also see the evolution of our understanding of the requirements of a functional cervical arthroplasty device.

Prestige Cervical Disc System (Medtronic, Memphis, TN, USA)

The first modern cervical artificial disc device was designed by B. H. Cummins in the Department of Medical Engineering at the Frenchay Hospital in Bristol, UK, in 1989 (Cummins et al. 1998). The first design was a stainless steel two-piece metal-on-metal, ball-on-socket device with anteriorly placed anchoring screws. This so-called Bristol-Cummins artificial cervical joint has subsequently experienced several design improvements. Later on named the Frenchay cervical disc, the device was eventually bought by Medtronic and redesigned to “Prestige” in 1998. The major design improvement was a change of the concave articulating surface from a

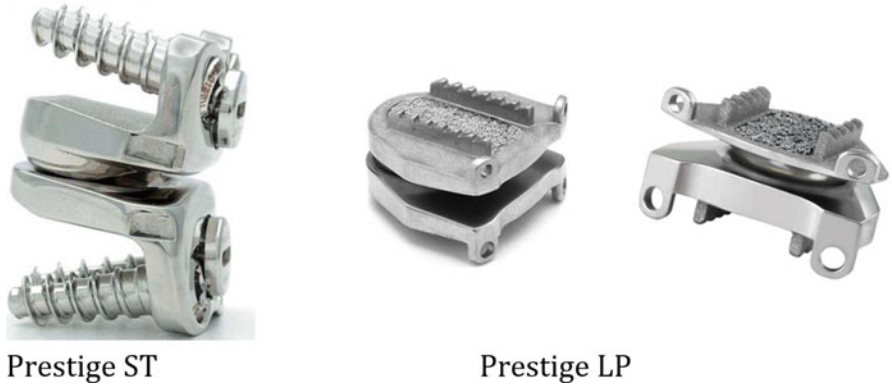

Fig. 4 The Prestige ST and Prestige LP artificial discs

Fig. 5 The Bryan disc

hemispheric cup to a more ellipsoid saucer, allowing for additional freedom of movement, in particular a small amount of anteroposterior translation coupled with flexion and extension. The screw locking mechanism was also changed to a lower profile with a locking mechanism designed to prevent screw pullout. With the fifth generation called the Prestige LP, it has become one of the most widely and extensively studied artificial discs. It has evolved from a stainless steel ball-on-socket device with anterior plate/screw fixation to a titanium ceramic composite using two small keels for low-profile fixation (Fig. 4).

Bryan Cervical Disc (Medtronic, Memphis, TN, USA)

Contrary to the Prestige artificial disc, the Bryan cervical disc (Fig. 5) that was invented in the late 1990s by Vincent Bryan was initially designed as a composite metal-on-plastic design. More adherent to low-friction principles of tribology, it consists of a polyurethane core between two titanium alloy shells, allowing for unrestrained motion and shock absorption. The titanium shells are covered by a porous surface that promotes bony ingrowth. The whole implant is contained in a polyurethane membrane designed to prevent shedding of wear debris. Specific to the Bryan system is the surgical implantation technique that necessitates a specific milling of vertebral end plates that guarantees initial implant stability. As with the Prestige disc system, substantial clinical data with the use of the Bryan disc are available due to the large number of devices implanted and long follow-up (Goffin et al. 2003; Anderson et al. 2004.).

ProDisc-C (Centinel Spine, USA)

Analogous to the lumbar ProDisc-L, the ProDisc-C (Fig. 6) is a uniarticulating ultrahigh-molecular-weight polyethylene (UHMWPE)-on-cobalt chrome ball-in-socket design. Short-term fixation stability is achieved by a protruding midline keel on the end plate surfaces of the device.

Fig. 6 The ProDisc-C disc

Fig. 7 The PCM disc

Porous Coated Motion (PCM) (Nuvasive, San Diego, CA, USA)

Different from the previous designs, the PCM (Fig. 7) is a uniarticulating two-piece non-constrained device. The initial fixation to the vertebrae is achieved by the curved design and serrations of the implant end plates, while long-term fixation is provided by bony ingrowth into its titanium and calcium phosphate surface. The articulation of this implant is UHMWPE-CoCr combination. Specific to this device is the lack of inherent range of motion limitations due to its design which relies on gliding motion. The motion limitation of this unconstrained device is dependent upon the surrounding soft tissues and facet joints.

Mobi-C Cervical Disc (Zimmer, USA)

The Mobi-C cervical disc (Fig. 8) is a combination of two titanium end plates and a polyethylene core in a semi-constrained design. The specific characteristic of this device is the presence of two peripheral stops incorporated in the construct of the inferior titanium plate that limits the mobility of the polyurethane insert.

Discover (Centinel Spine, USA)

The Discover artificial cervical disc (Fig. 9) has a fixed core ball-in-socket joint with articulating surfaces of titanium alloy and a cross-linked UHMWPE core. It offers an inherent 7° of structural lordosis. The immediate fixation is provided by six 1mm fixation teeth, while the titanium plasma and hydroxyapatite coating provides for better bony ingrowth and long-term fixation of the device.

Preoperative Planning

Irrespective of the device to be used, and consistent with good surgical practice, a thorough history and clinical examination and preoperative assessment of the patient's symptoms and signs, as well as a preoperative radiological work-up, must be undertaken. In preparation for cervical arthroplasty surgery, apart from standard C-spine X-rays showing the patient in the neutral standing position (particularly potentially useful during the operative procedure – described below) and MRI scans delineating the localization and characteristics of pathology as well as of neural structures, flexion and extension X-rays are necessary. If available, a CT scan is of use for evaluation of facet joint degenerative changes.

Knowledge of the normal lordotic curvature of the patient's cervical spine, as assessed by the preoperative neutral standing lateral X-ray, is of paramount importance when positioning the patient on the operating table. Failure to position the patient correctly with insufficient extension or overextension of the neck is a crucial mistake that

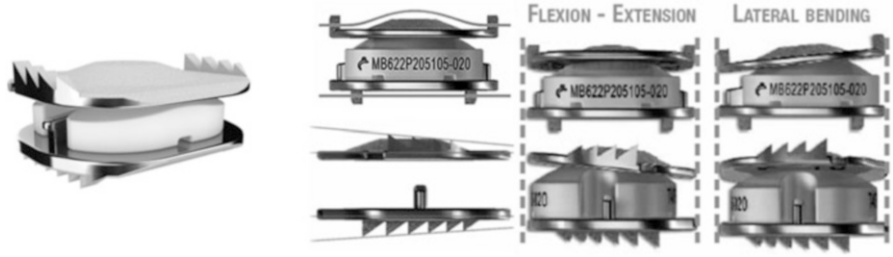

Fig. 8 The Mobi-C cervical disc

Fig. 9 The Discover disc

can occur even before initiating the surgical procedure itself. Measuring the purported implant size on preoperative X-rays can give the surgeon an idea of whether adequate end plate preparation has been made at the completion of neural decompression.

Surgical Technique

Positioning

Since indications for artificial disc replacement surgery differ from the standard ACDF indications that encompass a much larger spectrum of cervical spine degenerative diseases, the surgical nuances that differ are numerous and present in each step of the procedure starting with patient positioning. When planning total disc replacement surgery, it is absolutely mandatory to try and achieve as neutral a position as possible to maintain a midline position and natural lordotic curvature. Midline position is required for accurate coronal alignment and midline placement of the implant in order to minimize adjacent segment stresses and guarantee maximum duration of implant function. The head of the patient must not be rotated to either side. One way of assessing the degree of flexion/extension is to superimpose the preoperative X-ray of the patient taken when standing to the one taken intraoperatively during positioning. Hyperextension during surgery, for example, can lead to unintended AP translation inside the device resulting in suboptimal postoperative implant range of motion.

The head is maintained in the desired position by a self-retaining tape placed over the patient's forehead with care taken not to leave the eyes unprotected (avoided by applying ointment) should they unintentionally open under the drapes during surgery. The neck must not be left unsupported; usually an appropriate pad or a roll of cotton compresses is put under the neck to match its curvature, thus offering support during surgery (Fig. 10).

Positioning Pearls

- Ensuring a centered head position and midline cervical spine alignment is crucial for successful arthroplasty device implantation.
- The head should be taped to the surgical table to prevent any movement during surgery.
- Final positioning before draping can be checked by X-ray to ensure optimal alignment and lordotic curvature have been achieved.

Positioning Pitfalls

- Inadvertent rotation of the cervical spine during surgery can lead to improper implant

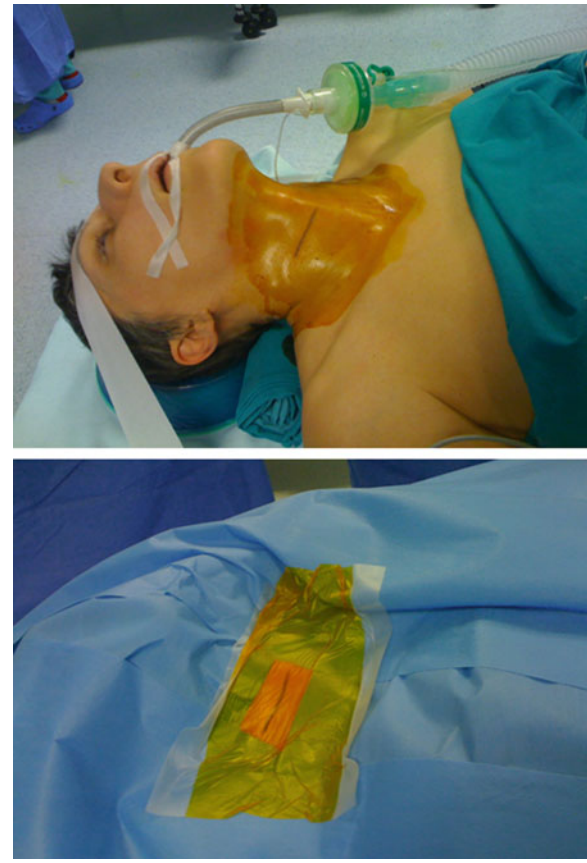

Fig. 10 Proper patient positioning for performing cervical disc arthroplasty. Note the placement of the mechanical ventilation tube in the opposite corner of the mouth, the position of the tape used to immobilize the head, and the roll of cotton pads that provide support for the neck in a neutral position

positioning and incorrect stress on the device resulting in possible suboptimal functionality of the prosthesis, neck pain, and even implant migration.

Approach

Depending upon the implant used, different dedicated sets of surgical instruments are present.

As with classical ACDF, the side of approach depends on the preference of the surgeon but also upon patient characteristics. A classical anterolateral approach to the cervical spine is undertaken. Since the vast majority of arthroplasty surgeries performed are for single-level disc disease, a classical approach through a horizontal incision concealed in a skin crease at the level of the conic ligament is undertaken. Care must be taken to minimize any unnecessary tissue trauma and bleeding, especially in the plane of the prevertebral fascia in order to minimize formation of heterotopic ossification. Instead, only mobilization of the medial margins of the longus colli muscle is undertaken with a Penfield No. 4 instrument or a similar dissector in order to visualize the uncovertebral joints and establish the midline. A marker is inserted into the disc, and fluoroscopy is performed to confirm the surgical level.

Approach Pearls

- For patients with short neck and for surgery on lower levels (C6–C7), shoulders should be gently pulled down and taped to the surgical table in a craniocaudal direction to ensure operative level X-ray visualization.
- The skin incision should be made using natural skin crests if visible, to ensure a better cosmetic outcome.

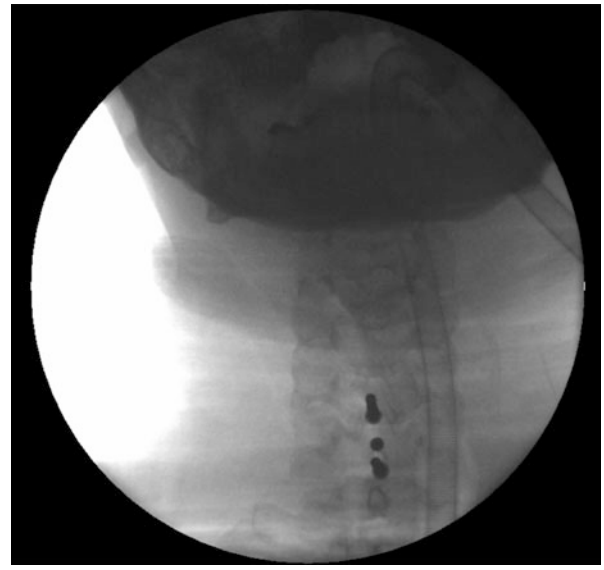

Fig. 11 Diagram and intraoperative fluoroscopy showing the placement of midline pin(s). Placement of the midline pin either in the disc or vertebra should be done equidistant from both uncovertebral joints. Radiographic confirmation of this position is mandatory

- Deep cervical fascia should be widely dissected in respect to the craniocaudal direction to minimize retractor compression to adjacent structures.
- Meticulous hemostasis must be achieved at all steps during surgery to avoid placement of drainage at the time of closure.

Approach Pitfalls

- Extensive electrocautery of the longus colli muscle must be avoided in order to minimize tissue trauma and scar formation, which can predispose to heterotopic ossification.

Midline Determination

Irrespective of the implant type, establishing the midline is of crucial importance for the long-term success of surgery. As previously stated, this is done by identifying the middle of the distance from the two uncovertebral joints while inflicting minimal trauma to surrounding soft tissue. Radiographic verification of the midline position of pins on adjacent vertebrae is performed by fluoroscopy after positioning a midline pin either in the disc itself or in the body of the adjacent vertebrae. Care must be taken not to misinterpret the midline alignment on fluoroscopy, and this is verified when both the pin and spinous process are aligned in a projection perpendicular to the intervertebral space (Fig. 11).

Midline Determination Pearls

- Longus colli muscle dissection should be performed with the use of a dissector to the level where both uncovertebral joints are fully visible, facilitating the determination of the true midline.
- When assessing the midline position of pins by fluoroscopy, it is necessary for the pins to be in line with the superimposed spinous processes of the corresponding vertebrae.

Placement of Pins

Retractor pins are then placed in the adjacent vertebral bodies (Fig. 12). This can be done with the aid of a guiding system. In this manner parallel placement and therefore an even and parallel retraction of both distractor pins are facilitated. If a dedicated guidance system is not available, care of must be taken to assure the placement of the vertebral body pins as close as parallel to one another as possible.

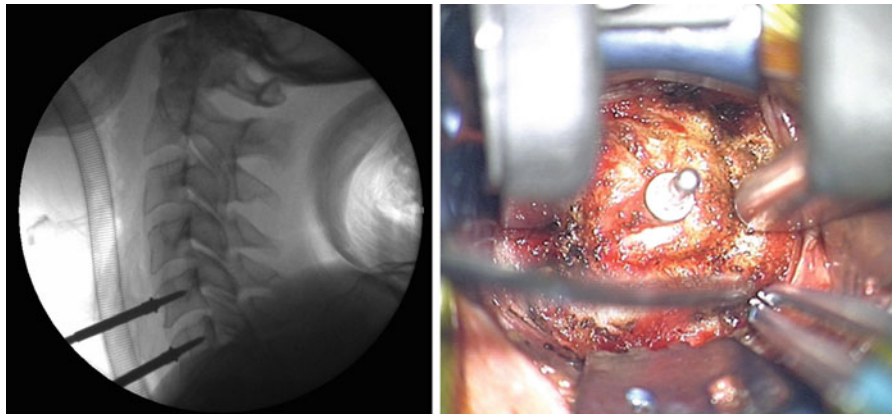

Fig. 12 Intraoperative fluoroscopy and intraoperative photograph showing positioning of the distractor pins

Pin Placement Pearls

- Parallel placement of pins will ensure equal distraction forces to be applied on both vertebrae.
- Both pins must be of same length and diameter.
- Pins must be placed in the mid-portion of the vertebral bodies, parallel to the end plates.

Pin Placement Pitfalls

- It is important not to overdistract, because overdistraction can put additional stress on facet joints leading to either postoperative neck pain or possible degeneration of the facets which at the end can diminish functioning of the prosthesis.

Discectomy

Initial partial discectomy is performed with the pins in place and before their distraction. The discectomy is then finished in a stepwise fashion, with minimal increments in vertebral body distractions over the pins as the discectomy is completed. Overdistraction must be avoided, since this can lead to implantation of an oversized device, leading to excessive distractive stress on the facet joints and postoperative pain and failure of motion preservation.

It is important to remove all residual disc material to the posterior longitudinal ligament and laterally to both uncovertebral joints. Removal of the posterior longitudinal ligament is always necessary, as well as removal of any osteophytes protruding into the spinal canal. However, all unnecessary bone drilling should be avoided and the operative field thoroughly rinsed with saline in order to flush away any bone debris.

Discectomy Pearls

- Removal of the posterior longitudinal ligament is necessary, in order to visualize adequately the decompression of neural structures.
- Additional foraminotomy is usually not required because most cases are limited to soft disc herniation; however, it is crucial to see the entire foramen and the nerve within it and to check for any residual compression using a probe or a nerve hook.

End Plate Preparation

Nuances of end plate preparation differ based on the type of implant used, and manufacturers' advice should be followed. Generally, the end plates should be prepared flat and shaped to match as closely as possible the curvature or angulation of the implant end plate geometry. Implants using keels as means for immediate anchoring have the inherent risk of provoking vertebral body fractures especially in the setting of performing arthroplasty surgery on two adjacent levels or next to a previous fused segment,

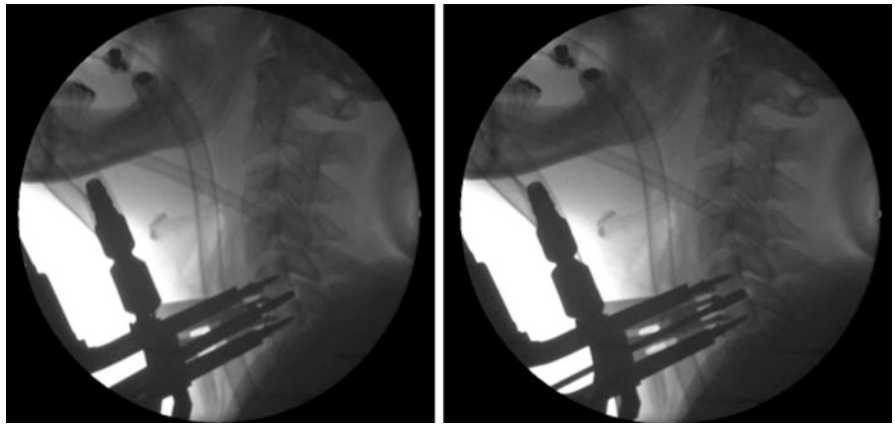

Fig. 13 Intraoperative fluoroscopic visualization when choosing the appropriate footprint size

so care must be taken not to be overly aggressive in preparation for their positioning. Newer generation devices use small spurs or teeth for immediate implant fixation which is generally less traumatic to the bony end plates.

Final end plate preparation is achieved with the use of appropriately sized rasps, with which any residual cartilaginous tissue impeding bony ingrowth into the implant end plates can be removed. Care must be taken not to impose injury to the subchondral bone. The superior end plate usually is concavely shaped, and this surface can be carefully flattened both anteriorly and posteriorly in order to accommodate the implant surface. The end plate of the lower vertebra should be usually flattened only posteriorly. At the end of the endplate preparation phase, both vertebral surfaces should be parallel to one another. A thorough irrigation is performed again.

End Plate Preparation Pearls

- When using prosthesis featuring a predetermined lordotic angle, achieving absolute parallelism during end plate preparation is mandatory; failure to do so may lead to loss of lordotic shape of the prosthesis.

Footprint Size

Choosing the right size of the implant in terms of endplate coverage is the best way to avoid implant subsidence as well as heterotopic ossification. The greater the coverage area, the lesser the chance that the implant will injure the adjacent bone and migrate. In the setting of various implant sizes available, the largest implant that still fits into the intervertebral space without protruding should be used.

Footprint Size Pearls

- Checking the appropriate footprint size is done exclusively under fluoroscopy (Fig. 13).
- The largest footprint size that does not enter the uncovertebral joints is to be chosen.
- When checking for footprint size, the template itself must be positioned parallel to the distraction pins (Fig. 14).

Disc Trial

To further optimize disc implant selection, several sets include disc trials that mimic the final disc implant and can be assessed under fluoroscopy in terms of height, coverage, and positioning.

Disc Trial Pearls

- It is of primary importance that the midline of the trial prosthesis matches the midline of the vertebral body, because this in the end will affect the center of rotation of the implant; again, this can be achieved only by fluoroscopic guidance.

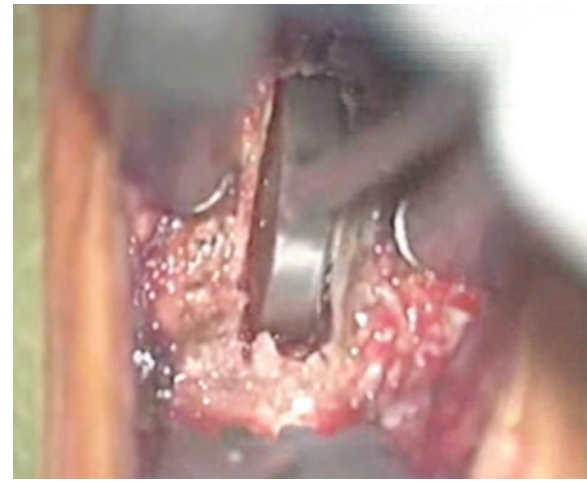

Fig. 14 Intraoperative image showing the proper position of the probe when checking adequacy of footprint size

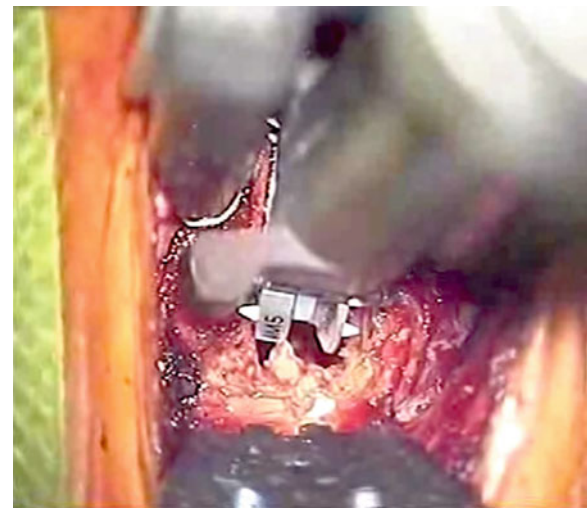

Fig. 15 Intraoperative photograph showing implantation of the Discover disc

Implant Insertion

Implant placement (Fig. 15) steps must be followed as described by the manufacturer. Any unnecessary manipulation of the implant should be avoided. Also, the simultaneous use of a burr and any metallic suction devices or similar metallic instruments during any surgical step should be performed with care. Contact of the burr with such an instrument can provoke formation of metal debris which can over the course of years lead to implant scratching and accelerated wear.

Final position (Fig. 16) must be checked by AP and LL fluoroscopy and any further positioning adjustment made accordingly. Since these implants are designed to last for millions of cycles of flexion and extension, translational movement, and rotation, any suboptimal placement should not be tolerated.

Implant Insertion Pearls

- Malpositioning of the prosthesis leads to prosthesis malfunction, and should such a malpositioning be verified at implantation, a reinsertion should be undertaken. For prosthesis using keels, this often cannot be done without significant injury to the cortical bone. Therefore prostheses using lower profile anchoring features, such as teeth or spurs, are advantageous, particularly for surgeons with less experience in cervical arthroplasty.

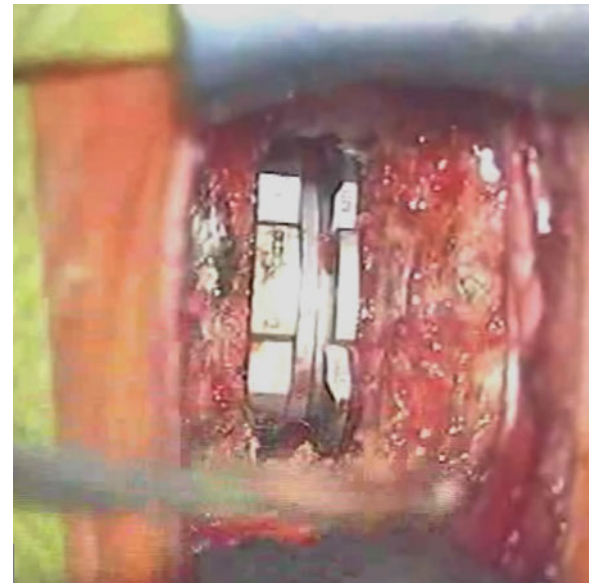

Fig. 16 Intraoperative photograph showing final position of the Discover disc

Wound Closure

After the device insertion is completed, all pins and retractors should be removed and fluoroscopy undertaken to check the final implant positioning. If the implant position is optimal, the wound can be irrigated and inspected for any bleeding. Hemostasis should be meticulously performed, and drainage for one-level surgery is usually not required. Only the platysma is sutured, as well as the subcutaneous layer using a 4–0 resorbable suture. Dermabond is applied on the skin, so that no particular restrictions regarding the skin incision site are necessary.

Postoperative Care and Follow-Up

Patients are encouraged to be upright and walk 3–4 h after surgery and are usually discharged the same or the following day. Administering pain medication as needed as well as NSAIDs for 1–2 weeks after surgery is advised. Wearing of a cervical collar is not recommended.

Follow-up in our practice is usually scheduled at 3, 6, and 12 months after surgery, with dynamic X-rays only.

Patients are also advised to come for further postoperative follow-up 24, 48, 72, and 96 months. The purpose is to check for possible heterotopic ossification that may occur during the patient's postoperative course and to follow and understand long-term outcome of both the patient and the device.

Conclusions

Modern cervical disc arthroplasty surgery started in 2001 in Belgium with the work of Goffin. Since then, cervical disc arthroplasty (CDA) has become a standard procedure in many orthopedic and neurosurgical departments all over the world. Several meta-analyses and randomized control trials showed that CDA is an effective and safe surgical procedure for the treatment of single-level cervical disc disease. Furthermore, in some studies, CDA was found to be superior to ACDF in terms of neck and arm pain, neurological success, and range of motion at the operated level and when assessing for secondary surgical procedures.

CDA is a procedure that has its own history in terms of both technological and surgical

development. It has a significant role in our present spinal surgery armamentarium and hopefully a bright future. Evaluation of new technology is an ongoing process, and we have to be careful and prudent in its implementation, but we also have a reason to be optimistic.

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Cervical Total Disc Replacement: Expanded Indications

44

Pierce D. Nunley

Contents

Abstract

Cervical total disc replacement (cTDR) was first used in the 1960s with little success. Widespread use began in the early 2000s, with multiple devices approved in the United States (US) and outside the US (OUS). The US regulatory process, the Investigational Device Exemption (IDE) trial, slows the adoption of some technology in the USA including cTDR. The design, including strict inclusion/exclusion, of IDE trials results in the most compelling, and highest level of evidence data in support of cTDR. The strict patient selection for the IDE trials continues to impact clinical use, as the US indications for use of cTDR remain restrictive compared to OUS. Literature supporting expanded indications of cTDR is limited to low level of evidence and small patient populations from mostly OUS sources. OUS surgeons have many years (10+) of experience with expanded indications, so we will also explore their experiences with cTDR. The reality in the USA is that approval of expanded indications will likely not occur without another IDE trial. What evidence is necessary for US surgeons to adopt expanded indications in their practice?

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Keywords

Cervical total disc replacement · Cervical arthroplasty · Cervical indications

Brief Worldwide History of cTDR

The first cervical total disc replacement (cTDR) was implanted in 1966 by the Swedish surgeon, Ulf Fernstom. The stainless steel ball bearing, known as the Fernstrom ball, was plagued with high failure rates, so approximately 75 were implanted before use was discontinued (Fernström 1966; Fisahn et al. 2017). In 1989, Cummins (Bristol, UK) developed a stainless-steel artificial disc consisting of metal on metal ball and socket device with anchoring screws. One more redesign, following high failure rates of the original Cummins design, produced the Frenchay cervical disc. The first with promising clinical outcomes, the Frenchay disc, was purchased by Medtronic (Medtronic, Minneapolis, MN, USA) and became the Prestige ST cervical disc (Cummins et al. 1998; Wigfield et al. 2002). The Bryan disc was designed in the USA by Vincent Bryan in 1992. The Bryan disc design was markedly different than Prestige, with two titanium alloy endplates and a polyurethane core filled with saline (Basho and Hood 2012). During this time period, another disc, ProDisc-C, was designed by a French surgeon, Dr. Thierry Marnay. ProDisc-C brought a third unique design to the cTDR market. The device was composed of cobalt-chromium-molybdenum and ultra-high molecular weight polyethylene (UHMWPE) articulating surface, with two keels to facilitate anchoring to the vertebral endplates (Baaj et al. 2009).

The 1990s and early 2000s experienced gaining momentum for design of new cTDR devices, but design was only a beginning for cTDR technology. Regulatory approval is required for cTDR devices in the country of distribution, although these approval requirements vary widely. In addition to approval of the device, many regulatory agencies will also approve the specific indications for use of the device.

Development of Indications

The development of medical device patient indications differs widely throughout the world. We will address the US indications and the OUS indications separately.

The USA

In the USA, the FDA regulates cTDR as a Class III medical device, requiring a large-scale (multicenter, prospective, controlled, and randomized) investigational device exemption (IDE) clinical trial for approval. The high-quality, controlled nature of these trials renders level 1 evidence comparing cTDR to anterior cervical discectomy and fusion (ACDF). During these trials, patient eligibility criteria are strict. Upon approval the manufacturer in conjunction with the FDA issues a document, "Instructions for Use" (IFU) that includes indications, contraindications, warnings, and precautions specific to the cTDR device. For purposes of this chapter, we will refer to indications, contraindications, warnings, and precautions, simply as "indications." The basis for the cTDR indications is the patient population included in the clinical trial, supported as level 1 evidence. Among the seven approved cTDR devices in the USA, the study populations and therefore the indications remain relatively homogeneous. In the USA, surgeons are allowed to operate on patients "off-label" (outside of the indications), but many surgeons choose to respect the indications based on the extensive data and high level of evidence that supports them. Additionally, US reimbursement remains a challenge even for on-label use of cTDR, so insurance approval of off-label use is rare.

OUS

OUS the regulatory approval process varies between countries, but largely these do not require highly controlled or high level of evidence trials for approval. Therefore, post-approval indications are at the discretion of the surgeon and tend to be

more expansive. In general, the OUS reimbursement landscape is also less restrictive, allowing the surgeon and patient to determine the best treatment option without coverage as a factor.

The focus of this chapter will be the current US indications and what evidence exists to expand these indications. Many countries OUS already accept broader indications for cTDR, but should and will the USA adopt these expanded indications?

US Current Indications

US cTDR patient indications remain narrow, but highly supported with level 1 evidence. While each cTDR device has slight variation in the approved indications, the following are common among the cTDR devices:

- Single or two contiguous levels between C3 and C7 for conditions
  - Intractable radiculopathy (with or without neck pain)
  - or myelopathy
  - and at least one of the following:
    herniated nucleus pulposus
    spondylosis (defined by osteophytes)
    visible loss of disc height compared to adjacent levels
- Failure of 6 weeks of conservative therapy
- Skeletally mature patients

Additionally, the following relevant (not fully inclusive listing) contraindications and/or warnings and precautions exist for guidelines against the use of cTDR:

- Prior cervical spine surgery, including prior surgery at the index level
- More than two disease levels requiring surgery
- Severe facet joint degeneration
- Segmental instability (translation >3.5 mm and/or $>11^\circ$ angular difference to that of either adjacent level)
- Disc height less than 3 mm measured from the center
- Significant kyphotic deformity or significant reversal of lordosis
- Neck pain alone

The US data and indications exclude large subsets of the population, and the most heavily debated include hybrid treatment (adjacent to a prior or concurrent fusion) and treatment for greater than two levels.

Evidence to Expand US Indications

For the FDA to officially expand US indications, level 1 evidence collected as part of an IDE would be required with the current regulatory cTDR classification. But for surgeons, what evidence is compelling enough to expand indications within your practice?

The published literature on expanded indications is a lessor level of evidence than the data published from the IDE studies. However, several of these studies are robust and provide valuable insight into expanded use of cTDR.

An analysis conducted by Auerbach used the US indications/contraindications of cTDR for Prestige, ProDisc-C, PCM, and Bryan to group patients requiring cervical spine surgery. Patients were grouped into three categories: (1) patients with direct contraindications, (2) qualified cTDR patients, and (3) qualified patient if indications were expanded to include clinical adjacent segment pathology (CASP). Of 167 patients, 95 were contraindicated, with 7/95 that would have qualified if CASP were included. It is noteworthy that the most common exclusion criteria were greater than two operative levels requiring surgery (47 patients). Only the remaining 72/167 patients were qualified to receive a cTDR (Auerbach et al. 2008). Adjacent to a previous fusion and required surgical levels greater than 2, remain a contraindication in the USA, and it could impact over 50% of patients presenting for cervical spine surgery.

Twenty patients were prospectively enrolled in a study in China for treatment at one or two levels with Bryan cTDR. Unlike in the US trials, the two-level treatment was not restricted to

contiguous levels. Clinical outcomes were favorable through 4 years, with no reported serious complications (Zhang et al. 2013). Another Chinese study prospectively enrolled 48 patients treated with Bryan at one, two, and three levels. Clinical outcomes remain favorable through 10 years, although reported heterotopic ossification (HO) rates are high, 69.0%. These HO rates are not categorized into grades, as is typically in the USA, so the true magnitude and impact are unclear (Zhao et al. 2016).

PCM cTDR has been analyzed and reported with expanded indications in several Brazilian studies. A 2007 study included patients treated at one ($n = 72$), two ($n = 53$), three ($n = 12$), and four ($n = 4$) cervical levels (not required to be contiguous) between C3 and T1. There was no exclusion for prior cervical fusion, resulting in 11 one-level and 9 multilevel patients treated with PCM as a revision to a failed fusion, and 12 one-level patients and 9 multilevel patients were treated with PCM adjacent to a prior fusion. Results were significantly improved for both groups, with significantly more improvement in the multilevel cohort (Pimenta et al. 2007). The authors found that the incidence of HO in this population was low, 7.7% through 6 years. While higher HO did correlate to loss of motion, clinical outcomes were not impacted (Pimenta et al. 2013).

A similar study in Brazil used CT results to analyze facet degeneration through 5 years postoperatively. Study enrollment criteria were similar to the previous study, prior fusions were not excluded, and patients were operated at one ($n = 72$), two ($n = 67$), three ($n = 17$), and four ($n = 6$) cervical levels (not required to be contiguous) between C3 and T1. Results indicate there is facet joint degeneration, although minimal, 14% with grade 3 or 4 degeneration (Oliveira et al. 2011).

In France, Mobi-C cTDR has been studied in a large prospective, non-controlled population using expanded indications. Patients were treated at one ($n = 175$), two ($n = 51$), three ($n = 4$), and four ($n = 1$) levels from C3 to T1 with outcomes reported through 2 years. Similar to the PCM studies, prior fusions, even at the index level, were not excluded. Of one-level patients, 21 (with 28 fused levels) had prior cervical fusions, with 18 of these adjacent to the index level. Of multilevel patients (2, 3, and 4 levels) 5 (with 5 fused levels) had prior cervical fusions, with 3 adjacent to the index level and 2 at the index level. Outcomes for both groups were favorable, with no significant difference between the one-level and multilevel groups (Huppert et al. 2011).

Forty-eight patients treated with Bryan cTDR at one-level were retrospectively reviewed in Korea. Twelve of the 48 patients were treated with Bryan adjacent to a fusion (hybrid). Although postoperative kyphotic changes were noted radiographically, the differences were not significant and clinical outcomes remain improved through the 11.8 month mean follow-up (Yoon et al. 2006).

The literature on expanded indications, while compelling, is of lessor evidence than the robust and highly controlled trials that are more common in the USA.

The evidence to expand US indications is not all based on published literature; it is also based upon surgeon experience. Many OUS and some US surgeons are regularly performing cTDR operations outside of the US indications including patients older than 75, greater than two operative levels, replacement of a failed fusion, adjacent to a fusion, and noncontiguous or "skip" levels.

Conclusions

The use of cTDR as an alternative to cervical fusion has gained momentum since the early 2000s and has seen even more widespread support in the last 10 years. Although still considered a novel technology, the number of implantations and supporting literature is abundant. However, the worldwide indications for use of cTDR differ widely. The typical US surgeon remains conservative in patient selection for cTDR, while OUS surgeons commonly expand the patient selection to include more conditions. Continued research, particularly level 1 and 2 evidence studies,

focused on expanded indications will help to appropriately advance cTDR, in an evidence-based fashion.

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Cervical Total Disc Replacement: Heterotopic Ossification and Complications

45

Michael Paci and Michael Y. Wang

Contents

Abstract

Cervical total disc replacement (CTDR) can be complicated by the occurrence of heterotopic ossification (HO). HO occurs when bone formation happens in tissues where it is not normally present. It is graded radiographically and develops on a spectrum, from ossification anterior to the cervical spine to ossification involving the articulating surfaces and causing an effective fusion. The true incidence of HO after CTDR is still under debate, with rates reported in the literature varying from approximately 20–90% of patients. The exact causes of HO are still unknown, but associations have been found with male gender, older age, type of prosthesis used, multilevel surgery, and surgical technique. The presence of HO after CTDR has not been correlated with worse clinical outcomes. There is no evidence to date to support a specific strategy to prevent HO, but prescribing a short course of nonsteroidal

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anti-inflammatory drugs (NSAIDs) is often done. CTDR is also associated with other complications, including complications that can occur during the anterior approach to the cervical spine, complications related to the prosthesis used and adjacent segment disease.

Keywords

Cervical disc replacement · Heterotopic calcification · Anterior cervical approach · Prosthesis-related complication · Adjacent segment disease

Introduction

Cervical total disc replacement (CTDR) has become a procedure of choice in select patients with one-level and two-level, symptomatic cervical spondylosis for whom motion preservation is an important goal. As detailed elsewhere in this book, this procedure has been shown to have benefits when compared to the more traditional anterior cervical discectomy and fusion (ACDF). It also carries some risks and these will be explored in the current chapter. In particular, we will discuss heterotopic ossification (HO), including its definition, its grading, prevalence after CTDR, risk factors for developing it, and methods to prevent it. We will also discuss more general risks associated with the anterior approach needed to perform a CTDR, as well as specific risks related to the different types of implants use in CTDR.

Heterotopic Ossification

Definition

Heterotopic ossification is a process by which bone and calcifications are deposited in tissues in which they are normally not present. This is known to occur in the context of trauma (such as brain trauma and spinal cord injury), as well as in the setting of arthroplasty, including hip replacement and CTDR (Shehab et al. 2002). In the setting of arthroplasty, the amount of bone formed and its location in relation to the articulating surfaces can threaten the range of motion of the joint involved. The exact pathophysiology of HO is still not well understood. It is clear however that a process of bone deposition can be triggered when bony fragments or shavings fall into contact with certain mesenchymal tissues such as muscle or fascia. It is thought that the presence of bony fragments in such tissues, with their accompanying osteoblasts and bone morphogenic proteins, can lead to the abnormal differentiation of mesenchymal cells into osteoblasts (Balboni et al. 2006). This in turn can lead to new bone formation.

Grading

A well-known grading system for heterotopic ossification following hip arthroplasty was classified in 1973 by Brooker et al. This system was based on the radiographic appearance of HO in relation to the hip joint. McAfee et al. (2003) adapted this grading system for HO in the setting of lumbar disc replacement. Mehren et al. (2006) further adapted this classification for HO in the setting of CTDR.

HO in CTDR is classified based on its radiographic appearance and the extent to which it involves the disc space and its movement (Mehren et al. 2006). Grade 0 is given when no HO is visible. Grade 1 is given when some HO is seen anterior to the vertebral column but not in the disc space. Grade 2 is given when HO starts to appear within the disc space, but no bridging osteophytes are visible yet. Grade 3 is given when bridging osteophytes have formed across the disc space, but some movement is still possible. Finally, grade 4 is given when the level treated by CTDR is entirely fused because of HO, and no movement is possible.

Occurrence of HO After CTDR

The exact incidence of HO after CTDR is still not well established. Different studies have presented widely varying data on this phenomenon. Leung

et al. (2005) observed a cohort of 90 patients who underwent CTDR. They found that 17.8% of patients developed HO at 12 months postoperatively, with 6.7% showing grade 3 or 4 HO. Heidecke et al. (2008) presented a cohort of 54 patients treated with CTDR (59 levels treated). Of these, 29% showed evidence of HO at 2 years of follow-up. Similarly, Lee et al. (2010) present a cohort of 48 patients treated with one-level CTDR. They reported that 27.1% of patients had developed HO at a mean follow-up time of 14 months. On the other end of the spectrum, Mehren et al. (2006) showed a much higher level of HO formation after CTDR. In their group of 54 patients treated with CTDR (77 levels treated), 66.2% of levels demonstrated evidence of HO at 1 year of follow-up. Park et al. (2013) present even higher figures with a 94.1% incidence of HO at 24 months in a cohort of 75 patients treated by CTDR.

It is clear that the rates of reported HO after CTDR vary significantly. The cohort studies presented are all relatively small, and the patient populations from each group likely differ significantly from one another as well.

Interestingly, it seems that the rate of HO after CTDR may increase with time after the initial intervention. This seems intuitively logical as it mirrors the natural history of cervical spondylosis in which osteophyte formation progresses over time at a diseased segment until the segment is fused. Suchomel et al. (2010) present data that support this idea. They followed a group of 54 patients (65 levels) treated with CTDR over a period of 4 years. At 6 months, 9% of levels showed grade 3 HO, and none showed grade 4 HO. By 4 years, 45% showed grade 3 HO, and 18% showed grade 4 HO.

Risk Factors for Developing HO After CTDR

Risk factors associated with the development of HO after CTDR remain under investigation. Older age, male gender, two-level CTDR, surgical technique, and type of prosthesis have been associated with HO in various studies that have examined this phenomenon.

Yi et al. (2013) presented a cohort of 170 patients who underwent CTDR with a minimum follow-up of 12 months. They reported a 40.6% rate of HO at follow-up. They found that male gender conferred an odds ratio of 2.117 of developing HO when compared to female gender. They also found that prosthesis type was associated with HO in their cohort. Compared to patients who received a Bryan disc (Medtronic, USA), patients who received a Mobi-C (LDR Medical, France) or ProDisc-C (Synthes, USA) had a significantly increased rate of HO (odds ratios of 5.262 and 7.449).

Leung et al. (2005) also examined possible risk factors for the development of HO in their cohort. They found a significant association between the development of HO and male gender. Additionally, they reported an association between age and HO, with older patients having an odds ratio of 1.10 of developing it as compared to younger ones.

Wu et al. (2012) studied whether two-level CTDR was a risk factor for HO as compared to one-level CTDR. Their hypothesis was that patients needing treatment at two levels were more likely to have more advanced spondylosis in their cervical spine and would thus be more at risk for HO. They presented a cohort of 70 patients who were followed for an average of approximately 46 months. Forty-two patients underwent a one-level procedure, whereas 28 underwent a two-level procedure. The authors found that 75.0% of the patients treated at two level developed HO, as compared to 40.5% for those treated at one level, and this was statistically significant ($p = 0.009$). They argue that this confirms their hypothesis and that patients treated at two-levels had more advanced cervical spondylosis that continued to progress postoperatively.

As previously noted, Park et al. (2013) presented a very high rate of HO in their cohort of patients treated with CTDR (94.1%). They argue that surgical technique can play a role in the development of HO as patients in their cohort were treated by two surgeons with a slightly different technique and one was associated with a significantly higher level of HO. Indeed, one surgeon was described as using a ball-type burr,

whereas the second was described as using a diamond-tipped burr. Patients who underwent the procedure with the second surgeon had an odds ratio of 3.33 of developing HO as compared to those who were operated by the first one. The authors discuss that the differing burr types and techniques may have led to a different amount of bony exposure, thus leading to differing HO rates.

Clinical Significance of HO

Given that HO occurs in a significant proportion of patients who undergo CTDR, and that it seems to progress with time, many authors have questioned whether it defies the purpose of the procedure itself. Indeed, the choice of CTDR over a more traditional ACDF is usually made with the intent to preserve motion. However, higher grades of HO are known to restrict the implanted prosthesis' motion, thus resulting into something more akin to a fused level from an ACDF.

As previously discussed, Lee et al. (2010) presented a small cohort of 48 patients who underwent CTDR, with a rate of HO of 27.1%. They examined the clinical outcomes of patients with HO and compared them to those without. They did not find any significant differences in pain as quantified by the visual-analog scale (VAS), in function as quantified by the Oswestry Disability Index (ODI) or in range of motion (ROM) as quantified radiographically. These results are however limited by the overall short patient follow-up and the fact that they did not have any patients who presented with grade 4 HO.

Tu et al. (2011) also compared the clinical outcomes of patients with and without HO after CTDR. They present a cohort of 36 patients (52 levels treated) followed for approximately 27 months. They report a rate of HO of 50%. They did not find a significant difference in VAS scores or in Odom outcome criteria in patients who developed HO compared to those who didn't. These results are however also of limited value given the small group of patients presented, the short follow-up and that there was only one patient who developed grade 4 HO.

More studies are needed to better evaluate the effect of HO on patient outcomes. It is however not surprising that patient-reported outcomes such as the VAS score or the Odom criteria have not been shown to differ between patients with and without HO. HO usually does not lead to neural compression. The relief of arm pain achieved during surgery should therefore not be affected by HO. Further, as CTDR was shown to be as effective as ACDF for treatment of such symptoms, even patients with grade 4 HO would be expected to report overall good outcomes. It remains to be seen whether the gradual loss of motion at a CTDR level would eventually lead to clinical deterioration, in particular, in an increase of mechanical neck pain. There is no available evidence to support this at this time.

Prevention of HO

There are currently no evidence-based methods to treat or prevent HO after CTDR. The current practice in our department is to prescribe patients a 1-week course of low-dose indomethacin, discourage the use of any neck collar or brace postoperatively, and encourage a regimen of physiotherapy and light exercise.

Most studies examining possible methods to prevent HO in arthroplasty were carried out in the setting of hip arthroplasty. Radiation therapy and nonsteroidal anti-inflammatory drugs (NSAIDs) have both been shown to be effective methods of preventing HO in patients undergoing hip arthroplasty (D'Lima et al. 2001).

Given the high morbidity of radiation when it is given to the soft tissues of the neck, it is not a reasonable therapeutic option for prevention of HO after CTDR. Indomethacin, which can be contraindicated if patients are known to have a history of renal disease or peptic ulcer disease, nevertheless has a much lower-risk profile. Tu et al. (2015) present a retrospective review of a cohort of 75 patients (107 levels) treated with CTDR. Patients were followed up for a mean of approximately 38 months. The authors examined the rate of HO between those who were given NSAIDs post-op and those who were not.

Although they found a lower rate of HO in the NSAIDs taking group (47.2% vs. 68.2% for those who did not take them), this was not statistically significant. They also found a lower rate of prostheses that had undergone arthrodesis in the NSAIDs taking group (13.2% vs. 22.7% in those who did not take them), but this was not significant either. Both groups had similar VAS scores for neck and arm pain at follow-up, as well as similar Neck Disability Index (NDI) scores. This data therefore does not seem to indicate any clinical benefit from NSAIDs after CTDR. As most of the data presented in this chapter, this data comes from a small retrospective cohort, and this limits its value.

One prevention strategy which is advocated by many authors is the copious irrigation of the wound during surgery. This is done to clear out bone fragments and shavings from the surgical site in order to limit the induction of bone formation that could be triggered by such remnants. Leung et al. (2005) and Tu et al. (2011) advocate for this strategy. Although it makes sense based on our current understanding of the pathophysiology of HO, it is not supported by any evidence to date. Further, as discussed by Lee et al. (2010), most surgeons already irrigate the wound extensively to reduce the rate of infection. This step may therefore not be a factor in the development of HO.

Other Complications Related to CTDR

Complications Related to the Anterior Approach

Although there are technical differences between CTDR and ACDF, the initial approach and neural decompression are essentially the same. As such, complications related to these steps are also similar. CTDR starts with an anterior neck dissection through the natural planes between the trachea and esophagus medially and the sternocleidomastoid and the carotid sheath laterally. This dissection is taken down to the anterior surface of the cervical vertebral column, at which point the proper disc level is identified and the discectomy and neural decompression can commence.

Many structures can be injured from the time of incision to the end of the neural decompression. We usually quote a rate of serious complications (such as neural injury, paralysis, vertebral artery injury) of less than 1% and a combined rate of 3–5% for all other possible complications.

Possible complications that are regularly discussed with patients preoperatively include infection, hematoma, hoarseness from recurrent laryngeal nerve injury, dysphagia from retraction on the esophagus, soft tissue injury in the neck (including esophagus and airway), cerebrospinal fluid leak, nerve injury, paralysis, and complications from anesthesia. More unusual complications can include Horner's syndrome from a too lateral dissection, superior laryngeal nerve injuries from high cervical dissection resulting in a risk of aspiration, and vertebral artery injury. C5 nerve root palsies are also possible from an anterior approach.

In a retrospective review of a cohort of 1015 patients who underwent ACDF at their institution, Fountas et al. (2007) reported the incidence of complications relating to the anterior approach to the cervical spine. They found the overall rate of morbidity to be of 19.3%. The main postoperative complications included dysphagia (9.5%, mostly transient), hematoma (5.6%), laryngeal nerve palsy (3.1%), dural tear (0.5%), esophageal perforation (0.3%), worsening myelopathy (0.2%), wound infection (0.1%), and mortality (0.1%). These are all complications that can also be associated with CTDR.

Complications Related to the Prosthesis

Although the rate of complications associated with the implanted prosthesis in CTDR seems to be very low, several issues have been reported. As each different type of prosthesis has a different design, the issues that have been reported vary from one type to another.

In their preliminary report on CTDR using the Bryan disc (Medtronic, USA) in a group of 60 patients, Goffin et al. (2002) reported that they identified possible device migration of more

than 2 mm but less than 3 mm in two patients. In their follow-up report, the same group reported a third case of device migration (Goffin et al. 2003). The authors attributed this phenomenon to inadequate initial milling of the vertebral body endplates when inserting the device. Indeed, one of the steps to implanting a Bryan disc involves inserting a milling/drilling device between both endplates and compressing them over this drill so that they can acquire the proper concavity to accept the prosthesis. Issues with this step of the surgery can therefore lead to improper placement and subsequent migration.

Some prostheses have a metal keel that must be implanted in the vertebral body, and this has been a source of complications as well. The ProDisc-C (Synthes, USA) is composed of two articulating surfaces which are each connected to a keel that must be inserted in the vertebral bodies above and below the disc space being treated. Shim et al. (2007) report a case of CTDR during which the vertebral bodies involved both fractured posteriorly when the authors were using a chisel to prepare them to receive the device's superior and inferior keels. They identified this intraoperatively and were able to remove any bone fragments that were compressing the thecal sac. Tu et al. (2012) present a similar situation in which the superior vertebral body was found to have a sagittal split fracture after the insertion of a ProDisc-C device. The patient was treated conservatively. See Fig. 1 for an example of a keel-based prosthesis.

We found two reports of outright device failure because the hardware's material fissured or cracked. Fan et al. (2012) present a case of Bryan disc failure, in which the prosthesis itself was found to have developed a fissure 8 years after implantation. Similarly, Nguyen et al. (2011) present a case of CTDR in which a prosthesis with a ceramic surface was found to have cracked leading to recurrent symptoms.

Interestingly, we also found one report in which a patient developed an inflammatory reaction to the implant, and this was assumed to be because of intolerance or allergy to the material used. Cavanaugh et al. (2009) report that a patient who underwent a one-level CTDR returned 6 months postoperatively with recurrence of symptoms. Imaging revealed a mass behind the implant which turned out to be inflammatory tissue at reoperation. The authors conclude that the patient was likely hypersensitive to one of the components of the implant.

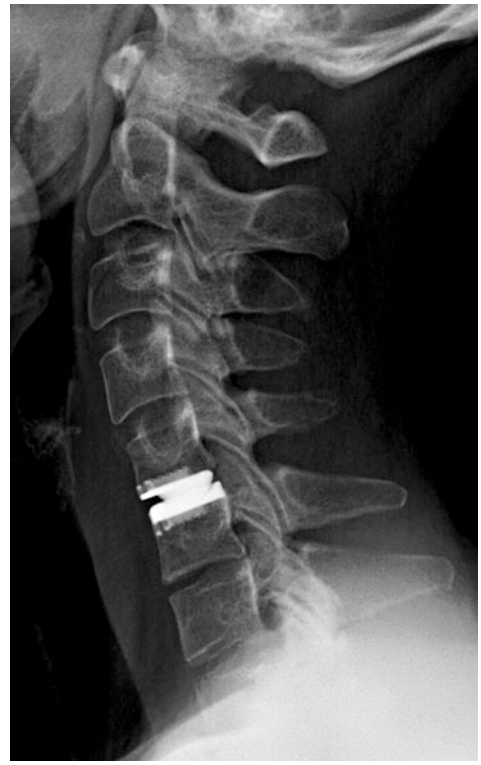

Fig 1 This lateral cervical radiograph demonstrates a keel-based prosthesis, the ProDisc-C (Synthes, USA). This patient did not suffer any complications during surgery and has not developed any HO

Adjacent Segment Disease

The main goal of CTDR is to preserve motion at the operated level. In theory, this preserved motion is also supposed to decrease the incidence of adjacent segment disease (ASD). This issue remains controversial, however, with differing reports of long-term outcomes when CTDR is compared to ACDF.

Robertson et al. (2005) compared the incidence of ASD at 24 months postoperatively in a group of patients who underwent CTDR to that of a group

of patients who underwent ACDF in a prospective clinical trial. This trial included 74 patients undergoing CTDR and 158 patients undergoing ACDF. The authors found that at 2 years of follow-up, the CTDR group showed a significantly lower rate of ASD compared to the ACDF group (17.5% vs. 34.6%, $p = 0.009$).

A different conclusion was however reached by the group of Nunley et al. (2012). They analyzed the data from three prospective randomized trials comparing CTDR to ACDF. Their pooled data resulted in a cohort of 113 patients who underwent ACDF and 57 patients who underwent CTDR. The authors found that at a median follow-up of 42 months, both groups showed a similar rate of ASD (14.3% vs. 16.8%, annual rate of 3.23% in the ACDF group and 3.77 in the CTDR group).

A more recent paper by Janssen et al. (2015) presents longer follow-up data of a randomized controlled trial of CTDR versus ACDF. They present data at 7 years of follow-up for 79 patients who underwent CTDR and 73 patients who underwent ACDF. The authors found that significantly more patients in the ACDF group had to undergo revision surgery for ASD than in the CTDR group (13 vs. 6 patients).

Although it remains controversial as to whether CTDR leads to lower rates of ASD than ACDF, ASD is a phenomenon that does occur with CTDR, and we believe it should be discussed with patients.

Conclusion

CTDR can be complicated by HO, as well as by issues related to the anterior approach to the cervical spine, by issues with the prosthesis used and by ASD. Nonetheless, the data presented in this chapter demonstrate that CTDR is an overall safe procedure and that HO has a limited effect on clinical outcomes. More research is needed to better delineate the exact pathophysiology of HO as well as its natural history. We believe that it is only once the phenomenon is better understood that effective strategies to prevent it will be found.

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Lumbar TDR Revision Strategies

46

Paul C. McAfee and Mark Gonz

Contents

Abstract

At the University of Maryland St Joseph Medical Center (UMSJMC), we have become a tertiary referral center for revision anterior retroperitoneal and transperitoneal approaches. To date we have performed over 500 repeat anterior approaches and over 100 revisions for failed lumbar arthroplasty referred from Elsewhere General.

With current lumbar TDR designs, the lumbar spine is approached anteriorly for numerous reasons. These include (1) minimal morbidity allowing for short recovery times; (2) unobstructed visualization of the disc space, allowing for total discectomy and accurate implant sizing; (3) the absence of the need to enter or retract posterior neural structures in the spinal canal; and (4) the familiarity of territory for many spine and vascular surgeons. Accordingly, the approach-related risks are both predictable and relatively low. In contrast, revision approaches to the anterior lumbar spine are about six times higher risk for major bleeding or thromboembolic complications due to

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adhesion formation, which prevent accurate identification of the great vessels. The anterior lumbar spine therefore remains a relatively facile approach as an index procedure but is fraught with potential complications in any revision situation. In our experience, many failures of lumbar disc replacement could have been avoided as they can be traced to surgeon-specific factors (as opposed to patient-specific factors) such as incomplete discectomy, improper device insertion, or inappropriate indications.

Our approach for revisions is to over-prepare – assume you will have suboptimal visualization between fascial planes. This means we place ureteral stents to palpate the ureters. In addition, in the event of inadvertent entering of the ureter, the stent facilitates suture repair by acting as a conduit in the early postoperative period. Occasionally for high-risk cases, we also prophylactically cannulate the femoral vessels. This allows faster intraoperative endovascular passage of balloons intraoperatively to assist hemostasis. In addition we can pass covered vascular stents up from the femoral vein and artery in an endovascular technique in the event of friable vessels with limited exposure in a deep retroperitoneal revision.

Keywords

Revision disc replacement · Spinal deformity · Spinal reconstruction

Key Points

1. Revision lumbar anterior retroperitoneal approaches are perhaps the most risky procedures in spinal surgery due to adhesions and difficult visualization of the very friable lumbar veins.
2. It behooves the spine surgeon to have a great working relationship with a vascular specialist and to over-prepare for repeat anterior retroperitoneal approaches.
3. Removal of the prosthesis requires being able to distract the disc space to gain working room between the vertebral endplates.

Introduction

One of the key considerations in approach for surgery in failed total disc replacement is to be able to differentiate between "pilot error" (suboptimal surgical technique) and inherent problems with the technology (metal-on-metal wear debris, osteolysis, poor ingrowth fixation, etc.). The best method for distinguishing inherent shortcomings of the technology is to present the immediate postoperative radiographs to a consensus group of experts – if the experts can predict the subsequent mode of failure, then one is dealing with a complication in surgical technique. However, if a consensus group of experts cannot predict the eventual mode of failure, then the complication is due to an inherent problem in the prosthetic design or biomaterials (Fig. 1).

Implant Failure: UHMWPE Core

Polyethylene core fractures, core dislocations, or implant breakage have been more common with UHMWPE implants. Instances of excessive polyethylene wear and osteolysis have been quite rare and have uniformly occurred in patients implanted before US FDA approval. David reported a case of polyethylene failure due to oxidation 9.5 years following implantation. Similarly, as reported in the largest series of TDR failures reported to date, there was one case of detectable polyethylene core wear noted 12 years postoperatively. Since 1997, an industry-wide enhancement to the sterilization process of polyethylene, whereby irradiation occurs in an inert gas such as nitrogen rather than air, has resulted in dramatically improved wear characteristics due to a reduction in the incidence of oxidation. This results in an increase in cross-linking or highly cross-linked UHMWPE – this improves wear characteristics but increases the brittleness of the core implant. This corrective preventative action of avoiding polymerization and reducing the UHMWPE wear rate was born out of the total hip implant experience on partially cross-linked UHMWPE. In contrast to the above cases, analysis of a retrieved polyethylene core from a

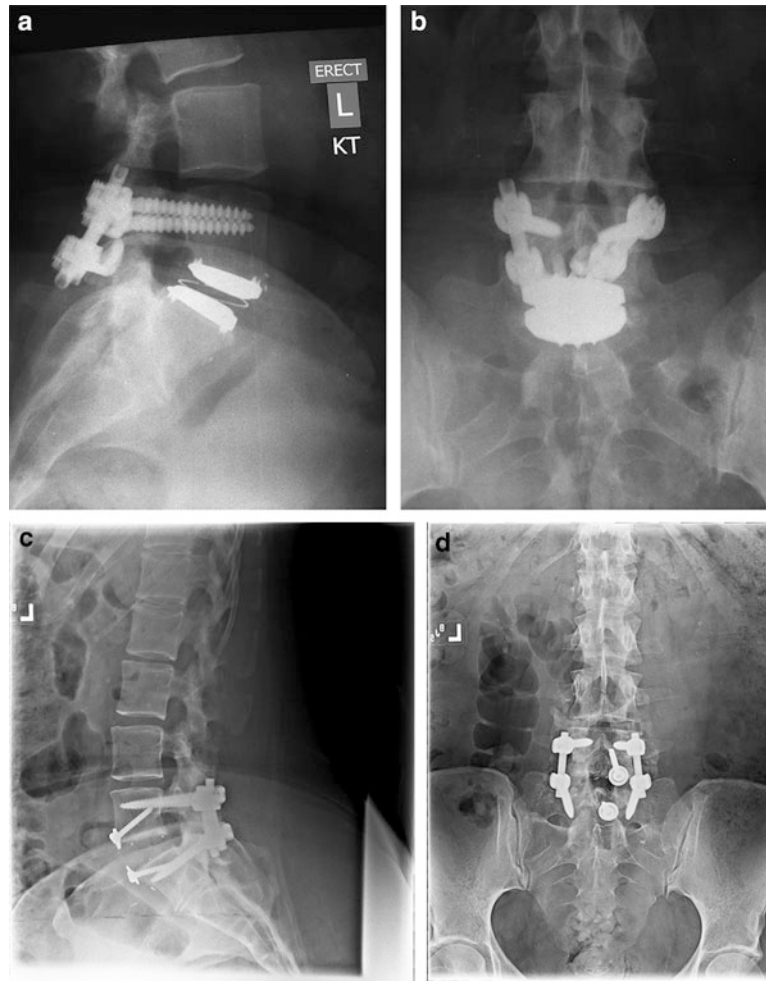

Fig. 1 These are the lateral (**a**) and the anteroposterior (**b**) radiographs of a 56-year-old woman who demonstrated a serum-confirmed nickel allergy shortly after implantation of this L5–S1 cobalt-chrome alloy arthroplasty. She also had undergone posterior fixation of an L5 spondylolysis with instrumentation from Elsewhere General. We performed anterior removal of the prosthesis and anterior lumbar interbody fusion at L5–S1 using allograft with buttress screws. The posterior instrumentation was revised into L5–S1 conventional pedicle instrumentation for increased stability. The lateral (**c**) and anteroposterior (**d**) radiographs demonstrate a stable 360 fusion and instrumentation. We advocate a combined front and back approach for most revisions following arthroplasty revision. The patients' metal allergy resolved

revision surgery performed for bone-implant loosening 1.6 years postoperatively in a patient implanted post-1997 demonstrated low levels of oxidation with mechanical properties that were not substantially degraded. At the time of this writing, there are only two published cases of anterior dislocation of the polyethylene inlay of a ProDisc artificial disc replacement. We have had over ten cases of posterior core dislocations presented from Elsewhere General. These are some of the most difficult revisions as the patients present with severe pain, pressure of the core on the cauda equina, and leg weakness. The key surgical step in the revision technique is to be able to insert a skeletal distraction device between the failed vertebral bodies to be able to distract the disc space. This is analogous to a Caspar distractor in the cervical spine. One has to distract the lumbar disc space to increase the working space in order to atraumatically remove the failed implant. Invariably we remove the core first and then reach vertebral endplate, in succession. With a keeled prosthesis, the loosening of the metal-bone ingrowth is achieved with a narrow osteotome.

Porous Ingrowth Failure and Loosening

Metal-bone interface complications account for the greatest number of failures of lumbar disc replacement, and the mode of failure depends on the type of device. Sagittal vertebral body

fractures can occur with keeled devices because the keel slot creates a stress riser in the bone. Two-level implantations in which keel slots are introduced into the superior and inferior aspects of the intercalated vertebra are at highest risk for this complication. To reduce this risk, the MAVERICK keel has been reduced from 11 mm to 7 mm[19]. In contrast, implants with smaller "anchors" at the bone-implant interface, such as the CHARITE, in which six 3 mm teeth engage the vertebral endplate, exhibit a greater tendency to migrate or dislodge if improperly placed. In the CHARITE US IDE study, there were 15 of 347 implantations that required removal, and none of these had been inserted in the "ideal" position[3]. Regardless of the design, TDR placement anterior to the center of rotation, especially in a hyperlordotic segment, will have a tendency to migrate or dislocate anteriorly due to excessive shear. Spondylolysis and spondylolisthesis present a biomechanically less stable environment for TDR and explain some of the early failures by migration and should be considered an absolute contraindication to lumbar TDR. Damage to the vertebral endplate during insertion, placement of a TDR in an osteoporotic spine, inaccurate positioning, and insertion of an implant that is too small are all factors that can contribute to TDR subsidence. In van Ooij and coworkers' report of 27 complications of the CHARITE device, there were 16 cases of subsidence. The cause, prevalence, or incidence of these failures could not be determined as the study was retrospective without mention of the total number of cases. Strict adherence to indications, surgeon education, and DEXA with preoperative correction of osteoporosis should theoretically reduce the incidence of this complication (Fig. 2).

Spinal instability has a greater tendency to occur in multilevel implantations. Preoperative scoliosis is a relative contraindication to TDR; however, subtle coronal and sagittal plane deformities may not be taken into account. TDR insertions in these scenarios will likely exacerbate rather than reduce any deformity because stabilizing structures such as the anterior and posterior longitudinal ligament as well as the majority of the annulus are removed during the implantation. Even in the well-aligned spine, incomplete discectomy and "off-axis" TDR placement at one level can create an "off-axis" situation at the next level (a so-called Z deformity). Thus when more than one vertebral level is to be implanted, device placement errors will tend to be compounded at sequential levels of insertion resulting in a "Z deformity." The principle concept is that cervical disc replacement adds inherent rotational stability to the cervical spine – unfortunately lumbar TDR adds to rotational instability to the lumbar spine. This is well documented by McAfee et al. in our laboratory (McAfee et al. 2006b) due to the posterior position of the lumbar facets, the relatively small cross-sectional area of the lumbar facets, and the relative importance of the anterior longitudinal ligament (ALL) in the lumbar spine body. For these three reasons, multiple levels of cervical TDR increase the cervical spine stability, whereas multilevel lumbar TDR decreases lumbar spine stability postoperatively.

Wear Debris and Cytokine Reaction: Prosthetic Inflammatory Response

Particulate debris generated from virtually any articulating biomaterial is characterized by macrophage recruitment and pro-inflammatory cytokine release. The culmination of this cascade is matrix metalloproteinase activation, which leads to bone resorption and osteolysis. Osteolysis is a well-documented complication of total joint replacement; however, most investigators agree that it will not be prevalent following TDR. One reason for the potentially reduced risk in the spine is the fact that the intervertebral disc lacks a surrounding synovial space, the key source for macrophages, and other inflammatory cells. The second reason is the relatively reduced range of motion and, hence, reduced volumetric wear in TDR compared with typical diarthrodial joint replacement. With over 20 years of global experience and over 10,000 TDR implantations worldwide, there are only anecdotal reports of osteolysis, and to our knowledge, only one has been documented histologically. Heterotopic

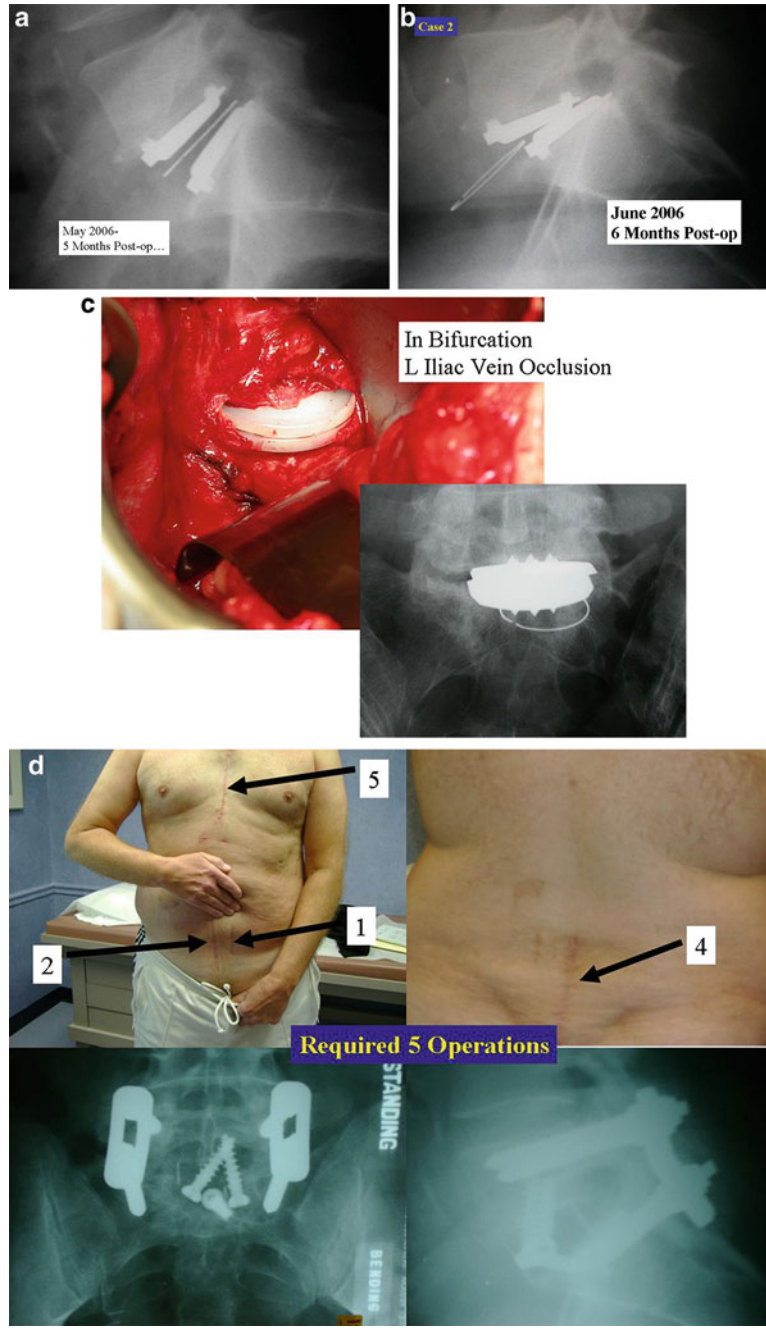

Fig. 2 (**a**) This 51-year-old executive underwent L5–S1 CHARITE disc replacement without incident. (**b**) Unfortunately 6 months following the surgery, he bent forward to pick up a heavy object, and he displaced the UHMWPE core of the prosthesis anteriorly. (**c**) A venogram was performed as part of the diagnostic workup of the anticipated revision surgical procedure. It demonstrated complete occlusion of the left iliac vein. This required insertion of an IVC umbrella at the start of the anterior revision procedure to avoid pulmonary embolism. (**d**) Following anterior and posterior arthrodesis and instrumentation at L5–S1, the patient also required CABG. In total the patient required five operative procedures. The illustration indicates no further migration of spinal instrumentation in this complicated patient requiring anticoagulation

ossification (HO) surrounding lumbar TDR implants has been classified previously by McAfee and colleagues in preparation for the CHARITE US IDE trial. In this trial, the incidence of HO was 4.3%; however, the presence of HO did not have any impact on flexion-extension range of motion or clinical outcome. We know of no other lumbar TDR trial in which the presence of HO has been systematically evaluated; however, isolated cases of periannular ossifications have been reported. To be fair, however, the imaging characteristics of the lumbar devices,

which are typically cobalt-chrome or stainless steel alloys, do not allow for identification of all but the larger amounts of periannular bone formation.

Nerve Root Compression from Implant Migration

Nerve root compression is occasionally found in cases of lumbar TDR when compared with fusion controls in prospective randomized evaluation. Most cases of revision surgery in the CHARITE US IDE trial involved reoperation with laminectomy and foraminotomy for new neurologic symptoms in the lower extremities. After any anterior discectomy and instrumentation, patients should be asked if they have any "new" pain in their legs that was not present preoperatively, and a thorough neurologic examination should be performed in the postanesthesia care unit. If there are any new neurological complaints or physical exam findings (i.e., motor or sensory loss), a CT scan with myelographic contrast should be performed to assess positioning of the implant and ensure that a hematoma, bone fragment, or disc material is not present in the spinal canal or neuroforamina. MRI is not particularly helpful postimplantation due to metal artifact obscuring the regions of greatest interest. By rapidly diagnosing the cause for new neurologic symptoms with appropriate imaging, early revision such as implant repositioning is possible. Neurologic injury without radiographic abnormalities is a complication that typically presents with left-sided leg pain in the L4 or L5 dermatome. First reported by Thalgott and *colleagues*, this complication has been thought by some to be due to excessive retraction of the lumbar plexus during the retroperitoneal exposure[26]. The lumbar plexus is at highest risk when exposing the L4–L5 disc space. To mobilize the left common iliac vein to the patient's right side, the iliolumbar vein(s) needs to be identified and ligated as it courses dorsally between the lumbar nerve roots located under the psoas muscle. Alternatively, such symptoms have been thought to be sympathetic mediated and result from the vascular exposure, as similar symptoms may be seen following non-spinal vascular dissections. In either case, whatever the etiology, the dysesthetic pain pattern typically resolves after 6–8 weeks; however, corticosteroid selective nerve root blocks may help minimize the symptoms. Notwithstanding, the burden of proof remains to demonstrate that the acquired symptoms are not due to new nerve root compression, which may be remedied with further surgery.

Biomechanical Instability

Excessive motion is a phenomenon that is not a prevalent mode of failure for TDR but likely underdiagnosed. It is defined as motion exceeding the natural motion arc in six degrees of freedom from the native motion in a specific patient's functional spinal unit. This motion results in subclinical instability that the body senses and in turn attempts to combat. This can present with postoperative muscle spasms and unexplained and chronic postoperative pain. It is a diagnosis of exclusion. The TDR is typically in excellent position without signs of dislodgement, dislocation, or subsidence. The hallmark is significant hypertrophy of the facet joints. Because the workup algorithm follows closely to ruling out spondylolysis, a CT scan can be very helpful in characterizing this hypertrophy. To determine surgical candidacy following exhaustive conservative management which typically includes long-acting narcotics, local facet blocks are the major objective tool to assess pain relief. Care must be taken to counsel the patient to give feedback following the injections to pay close attention to the duration of relief that may ensue corresponding to the half-life of Marcaine. If the patient notices a significant decrease in pain, a stabilizing procedure in the form of a posterolateral fusion with instrumentation can be discussed as an option of treatment. There is presently no way of predicting which patients will be affected by this phenomenon. Some surgeons have pointed to facet orientation as a predisposition. Especially at L5–S1, more sagittally oriented facets in conjunction with sacral inclination can predispose to increased

facet forces and this mode of failure. When diagnosed properly with facet blocks, patients have had resolution of pain and spasms and likewise weaned off of narcotics completely.

Vascular Revision Strategies

Revision total disc replacement is a potentially life-threatening procedure and should be reserved for indications that justify the increased risk.

Revision anterior exposure within 2 weeks of TDR incurs relatively little additional morbidity because adhesion formation is minimal. For this reason, surgeons should have a low threshold for revising implants that are clearly malpositioned or exhibit early migration within this 2-week time frame. If the prosthesis can be repositioned or revised to another TDR, without damage to host bone, it seems reasonable to do so. Beyond this period of time, a revision strategy must be individualized to the particular clinical situation. A posterior instrumented fusion with or without a decompressive laminectomy is currently the most effective salvage procedure. Preoperative planning is critical to a successful anterior revision. The authors analyze the cause for failure to establish individual goals for the revision. Corrections such as polyethylene replacement, size, or position changes are relatively easy to anticipate. Appropriate patient counseling regarding the increased risks, potential for changes, or need to abort the original plan for safety considerations is also critical. Reviewing the initial operative reports, clinic notes, and original indications can be particularly enlightening if a revision to a TDR is contemplated. If a patient failed to meet indications for a TDR at the index procedure, it is unlikely that they will meet indications at the revision. Patients with significant host bone loss, deformity, or instability should be revised to an interbody arthrodesis.

In our experience, major vascular injury, deep venous thrombosis, and potential ureteral injury are at particularly increased risk in the anterior revision scenario, and our operating room preparation strives to mitigate these risks (McAfee et al. 2003, 2006a, 2006b). Ureteral stenting is easily performed preoperatively and is valuable not only for intraoperative identification of the ureter but also for maintaining ureteral patency during the healing phase if an injury were to occur. Significant reduction in the somatosensory-evoked potentials of one leg may be the first indicator of excessive arterial retraction, and for this reason, we routinely utilize this form of somatosensory (SSEP) monitoring. Placing a pulse oximeter probe on the great toes is another form of monitoring that can assist in detecting excessive arterial retraction or occlusion. Often temporary relaxation of the retractors will result in normalization of the SSEP or pulse oximeter readings. We currently insert inferior vena cava (IVC) filters preoperatively as postoperative lower extremity duplex evaluations have missed a deep venous thrombosis (DVT) in the pelvic great vessels which progressed to a postoperative pulmonary embolism (PE) (Tortolani et al. 2006). Finally, we prepare the inguinal region into the operative field through which percutaneous vascular access wires are placed into the right and left femoral veins. If an injury to one of the venous great vessels occurs, balloon catheters can be inflated to tamponade and control bleeding in a timely fashion.

The specific revision surgical approach depends on the reason for failure and the original surgical approach; however, the currently available options include posterior decompression, posterior decompression and instrumented fusion, anterior TDR removal and fusion, or anterior TDR removal and reinsertion. Usually anterior TDR removal and conversion to fusion is the safest salvage strategy because gaining the exposure necessary to implant a new disc replacement is rarely possible due to adhesion formation. Our attitude is we perform anterior and posterior arthrodesis for L4–L5 revisions because we want this to be the absolute last time the great vessel dissection should ever be required. Anterior interbody fusion devices typically require less exposure and can be inserted obliquely across the disc space. This can be extremely handy when the only accessible area to the disc is to one side. Revision to a TDR is no longer a consideration in our experience in the lumbar spine.

Revision anterior exposures should always be performed with an experienced vascular access surgeon, and gaining access via a virgin territory is desired but rarely possible. At L5–S1, if a left-sided retroperitoneal approach was utilized at the index procedure, then transperitoneal or right-sided retroperitoneal approach can be considered. Conversely, if a transperitoneal approach was used at the index procedure, then a right- or left-sided retroperitoneal exposure can be considered. L4–L5 and higher is always more challenging because the left-sided retroperitoneal approach is virtually always utilized during the initial exposure. Transperitoneal and right-sided approaches are technically far more demanding at L4–L5 because of the central to right-sided position of the IVC. For this reason, anterior revisions to L4–L5 should be performed via a transperitoneal or through the same left-sided retroperitoneal approach. By identifying the left psoas muscle, one can generally palpate the lateral border of the lumbar spine, and, from this point, a subperiosteal dissection can facilitate safe exposure toward the midline and beyond. In the end, the experience and comfort level of the access surgeon will be as, if not more, important than the type of approach used during the index procedure.

Given the aforementioned technical challenges, the most common salvage procedure for failed TDR is posterior instrumented fusion with pedicle screws. This technique essentially locks the prosthesis from any further movement and allows for bone grafting in the posterolateral intertransverse region. Cunningham et al. found that pedicle screws alone combined with a lumbar disc replacement were not found to be statistically different biomechanically from pedicle screws and a femoral ring allograft. Posterior hemilaminectomy or laminotomy without fusion is an alternative for focal disc or bone displacements into the spinal canal; however, extreme care must be taken to avoid destruction of stabilizing structures like the facet joints.

Conclusions

Lumbar TDR is a safe and effective treatment option for appropriately selected patients with lumbar degenerative disc disease. Bone-implant failures can be prevented by strict adherence to FDA indications and accurate placement of the device. For at least one device, suboptimal positioning has been correlated with worse patient outcome, a finding which will likely be borne out for other TDR designs. Device failures for current designs are rare and are characterized by polyethylene fracture or dislocation. Anterior revision surgery with an experienced access surgeon and preoperative placement of ureteral stents, vena cava filters, percutaneous vascular access wires, and spinal cord monitoring can reduce the risks of major vessel injury or thrombosis.

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Posterior Lumbar Facet Replacement and Interspinous Spacers

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Taylor Beatty, Michael Venezia, and Scott Webb

Contents

Abstract

Motion preservation technology in the lumbar spine is not confined to lumbar disc arthroplasty. Pathology involving the posterior elements of the lumbar spine is often the source of pain generation and stenotic symptoms. Posterior-based motion preservation systems fall under two categories: facet arthroplasty and posterior dynamic stabilization (PDS). Several devices have gone through clinical trials since initial introduction in the early 1990s for PDS systems and mid-2000s for facet arthroplasty systems presenting viable alternatives to lumbar fusion. Understanding the anatomy and the biomechanical forces acted on the lumbar region has led to the creation of these devices with goals of symptomatic relief, motion preservation, and prevention of adjacent segment disease.

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Introduction

There has been significant advancement in spinal implants and the treatment of spinal pathology over the last few decades, including a resurgence of motion preservation and joint arthroplasty. While we still have much to learn concerning the pain generators and correlating pathology of the lumbar spine, procedures such as total facet arthroplasty and posterior dynamic stabilization allow for additional tools in a surgeon's armamentarium.

Historically, the standard of care for degenerative pathology with instability of the lumbar spine has been fusion with or without instrumentation. Dynamic stabilization has emerged as a viable alternative to the standard of care. To begin addressing some of the concerns with fusion, posterior dynamic stabilization was introduced beginning with the development of the Graf ligament in 1989 and subsequently the Dynesys (Zimmer Spine, Minneapolis, MN) in 1994. The facet joints have also been targeted as another potential pain generator of the lumbar spine. Total facet arthroplasty has arisen as a treatment option for spinal stenosis as well as degenerative spondylolisthesis, allowing for an alternative to spinal fusion and the ability to address the facet joints as possible lumbar pain generators.

Throughout this chapter, we will review the biomechanical basis as well as clinical literature supporting the role of posterior-based dynamic stabilization (PDS).

Facet Anatomy and Biomechanics

The facet joint is critical to the proper motion of the functional spine unit which consists of the disc, the facet joints, and the ligaments. The motion at each segment is determined by the health of each of these components. Each vertebral segment interacts with the adjacent vertebral segment by means of five articulating joints; the disc and the four facet joints at each level. These components share the loads as they are transmitted through the spine. The facet joint acts like a cam with a multi-radius arc of motion that is engaged as the spine moves. This assists with proper spinal motion, protection of neurologic structures, and transferring of load through the spinal column (White and Panjabi 1978). These diarthrodial, synovial joints bear weight in both compression and shear providing functional range of motion (ROM) while limiting excessive ROM. They help to protect the lumbar disc from excessive stress. Due to this mutualistic nature of disc and associated facets, the degenerative changes in the disc lead to increased loads and progression of degeneration in the facets (Webb and Holen 2008) (Fig. 1). The loads are transferred through each component, and as the spine ages, their interaction with each other changes. The loads transferred are going to vary depending on the health of the segment.

Lumbar facets require high load transmission and therefore are significantly larger than cervical facets. ROM is limited in the lumbar segment with the focus in flexion and extension. The ability of the facets to share the load with the intervertebral disc is position dependent with a load sharing of 0% in full flexion to 33% in full extension (Panjabi et al. 1989). The facets are located more centrally with an adducted positioning to prevent hyperextension and rotational torsion (Webb and Holen 2008). The amount of sagittal angulation increases as you move caudally in the lumbar spine. In childhood, the facets are angled more posteriorly with a transition to a more sagittal position with age; this can be a factor in many of the facet-related issues (Scoles et al. 1988). The lumbar facets main function is to prevent anterior shear which has been proven to damage the intervertebral disc (Reily 2011). Resistance increases toward the endpoint of motion. This gradual increased resistance protects the joint and the adjacent structures by

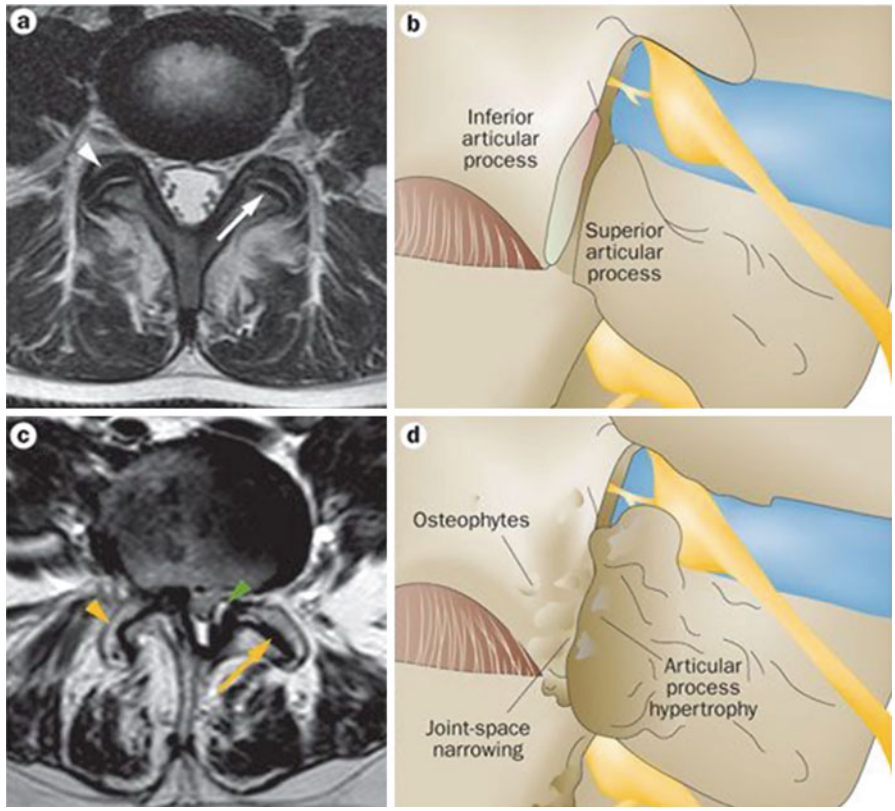

Fig. 1 Normal facet joints and advanced facet joint osteoarthritis. (**a**) T2-weighted axial MRI image of normal facet joints with no joint-space narrowing (white arrow), and no osteophytes or articular process hypertrophy (white arrowheads). (**b**) Normal facet joints. (**c**) T2-weighted axial MRI image of osteoarthritic facet joints with joint-space narrowing (yellow arrow), osteophytes and articular process hypertrophy (yellow arrowhead). Facet joint osteoarthritis, disc-bulging, and a facet joint synovial cyst (green arrowhead) in combination lead to stenosis of the central canal and lateral recesses. (**d**) Osteoarthritic "facet joints." (Gellhorn et al. 2013)

providing a soft stop. When anterior shear load is applied suddenly, the facets carry 1/3 of the load, while the disc carries 2/3 of the load; when the load is applied over time, the majority of the load is carried by the facets (White and Panjabi 1978). Nachemson (1960) used pressure transducers and determined that the facets carry approximately 15% of vertical load in the lumbar spine. Yang and King (1984) established the mechanism of facet transmission of axial load in cadaveric specimens by the use of an intervertebral load cell with results demonstrating a normal facet carrying 3–25% of the load, while an arthritic joint could carry as much as 47%.

The facets are surrounded by capsules that are innervated by type I, II, and III mechanoreceptors. This neural input allows for positional feedback for postural control. Destruction of this innervation may also be a key role in the disease process (Webb and Holen 2008). Cavanaugh et al. (1996) concluded that these nerves are activated by capsular stretch and by neurogenic and non-neurogenic modulators of inflammation, including substance P, bradykinin, and phospholipase A2. Facet joint surfaces are covered with hyaline cartilage that undergoes degenerative changes to its mechanical properties similar to the processes that occur in other joints. The loss of articular cartilage leads to spur formation thought to stabilize the joint. The degenerative process also leads to loss of control of anterior shear forces, facet subluxation, and increased

anterior-posterior translation (Reily 2011). This begins early in the degenerative process with the loss of 1 mm of cartilage in the facet joint being shown to significantly increase the translational motion (Reily 2011). Degeneration and inflammation lead to pain with joint motion that causes restriction and thus deconditioning.

It is important to understand how each component of the functional spinal unit performs and how each component interacts and the impact when they begin to fail. The functional spinal unit has a neutral zone where the axial force transmitted by the spine is stiffer at the extreme range of motion and less stiff near the neutral position. In other words, it requires more force to move the functional spinal unit from the neutral zone to the endpoints of motion. When one looks at the facet joint, it is apparent that degenerative changes as well as surgical intervention such as in a fusion or disc arthroplasty changes the way the facet joints at the index level and adjacent levels behave. Facet joints can be overloaded if the surgical intervention substantially changes the way the disc behaves as in a disc replacement. With a fairly non-constrained lumbar disc arthroplasty, one might expect increased facet stresses. In a fusion, the adjacent segment will experience increased loads across the facet joint. It is important to consider the impact of any surgical procedure on the overall motion of each lumbar segment and the long-term potential impact.

Rationale and Biomechanics of Facet Arthroplasty Systems

The potential benefit of posterior motion preservation devices is load sharing with the anterior and other posterior structures. Additionally, by removing pathologic structures, the symptoms associated with the facet joints including local pain symptoms can be reduced while decompressing the neural structures. The goal of posterior motion preservation devices should be to preserve motion and, by load sharing with adjacent segments, slow the degeneration of these adjacent segments compared to fusion.

Artificial facet joints should provide stability similar to the native facet joint. Ideally the design will include measures to cause the artificial facet joint to behave similar to the native joint to include resistance to flexion and extension forces. Wear of the articular surfaces should also be minimal. Robust fixation to the spine is also critical. In the case of facet replacement, there have been different types of fixation. The Total Facet Arthroplasty System (Archus Orthopedics, Redmond, WA) was a cemented implant in an attempt to enhance the fixation to the vertebral body in a potentially osteoporotic patient. Subsequent implants ACADIA (Globus Medical, Audubon, PA), and TOPS (Premia Spine, Philadelphia, PA) are screw-based implants with coatings or texturing of the screws.

Kinematically all the facet joint replacement devices have done testing that indicates that if a functional spinal unit is destabilized with the removal of the facet joints the kinematics of that segment is restored with the utilization of a facet arthroplasty implant (Fig. 2). When the facet arthroplasty implants were tested in vivo and compared to fusion constructs with loads applied, the facet arthroplasty group experienced much lower implant stresses than the fusion implant (Webb and Holen 2008).

Kinematics

- The TFAS™ effectively
  - stabilizes motion in flexion and lateral bending
  - restores the motion in extension
  - limits the motion in axial rotation
- TFAS™ restored motion of an unstable FSU to that of an intact FSU allowing considerable range of motion in all directions when compared to the intact condition

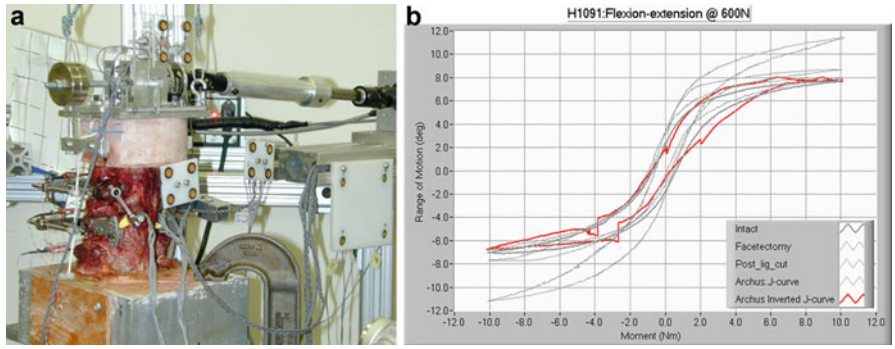

Fig. 2 Kinematic testing (**a**) demonstrated that TFAS effectively stabilized motion in flexion and restores motion in extension of an unstable functional spine unit to that of an intact unit (**b**)

History of Facet Arthroplasty Systems

The goal of posterior lumbar facet replacement systems is to use an alternative to fusion for facet degeneration and stenosis that allows for full decompression and stability while maintaining near physiologic motion (Zhu et al. 2007). The earliest facet replacements can be traced back to the 1980s, with the majority of these implants focused on articular surface replacement similar to the implants for peripheral joints (Serhan et al. 2011).

The TFAS was the initial facet replacement system to enter US investigational device exemption (IDE) in the mid-2000s. Other facet replacements soon followed including the Acadia by Facet Solutions and TOPS by Implant. They were all uniquely designed with different features to address the replacement of a facet joint in a wide decompression necessary to treat significant lumbar stenosis.

Total Facet Arthroplasty System (TFAS)

The first patient in the US IDE clinical trial of the Total Facet Arthroplasty System (TFAS) was performed on August 26, 2005 by Dr. Scott Webb (Figs. 3 and 4). This was the first time a total facet replacement had ever been performed in the United States. The TFAS implant was indicated in patients with lumbar spinal stenosis presenting predominantly with neurogenic claudicatory symptoms that required a wide decompression and stabilization.

The Total Facet Arthroplasty System (TFAS) is metal-on-metal joint prosthesis intended to provide stabilization of lumbar spinal segments in skeletal mature patients as an adjunct to a laminectomy/laminotomy/neural decompression and facetectomy in the treatment of single-level stenosis. Additional indications include degenerative facets at the index level with or without instability. Up to a Grade 1 degenerative spondylolisthesis could be present.

Due to the typical age group of patients with spinal stenosis and neurogenic claudication, the implant was designed to be implanted with cement fixation.

The implant's modularity allowed for a great deal of potential variability (Fig. 5).

Initial midterm clinical data of the US IDE trial demonstrated successful restoration of motion and clinically significant reduction of preoperative symptoms. ZCQ symptom and ZCQ function scores improved by 84% and 81% compared to preoperative scores in the 79 TFAS IDE patients. VAS back and leg pain scores improved in 73 of 79 and 75 of 79, respectively. Radiographic analysis showed all devices to be intact and functioning at time of follow-up (Sachs et al. 2008).Unfortunately,

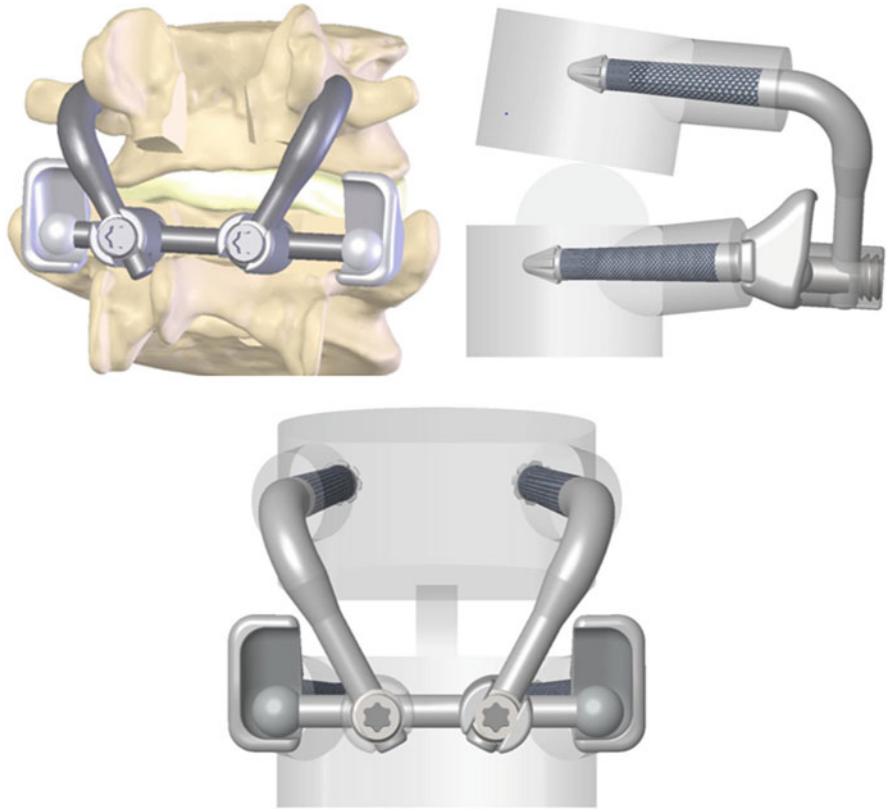

Fig. 3 Total Facet Arthroplasty System (Archus Orthopedics, Redmond, WA) (attempted to obtain permission from Archus Orthopedics but company no longer exists)

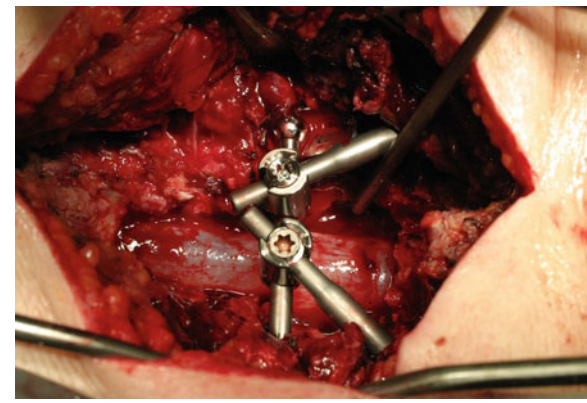

Fig. 4 Intraoperative imaging of TFAS (Scott Webb)

volume wear of metal debris in the TFAS implant was found to be comparable to metal-on-metal hip (M-o-M) implants in regard to particle size and distribution. The fear of similar outcomes despite significantly different biomechanics led to the removal of the product from the market. TFAS pioneered facet arthroplasty and demonstrated safety and efficacy in a small number of patients with limited follow-up.

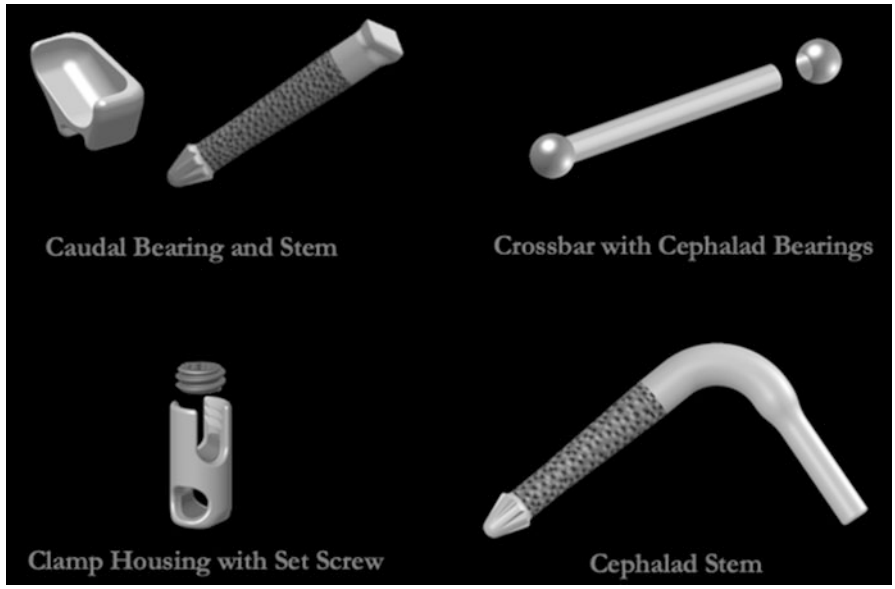

Fig. 5 TFAS components allowed for significant variability creating a custom fit for patient's anatomy

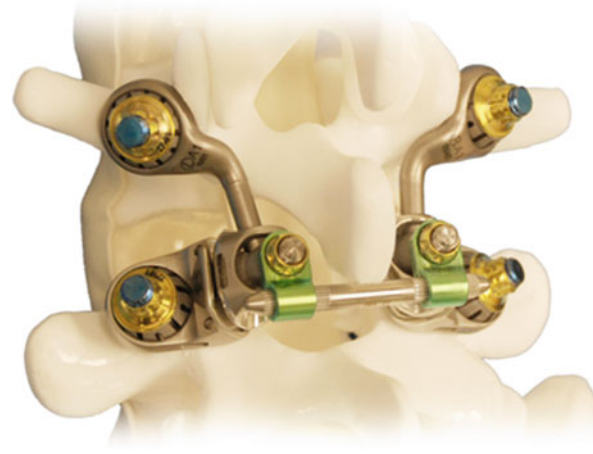

Fig. 6 ACADIA Facet Replacement System (AFRS) (Globus Medical, Audubon, PA)

ACADIA Facet Replacement System (AFRS)

The ACADIA Facet Replacement System (AFRS) (Globus Medical, Audubon, PA) formerly Anatomic Facet Replacement System (Facet Solutions, Logan, UT) evolved under the basic principles of other articulating synovial joint implant systems with a focus on restoring normal ROM with a uniform distribution of forces (Carl et al. 2008) (Fig. 6). International clinical evaluations began in São Paulo, Brazil, in 2005 with approval in the United States for FDA IDE study coming in 2006. AFRS was also intended to provide stabilization of spinal segments in skeletally mature patients as an adjunct to laminectomy, laminotomy, and facetectomy in the treatment of single level, L3–4 or L4–5, degenerative disease of the facets with or without instability including Grade I degenerative

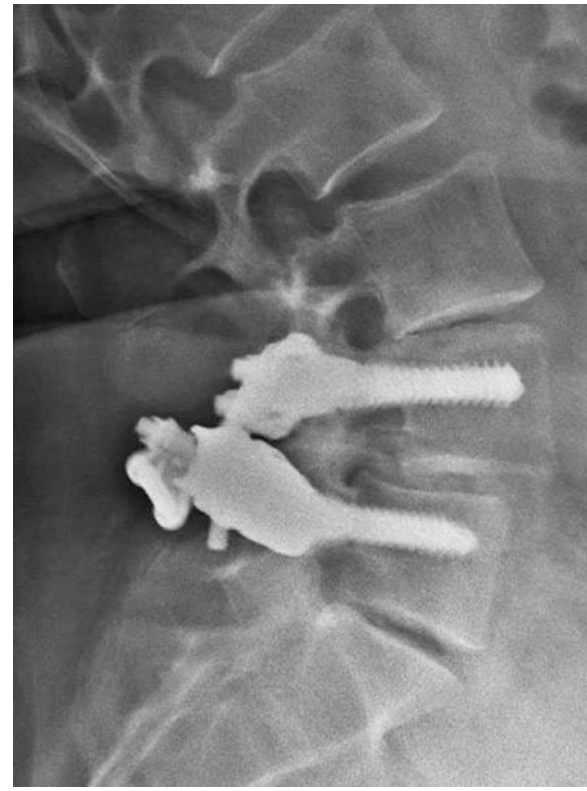

Fig. 7 Postoperative extension radiograph of ACADIA in a patient with a Grade 1 spondylolisthesis (Scott Webb)

spondylolisthesis with objective evidence of neurologic impairment, central or lateral spinal stenosis (Carl et al. 2008).

The device, like the TFAS system, is a pedicle-screw-based construct with superior and inferior facet implants with articulating surfaces made of cobalt-chromium-molybdenum. Unlike the spherical bearing TFAS system, AFRS creates metal-on-metal articulation that resembles the anatomic structure of the facet joint. A crossbar links the left and right inferior facet implants providing construct stability (Carl et al. 2008). Pedicle screws are made of titanium alloy with hydroxyapatite coatings that allow for improved bone-implant interface (Fig. 7). The polyaxial junction of the implant accommodates for $\pm 15^{\circ}$ of variability in pedicle screw placement (Goel et al. 2007).

Preliminary outcomes of the US IDE study involving 162 ACADIA patients demonstrate improvement in ZCQ, ODI, and VAS scores at 2 and 4 years post-op similar to posterior lateral fusion patients. Surgical intervention at subsequent levels occurred in 8% of ACADIA patients and 7.4% of PLF patients (Myer et al. 2014). Ultimately, the IDE trial was terminated in 2017, also due M-o-M wear debris concerns.

Total Posterior Arthroplasty System (TOPS)

The Total Posterior Arthroplasty System (TOPS) (Premia Spine, Philadelphia, PA) is a dynamic facet arthroplasty prosthesis designed to restore segmental stability following extensive posterior decompression, including facet joint resection, while maintaining near anatomic motion (Anekstein et al. 2009) (Fig. 8). The device replaces the degenerated facets and bony elements removed during decompression of the stenotic level without sacrificing motion. The TOPS device differs from previous facet replacement systems as it does not resemble an anatomic

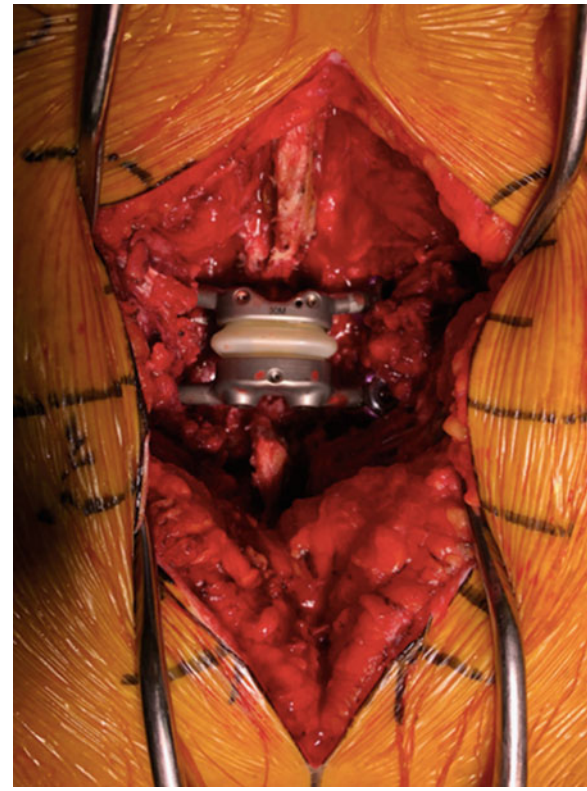

Fig. 8 Intraoperative imaging of Total Posterior Arthroplasty System (TOPS) (Premia Spine, Philadelphia, PA) (Scott Webb)

facet joint. The primary indication is symptomatic lumbar stenosis secondary to Grade 1 degenerative spondylolisthesis.

TOPS uses a cannulated pedicle-screw-based implant with superior and inferior titanium constructs fixed to a flexible, polycarbonate urethane (PCU) articulating core. The double horizontal crossbar connects pedicle screws of the same vertebrae creating better load sharing and eliminates screw head torque (Myers et al. 2008). The internal configuration of the bumper limits motion by dissipating energy during load sharing (McAfee et al. 2007). The central core is attached to all four pedicles stabilizing rotation and lateral bending as well as significantly decreasing the load transfer to adjacent segments (McAfee et al. 2007) The PCU bumper acts as a limiter of motion but also absorbs shock in the vertical axis; it incorporates a PEEK ribbon that acts as a restraint for excessive flexion. The boot creates a closed compartment that prevents wear debris from entering the spinal canal which was a major fear of product designers after the issues surrounding M-o-M hip prosthetics (Anekstein et al. 2009) (Fig. 9).

Initial investigational studies with the TOPS device began internationally in 2005, with the first US IDE study under FDA investigation beginning shortly afterward in 2006. Initial results of the study were very promising. McAfee et al. (2007) reported on 29 patients in the initial international study who had met criteria for single-level decompression and fusion of the lumbar spine underwent facet replacement. Outcomes were based on VAS, ODI, and ZCQ scores at 6 weeks, 3 months, 6 months, and 1 year. Preliminary data demonstrated improvement in all three scores and no device-related events or hardware failure. CT scans at 3 months and 1 year demonstrated no signs of subsequent disc height loss at treatment level or adjacent levels. The TOPS device has undergone some minor changes in the structure of the system and is currently undergoing a second IDE study which began in January 2017 (ClinicalTrials.gov 2017).

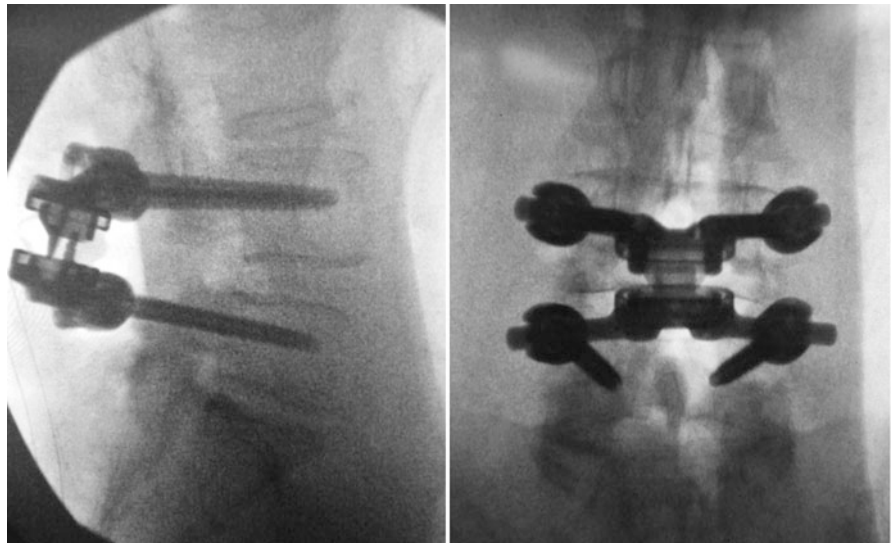

Fig. 9 Intraoperative fluoroscopic imaging (lateral and PA) of second generation of TOPS device (Scott Webb)

The TOPS device is the only posterior facet replacement device still in active US IDE study.

Interspinous Devices (ISD)

Interspinous devices have been primarily used to treat lumbar central stenosis with concomitant neurogenic claudication. These devices result in indirect decompression of the canal and neuroforamen. These devices are typically used in conjunction with decompressive surgery. Earliest documentation off interspinous devices was in the 1950's at which time metal "plugs" were placed between the spinous processes. Senegas et al. described one of the early interspinous spacers in 1988. This was a titanium device that was held to the spinous processes with Dacron tape. This was later redesigned as the Wallis Implant (Abbott Spine, Austin, TX) which used a PEEK material instead of the previous titanium. One of the more popular devices, the X-Stop (Medtronic, Minneapolis, MN) device received FDA premarket approval in 2005, initial studies were very promising, but as later data came out there appeared to be high rates of complications. Medtronic discontinued this device in 2015. The DIAM system (Device for Intervertebral Assisted Motion) (Medtronic Sofamor Danek, Memphis, TN) is another abandoned interspinous device. It is an "H-"shaped device secured by a cord to the spinous processes. The latest device to gain traction in the US market is the Coflex device (Paradigm Spine, New York, New York) (Fig. 10). The FDA has approved Coflex for 1–2 level stenosis in the lumbar spine, with some clinical data promising compared to traditional fusion. Superion (Vertiflex, Carlsbad, CA) is an interspinous device that is delivered percutaneously, similar to devices such as the X-Stop (Fig. 11). In 2015, a randomized controlled trial comparing the Superion to the X-Stop demonstrated a statistically significant benefit to the Superion over the X-Stop at 36 months.

Interspinous devices were primarily developed to treat lumbar spinal stenosis resulting in neurogenic claudication. Patients with these symptoms tend to improve with flexion; therefore these devices place the spinal segment into slight flexion or kyphosis (Richards et al. 2005). There is not compelling data to support ISD over traditional open laminectomy decompression, but it does offer an alternative to an open surgical procedure (Senegas et al. 1988). This may be an attractive alternative for elderly patients with medical comorbidities and higher surgical risk.

Fig. 10 Coflex device (Paradigm Spine, New York, New York)

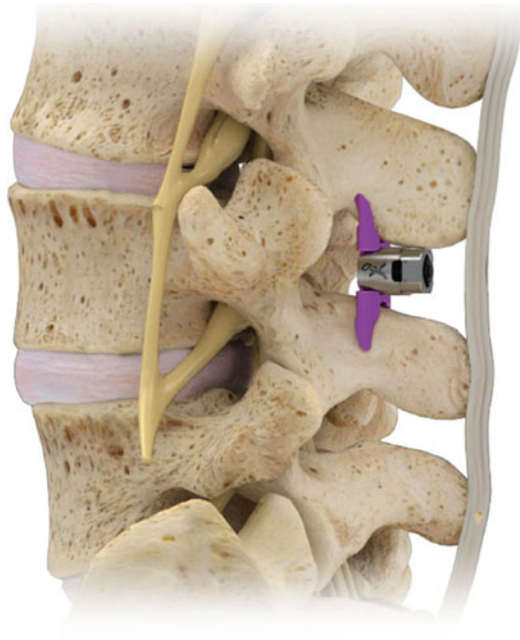

Fig. 11 Superion Image provided courtesy of Boston Scientific. ©2020 Boston Scientific Corporation or its affiliates. All rights reserved

Conclusions

The role for motion preservation by means of facet arthroplasty and dynamic stabilization in lumbar spine surgery continues to evolve. Posterior facet remains in active FDA IDE study with promising early results for the treatment of spinal stenosis secondary to degenerative spondylolisthesis. Pedicle-screw-based posterior dynamic stabilization systems have largely fell out of favor. Interspinous spacers have developed a niche in the minimally invasive treatment of spinal stenosis. Overall, the use of posterior arthroplasty for the treatment of lumbar spine pathology remains in its relative infancy, and further study is warranted in defining its role in the future.

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Cervical Arthroplasty: Long-Term Outcomes

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Contents

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Abstract

Cervical disc arthroplasty (CDA) attempts to preserve normal motion at adjacent segments and in doing so may decrease the incidence of adjacent segment degeneration in comparison with cervical arthrodesis. Since 2006, the United States Food and Drug Administration (FDA) has approved seven CDA prosthetic devices for surgical management of symptomatic cervical spondylosis and disc herniation (seven for 1-level disease and two for two-level disease). Motion-preserving CDA has showed great promise with equivalent quality-of-life outcomes in many long-term comparative studies. Currently, follow-up duration of up to 10 years is available from some of the FDA trials comparing CDA to arthrodesis. In general, study findings have consistently demonstrated that both techniques result in significant clinical improvement by roughly 3 months post-op and that improvement may be maintained at final follow-up. Overall, there exists robust data to support CDA as a viable alternative to arthrodesis in select patients. However, complications such as heterotopic ossification have been reported. In this chapter, we review CDA, with an emphasis on highlighting the published long-term outcomes and complications for this motion-preserving operation in comparison with arthrodesis.

Keywords

Degenerative disc disease · Cervical spondylosis · Disc herniation · Anterior cervical discectomy and fusion · Cervical disc arthroplasty · Heterotopic ossification · Artificial cervical disc · Motion preservation · Adjacent segment degeneration or disease · Bryan cervical disc · Prestige cervical disc · Prestige ST · Prestige LP · Porous Coated Motion · ProDisc-C · Mobi-C · Kineflex-C · Secure-C · Discover artificial cervical disc

Introduction

Degenerative disc disease involving the cervical spine is part of the normal aging process (Traynelis 2004). When degenerative changes occur gradually, they may be asymptomatic; however, in a subset of patients, cervical spondylosis or disc herniation may result in compression of nerve roots or the spinal cord, resulting in radiculopathy, myelopathy, or both (Traynelis 2004). A common surgical treatment for patients with symptomatic cervical spondylosis or disc herniation is anterior cervical discectomy and fusion (ACDF) (Alvin et al. 2014). The ACDF procedure, first described over 50 years ago, has been shown to be safe and clinically efficacious (Alvin et al. 2014; Cloward 1959; Smith and Robinson 1958). However, there is debate about further degeneration at adjacent segments after fusion surgery (Gao et al. 2013; McAfee et al. 2012; Xing et al. 2013; Yin et al. 2013). Specifically, it is currently unclear if adjacent segment degeneration is part of the natural history of cervical spondylosis or whether it is related to the adjacent fused levels. Some studies have shown an average 3% reoperation rate, while other studies report revision rates exceeding 10% after 2 years to treat complications related to the index fusion operation (Hilibrand et al. 1999; Yin et al. 2013). By preserving physiologic cervical motion, one of the goals of CDA is to reduce the incidence of adjacent segment degeneration while maintaining the highly effective results of ACDF in maintenance or improvement of neck pain, arm pain, and myelopathy (Alvin et al. 2014).

The initial clinical experience with CDA began in the 1960s with Ulf Fernstrom, a Swedish surgeon, implanting stainless steel ball bearing prosthetic devices following laminectomy (Fernstrom 1966; Fisahn et al. 2017). A high failure rate and concern for hypermobility and device migration into adjacent vertebral cancellous bone ultimately led the industry back to favoring ACDF (Bertagnoli et al. 2005; Fernstrom 1966; Fisahn et al. 2017). Then later in the 1980s, CDA returned with a design by Cummins, who was developing an artificial disc to address the shortcomings of ACDF regarding motion preservation and adjacent segment degeneration. Cummins' artificial cervical disc was developed in collaboration with the Department of Medical Engineering at Frenchay Hospital in 1989, and resulted in improved clinical outcomes after implantation in appropriately selected patients (Cummins et al. 1998; Traynelis 2004; Wigfield et al. 2002b). After performing the index decompression or discectomy, the main advantage of CDA in comparison to ACDF is the possibility for postsurgical segmental motion preservation, which may prevent the occurrence of adjacent segment degeneration and disease (Alvin et al. 2014).

Since 2006, the United States Food and Drug Administration (FDA) has approved seven CDA prosthetic devices for surgical management of symptomatic cervical spondylosis and disc herniation at a single level (Coric et al. 2018; Gornet et al. 2016). In 2007, the Prestige ST (Medtronic Inc.), a metal-on-metal device made from stainless steel, was the first CDA device to receive FDA approval (Mummaneni et al. 2007). A later version with a low profile modification, the Prestige LP (Medtronic Inc.), was made from a titanium ceramic composite and received FDA approval in 2014 (Gornet et al. 2015). The other five FDA-approved devices are metal (cobalt-chrome or titanium alloy)-on-polymer (polyethylene or polyurethane) designs and include (by order of FDA approval for single-level CDA) ProDisc-C (2008; Synthes Spine), Bryan (2009; Medtronic Inc.), Porous Coated Motion (2012; Cervitech), Secure-C (2012; Globus Medical), and Mobi-C (2013; LDR Medical) (Heller et al. 2009; Hisey et al. 2014; Murrey et al. 2009; Phillips et al. 2013; Vaccaro et al. 2013). Two of these devices, the Prestige LP and Mobi-C, have since received FDA approval for CDA at two adjacent levels.

More recently, long-term studies have been published for these FDA-approved artificial discs and suggest CDA is safe and clinically efficacious in appropriately selected patients. Currently, follow-up duration of up to 10 years is available from some of the FDA trials comparing CDA to ACDF. In general, study findings have consistently demonstrated that both CDA and ACDF result in significant clinical improvement by roughly 3 months post-op and that improvement may be maintained at final follow-up (Davis et al. 2015; Heller et al. 2009; Hisey et al. 2016; Phillips et al. 2013; Radcliff et al. 2016a; Vaccaro et al. 2013; Zigler et al. 2013). CDA was found to produce noninferior results in all the studies for certain outcome variables and even demonstrated statistical superiority for some outcome measures. For single-level CDA, four of the seven discs (Prestige ST, Prestige LP, Bryan, and Secure-C) demonstrated superiority in overall success. Prestige ST showed superiority in three of four outcome variables (neurological success, revision surgery, and overall success), while the other discs showed superiority in ≤ 2 variables (Prestige LP, neurological and overall success; Bryan, Neck Disability Index [NDI] and overall success; Secure-C, revision surgery and overall success; and Pro-Disc C, revision surgery). The Porous Coated Motion (PCM) and Mobi-C discs demonstrated noninferiority for all outcome variables. For two-level (adjacent) CDA, Prestige LP and Mobi-C demonstrated superiority in three outcome variables (NDI, secondary surgery, and overall success), but not neurological success (Turel et al. 2017).

Although the aforementioned devices have met rigorous outcome requirements for FDA approval, there have been reports of complications such as heterotopic ossification (HO; abnormal bone formation around or within the intervertebral disc space) and/or implant migration (Gao et al. 2013; McAfee et al. 2012; Xing et al. 2013; Yin et al. 2013). Therefore, in this review, in addition to summarizing long-term

outcomes, we also report complications associated with CDA for the FDA-approved discs. Although not FDA-approved, we also report outcomes and complications for the Discover artificial cervical disc (DePuy Spine) due to its widespread use outside the United States (OUS). At the end of each section, we specifically report outcome variables (NDI, Visual Analogue Scale [VAS] neck score, VAS arm score, Short Form-36 Health Survey Physical and Mental component scores [SF-36 PCS; SF-36 MCS]) comparing CDA and ACDF, when available. Outcomes for two-level adjacent CDA are also summarized for the FDA-approved Prestige LP and Mobi-C discs.

Bryan Cervical Disc

Vincent Bryan designed the Bryan cervical disc (Medtronic Inc.) in the United States in 1992 (Basho and Hood 2012). The Bryan cervical disc (Fig. 1a) is a non-constrained device consisting of a low-friction, wear-resistant, polyurethane nucleus housed between titanium plates (Bryan 2002). These titanium plates have convex porous ingrowth surfaces that function to support bony fixation of adjacent vertebral end plates. Consistent with the goal of motion preservation, the Bryan disc was designed to allow normal or physiologic range of motion, as well as coupled motion in cervical flexion/extension, lateral bending, rotation, and translation (Bryan 2002). Several studies have reported significant improvement in postoperative standardized outcomes scores (NDI, VAS scores, and SF-36 scores) for Bryan CDA in comparison with ACDF, for both single- and two-level procedures in patients with discogenic cervical radiculopathy and/or myelopathy (although the Bryan disc is not FDA-approved for multilevel CDA) (Cheng et al. 2009, 2011; Coric et al. 2006, 2013; Garrido et al. 2010; Goffin et al. 2003, 2010; Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Lafuente et al. 2005; Leung et al. 2005; Quan et al. 2011; Robertson et al. 2005; Sasso et al. 2007a, b, 2011; Tu et al. 2011; Walraevens et al. 2010; Yang et al. 2008; Zhang et al. 2012). Table 1 summarizes Bryan CDA outcomes data (Alvin et al. 2014; Anderson et al. 2004; Bhadra et al. 2009; Bryan 2002; Cheng et al. 2009; Coric et al. 2006, 2010, 2013; Ding et al. 2012; Duggal et al. 2004; Garrido et al. 2010; Goffin et al. 2003, 2010;

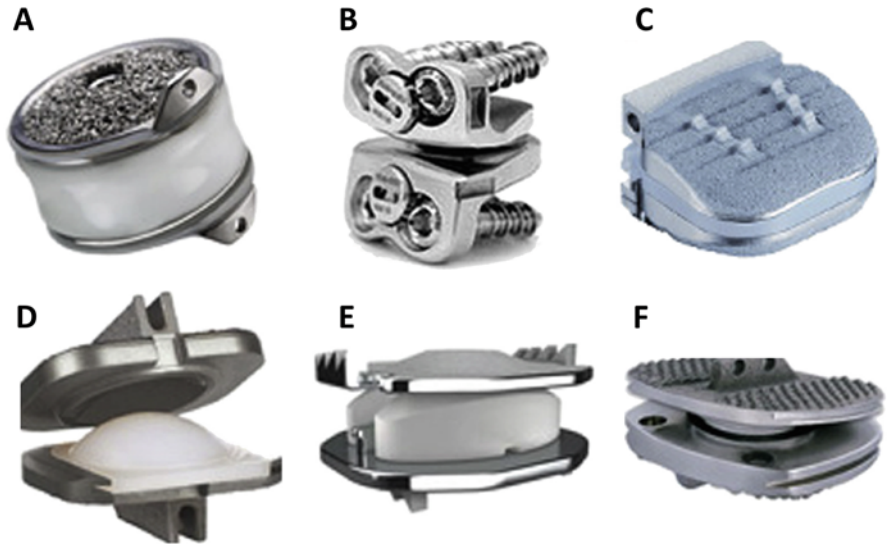

Fig. 1 (**a**) Bryan disc, (**b**) Prestige disc, (**c**) Porous Coated Motion (PCM) disc, (**d**) ProDisc-C disc, (**e**) Mobi-C disc, and (**f**) Kineflex-C disc. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014)

Table 1 Summary of single- and multilevel Bryan disc arthroplasty outcomes for symptomatic cervical spondylosis or disc herniation. Recreated and modified from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Anderson et al. 2004; Bhadra et al. 2009; Bryan 2002; Cheng et al. 2009; Coric et al. 2006, 2010, 2013; Ding et al. 2012; Duggal et al. 2004; Garrido et al. 2010; Goffin et al. 2003, 2010; Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Kim et al. 2008, 2009; Lafuente et al. 2005; Lee et al. 2010; Leung et al. 2005; Pickett et al. 2004, 2006; Quan et al. 2011; Ren et al. 2011; Robertson et al. 2005; Ryu et al. 2010; Sasso et al. 2007a, b, 2011, 2017; Sekhon 2003; Sekhon et al. 2005; Shim et al. 2006; Tu et al. 2011; Walraevens et al. 2010; Wang et al. 2008; Yang et al. 2008; Yoon et al. 2006; Zhang et al. 2012)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/ arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Sasso 2017	RCT	47 (single level)	120 mos	Imp	Imp/Imp			Ib
Coric 2013	RCT	74 (single level)	72 mos	Imp	Imp/Imp			Ib
Zhang 2012	RCT	120 (single level)	24 mos	Imp	Imp/Imp			Ib
Sasso 2011	RCT	463 (single level)	48 mos	Imp	Imp/Imp	Imp	Imp	Ib
Cheng 2009	RCT	65 (all multilevel)	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Garrido 2010	RCT	47 (single level)	48 mos	Imp	Imp/Imp	Imp	Imp	Ib
Heller 2009	RCT	463 (single level)	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Sasso 2007	RCT	115 (single level)	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Hacker 2005	RCT	46 (single level)	12 mos	Imp	Imp/Imp	Imp	Imp	Ib
Coric 2006	RCT	33 (single level)	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Quan 2011	PC	21 (6 multilevel)	96 mos		Imp/Imp			IIb
Ren 2011	PC	45 (6 multilevel)	35 mos	Imp				IIb
Coric 2010	PC	98 (13 multilevel)	24 mos	Imp				IIb
Goffin 2010	PC	98 (9 multilevel)	72 mos	Imp	Imp/Imp	Imp	Imp	IIb
Ryu 2010	PC	36 (single level)	24 mos	Imp	Imp/Imp			IIb
Walraevens 2010	PC	89 (single level)	48 mos					IIb
Bhadra 2009	PC	60 (single level)	31 mos		Imp/Imp			IIb
Heidecke 2008	PC	54 (5 multilevel)	24 mos					IIIb
Kim 2008	PC	47 (8 multilevel)	24 mos	Imp	Imp/Imp			IIb
Wang 2008	PC	59 (single level)	24 mos	Imp	Imp/Imp			IIb
Yang 2008	PC	19 (3 multilevel)	24 mos		Imp/Imp			IIb
Pickett 2006	PC	74 (21 multilevel)	24 mos	Imp	Imp/Imp	Imp	Imp	IIb
Robertson 2005	PC	74 (single level)	24 mos		Imp/Imp	Imp	Imp	IIb
Sekhon 2005	PC	15 (5 multilevel)	24 mos		Imp/Imp			IIb

(continued)

Table 1 (continued)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/ arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Lafuente 2005	PC	46	12 mos	Imp	Imp/Imp	Imp	Imp	IIb
Pickett 2004	PC	14 (1 multilevel)	24 mos	Imp		Imp	Imp	IIb
Duggal 2004	PC	26 (4 multilevel)	12 mos	Imp		Imp	Imp	IIb
Anderson 2004	PC	136 (30 multilevel)	12 mos			Imp	Imp	IIb
Goffin 2003	PC	143 (43 multilevel)	12 mos			Imp	Imp	IIb
Bryan 2002	PC	97 (single level)	24 mos			Imp	Imp	IIb
Ding 2012	R	32 (included multilevel)	49 mos	Imp	Imp/Imp	Imp	Imp	IIb
Tu 2011	R	36 (16 multilevel)	27 mos		Imp/Imp			IIb
Lee 2010	R	48 (single level)	14 mos		Imp/Imp			IIb
Kim 2009	R	51 (12 multilevel)	19 mos	Imp	Imp/Imp			IIb
Shim 2006	R	47 (8 multilevel)	6 mos	Imp	Imp/Imp			IIb
Yoon 2006	R	46 (single level)	12 mos	Imp	Imp/Imp			IIb
Leung 2005	R	90	12 mos			Imp	Imp	IIb
Sekhon 2003	R	7 (2 multilevel)	6 mos	Imp	Imp/Imp			IIb

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Kim et al. 2008, 2009; Lafuente et al. 2005; Lee et al. 2010; Leung et al. 2005; Pickett et al. 2004, 2006; Quan et al. 2011; Ren et al. 2011; Robertson et al. 2005; Ryu et al. 2010; Sasso et al. 2007a, b, 2011, 2017; Sekhon 2003; Sekhon et al. 2005; Shim et al. 2006; Tu et al. 2011; Walraevens et al. 2010; Wang et al. 2008; Yang et al. 2008; Yoon et al. 2006; Zhang et al. 2012). The vast majority of these studies had follow-up duration of up to 2 years; however, some had over 6 years of clinical and radiographic follow-up (Pointillart et al. 2017; Quan et al. 2011).

Long-Term Outcomes for Single-Level Bryan CDA Versus ACDF

In 2012, Zhang and colleagues reported 24-month outcomes for Bryan CDA versus ACDF. Study results demonstrated no significant differences between treatment groups based on mean NDI or median VAS scores (Zhang et al. 2012). These results are consistent with a study by Coric and colleagues (with average follow-up 72 months) that also demonstrated no significant differences between groups based on mean NDI or median VAS scores (Coric et al. 2013). In contrast, Sasso and colleagues reported significantly greater improvement in the CDA cohort based on NDI, VAS neck and arm pain scores, and SF-36 PCS and MCS scores at 48 months post-op (Sasso et al. 2011). Sasso and colleagues also reported an advantage for CDA in comparison with ACDF as measured by 7- and 10-year NDI scores (Sasso et al. 2017). The same authors reported CDA having an advantage over ACDF based on 7-year VAS neck and arm pain scores; however, the comparison was no longer significant at final 10-year follow-up (Sasso et al. 2017).

The data from these studies suggests that Bryan CDA is at least a viable alternative to ACDF for symptomatic cervical spondylosis and/or disc prolapse. The data also suggests that there is a lower incidence of secondary surgery after CDA (Cheng et al. 2009, 2011; Coric et al. 2006, 2013; Garrido et al. 2010; Goffin et al. 2003, 2010; Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Lafuente et al. 2005; Leung et al. 2005; Quan et al. 2011; Robertson et al. 2005; Sasso et al. 2007a, b, 2011; Tu et al. 2011; Walraevens et al. 2010; Yang et al. 2008; Zhang et al. 2012). A study by Shang and colleagues that focused on "skip" cervical spondylosis provided more evidence for the benefits of Bryan CDA over ACDF (Shang et al. 2017). Also, in a study that utilized a workers' compensation patient cohort, a greater number of CDA patients returned to work at 6 weeks and 3 months after surgery compared to ACDF (Steinmetz et al. 2008).

However, despite the demonstrated benefits of Bryan CDA over ACDF, complications were still reported (Cheng et al. 2009, 2011; Coric et al. 2006, 2013; Garrido et al. 2010; Goffin et al. 2003, 2010; Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Lafuente et al. 2005; Leung et al. 2005; Quan et al. 2011; Robertson et al. 2005; Sasso et al. 2007a, b, 2011; Tu et al. 2011; Walraevens et al. 2010; Yang et al. 2008; Zhang et al. 2012). For example, new anterior osteophyte formation or enlargement, increased narrowing of the intervertebral interspace, new adjacent degenerative disc disease, and calcification of the anterior longitudinal ligament were reported radiological findings indicative of post-CDA adjacent-level disease (Robertson et al. 2005; Yi et al. 2009). The incidence of heterotopic ossification (HO) causing restricted range of movement of the artificial disc prosthesis appears to increase with time, especially in multilevel (bilevel) CDA. Longer follow-up duration after CDA, gender, and age were noted to be risk factors in the development of HO after CDA (Leung et al. 2005).

Preoperative cervical kyphosis is a contraindication to CDA; therefore, post-CDA alignment has been an important topic of interest (Leven et al. 2017; Nunley et al. 2018). Using Bryan CDA for patients with single- and/or two-level symptomatic disc disease, Kim and colleagues studied postsurgical sagittal alignment of the functional spinal unit (FSU), as well as overall sagittal balance of the cervical spine (Kim et al. 2008). Their results demonstrated that Bryan CDA resulted in preserved motion of the FSU, and although the preoperative lordosis (or kyphosis) of the FSU could not always be maintained at during follow-up, the overall sagittal balance of the cervical spine was usually preserved (Kim et al. 2008). Pickett and colleagues reported similar results. Specifically, they also demonstrated preserved motion of the FSU after CDA. Although both the end plate angle of the treated disc space and the angle of the FSU became kyphotic after CDA, overall cervical spine sagittal alignment was preserved (Pickett et al. 2004). Other authors have found that cervical spine sagittal alignment became kyphotic after surgery, but overall lordosis was restored at a later time on follow-up imaging (Yoon et al. 2006). Possible causes of kyphotic changes included "over-milling" at the dorsal end plate, suboptimal angle of disc insertion, structural absence of lordosis in the Bryan disc prosthesis, removal of the posterior longitudinal ligament, and preexisting cervical kyphosis (Yoon et al. 2006).

Cummins/Bristol and Prestige Cervical Discs

Authors of both single- and multicenter studies have reported statistically significant improved postoperative outcomes for Prestige CDA (Fig. 1b), as well as reduced rates of secondary surgery compared to ACDF (Burkus et al. 2010, 2014; Lanman et al. 2017; Mummaneni et al. 2007; Peng et al. 2011; Porchet and Metcalf 2004; Riina et al. 2008; Robertson and Metcalf 2004). In addition to improved neurological success and outcomes, some studies have also demonstrated that Prestige CDA may restore segmental lordosis and preserve segmental motion (Peng et al. 2011). The follow-up duration for many of these studies was 2 years, but up to 7 years of follow-up data was reported (Lanman

Table 2 Summary of single-level Prestige disc outcomes for symptomatic cervical spondylosis or disc herniation. Recreated and modified from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Burkus et al. 2010, 2014; Gornet et al. 2015, 2016, 2017; Lanman et al. 2017; Mummaneni et al. 2007; Peng et al. 2011; Porchet and Metcalf 2004; Riew et al. 2008; Riina et al. 2008; Robertson and Metcalf 2004)

Author/Device	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Gornet 2016 Prestige LP	RCT	545	84 mos	Imp	Imp/Imp	Imp	Imp	Ib
Gornet 2015 Prestige LP	RCT	545	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Burkus 2014 Prestige ST	RCT	541	84 mos	Imp	Imp/Imp	Imp		Ib
Burkus 2010 Prestige ST	RCT	541	60 mos	Imp	Imp/Imp	Imp		Ib
Riew 2008 Prestige ST	RCT	199	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Mummaneni 2007 Prestige ST	RCT	541	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Porchet 2004 Prestige II	RCT	49	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Peng 2011 Prestige LP	PC	115 (includes 1–3 levels)	24 mos	Imp	Imp/Imp	Imp	Imp	IIb
Riina 2008 Prestige ST	PC	19	24 mos	Imp	Imp/Imp			IIb
Robertson & Metcalf 2004 Prestige I	PC	14	48 mos	Imp	Imp/Imp	Imp	Imp	IIb

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Table 3 Summary of two-level (adjacent) Prestige LP disc outcomes for symptomatic cervical spondylosis or disc herniation. (Gornet et al. 2017; Lanman et al. 2017)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Lanman 2017	RCT	397	84 mos	Imp	Imp/Imp	Imp	Imp	Ib
Gornet 2017	RCT	397	24 mos	Imp	Imp/Imp	Imp	Imp	Ib

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

et al. 2017). Tables 2 and 3 summarize Prestige CDA outcomes data (Burkus et al. 2010, 2014; Gornet et al. 2015, 2016, 2017; Lanman et al. 2017; Mummaneni et al. 2007; Peng et al. 2011; Porchet and Metcalf 2004; Riew et al. 2008; Riina et al. 2008; Robertson and Metcalf 2004). Below, we highlight key design steps in the history of Prestige CDA and then summarize one- and two-level outcomes data for Prestige CDA versus ACDF.

In the late 1980s, Cummins introduced a simple ball-and-socket prosthetic cervical joint in an attempt to address some of the problems associated with ACDF (Cummins et al. 1998; Wigfield et al. 2002b). His efforts, in collaboration with the Department of Medical Engineering at Frenchay

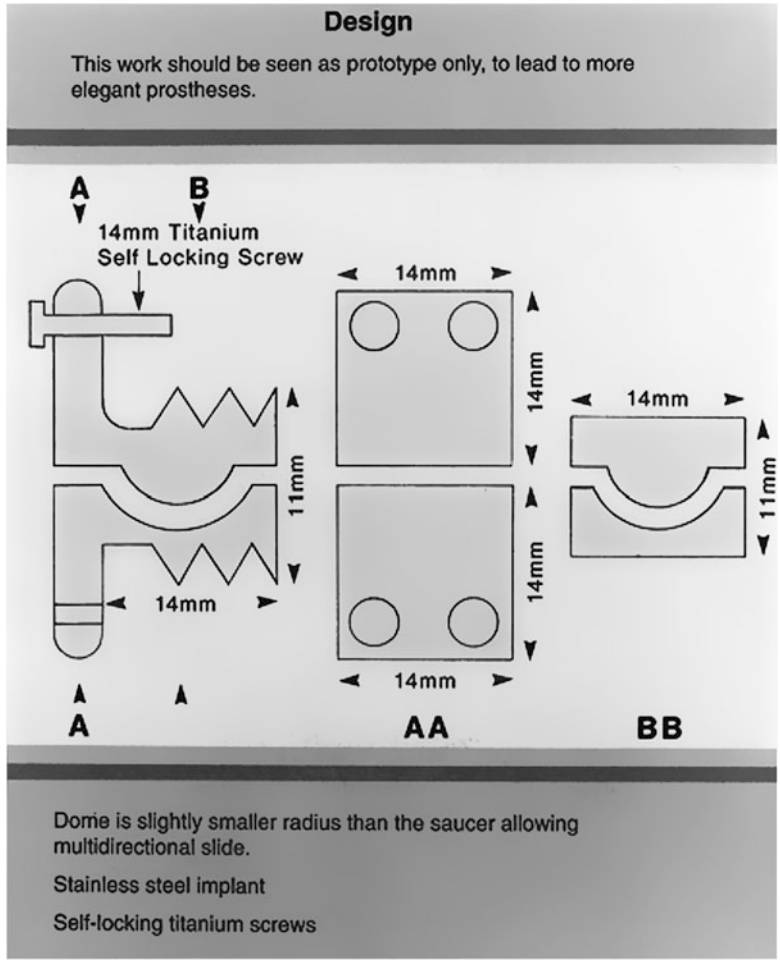

Fig. 2 Prototype design of the Prestige artificial cervical disc composed of stainless steel (made by Mr. Colin Walker at Frenchay Hospital). (Recreated from Cummins et al. Surgical experience with an implanted artificial cervical joint. Journal of Neurosurgery. (Cummins et al. 1998))

Hospital, led to the development of a prosthetic cervical disc constructed entirely of stainless steel with congruent surfaces and no point loading (Fig. 2) (Cummins et al. 1998; Traynelis 2004; Wigfield et al. 2002b). The Cummins disc occupied 11 mm of the intervertebral space and was secured to the vertebral bodies above and below the index level with screws (Traynelis 2004). Between 1991 and 1996, 22 Cummins discs were implanted in 20 "end-stage" patients who lacked motion over multiple cervical levels because of congenital block vertebrae or prior surgical fusion. On follow-up, two patients lacked motion at the index level. This was attributed to the relatively large implant size which may have caused over-distraction of the facet joints (Cummins et al. 1998). Although there were implant problems such as screw breakages, patients experienced clinical improvement (those with radiculopathy improved, and those with myelopathy improved or stabilized) (Cummins et al. 1998).

The work of Cummins set the foundation for the development of the next generation of artificial cervical discs. The next CDA device was developed in 1998 and was referred to as the Frenchay artificial cervical joint (Fig. 3) (Traynelis 2004; Wigfield et al. 2002b).

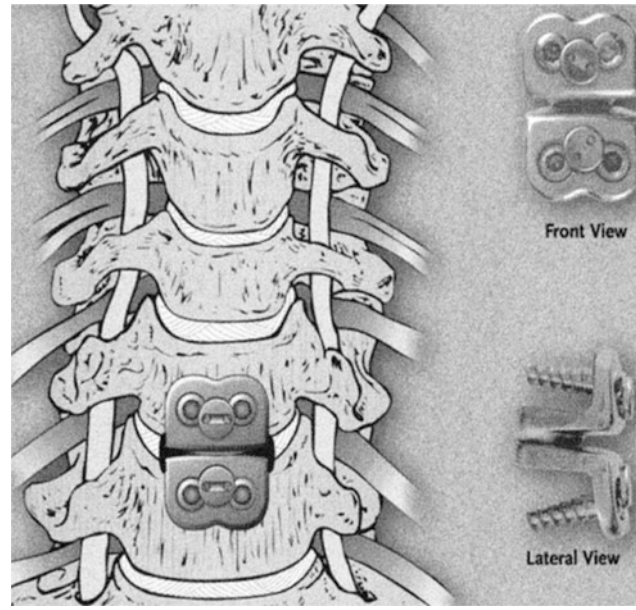

Fig. 3 The two articulating components of the Frenchay artificial cervical joint (or Prestige I) are shown with the bone and locking screws. (Recreated from Wigfield et al. The New Frenchay Artificial Cervical Joint: Results From a Two-Year Pilot Study. Spine (Phila Pa 1976). (Wigfield et al. 2002b))

Medtronic ultimately purchased the Frenchay disc, and it was renamed as Prestige (Medtronic Inc.) (Nunley et al. 2018). This device had some similarities to the prior Cummins joint but was redesigned with a trough rather than a ball-and-socket for articulation. Also, the lower component of the joint was redesigned for translation within three degrees of freedom for both translation and rotation (Wigfield et al. 2002b). Together, these design changes allowed more physiologic motion (anterior-posterior translation coupled with flexion/extension) (Traynelis 2004; Wigfield et al. 2002b). Wigfield and colleagues prospectively evaluated the Frenchay artificial joint in a cohort of 15 patients with cervical radiculopathy or myelopathy from cervical disc herniation or posterior vertebral body osteophytes (Wigfield et al. 2002b). Over the duration of their 2-year study, the Frenchay CDA maintained motion and intervertebral height at the index levels, there were no cases of dislocation screw backout, and clinical outcomes scores improved (Wigfield et al. 2002b).

The next iteration of Prestige CDA, Prestige II, was developed in 1999 (Traynelis 2004). This device had roughened end plate surfaces to promote bony ingrowth for long-term stability (Traynelis 2004). The Prestige II was the first artificial cervical disc to be compared to ACDF (non-instrumented arthrodesis with autograft) in a prospective randomized trial of patients with symptomatic single-level primary cervical disc disease (Porchet and Metcalf 2004; Traynelis 2004). Data after 2 years of follow-up demonstrated improvement in most outcome measurements that favored CDA over ACDF (Porchet and Metcalf 2004). Also, motion analysis demonstrated favorable results in the CDA cohort (motion was maintained in the CDA cohort compared to ACDF patients who displayed no significant motion) (Porchet and Metcalf 2004).

The next Prestige disc, Prestige ST, became available in 2002 (Traynelis 2004). The surfaces of the device contacting the end plates were grit-blasted to promote bone osteointegration (Traynelis 2004). In comparison with its predecessor, there was a 2 mm reduction in the height of the device's anterior flanges (Traynelis 2004). The Prestige ST ball-and-trough articulation design, combined with its angulation between the base and anterior portions of the device, allowed more physiologic motion comparable to normal cervical vertebrae (Traynelis 2004). Mummaneni and colleagues performed a

multicenter, prospective, randomized, non-inferiority clinical trial comparing the Prestige ST to ACDF (Mummaneni et al. 2007). The Prestige CDA patients maintained physiological segmental motion and had improved clinical outcomes (summarized below) and reduced rates of secondary surgery compared to ACDF (Mummaneni et al. 2007). Burkus and colleagues demonstrated that the Prestige ST disc maintained improved clinical outcomes (summarized below) and segmental motion after implantation after 5 years post-op (Burkus et al. 2010). Rates of reoperations for adjacent segment degeneration trended lower in the CDA cohort in comparison with the ACDF group, but the differences were not statistically significant (Burkus et al. 2010).

The Prestige LP is the latest generation in the Prestige family of cervical discs (Traynelis 2004). The FDA-approved Prestige LP disc (for both single- and two-level symptomatic cervical spondylosis or disc herniation) is a non-constrained ball-in-trough, metal-on-metal articulation made of a titanium ceramic composite. The unique titanium ceramic composite material is highly durable and results in less artifact during CT and MRI scans (Traynelis 2004). Also, the porous titanium plasma spray coating on the end plate surface facilitates bone ingrowth and long-term fixation (Traynelis 2004). Long-term outcomes for the Prestige family of discs are summarized below.

Long-Term Outcomes for Single-Level Prestige CDA Versus ACDF

Prestige LP: In 2015, Gornet and colleagues reported 24-month outcomes for Prestige LP CDA versus ACDF: NDI and VAS neck and arm scores were noninferior, and SF-36 MCS was noninferior as well as statistically superior (Gornet et al. 2015). Gornet and colleagues reported continued success for Prestige LP CDA versus ACDF at 84 months: NDI and VAS scores were still noninferior, SF-36 PCS was noninferior, and SF-36 MCS was noninferior as well as statistically superior (Gornet et al. 2016).

Prestige ST: Outcomes at 24 months for Prestige ST CDA versus ACDF demonstrated no differences in NDI, VAS neck score (which had been significantly better for the CDA group at 12 months), VAS arm score, and SF-36 PCS and MCS (Mummaneni et al. 2007; Riew et al. 2008). Burkus and colleagues reported outcomes at 60 months for Prestige ST CDA versus ACDF: NDI was significantly better, VAS neck score was significantly better, VAS arm score had no significant difference, SF-36 PCS had no significant difference, and SF-36 MCS comparison was not reported (Burkus et al. 2010, 2014). Later in 2014, Burkus and colleagues reported 84-month outcomes for Prestige ST CDA versus ACDF, and the results were similar to previously reported 60-month outcomes except the SF-36 PCS score for the CDA group was now significantly improved compared to the ACDF treatment group (Burkus et al. 2014).

Prestige II: In 2004, Porchet and colleagues reported outcomes at 24 months for Prestige II CDA versus ACDF: NDI was statistically equivalent, VAS neck score statistical equivalence could not be shown between treatment groups, VAS arm score was statistically equivalent, and no significant differences were demonstrated for SF-36 PCS and MCS (Porchet and Metcalf 2004).

Long-Term Outcomes for Two-Level Adjacent Prestige LP CDA Versus ACDF

Gornet and colleagues reported 24-month outcomes for Prestige LP CDA versus ACDF at two levels: NDI was statistically superior, VAS neck score was noninferior, VAS arm score was noninferior, SF-36 PCS was noninferior, and SF-36 MCS was not reported (Gornet et al. 2017). Lanman and colleagues reported similar results for 84-month CDA outcomes: VAS neck score was statistically superior, SF-36 PCS was statistically superior, and SF-36 MCS was noninferior (Lanman et al. 2017). Although there was no statistically significant difference in the overall rate of implant- or procedure-related

adverse events for up to 84 months post-op, the trend favored the CDA treatment cohort (Lanman et al. 2017).

Porous Coated Motion (PCM) Cervical Disc

The Porous Coated Motion (PCM) device (Cervitech) is a non-constrained artificial cervical disc that was originally invented by McAfee and then was improved upon by Helmut Link and Arnold Keller (Fig. 1c) (Pimenta et al. 2004). It has a unique biomechanical design feature that incorporates a large radius ultrahigh-molecular-weight polyethylene bearing surface attached to the inferior vertebrae. This allows the device more physiologic translational motion in an arc, which is consistent with the natural motion of the cervical spine (Pimenta et al. 2004). The porous ingrowth material is composed of two ultra-thin layers of titanium with electrochemically coated calcium phosphate (Pimenta et al. 2004). The pore size was designed to match the bony trabecular architecture of the cervical vertebra (Pimenta et al. 2004).

Pimenta and colleagues reported the results of a pilot study performed between December 2002 and October 2003 in which 82 PCM devices were implanted in 53 patients. Significant improvements in all scores were seen postoperatively (NDI, VAS pain scores, and Treatment Intensity Gradient Test). One device migration of 4 mm was seen at 3 months and was observed (no reoperation). Eighty percent of patients had a good or excellent result at 1 week, improving to 90% of patients having a good or excellent result by 1 month (Odom's criteria), and this result remained stable 3 months after surgery (Pimenta et al. 2004). Later in 2007, Pimenta and colleagues published the first prospective CDA study to show significantly improved clinical outcomes for multilevel compared to single-level CDA (PCM disc) (Pimenta et al. 2007). Table 4 is a summary of PCM CDA outcomes data (Alvin et al. 2014; Delamarter et al. 2010; Phillips et al. 2009, 2013, 2015; Pimenta et al. 2004, 2007).

Long-Term Outcomes for Single-Level PCM CDA Versus ACDF

The FDA randomized controlled trials comparing PCM CDA vs. ACDF were performed by Phillips and colleagues (Phillips et al. 2013, 2015). The study cohort consisted of patients 18–65 years of age with single-level symptomatic cervical spondylosis (radiculopathy and/or myelopathy) unresponsive to nonoperative treatment. This included patients with prior non-adjacent or adjacent single-level fusion operations. The 24-month outcomes demonstrated that NDI was significantly better, VAS neck and arm scores were not significantly different, and SF-36 PCS and MCS were not significantly different for PCM CDA compared to ACDF (Phillips et al. 2013). The patients with PCM CDA had lower rates of prolonged dysphagia, greater patient satisfaction, and superior overall success compared to ACDF (Phillips et al. 2013).

In 2015, Phillips and colleagues reported 60-month outcomes for PCM CDA vs. ACDF: NDI was significantly better, VAS neck score was significantly better, VAS arm score was not significantly different, and SF-36 PCS and MCS were significantly better (Phillips et al. 2015). PCM CDA patients also had a lower rate of radiographical adjacent-level degeneration and a trend toward fewer secondary surgeries (Phillips et al. 2015). The authors interpreted the results of these studies to support PCM CDA as a viable and sustainable alternative to ACDF in appropriately selected patients (Phillips et al. 2015).

ProDisc-C Cervical Disc

The ProDisc-C (Synthes Spine) is an artificial cervical disc designed with these principles in mind: implant stability, ease and safety of insertion, minimal end plate disruption, and optimization of functional range of motion (Fig. 1d). These principles and design characteristics were investigated in several studies, and clinical outcomes are summarized in

Table 4 Summary of single- and multilevel Porous Coated Motion (PCM) disc outcomes for symptomatic cervical spondylosis or disc herniation. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Phillips et al. 2009, 2013, 2015; Pimenta et al. 2004, 2007)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Phillips 2015	RCT	110	60 mos	Imp	Imp/Imp	Imp	Imp	Ib
Phillips 2013	RCT	342	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Phillips 2009	PC	152	12 mos	Imp	Imp/Imp			IIb
Pimenta 2007	PC	140 (69 multilevel)	NR	Imp	Imp/Imp	NR	NR	IIb
Pimenta 2004	PC	53 (25 multilevel)	NR	Imp	Imp/Imp	NR	NR	IIb

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Table 5 Summary of single- and multilevel ProDisc-C disc outcomes for symptomatic cervical spondylosis or disc herniation. Recreated and modified from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Bertagnoli et al. 2005; Chin et al. 2017; Delamarter et al. 2010; Janssen et al. 2015; Kelly et al. 2011; Kesman et al. 2012; Mehren et al. 2006; Murrey et al. 2009; Nabhan et al. 2007; Peng et al. 2009; Suchomel et al. 2010; Zigler et al. 2013)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Janssen 2015	RCT	209	84 mos	Imp	Imp/Imp	Imp	Imp	Ib
Zigler 2013	RCT	209	60 mos	Imp	Imp/Imp	Imp	Imp	Ib
Kesman 2012	RCT	44	84 mos	Imp	Imp/Imp	Imp	Imp	Ib
Kelly 2011	RCT	199	24 mos					Ib
Delamarter 2010	RCT	345	48 mos	Imp	Imp/Imp	Imp	Imp	Ib
Murrey 2009	RCT	209	24 mos	Imp	Imp/Imp	Imp	Imp	Ib
Nabhan 2007	RCT	49	12 mos		Imp/Imp			Ib
Suchomel 2010	PC	54 (10 multilevel)	48 mos		Imp/Imp			IIb
Mehren 2006	PC	54 (20 multilevel)	12 mos	Imp	Imp/Imp			IIb
Bertagnoli 2005	PC	16 (4 multilevel)	12 mos	Imp	Imp/Imp			IIb
Peng 2009	R	166	24 mos	Imp	Imp/Imp			IIb
Chin 2017	R	110	24 mos	Imp	Imp/Imp			III

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Table 5 (Alvin et al. 2014; Bertagnoli et al. 2005; Chin et al. 2017; Delamarter et al. 2010; Janssen et al. 2015; Kelly et al. 2011; Kesman et al. 2012; Mehren et al. 2006; Murrey et al. 2009; Nabhan et al. 2007; Peng et al. 2009; Suchomel et al. 2010; Zigler et al. 2013). The

specific advantages of the ProDisc-C device include the absence of anterior plate fixation hardware, preservation of osseous end plates, immediate keel fixation stability, and the possibility of multilevel application. Biomechanically, the ProDisc-C implant is considered to represent a ball-and-socket/semi-constrained design with a fixed axis of rotation (Bertagnoli et al. 2005). DiAngelo and colleagues performed an in vitro biomechanical study to compare the effects of ProDisc-C CDA and ACDF in a multilevel human cadaveric model. Their results demonstrated that ACDF decreased motion at the index level in comparison with CDA (DiAngelo et al. 2004). The reduced motion at the index level was compensated at adjacent segments by an increase in motion. ProDisc-C CDA did not alter the motion patterns at either the index or adjacent levels compared with control (except in extension) (DiAngelo et al. 2004). Long-term outcomes from the FDA trials comparing ProDisc-C CDA to ACDF are summarized below.

Long-Term Outcomes for Single-Level ProDisc-C CDA Versus ACDF

In 2007, Nabhan and colleagues reported no significant difference in 12-month VAS neck and arm scores for ProDisc-C CDA versus ACDF (Nabhan et al. 2007). Later in 2009, Murrey and colleagues reported no significant differences in all outcome variables (NDI, VAS neck and arm scores, SF-36 PCS and MCS) at 24 months post-op (Murrey et al. 2009). This trend continued in 2010 with Delamarter and colleagues reporting 48-month outcomes for ProDisc-C CDA versus ACDF: NDI and VAS neck and arm scores were still not significantly different (Delamarter et al. 2010). However, in 2013, Zigler and colleagues reported 60-month outcomes for ProDisc-C CDA vs. ACDF and found that NDI and VAS neck scores were significantly better (VAS arm score, SF-36 PCS, and SF-36 MCS were not significantly different) (Zigler et al. 2013). Then at 84 months post-op, two studies demonstrated no significant difference in all outcome variables for ProDisc-C CDA versus ACDF (Janssen et al. 2015). For these two studies, the VAS and SF-36 scores showed noninferiority of the Prodisc-C group, which trended toward statistical superiority (Kesman et al. 2012).

Mobi-C Cervical Disc

The Mobi-C cervical artificial disc (LDR Medical) is a semi-constrained, bone-sparing prosthetic device (Fig. 1e) (Davis et al. 2015; Kim et al. 2007). The implant is composed of two cobalt-chromium-molybdenum alloy shells with an ultrahigh-molecular-weight polyethylene mobile insert facilitating five independent degrees of freedom (Davis et al. 2015; Kim et al. 2007). The mobility of the polyethylene insert decreases the transmission of the constraints on the bone-implant interface and reduces the constraints of the posterior facet joints (Kim et al. 2007). The implant has lateral self-retaining, incline-shaped teeth that were designed to support reliable vertebral end plate anchorage and stability (Kim et al. 2007). Tables 6 and 7 summarize Mobi-C CDA outcomes data (Bae et al. 2015; Beaurain et al. 2009; Davis et al. 2013, 2015; Guerin et al. 2012; Hisey et al. 2014, 2015, 2016; Huppert et al. 2011; Kim et al. 2007; Lee et al. 2012; Park et al. 2008, 2013; Radcliff et al. 2016a). The Mobi-C disc has FDA approval for both single- and two-level symptomatic cervical spondylosis and/or disc disease. Long-term outcomes from the FDA trials are summarized below.

Long-Term Outcomes for Single-Level Mobi-C CDA Versus ACDF

Hisey and colleagues reported 24-, 48-, and 60-month outcomes in multicenter, prospective, randomized, controlled FDA investigational device exemption clinical trials comparing Mobi-C CDA to ACDF in the treatment of

Table 6 Summary of FDA single-level (and other multi-level) Mobi-C cervical disc outcome studies. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Bae et al. 2015; Beaurain et al. 2009; Davis et al. 2013, 2015; Guerin et al. 2012; Hisey et al. 2014, 2015, 2016; Huppert et al. 2011; Kim et al. 2007; Lee et al. 2012; Park et al. 2008, 2013; Radcliff et al. 2016a)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Hisey 2016	RCT	245	60 mos	Imp	Imp/Imp			Ib
Hisey 2015	RCT	245	48 mos	Imp	Imp/Imp			Ib
Hisey 2014	RCT	245	24 mos	Imp	Imp/Imp			Ib
Lee 2012	PC	28 (9 multilevel)	24 mos	Imp	Imp/Imp			IIb
Huppert 2011	PC	231 (56 multilevel)	24 mos	Imp	Imp/Imp	Imp	Imp	IIb
Beaurain 2009	PC	76 (9 multilevel)	24 mos	Imp	Imp/Imp	Imp	Imp	IIb
Park 2013	R	75 (16 multilevel)	40 mos	Imp	Imp/Imp			IIb
Park 2008	R	53	20 mos	Imp	–/Imp			IIb
Kim 2007	R	23 (7 multilevel)	6 mos		Imp/Imp			IIb

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Table 7 Summary of FDA two-Level Mobi-C cervical disc outcomes for symptomatic cervical spondylosis or disc herniation. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Bae et al. 2015; Beaurain et al. 2009; Davis et al. 2013, 2015; Guerin et al. 2012; Hisey et al. 2014, 2015, 2016; Huppert et al. 2011; Kim et al. 2007; Lee et al. 2012; Park et al. 2008, 2013; Radcliff et al. 2016a)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Radcliff 2016	RCT	330	60 mos	Imp	Imp/Imp			Ib
Bae 2015	RCT	413 (225 multilevel)	48 mos	Imp	Imp/Imp			Ib
Davis 2015	RCT	291	48 mos	Imp	Imp/Imp			Ib
Davis 2013	RCT	330	24 mos	Imp	Imp/Imp			Ib
Guerin 2012	PC	40	24.3 mos	Imp	Imp/Imp	Imp	Imp	IIb

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PC* prospective cohort, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

symptomatic degenerative disc disease in the cervical spine (single level). The results demonstrated similar findings at each of these time points, namely, there were no significant differences in NDI or VAS neck and arm scores (Gornet et al. 2015; Hisey et al. 2014, 2015).

Table 8 Summary of single-level Kineflex-C cervical disc outcomes for symptomatic cervical spondylosis or disc herniation. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Coric et al. 2011, 2013, 2018)

Author	Design	n	Follow-up	NDI	VAS neck/arm	SF-36 PCS	SF-36 MCS	Design LoE
Coric 2018	RCT	269	60 mos	Imp	Imp/Imp			Ib
Coric 2013	RCT	74	48 mos	Imp	Imp/Imp			Ib
Coric 2011	RCT	269	24 mos	Imp	Imp/Imp			Ib

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Table 9 Single-level Secure-C cervical disc outcomes for symptomatic cervical spondylosis or disc herniation (Vaccaro et al. 2013)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Vaccaro 2013	RCT	380	24 mos	Imp	Imp/Imp	Imp	Imp	Ib

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

Long-Term Outcomes for Two-Level Adjacent Mobi-C CDA Versus ACDF

In 2013, Davis and colleagues reported 24-month outcomes for Mobi-C CDA versus ACDF at two adjacent levels: NDI was significantly better, and although VAS neck score was significantly improved at 3 and 6 months postoperatively, there were no statistically significant differences at any other time point. Also, there were no significant differences between treatment groups for VAS arm scores at any time point (Davis et al. 2013). Later in 2015, Davis and colleagues reported similar results at 48 months post-op: NDI was significantly better, but there were no significant differences in VAS neck and arm scores between treatment groups (Davis et al. 2015). For 60-month outcomes, Radcliff and colleagues reported that NDI was significantly better, and although there was more improvement in VAS neck and arm scores for the CDA group, the difference was not statistically significant (Radcliff et al. 2016a).

Kineflex-C Cervical Disc

The Kineflex-C artificial cervical disc (SpinalMotion Inc.) is a cobalt-chrome on cobalt-chrome alloy (metal-on-metal) semi-constrained device (Fig. 1f) (Coric et al. 2011). It is composed of three pieces (two end plates and a mobile center that translates within a retention ring). There is a midline keel on the device's end plate that provides immediate fixation, and the end plates are coated with a titanium plasma spray to promote bony ingrowth for long-term fixation (Coric et al. 2011). Table 8 summarizes Kineflex-C CDA outcomes data (Coric et al. 2011, 2013, 2018). Long-term outcomes for the FDA trials comparing Kineflex-C CDA and ACDF are summarized below.

Long-Term Outcomes for Single-Level Kineflex-C CDA Versus ACDF

Coric and colleagues reported 24- and 48-month outcomes for Kineflex-C CDA versus ACDF and found no significant differences between treatment groups based on NDI or VAS scores (Coric et al. 2011, 2013). However, clinical success (maintenance or improvement in neurological exam, minimum of 20% improvement in NDI, no device failure, no reoperation at the index level, no major device-related adverse event) was significantly higher in the Kineflex-C group compared to ACDF (Coric et al. 2011). Recently, Coric and colleagues reported clinical

Table 10 Summary of single- and multilevel Discover disc outcomes for symptomatic cervical spondylosis or disc herniation. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Du et al. 2011; Fang et al. 2013; Li et al. 2013; Miao et al. 2014; Rozankovic et al. 2017; Shi et al. 2016; Skeppholm et al. 2015)

Author	Design	Study size	Follow-up duration	NDI	VAS neck/ arm scores	SF-36 PCS	SF-36 MCS	Design LoE
Rozankovic 2017	RCT	105	24 mos	Imp	Imp/Imp			Ib
Skeppholm 2015	RCT	137 (43 multilevel)	24 mos	Imp	Imp/Imp			Ib
Shi 2016	PC	128	24 mos	Imp				IIb
Miao 2014	PC	79 (23 multilevel)	31.6 mos		Imp/Imp			IIb
Li 2013	PC	55	24 mos	Imp	Imp/Imp			IIb
Du 2011	PC	25 (1 multilevel)	15 mos	Imp	Imp/Imp			IIb
Fang 2013	R	18	15 mos		Imp/Imp			IIb

Imp improved, *LoE* level of evidence, *MCS* mental component score, *NDI* neck disability index, *PCS* physical component score, *R* retrospective, *RCT* randomized controlled trial, *SF-36* short form-36, *VAS* visual analogue scale

success was significantly improved for the Kineflex-C CDA group compared to ACDF at 60 months post-op (Coric et al. 2018). Also, the results demonstrated there were no significant differences between treatment groups in terms of reoperation/revision surgery or device-/surgery-related adverse events during the 5 years of follow-up (Coric et al. 2018).

Secure-C Cervical Disc

The selectively constrained Secure-C artificial cervical disc (Globus Medical) is an anterior articulating intervertebral device comprised of two cobalt-chrome alloy serrated end plates and a sliding polyethylene central core. The end plates have a titanium plasma spray coating on its bone-contacting surface to promote long-term bony ingrowth (Vaccaro et al. 2013). The Secure-C artificial cervical disc is designed for motion in flexion/extension up to 30 ± 15°, lateral bending up to 20 ± 10°, and sagittal translation of up to ±1.25 mm (Vaccaro et al. 2013). There is less available FDA trial outcomes data (compared to the aforementioned discs) comparing Secure-C CDA to ACDF (Table 9) (Vaccaro et al. 2013).

Long-Term Outcomes for Single-Level Secure-C CDA Versus ACDF

Overall success results (improvement of at least 25% in baseline NDI, no device failure requiring revision, and absence of major complications [major vessel injury, neurological damage, or nerve injury]) demonstrated statistical superiority of the randomized Secure-C group compared with the randomized ACDF group at 24 months post-op (Vaccaro et al. 2013). There was noninferiority of the randomized Secure-C group at all postoperative time points (up to 24 months) for both (1) 25% or more and (2) 15-point or more improvement in NDI (Vaccaro et al. 2013). Also, the study demonstrated statistical noninferiority of Secure-C compared to ACDF for VAS neck and arm pain scores (and also statistical superiority for VAS neck pain) (Vaccaro et al. 2013).

Discover Cervical Disc

The non-constrained Discover artificial cervical disc (DePuy Spine) is an MRI-compatible ball-and-socket design consisting of two end plates manufactured from titanium alloy and

a polyethylene core (Du et al. 2011; Shi et al. 2016). The inferior end plate is a two-piece design with an ultrahigh-molecular-weight polyethylene insert and features a spherical bearing surface that allows motion in all rotational directions (Du et al. 2011). The Discover disc has a 7° lordotic angle split evenly between the superior and inferior end plates for restoration of lordosis at the index level (Du et al. 2011). Table 10 summarizes Discover CDA outcomes data (Du et al. 2011; Fang et al. 2013; Li et al. 2013; Miao et al. 2014; Rozankovic et al. 2017; Shi et al. 2016; Skeppholm et al. 2015). In contrast to the aforementioned artificial cervical discs, the Discover disc is not approved by the FDA; however, its widespread use for CDA warrants a brief summary of its outcomes.

Long-Term Outcomes for Single- and Multilevel Discover CDA Versus ACDF

In 2017, Rozankovic and colleagues reported 24-month outcomes for Discover CDA vs. ACDF (single level): NDI and VAS neck and arm scores were significantly improved compared to ACDF (Rozankovic et al. 2017). In contrast, Skeppholm and colleagues did not find significantly better 24-month outcomes for CDA compared to ACDF based on NDI scores. In contrast to the Rozankovic study, the Skeppholm study included patients with multilevel cervical disc degeneration who received CDA at adjacent levels, which could explain the difference in results (Skeppholm et al. 2015).

Summary of Complications Associated with Cervical Disc Arthroplasty

Biomechanical and clinical studies suggest that the rate of adjacent segment degeneration (ASDG; *radiographic* evidence of degeneration at the adjacent level) is significantly higher for ACDF compared to CDA (Baba et al. 1993; Chang et al. 2007; Coric et al. 2010; DiAngelo et al. 2003; Dmitriev et al. 2005; Eck et al. 2002; Matsunaga et al. 1999; Nunley et al. 2018; Park et al. 2011; Puttlitz et al. 2004; Reitman et al. 2004; Wigfield et al. 2002a). However, rates of adjacent segment disease (ASDI; development of new *clinical* symptoms correlating with adjacent segment degeneration) between CDA and ACDF continue to be debated. Jawahar and colleagues found no difference in the incidence of ASDI between CDA and ACDF. On the contrary, there has been growing evidence from other long-term follow-up studies and meta-analyses that suggest CDA may reduce ASDI and reoperation rates in comparison with ACDF (Gao et al. 2013; Ishihara et al. 2004; Jawahar et al. 2010; McAfee et al. 2012; Robertson et al. 2005; Upadhyaya et al. 2012).

Other adverse outcomes associated with CDA include heterotopic ossification (HO), delayed fusion around cervical disc prosthesis, asymmetric end plate preparation resulting in postoperative kyphosis, and reduction in caudal vertebral body height (Yi et al. 2010). Rates of HO with the FDA investigational device exemption publications have been reported, and grade 4 HO rates are as high as 13% (Gornet et al. 2016; Hisey et al. 2016; Janssen et al. 2015; Nunley et al. 2018; Radcliff et al. 2016a). Table 11 is a summary of the commonly reported complications associated with CDA in the literature (Alvin et al. 2014; Anderson et al. 2004; Beaurain et al. 2009; Bertagnoli et al. 2005; Bhadra et al. 2009; Bryan 2002; Cheng et al. 2011; Coric et al. 2006, 2011; Ding et al. 2012; Du et al. 2011; Duggal et al. 2004; Garrido et al. 2010; Goffin et al. 2003, 2010; Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Huppert et al. 2011; Kelly et al. 2011; Kesman et al. 2012; Kim et al. 2007, 2008, 2009; Lee et al. 2010; Leung et al. 2005; Li et al. 2013; Mehren et al. 2006; Mummaneni et al. 2007; Murrey et al. 2009; Nabhan et al. 2007; Park et al. 2008, 2013; Peng et al. 2009, 2011; Phillips et al. 2013; Pickett et al. 2004; Pimenta et al. 2004, 2007; Porchet and Metcalf 2004; Quan et al. 2011; Ren et al. 2011; Riew et al. 2008; Riina et al. 2008; Robertson and Metcalf 2004; Robertson et al. 2005; Ryu et al. 2010; Sasso et al. 2011; Sekhon 2003; Sekhon et al. 2005; Shim et al. 2006; Suchomel et al. 2010; Tu et al. 2011; Walraevens

Table 11 Summary of cervical disc arthroplasty complications. Recreated from Alvin et al. Cervical arthroplasty: a critical review of the literature. The Spine Journal. (Alvin et al. 2014; Anderson et al. 2004; Beaurain et al. 2009; Bertagnoli et al. 2005; Bhadra et al. 2009; Bryan 2002; Cheng et al. 2011; Coric et al. 2006, 2011; Ding et al. 2012; Du et al. 2011; Duggal et al. 2004; Garrido et al. 2010; Goffin et al. 2003, 2010; Guerin et al. 2012; Hacker 2005; Heidecke et al. 2008; Heller et al. 2009; Huppert et al. 2011; Kelly et al. 2011; Kesman et al. 2012; Kim et al. 2007; 2008, 2009; Lee et al. 2010, 2012; Leung et al. 2005; Li et al. 2013; Mehren et al. 2006; Mummaneni et al. 2007; Murrey et al. 2009; Nabhan et al. 2007; Park et al. 2008, 2013; Peng et al. 2009, 2011; Phillips et al. 2013; Pickett et al. 2004; Pimenta et al. 2004, 2007; Porchet and Metcalf 2004; Quan et al. 2011; Ren et al. 2011; Riew et al. 2008; Riina et al. 2008; Robertson and Metcalf 2004; Robertson et al. 2005; Ryu et al. 2010; Sasso et al. 2011; Sekhon 2003, 2005; Shim et al. 2006; Suchomel et al. 2010; Tu et al. 2011; Walraevens et al. 2010; Wang et al. 2008; Yang et al. 2008; Yoon et al. 2006; Zigler et al. 2013)

Author	Disc	HO (%)	ASDI (%)[a]	ASDG (%)[a]	Other (%)[a]
Cheng 2011	Bryan	2.4	None	None	Dysphagia (2.4)
Tu 2011	Bryan	50	None	None	None
Lee 2010	Bryan	27	None	None	None
Ryu 2010	Bryan	52.8	None	None	None
Yang 2008	Bryan	None	None	None	None
Shim 2006	Bryan	None	None	None	Op failure (17)
Hacker 2005	Bryan	None	(4.6)	None	Dysphonia (4.5)
Lafuente 2005	Bryan	None	None	None	Dysphonia (7)
Leung 2005	Bryan	17.8	None	None	None
Ding 2012	Bryan	None	None	23	None
Quan 2011	Bryan	47.6	19	19	None
Ren 2011	Bryan	4.4	None	None	None
Garrido 2010	Bryan	None	5	None	Reoperation (6.7)
Bhadra 2009	Bryan	13	None	None	None
Kim 2009	Bryan	None	None	None	None
Heidecke 2008	Bryan	29	None	None	None
Kim 2008	Bryan	None	None	None	None
Wang 2008	Bryan	None	None	None	None
Sasso 2007	Bryan	None	5.4	None	Reoperation (3.5)
Coric 2006	Bryan	None	None	None	None
Yoon 2006	Bryan	None	None	None	None
Duggal 2004	Bryan	None	None	None	None
Pickett 2004	Bryan	None	None	None	None
Sekhon 2003	Bryan	None	None	None	None
Zhang 2012	Bryan	12.5	1.6	None	Reoperation (1.6)
Sasso 2011	Bryan	None	4.1	None	Reoperation (3.7)
Coric 2010	Bryan	5.6	1.7	None	Reoperation (7.5)
Goffin 2010	Bryan	None	4.1	None	Reoperation (8.2)
Walraevans 2010	Bryan	34	None	None	None
Heller 2009	Bryan	None	None	None	Reoperation (2.5)
Pickett 2006	Bryan	2.7	None	None	Reoperation (5.4)
Robertson 2005	Bryan	None	1.3	17.5	None
Sekhon 2005	Bryan	None	None	None	None
Anderson 2004	Bryan	None	None	None	Reoperation (2.2)
Goffin 2003	Bryan	None	None	None	Reoperation (2.0)
Bryan 2002	Bryan	None	None	None	None
Peng 2011	Prestige	None	None	None	None
Riina 2008	Prestige	None	None	None	None
Burkus 2010	Prestige	3.2	2.9	None	Reoperation (10.5)

(continued)

Table 11 (continued)

Author	Disc	HO (%)	ASDI (%)[a]	ASDG (%)[a]	Other (%)[a]
Riew 2008	Prestige	None	None	None	Reoperation (1.9)
Mummaneni 2007	Prestige	None	1.1	None	Reoperation (1.8)
Porchet 2004	Prestige	None	None	None	None
Robertson 2004	Prestige	None	None	None	None
Phillips 2013	PCM	38	39.1	None	None
Pimenta 2007	PCM	0.7	None	None	Reoperation (2.2)
Pimenta 2004	PCM	None	None	None	None
Suchomel 2010	ProDisc-C	88	None	None	None
Peng 2009	ProDisc-C	None	None	None	None
Nabhan 2007	ProDisc-C	None	None	None	None
Mehren 2006	ProDisc-C	57	None	None	None
Bertagnoli 2005	ProDisc-C	None	None	None	None
Zigler 2013	ProDisc-C	None	None	None	Reoperation (2.9)
Kesman 2012	ProDisc-C	None	None	None	None
Kelly 2011	ProDisc-C	None	None	None	None
Murrey 2009	ProDisc-C	2.9	None	None	Reoperation (1.9)
Guerin 2012	Mobi-C	27.7	None	None	None
Lee 2012	Mobi-C	77.3	None	None	None
Park 2013	Mobi-C	94.1	None	None	None
Beaurain 2009	Mobi-C	67	None	9.1	Dysphagia (10.5)
Park 2008	Mobi-C	None	None	None	None
Kim 2007	Mobi-C	None	None	None	None
Huppert 2011	Mobi-C	62	None	None	Reoperation (2.6)
Coric 2011	Kineflex-C	None	None	9	Reoperation (5)
Li 2013	Discover	18	None	7.2	None
Du 2011	Discover	None	9	None	None

[a]Complication rate reported for the arthroplasty investigational cohort
ASDI adjacent segment disease, *ASDG* adjacent segment degeneration, *HO* heterotopic ossification, *PCM* porous coated motion

et al. 2010; Wang et al. 2008; Yang et al. 2008; Yoon et al. 2006; Zigler et al. 2013).

Metal Ion Toxicity

Articulating prosthetic implants are subject to wear and corrosion following implantation. An advantage of metal-on-metal bearings is the substantially lower volumetric wear debris when compared with conventional metal-on-polyethylene bearing couples. A concern regarding any metal-on-metal CDA (e.g., Prestige LP CDA) is that patients may have increased serum metal ion concentrations after surgery since implant wear can lead to local and systemic transport of metal debris (Coric et al. 2018; Gornet et al. 2016). Toxicology-related sequelae from chronically elevated metal ion levels have not been determined. In support of CDA, a 5-year randomized control trial (comparing single-level Kineflex-C CDA with ACDF) demonstrated that serum ion levels (cobalt and chromium) were significantly lower than the levels that merit monitoring (Coric et al. 2018). However, several case studies have reported some early local effects of wear debris (Cavanaugh et al. 2009; Gornet et al. 2016; Hacker et al. 2013).

Patient Selection

CDA is associated with high success rates when performed for appropriately selected patients. However, complications may occur with

improper patient selection, technical errors, or progression of underlying cervical disease (Leven et al. 2017; Nunley et al. 2018; Nunley et al. 2012). Current indications for CDA in the United States (largely dictated by FDA approval of the various prosthetic devices) include skeletally mature patients with cervical radiculopathy and/or myelopathy at a single or two adjacent levels without severe facet joint degeneration, instability, malalignment or kyphosis, or severe neck pain only (Leven et al. 2017; Nunley et al. 2018). Other contraindications include retrovertebral compression (i.e., congenital stenosis or ossification of the posterior longitudinal ligament) and spondyloarthropathies (ankylosing spondylitis) (Leven et al. 2017; Nunley et al. 2018). Patients with a severe axial neck pain due to facet degeneration should be counseled appropriately since these symptoms may not improve after CDA (Leven et al. 2017). Also, some authors have recommended a disc height of 3 mm or greater for adequate disc space access and removal (Ding and Shaffrey 2012). Placing an oversized implant into a collapsed disc space can potentially place excessive forces through the facet joints and lead to worsening of axial neck pain (Ding and Shaffrey 2012).

Cost Efficacy

Although many studies have demonstrated successful treatment with CDA, economic analysis and health costs are also important determinants for obtaining insurance coverage in the United States (Nunley et al. 2018). Therefore, recent studies have focused on analyzing the incremental cost-effectiveness of CDA in comparison with the ACDF. Ament and colleagues reported the incremental cost-effectiveness ratio of CDA compared to ACDF at 2 years post-op for two-level disease was $24954/quality-adjusted life year (QALY). This value is considered to be well within the commonly accepted threshold of $50000/QALY (Ament et al. 2014). Ament and colleagues updated their cost utility analysis at 5 years post-op and reported that the incremental cost-effectiveness ratio for CDA continued to remain below this $50000/QALY threshold (Ament et al. 2016).

In 2014, McAnany and colleagues analyzed 5-year outcomes data and reported cost benefits of CDA compared to ACDF (McAnany et al. 2014). The CDA cost-effectiveness ratio was $35976/QALY compared to $42618/QALY for ACDF (McAnany et al. 2014). In two studies by Radcliff and colleagues, the results suggested that CDA was also the more cost-effective treatment over ACDF (Radcliff et al. 2015, 2016b). Using 3-year data, they found that the total costs paid by insurers for CDA were $34979 compared to $39829 for ACDF. This difference may have been from readmissions and reoperations, which were higher for the ACDF cohort (Radcliff et al. 2015). In another study which analyzed 7-year data, Radcliff and colleagues reported continued cost benefits of CDA over a range of scenarios (Radcliff et al. 2016b).

In 2016, Ghori and colleagues performed a Markov analysis to evaluate the societal costs of ACDF versus CDA in a theoretical cohort of 45–65-year-old patients (Ghori et al. 2016). Their results demonstrated that the long-term costs for CDA were less expensive throughout the model's age range (Ghori et al. 2016). Factors driving lower costs included lower perioperative costs, earlier return to work, and lower reoperation rates (Ghori et al. 2016).

Conclusions

Total cervical disc replacement attempts to preserve normal motion at adjacent segments and in doing so may decrease the incidence of adjacent segment degeneration and disease. Motion-preserving CDA has showed great promise with equivalent quality-of-life outcomes to ACDF in many long-term comparative studies. However, complications such as heterotopic ossification have been reported to occur with some frequency, but the ultimate clinical consequences or implications (in comparison with ACDF) are yet to be determined. Overall, there exists robust data to support CDA as a

viable alternative to ACDF in select patients, but further investigation and continued long-term comparison between CDA and ACDF is warranted.

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Adjacent-Level Disease: Fact and Fiction

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Jonathan Parish and Domagoj Coric

Contents

Keywords

Adjacent disease · Arthroplasty · Cervical fusion · Disc replacement · Motion preservation

Introduction

The topics of adjacent segment (AS) degeneration and disease have been increasingly discussed with the development and adoption of motion preserving devices. AS degeneration is defined as new degenerative radiographic changes at a spinal level immediately above or below surgically treated levels. When this degeneration is associated with clinical symptoms, including radiculopathy, myelopathy, or mechanical instability, then the appropriate terminology is AS disease. Controversy exists as to whether AS disease is primarily due to the natural progression of an underlying degenerative process or an accelerated process due to increased forces placed on adjacent segments following fusion surgery. In theory, motion preserving devices would eliminate or significantly decrease any accelerated degeneration related to fusion and increased biomechanical stress. Both clinical and laboratory studies have addressed

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AS degeneration and disease as well as the factors leading to their development. In this chapter, we will review these studies as well as examine the evidence basis regarding the effect of motion preservation technology on the incidence of AS disease.

Historical Perspective

The etiology of AS disease has been controversial with some studies suggesting that fusion places significantly increased stress on adjacent segments while others arguing that AS disease is primarily due to the natural progression of underlying disease. Furthermore, there is debate over whether motion preservation devices with their ability to eliminate increased forces on the adjacent discs can decrease AS disease.

Historically, the annual incidence of AS disease following fusion is generally reported to range from 1.5% to 4.5% (Bohlman et al. 1993; Cauthen et al. 1998; Gore and Sepic 1998; Hilibrand et al. 1999). Hilibrand et al. (1999) reported on 409 total procedures in 374 patients followed for 10 years. In this series, symptomatic AS disease was defined as a combination of new radicular or myelopathy symptoms referable to an adjacent degenerated level on two consecutive office visits based on chart review and surgical records (a nonvalidated outcome measure). The annual incidence was 2.9% per year over the 10-year study period (range, 0.0–4.8% per year). In this frequently cited study, only 27 patients (6.6%) had adjacent level surgery with an annual adjacent level reoperation rate of 0.7%. A similar study by Goffin et al. (2004) evaluated long term outcomes in 180 patients with a mean follow-up of 30.9 months. 92% of patients had radiographic evidence of increased degeneration at long-term follow-up. Interestingly, age and number of levels fused showed no correlation with degeneration (Spearmen $r_s = -0.033$, $P = 0.660$ and Spearman $r_s = -0.011$, $P = 0.879$, respectively), but the length of time after operation was correlated with degeneration (Spearman $r_s = 0.156$, $P = 0.036$). This suggests a multifactorial etiology to AS degeneration given such a high incidence after fusion surgery, but the correlation with length of time after operation suggestive of natural progression.

Though these studies addressed the incidence of AS disease, they did not provide a definitive etiology. Biomechanical studies by Eck et al. (2002) were performed to evaluate the intradiscal pressure after cervical fusion. In cadaveric specimens, the authors found that increased intradiscal pressure resulted with normal range of motion after fusion. Increased segmental motion adjacent to fusion segment resulted in increased pressures. They were unable to make conclusions regarding increased intradiscal pressure and effect on normal degenerative changes. Additional biomechanical studies using a finite element model of the cervical spine by Lopez-Espina et al. (2006) showed significant increases in stress of up to 96% on the annulus, nucleus, and endplates of adjacent levels in fused (single and double level) versus normal cervical spines. The authors argued that increased rotation and stress may explain the disc degeneration and osteophyte formation after fusion.

The counter argument for natural progression of spinal degeneration over time is also well supported with radiographic and clinical data. Matsumoto et al. (1998) performed 497 MRI on asymptomatic subjects and found a significant occurrence of degenerative changes and age. In their initial study, 17% of men and 12% of women in their 20s had evidence of degenerative changes compared to 86% of men and 89% of women over 60 years of age. A follow-up of 223 of those patients showed progression of degenerative changes in 81.1% of patients with only 34.1% developing clinical symptoms. These studies suggest a rate of natural progression with age for AS degeneration. Similarly, Gore et al. (2002) followed 159 patients for 10 years with asymptomatic cervical disease. Radiographic degeneration was seen in 72 patients at initial imaging and degeneration progressed in 70 (97.2%) of these patients with15% of patients developing pain over the 10-year study period. These studies identify a clear progression of degeneration over time. In regard to the effect of cervical surgery on the

rate of AS degeneration, Lunsford et al. (1980) reported on 253 patients who underwent anterior cervical discectomy with and without fusion (ACD and ACDF). There was no difference in symptomatic relief and recurrence of symptoms. Further, there was no difference in subsequent development of AS degeneration requiring re-operation.

Motion Preservation Devices

Given the rate of AS degeneration and need for further surgery following fusion, motion preserving devices were developed to theoretically reduce effects of AS disease. Initially developed for the lumbar spine, artificial disc replacement has been performed to prevent loss of vertebral interspace height and reduce pain while maintaining motion. Cadaver studies by Wigfield et al. (2003) showed that artificial disc resulted in reduced stresses in the annulus of neighboring cervical segments compared to simulated fusion. These studies supported the theory that motion preservation resulted in less adjacent segment mechanical stress compared to fusion. The earliest clinical reports of disc replacement in the cervical spine were reported by Fernstrom in 1966. His device was used in a series of 32 patients with 74 cervical disc prosthesis reported by Reitz and Joubert (1964) with good results in all patients and preservation of mobility. The earliest reports of AS degeneration after artificial disc replacement were reported by Cummins et al. (1988). In 18 patients with 5-year follow-up, there was no reported adjacent joint degeneration and motion was preserved on flexion and extension x-ray films.

Motion Preservation Effect

Early US Investigational Device Exemption (IDE) trials of artificial disc replacement showed that results were equivalent in regard to neurologic outcome and surgical success, but data regarding AS degeneration was more difficult to assess given the short follow-up. Heller et al. (2009) reported on 24-month outcome for BRYAN cervical disc (Medtronic Sofamor Danek, Memphis, TN). 242 patients were randomized to the BRYAN cervical disc and 221 were in the control ACDF group. The rate of secondary surgical procedures at the treated level was 2.5% in the total disc replacement (TDR) patients and 3.6% in the fusion group though this was not statistically significant. Interestingly, composite overall success was achieved in 82.6% artificial disc patients and only 72.7% of fusion patients ($p = 0.010$). Another randomized, controlled IDE study by Mummaneni et al. (2007) enrolled 276 patients to arthroplasty with PRESTIGE ST cervical Disc System (Medtronic Sofamor Danek, Memphis, TN) and 265 patients to ACDF with 24-month follow-up. The groups showed similar improvement in validated outcome measures (NDI and VAS arm/neck pain scores), but the composite overall success rate was significantly higher at 24 months in the arthroplasty group than ACDF control group (79.3% vs. 67.8%, $p = 0.0053$). The reoperation rate in the arthroplasty group was lower (1.1% vs. 3.4%, respectively, $p = 0.0492$, log-rank test) for AS disease than the control group. Though these 2-year outcomes showed equivalence in this noninferiority statistical design and the effect on AS degeneration was promising, long-term studies of the effect on AS disease with motion preservation were still needed.

One of the earliest attempts to analyze AS disease following cervical artificial disc replacement was performed by Jawahar et al. (2010). In this study, a total of 93 patients were enrolled in 3 prospective randomized trials of artificial cervical discs. Patients showed equivalence in symptomatic relief (71% in TDA vs. 73.5% in ACDF). At last follow-up (median 36.4 months), 15% of patients with ACDF and 18% of TDA had clinical and radiographic AS disease which was not statistically different. A follow-up study by Nunley et al. (2012) included 170 patients with 3- and 4-year follow-up after treatment for 1 and 2-level cervical disc degeneration with cervical artificial disc or ACDF. AS degeneration and disease was reported in 16.5% of patients during follow-up ranging from 32 to 54 months (median 38 months)

though only 4.1% of patients required a second surgery at adjacent level. At 4 years, adjacent level degeneration-free rate was 76.7% in artificial disc group and 78.3% in the ACDF group, suggesting no difference in development of AS disease after arthroplasty.

Another study by Maldonado et al. (2011) prospectively studied 190 patients with a minimum of 3-year follow-up after ACDF or artificial disc to evaluate the incidence of AS degeneration. Radiographic evidence of AS degeneration was defined as new or enlarging anterior osteophytes or new or increased calcification of the anterior longitudinal ligament. AS degeneration was found in 10.5% of patients in the ACDF group and in 8.8% of patients in the arthroplasty group though this did not reach clinical significance ($p = 0.69$). This study did not address AS disease requiring operative intervention.

Another prospective, randomized IDE trial by Davis et al. (2015) followed 291 patients for 48 months after arthroplasty with MOBI-C cervical artificial disc (LDR Medical; Troyes, France) and ACDF. At 4-year follow-up, TDR group had significantly less AS degeneration than the ACDF group (41.5% vs. 89.5%, respectively, $p < 0.0001$). Re-operation at the index level was significantly lower for TDR group (4.0%) versus ACDF group (15.2%, $p < 0.0001$). Indication for TDR group re-operation was stenosis, device migration, poor endplate fixation, and persist neck and/or shoulder pain. The most common indication for re-operation in ACDF group was symptomatic pseudarthrosis. This study also did not address AS disease.

Studies addressing AS re-operation rate provide a more objective assessment of the effect of motion preservation on adjacent levels. In a single institution study by Coric et al. (2010) with 3 separate prospective randomized trials for artificial cervical discs, lower re-operation rates were observed for arthroplasty than fusion. 90 patients were randomized to ACDF (37 patients) or cervical disc arthroplasty (53 patients) with 2-year minimum follow-up (mean 38 months). Clinical success, defined as a composite measure of five separate components, was significantly higher in the arthroplasty group (85%) compared to the ACDF group (70%, $p = 0.035$). Adjacent level disease requiring re-operation occurred at a rate of 1.7% (0.5%/year) in the arthroplasty group which was lower (but not statistically significant) than the rate of 8.1% (2.6%/year) in the ACDF group. A multicenter randomized US FDA IDE trial also by Coric et al. (2011) addressed radiographic adjacent-level changes and re-operation rate. A total of 269 patients were enrolled with 135 patients randomized to TDR with the Kineflex-C disc and 133 to ACDF. There were no preoperative differences in the radiographic changes at adjacent levels. Radiographic deterioration was graded as none, mild, moderate, or severe. At 2-year follow-up, severe adjacent-level deterioration was evident in 24.8% of ACDF patients and only 9% in TDR group ($p < 0.0001$). Index-level re-operation rate was similar (5.0% TDR vs. 6.1% ACDF) and there was no significant difference in AS re-operation rate (7.6% for TDR and 6.1% for ACDF).

Given the low incidence of AS disease requiring re-operation, long term studies and large number of subjects are required to adequately assess the potential positive effect of motion preservation. A single institution study by Coric et al. included two devices (Bryan Disc or Kineflex/C) and enrolled 41 patients in CDR and 33 patients in ACDF control. A total of 63 patients had a minimum of 4-year follow-up. Both arthroplasty and ACDF patients showed a low rate of index level re-operation rate (2.4% vs. 0%, respectively) and adjacent level re-operation (4.9% vs. 3.0%, respectively) without statistically significant differences. Two studies have presented 7-year follow-up on arthroplasty outcomes. Vaccaro et al. (2013) reported a US FDA IDE trial of the SECURE-C device. At 24 months, patients in the arthroplasty group had statistically lower index level re-operations than ACDF (2.5% vs. 9.7%, respectively) and similar AS re-operation rate at 2-years (1.7% vs. 1.4% respectively). Recently, follow-up 7-year data was released that showed very significant differences in index and adjacent level re-operation rates. Index level re-operation rate was significantly lower in TDR group (4.2% vs. 15.3%). For AS re-operation rates, the incidence for cervical TDR was 4.2% compared to 16.0% in the ACDF group. Another long-term

7-year study by Burkus et al. (2014) reported on the efficacy of cervical disc replacement with Prestige Disc (Medtronic, Memphis, TN). 541 patients were randomized at 31 investigational sites to TDR or ACDF. At 84 months, surgery at the index level were lower for TDR than ACDF (4.8% vs. 13.7%, $p < 0.001$) as well as at adjacent levels (4.6% vs. 11.9%, $p = 0.008$).

Long term results have also been observed to be significant for 2 level cervical disc arthroplasty compared to ACDF. Radcliff et al. (2015) reported on 5-year results of TDR and ACDF for 2-level degenerative cervical disease. A total of 225 patients underwent 2-level TDR and 105 patients underwent 2 level ACDF. At 60-month follow-up, there were significantly fewer second surgeries in TDR group than in the ACDF group (71% vs. 21.0%, $p = 0.0006$). In regard to AS degeneration, there also were significantly less AS degeneration in TDR group than in the ACDF group (50.7% vs. 90.5%, $p < 0.0001$). Furthermore, there were significantly fewer AS reoperations in TDR group than in the ACDF group (3.1% vs. 11.4%, $p = 0.0004$). For TDR, the annual rate of AS re-operation was 0.6%/year which is similar to the actual re-operation rate (0.66%/year) reported by Hillebrand.

Radcliff et al. (2015) also reported on a "real-world" application of arthroplasty versus ACDF. A retrospective, matched cohort analysis of patients enrolled in a Blue Cross Plan assessed a "real-world" population with symptomatic cervical disease treated with TDR or ACDF. A total of 6635 patients in the ACDF group and 327 patients in the cervical TDR group. At 36 months, the incidence of reoperation at index level in TDR group was 5.7% compared to 10.5% in ACDF group ($p = 0.0214$). Further, AS re-operation rate was significantly lower for cervical TDR group compared to ACDF (3.1% vs. 11.4%, respectively). This study was performed outside of randomized trials and therefore represents "real world" outcomes supporting a lower incidence of index and adjacent level re-operation after cervical TDR than ACDF. Interestingly, this study also showed a significant reduction in all costs at 2 years of 12% in the TDR group ($34, 979 vs. ACDF $39,820).

Two meta-analysis have also addressed AS disease after cervical arthroplasty and ACDF. Upadhyaya et al. (2012) included 3 randomized, multicenter, US FDA IDE studies. A total of 621 patients received an artificial disc and 592 patients were treated with ACDF. At 24 months, 1098 patients were available for follow up. The rate of secondary surgery at the index level was significantly lower for arthroplasty with an RR of 0.44 (95% CI 0.26–0.77, $p = 0.004$, $I^2 = 0\%$). There was also a significant reduction in the adjacent-level reoperation risk favoring arthroplasty with an RR of 0.460 (95% CI 0.229–0.926, $p = 0.030$, $I^2 = 2.9\%$). McAfee et al. (2012) meta-analysis of the 3 FDA-approved TDR IDE studies above and PCM cervical disc (NuVasive Inc., San Diego, CA). A total of 1226 patients had a with minimum 2-year follow-up. Overall survivorship was defined as the absence of revision, reoperation, supplemental fixation, or device removal within 24-month follow-up period. Survivorship was achieved in 96.6% of arthroplasty patients (804 of 832) and 93.4% of ACDF patients (725 of 776). The difference in proportions was 3.2% (95% CI:1.1–5.3%, $P = 0.004$), suggesting that arthroplasty is superior to ACDF in regard to secondary surgical procedure. Unfortunately, this meta-analysis did not specifically address AS re-operation rate.

Conclusions

AS degeneration leading to re-operation is a multifactorial process. Factors contributing to the etiology of this process include: (a) the natural history of the underlying degenerative disease, (b) surgical technique, e.g., minimally invasive, muscle, and ligament sparing versus open procedures, (c) surgical decision-making, e.g., single versus multilevel surgery, (d) surgical procedure, i.e., fusion versus decompression alone versus arthroplasty, (e) patient specific factors such as overall sagittal balance. Due to inherently low incidence of AS re-operation following cervical spine surgery (<1%), long-term follow-up and/or large patient numbers are needed to demonstrate

statistically significant differences between procedures such as arthroplasty and fusion. Studies aim at detecting differences with only 2-year follow-up with less than several thousand patients are simply not powered to show statistically significant differences. Biomechanical studies have indicated cervical arthroplasty puts less stress on adjacent segments compared to fusion. Some prospective, randomized clinical studies indicate that arthroplasty decreases the rate of AS degeneration. Limited studies with long-term follow-up also support that arthroplasty may lead to less subsequent surgical intervention at index and adjacent segments. But continued long term data is required to confirm that this trend remains significant.

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Posterior Dynamic Stabilization

50

Dorian Kusyk, Chen Xu, and Donald M. Whiting

Contents

Abstract

Posterior dynamic stabilization (PDS) systems arose with the promise of stability without fixation. In particular, these systems address the two prevailing models of spinal biomechanics – the Panjabi model of the Neutral Zone and Mulholland-Segupta theory of abnormal load transmission. By both limiting the range of motion of the diseased level and off-loading the disc space of some axial stress, PDS systems hope to treat back pain while preserving motion. However, these design constraints post a significant design challenge, as demonstrated by the multiple models that have been visited over the years. Though a successful PDS system has yet to emerge, surgeons have found other ways to use the technology, including as an adjunct to improve fusion rates when paired with interbody devices.

Keywords

Posterior dynamic stabilization · Neutral zone · Fusion biomechanics · Graf ligament · Dynesys

Introduction

The question of the treatment of axial back pain, along with the concept of spinal instability, is still incompletely understood. The current gold

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standard is spinal fusion, which internally fixes spinal elements until a patient can undergo a boney fusion across the levels in questions. However, a spinal fusion will abnormally fix two spinal vertebral bodies, which not only reduce a patient's mobility, but increases the risk of developing adjacent level pathology.

To begin addressing these concerns, posterior dynamic stabilization (PDS) was introduced with the development of the Graf ligament in 1989 and the Dynesys in 1994 (Gomleksiz et al. 2012). The promise of these devices and the multiple iterations since was stability without fixation and therefore pain relief without the long-term repercussions of a rigid construct. However, enthusiasm for these devices has waned considerably in recent years given the mechanical failure of the devices and the failure of clinical success has become increasingly documented (Sengupta and Herkowitz 2012).

The following chapter will review some of the conceptual underpinnings of dynamic stabilization and its proposed benefits, briefly describe some of the key devices designed in this space along with lessons learned from them, and finally, discuss the current literature regarding the use of dynamic stabilization devices in hybrid constructs as a potential path forward with the technology.

Biomechanics of Dynamic Stabilization

Two prevailing theories of spinal biomechanics are used to explain low back pain, and PDS theoretically would address both as pain generators. Panjabi's model describes pain in terms of Neutral zone (NZ) and the range of motion (ROM) of vertebral segments (Panjabi 1992). In his 2003 paper, he described the NZ as the range of motion to which there is minimal resistance to vertebral motion. In the nonpathologic spine, the neutral zone encompasses a smaller ROM than the joint's painful zone – that is, the ligaments and other support structures of the spine limit vertebral motion before it causes pain. However, with ligament laxity or other pathology, the neutral zone of the spine can expand and permit positions of flexion and extension which are painful (Panjabi 2003). PDS seeks to reduce a patient's pain by restoring a more physiologic NZ. Where spinal fusion reduces the neutral zone to very limited motion, dynamic stabilization would theoretically restore a more natural NZ.

According to a second hypothesis, spinal instability should not be thought of as unnatural movement of the segment, rather as abnormal load transmission at the level. According to Mulholland and Segupta, disc degeneration makes it nonhomogeneous with areas with increasingly larger loads transmitted through the annulus. Load transmission therefore becomes uneven, which in turn leads to focal in-folding of endplate cartilage and subchondral bony trabeculae, analogous to a stone a shoe (Mulholland and Sengupta 2002; Simpson et al. 2001; Keller et al. 1989). PDS can help unload the disc space by providing a posterior tension band, ultimately reducing the back pain caused by the uneven load distribution. Some researchers argue that by unloading the disc, the patient will actually begin to repair the damage (Beckmann et al. 2019; Cho et al. 2010).

In addition to addressing the biomechanical foundations of back pain, PDS also aims to limit the risk of adjacent level disease. One of the largest limitations of a rigid fusion construct is the stress it places on levels above and below the initial pathology, likely due to an increased lever arm and the development of a nonphysiologic center of motion. This in turn leads to fractional increases in joint ROM, which in time develops to gross spinal instability and low back pain (Park et al. 2004). Put another way, hard fusion constructs force adjacent levels to expand their neutral zones to adjust to limited mobility, until the neutral zone of the adjacent level extends beyond the pain-free ROM of the joint. PDS would theoretically limit this risk by maintain a physiologic ROM at the diseased level and decrease the stress placed on adjacent levels (Bono et al. 2009; Aygun et al. 2017).

Though PDS devices have many theoretical advantages, it should be noted that these pose a significant design challenge. First, in order for a device to be considered a dynamic stabilization device, it must limit joint motion to a physiologic

range and unload the pathologic disk space. Additionally, the dynamic stabilization devices are fundamentally different from a fusion construct – whereas a traditional fusion construct needs to last just long enough for the patient's own bone remodeling to fuse across the segment, the PDS systems need to last indefinitely. Dilip Sengupta argues that these devices need to have uniform motion restriction and load-sharing throughout the ROM (Sengupta and Herkowitz 2012). Any asymmetry in load or motion would lead to an increase of stress on the device and lead to its premature failure.

PDS Devices

There are three main categories of PDS systems depending on the location of where the device is implanted. These focus on the pedicles, the facets, or the spinous processes.

Pedicle Based Systems

The Graf Ligament was one of the earliest pedicle based systems first reported in 1992 (Graf 1992). It was developed in Europe and used braided polyester cables looped around pedicle screws (Fig. 1). There have been several studies that have shown inconsistent outcomes of the device. One study reported patients undergoing the Graf ligamentoplasty doing clinically better in comparison to anterior lumbar interbody fusions (ALIFs) (Madan and Boeree 2003), while another showed worse outcome at 1 year and increased revision rate at 2 years with the Graf ligamentoplasty when compared to posterolateral fusions in the management of low back pain (Hadlow et al. 1998). As regards to patient satisfaction, studies have reported anywhere from 96% of patient feeling that the operation was worthwhile to 41% of patients stating they would not have chosen to have the operation again (Grevitt et al. 1995; Rigby et al. 2001).

The Dynesys system manufactured by Zimmer Spine uses nylon cords combined with plastic spacers (Fig. 2). In comparison to traditional posterior lumbar interbody fusions (PLIFs), the Dynesys was shown to offer similar improvement in clinical outcomes for lumbar degenerative disease. In addition, the Dynesys system was reported to have significantly less adjacent segment disease radiographically when compared to PLIFs and also offered more range of motion (ROM) (Zhang et al. 2016).

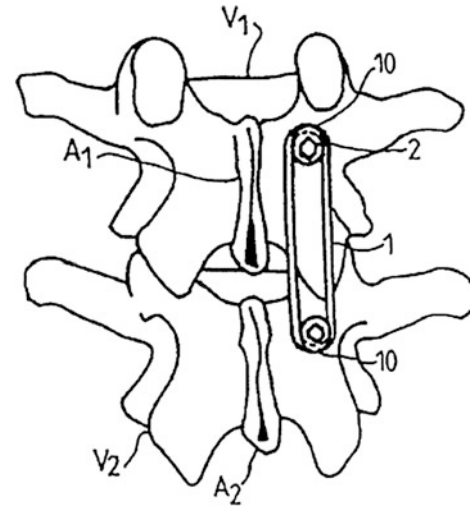

Fig. 1 Graf ligament. (Taken from original 1990 patent filing)

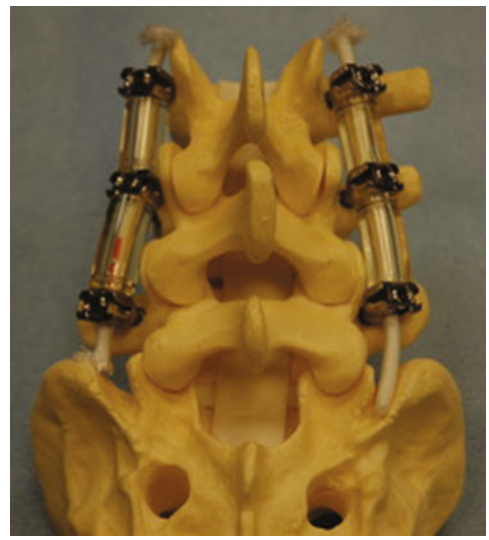

Fig. 2 Dynesys pedicle screws and spacer

The Dynamic Soft Stabilization (DSS) system uses pedicle screws with metal coils connecting the screws to control motion (Figs. 3 and 4). And the Isobar is essentially the tradition rod system but with a mobile joint within the rod.

Fig. 3 Dynamic soft stabilization (DSS) (Courtesy of Paradigm Spine, Device not available in the U.S.)

Facet Replacements

The majority of the facet replacement systems have some involvement of the pedicles, although the focus is on motion preservation at the facet joints. The Total Posterior Element Replacement (TOPS) system requires complete removal of the posterior elements for the device to be implanted and is anchored through the pedicles and is the only such device currently in active clinical study.

Interspinous Process Spacers

The Coflex system is the most common interspinous implant currently used in clinical practice. The device is a "U" shape allowing for distraction of the neuroforamina as well as controlled forward and backward bending. Previous studies have shown favorable outcomes with reports of 33% and 66% reductions in back pain and leg pain severities, respectively, with 95% satisfaction form patients (Errico et al. 2009).

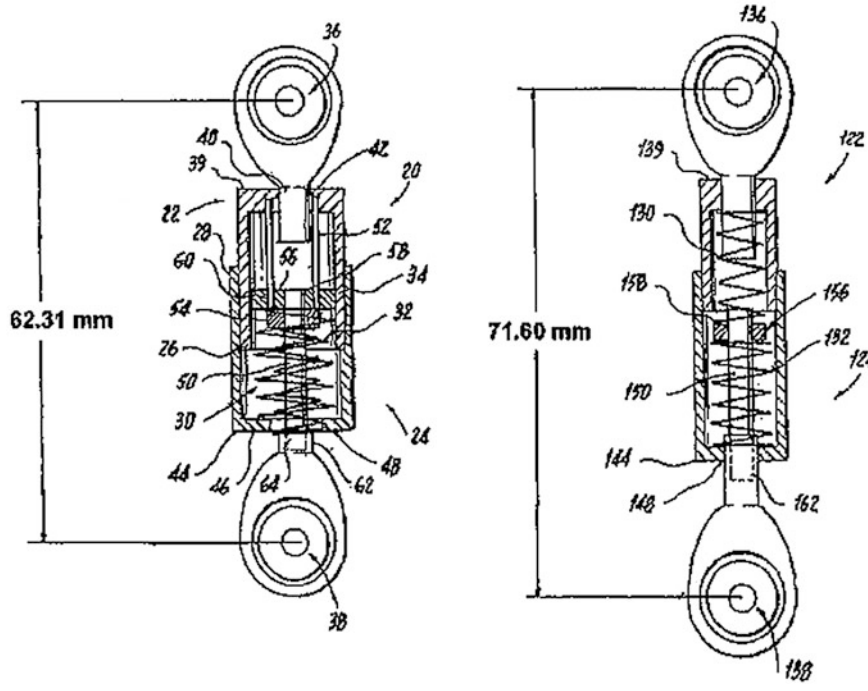

Fig. 4 DSS detail (Hildebrand and Trimm 2005)

This device does require a fair amount of laminotomy to be performed as well as drilling of the spinous processes for implantation with avoidance of posterior canal compression.

PDS as an Adjunct to Fusion

Given the long list of design requirements for a successful device, it is not surprising that in the United States, PDS devices have not been approved as a stand-alone construct. Instead, PDS devices are used as adjuncts to interbody devices to theoretically improve fusion rates.

The foundation of any fusion can be described by Wolff's Law (Wolff 1986), also known as the law of bone remodeling. In brief, Wolff's law describes cellular mechano-transduction – the conversion of mechanical stressors into biochemical signals. In the context of spinal fusion, the law implies that bone remodeling and growth may be enhanced through greater loading on the graft. Though rigid spinal fusion constructs are adequate in this regard, they are still plagued by high rates of pseudoarthrosis, and one reason may be the stress shielding phenomenon. If the pedicle screw-rod complex is too rigid, it can theoretically offload the anterior column. According to Wolff's law, that can only undermine the efficacy of fusion and could potentially play into rates of pseudoarthrosis. In contrast, PDS can maintain a controlled amount of motion when paired with an interbody. As the bone settles and remodels, the microadjustments allowed by a dynamic system can ensure a constant loading force on the anterior column and theoretically a better rate of fusion (Yu et al. 2016). Though this use of the PDS is contrary to the device's initial intent, it is a welcome windfall as the research community continues to search for the ideal motion preservation stabilization device.

Cross-References

► Design Rationale for Posterior Dynamic Stabilization Relevant for Spine Surgery

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Total Disc Arthroplasty

51

Benjamin Ebben and Miranda Bice

Contents

Abstract

The concept of total disc replacement in the spine has been present for decades because of the desire to maintain physiologic motion of spinal segments while treating underlying pain-generating pathology. There has been considerable evolution of this technology,

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with successes, failures, and the popularity of these procedures waxing and waning over time. Much in vitro and in vivo research has been done on both past and current devices to facilitate understanding of this technology and optimize utilization for clinical success and progress. This chapter describes some of the historical background, current uses and approved devices, surgical techniques, complications, revision options, and outcomes of both lumbar and cervical disc replacement.

Keywords

Lumbar disc replacement · Cervical disc replacement · Disc arthroplasty · Adjacent segment degeneration · Adjacent segment disease · Motion sparing · Spine arthroplasty · Artificial disc

Introduction

Historically, the initial management of painful degenerative spinal disc disease has been conservative and supportive measures. When these efforts fail to provide meaningful relief, decompression and arthrodesis is generally considered the accepted surgical intervention for its effectiveness in maintaining intervertebral height, establishing segmental stability, and improving pain. Overall, arthrodesis has proven quite successful over time. However, the reported reoperation rates cannot be ignored. These reoperations are frequently reported due to persistent or recurrent pain from symptomatic adjacent level degeneration or pseudarthrosis. Although heavily debated, current thought suggests that the complications associated with arthrodesis, namely, adjacent level disease, exist secondary to the alteration of normal spine biomechanics associated with the fusion of a previously mobile segment. There has been a considerable amount of literature dedicated to not only uncovering the presumed association between arthrodesis and adjacent level deterioration but also to investigating the biomechanical and biochemical basis behind this theoretical relationship.

In vitro cadaveric studies have demonstrated increased stresses at mobile segments adjacent to the site of fusion in the cervical spine. Eck et al. found that intradiscal pressure (IDP) increased significantly both cranial and caudal to a cervical fusion during flexion compared to an intact spine by 73% and 45%, respectively (Eck et al. 2002). Similarly, Chang and colleagues reported significantly elevated IDP in the cranial mobile segment during both flexion and extension following cervical fusion. These investigators also demonstrated effects on posterior element stress levels following cervical fusion and found that facet joint forces were significantly greater at both adjacent mobile segments during extension (Chang et al. 2007). A similar group of cadaveric biomechanical studies have been performed in the lumbar spine following instrumented arthrodesis with comparable findings of increased stress within the intervertebral discs and/or facet joints (Cunningham et al. 1997; Lee and Langrana 1984). Examination of intervertebral disc physiology shows that the health of this avascular structure is related to the relative concentrations of specific collagen and proteoglycan subtypes. The maintenance of this extracellular matrix is, in turn, reliant upon adequate diffusion of nutrients through the vertebral body cartilaginous endplate. It can be reasonably inferred that the discs within adjacent mobile segments exposed to chronically elevated intradiscal hydrostatic pressures following spinal arthrodesis may degenerate at an accelerated rate due to the disruption of this intricate metabolic balance (Buckwalter 1995; Hutton et al. 1998).

Long-term radiologic follow-up studies after spinal fusion have reported high incidences of adjacent level degenerative changes. In 2004, Goffin et al. published their radiologic findings for a series of 180 patients an average of 8 years following cervical interbody fusion. They found that 92% of the patients demonstrated an increase in degeneration score at adjacent levels at long-term follow-up. A suggestive trend of correlation, albeit not statistically significant, was appreciated between adjacent level radiologic degeneration and clinical outcomes (Goffin et al. 2004). Other authors have tried correlating these observed

radiologic changes with clinical outcomes. In a landmark study, Hilibrand and colleagues studied the development of new radiculopathy or myelopathy referable to mobile segments adjacent to previous anterior cervical arthrodesis in 374 patients available for 10-year follow-up. They reported a nearly 3% annual incidence of symptomatic adjacent segment degeneration and a Kaplan-Meier survival analysis predicted an overall prevalence of 25.6% within the first 10 years after the procedure. Twenty-seven patients underwent a second operation for fusion at the adjacent symptomatic level (Hilibrand et al. 1999). Ghiselli et al. studied adjacent segment disease in the lumbar spine and reported similar clinical outcomes. Fifty-nine of 215 patients, followed for an average of 6.7 years after posterior lumbar arthrodesis, developed symptomatic adjacent segment degeneration that warranted additional surgery. The authors reported a nearly 4% annual incidence of surgical intervention for adjacent segment disease and their survivorship analysis predicted that 36.1% of patients would have new disease requiring reoperation within the first 10 years following the index procedure (Ghiselli et al. 2004). There is a sizeable amount of literature further investigating clinical outcomes following spinal arthrodesis with a focus on defining its contribution to the development of symptomatic adjacent segment degeneration (Park et al. 2004; Gore and Sepic 1998).

Despite the substantial supporting data, no causation has been definitively proven. Randomized controlled trials investigating the relative rates of symptomatic adjacent segment disease with and without arthrodesis do not exist as it would be unethical to deny patients a fusion operation for a situation in which they would otherwise be indicated. Some experts would argue that adjacent segment degeneration is a consequence of natural history and can be expected as an inherent fate in a spine that has already shown signs of degenerative disease. To this end, studies have attempted to decipher the relative contributions of fusion and the natural aging process. Matsumoto et al. evaluated the pre-surgery and 10-year follow-up MRI images of 64 patients who underwent anterior cervical decompression and fusion (ACDF). They compared the observed radiologic changes to a group of asymptomatic volunteers who, likewise, underwent a baseline and 10-year follow-up MRI. The incidence of progression of degenerative disc disease was significantly higher in the ACDF group (Matsumoto et al. 2010). Nonetheless, this study was limited by differences in group characteristics including both a higher mean age and observed frequency of baseline MRI degenerative findings in the ACDF group. Interestingly, two of the landmark publications referenced earlier found that multilevel fusion is actually protective rather than promotive when it comes to adjacent segment degeneration. Hilibrand et al. discovered that only 12% of patients who underwent multilevel arthrodesis developed symptomatic adjacent segment degeneration, an odds ratio of 0.64 when compared to single level (Hilibrand et al. 1999). In the lumbar spine, mobile segments adjacent to single-level arthrodesis were three times more likely to develop symptomatic adjacent segment degeneration than segments adjacent to a multilevel arthrodesis (Ghiselli et al. 2004).

Another frequently studied complication of spine arthrodesis is the development of a symptomatic pseudarthrosis. There are established but quite variable rates of pseudarthrosis within the cervical and lumbar spine literature. Rates are technique-dependent and vary based on multiple factors including the use of an interbody device, fixation rigidity, whether or not instrumentation was performed, choice of graft, etc. Martin and colleagues used a registry of statewide (Washington) hospital discharges to investigate rates of reoperation following lumbar spinal surgery and found that the cumulative 11-year incidence of reoperation following an index fusion procedure was 20%. Of the 471 reoperations following an index fusion, 23.6% were associated with a coding of pseudarthrosis (Martin et al. 2007). A 47-article meta-analysis conducted to determine success and complication rates for lumbar spinal fusion found pseudarthrosis as the most frequently reported complication (14%). Authors also noted a positive relationship between satisfactory patient outcomes and achievement of solid

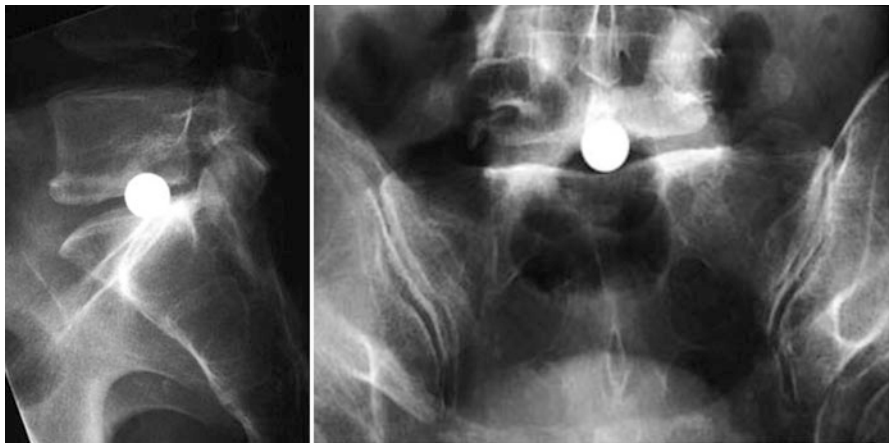

Fig. 1 Fernstrom Ball prosthesis. (Reprinted with permission from Szpalski et al. *Eur Spine J* 2002)

arthrodesis (Turner et al. 1992). A similar meta-analysis investigating the overall incidence of pseudarthrosis following fusion in the cervical spine found a much lower overall rate of 2.6% (Shriver et al. 2015). The true incidence of spine pseudarthrosis is probably underestimated as a percentage are asymptomatic and prompt no further diagnostic workup or additional management.

To combat the pitfalls discussed above that are associated with spinal fusion, the field of spinal arthroplasty and the concept of motion sparing spinal implants evolved. The growth of this field was heavily influenced by the technologic successes of motion-preserving joint prostheses for the treatment of degenerative joint disease in the hip and knee. Motion sparing technology could potentially circumvent the limitations of arthrodesis. In theory, by implanting a motion sparing prosthetic within the intervertebral space, accelerated adjacent segment degeneration could be mitigated. The potential for pseudarthrosis development could be eliminated with no attempt at surgical fusion. In addition, maintaining the mobility of the spinal segment could lead to preservation of normal spine biomechanics and could maximize patient motion, function, and improve clinical outcomes. Along these lines, investigators began to define the characteristics of an ideal spinal arthroplasty system which would include the reproduction of native disc viscoelastic properties, the reproduction of native disc motion characteristics, and the ability to withstand the mechanical and chemical environment of the intervertebral space.

A Swedish surgeon, Ulf Fernström, is historically credited with implantation of the first artificial disc in a human patient, and his experiences were published in the late 1960s and the early 1970s. His prosthesis was quite simple and consisted of a single, corrosion-resistant stainless steel ball bearing implanted into the center of the intervertebral disc space (Fig. 1). It is estimated that he implanted approximately 250 of these devices in total, both in the lumbar and cervical spine (Le et al. 2004; Basho and Hood 2012; Baaj et al. 2009). A duo of South African surgeons, impressed with Fernström's early results, also implanted 75 of these devices in the cervical spine during the same time period, for the treatment of intractable headache and cervico-brachialgia (Reitz and Joubert 1964). Ultimately, with longer-term follow-up, these mobile bearings failed miserably. The unconstrained nature created segmental spinal hypermobility, and the lack of endplate support resulted in a tendency for subsidence and migration into the superior endplate (Le et al. 2004). These early disappointments lead to a temporary abandonment of spinal arthroplasty surgical practice in favor of arthrodesis until the 1980s. Nonetheless, Fernström was ahead of his time in recognizing the potential benefits of motion sparing devices, and other researchers continued to investigate alternative designs.

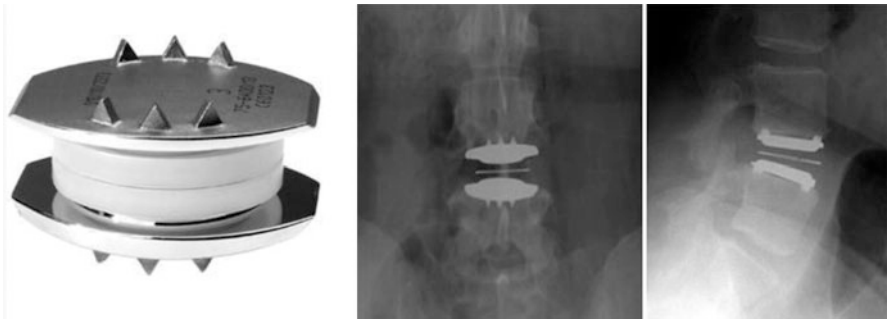

Fig. 2 Charite III prosthesis. (Reprinted with permission from Atkins, et al. *Lumbar Disc Arthroplasty.* In: Essentials of Spinal Stabilization. Holly L., Anderson P. (eds). Springer, Cham. 2017)

Multiple spine arthroplasty models were subsequently developed during the second half of the twentieth century, a majority of which were patented or published but never reached the stage of human implantation (Szpalski et al. 2002).

Spine arthroplasty then garnered renewed interest in 1984 after the maiden implantation of the German-engineered SB Charité I prosthesis, which was the first approved and commercially available lumbar total disc replacement system available in Europe (Link 2002). The SB Charité I was an unconstrained device featuring small, circular, polished steel alloy endplates with anchoring teeth for cementless fixation and a sliding ultrahigh molecular weight polyethylene (UHMWPE) core marked with a radio-opaque circumferential wire (Büttner-Janz et al. 1989). The sliding core allowed for a dynamic instantaneous axis of rotation that could translate during flexion and extension, more closely mimicking normal lumbar spinal motion (Bono and Garfin 2004). Similar to Fernström's ball bearing implants, the earliest SB Charité model lacked sufficient endplate contact surface area secondary to its undersized metal endplates and was noted to subside or migrate axially (Link 2002). This design flaw prompted development of a second version, the SB Charité II, with enlarged metal endplates. Problems with fatigue fractures ultimately lead to the third- and final generation Link SB Charité III (DePuy) device which started production in 1987 in Europe and eventually received FDA approval in the United States in 2004 after 2-year follow-up results from its investigational device exemption (IDE) randomized controlled trial showed noninferiority to lumbar arthrodesis (Fig. 2) (Blumenthal et al. 2005). Subsequent 5-year follow-up data showed a FDA-defined clinical success rate of 58% in the Charité group and 51% in the arthrodesis group (Guyer et al. 2009). Even longer-term follow-up and device retrieval studies have become increasingly available and shed light onto some of the device late failure mechanisms. Punt et al. published a case series analyzing late complications following SB Charité III disc implantation in a group of 75 unsatisfied patients that presented to their institution with persistent leg and back pain. Forty-six of the 75 patients ultimately ended up undergoing a salvage operation, and the authors were directly involved in 37 of these cases. They reported implant subsidence, adjacent disc degeneration, and index-level facet arthrosis as the three most common late complications. Of the 39 cases of observed implant subsidence, they estimated that 24 were secondary to an undersized prosthesis. The authors also reported on 8 cases of anterior-posterior migration and 10 cases of polyethylene core wire breakage (Punt et al. 2007). Van Ooij and colleagues reported very similar findings in their 27 patient case series (van Ooij et al. 2003). In a 2007 international multicenter retrieval study of 21 explanted SB Charité III implants from patients undergoing revision surgery due to persistent pain, Kurtz et al. analyzed polyethylene wear patterns and found the peripheral rim to be susceptible to pinching as evidenced by the observation of plastic

deformation, fracture, cracking, and other fatigue damage in most of the specimens (Kurtz et al. 2007). Current long-term clinical outcome data and the results of the most recent FDA IDE randomized controlled trials for the SB Charité III, its contemporaries, and its successors will be covered elsewhere in this chapter. Overall, however, the SB Charité III was quite successful and underwent widespread implantation for many years. It was removed from the US market in 2013 as part of a business decision when DePuy purchased Synthes and elected to sell its lumbar arthroplasty system, the ProDisc-L.

Currently, there are two FDA-approved lumbar arthroplasty systems. The Synthes ProDisc-L was developed concurrently with the SB Charité III in the late 1980s. Like the Charité, it underwent stepwise modifications from its initial design to the release of the current model, which received FDA approval in 2006. Unlike the Charité, the ProDisc-L is a semiconstrained device. There is a single articulating interface between a polyethylene bearing and the superior endplate. The polyethylene bearing is fixed to the inferior endplate and does not slide or translate as in the Charité. The ProDisc-L is secured to the neighboring vertebral bodies via a keel or midline sagittal fin (Bono and Garfin 2004). There is currently a considerable amount of longer-term follow-up studies (>5 years) supporting the use of this device in patients with lumbar degenerative disc disease. The ActivL (Aesculap Implant Systems) prosthesis received FDA approval in 2015 after its 2-year follow-up data showed noninferiority to the other two previously mentioned lumbar arthroplasty prostheses. This implant has been marketed as next generation in that it is designed to be inserted as a single unit, obviating the need for multiple spinal distractions. In addition, its polyethylene inlay is affixed to the inferior endplate in a way that permits a limited amount of translational motion (Garcia et al. 2015).

The technological triumphs in lumbar arthroplasty motivated the pursuit for a counterpart in the cervical spine. The first modern era artificial cervical disc was developed in the United Kingdom and was implanted in 1991. This device came to be known as the Cummins-Bristol and had two distinctive design features when contrasted to the previously discussed lumbar prosthetics: (1) a metal-on-metal articulation with no separate intercalary polyethylene bearing and (2) anterior flanges for the purpose of obtaining immediate anchoring screw fixation into the cranial and caudal vertebral bodies. Early results were quite poor and related to failure of the anterior screw fixation via screw pullout and screw fracture. Following modifications to screw hole positions and the addition of locking screw capabilities, a subsequent group of 20 patients, implanted with the device between 1991 and 1996, fared much better according to Cummins and colleagues. The authors reported that 75% of the patients experienced an improvement in preoperative symptoms and that 88% of the patients available for follow-up in 1996 had radiographic evidence of maintenance of index level motion (Le et al. 2004; Cummins et al. 1998). There were also four patients with persistent dysphagia attributed to the high profile of the anterior flanges. Two years later, a redesigned second-generation version of the Cummins-Bristol artificial disc, known as the Frenchay, was implanted into 15 patients as part of a pilot study (Fig. 3). The Frenchay's superior component "ball" remained hemispherical, while the inferior component "socket" was shallow and ellipsoid making for an incongruent articulation. Theoretically, this permitted the cranial vertebral body to passively align with the dynamic center axis of rotation as dictated by the facet joints. At 2 years, the prosthetic joints remained mobile with an average arc of 6.5° in flexion and extension, there were no cases of joint subluxation or subsidence, and there were 3 reoperations, only one of which involved explanation of the prosthesis for looseness (Wigfield et al. 2002). The Frenchay would eventually become the Prestige (Medtronic), which is one of the commercially available cervical total disc replacement systems on the market today. This device received US FDA approval in 2007, and the latest long-term (7-year) clinical outcome data has been very favorable showing a statistically significant greater overall success rate of 75% in the

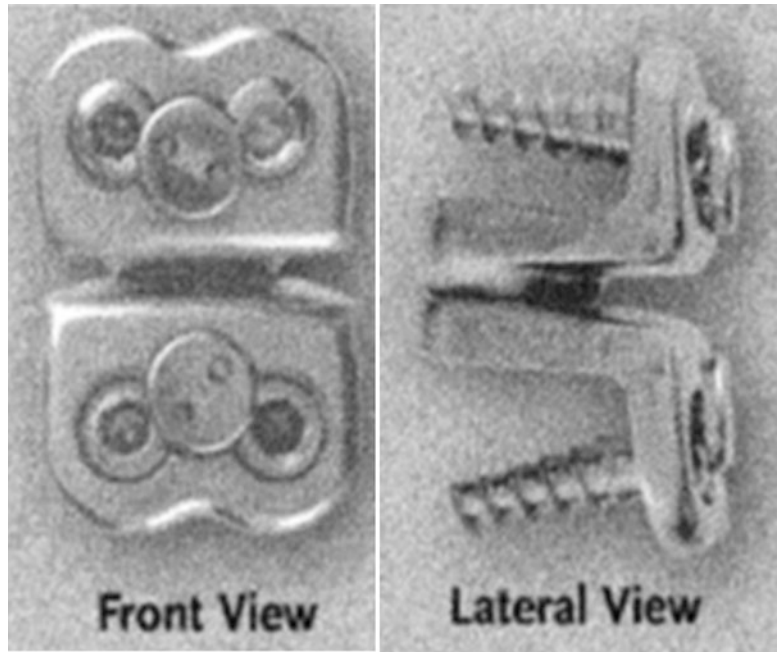

Fig. 3 Frenchay prosthesis. (Reprinted with permission from Buell, et al. Cervical Arthroplasty: Long-Term Outcomes. In: Handbook of Spine Technology. Cheng B. (eds). Springer, Cham. 2019)

arthroplasty group compared to 64% in the control arthrodesis group. These authors also reported maintenance of physiologic segmental angular motion at the index level and an index level secondary surgery 11-year cumulative rate of 4.8% compared to 13.7% in the arthrodesis group (Burkus et al. 2014).

Another unique, albeit unsuccessful, cervical arthroplasty concept is worthy of brief mention. The Pointillart cervical prosthetic entered the scene momentarily between 1998 and 1999, and its concept was influenced by unipolar hip replacement designs (Fig. 4). It featured a single titanium base piece which was anchored via screws into the caudal vertebral body and a carbon sliding cranial surface meant to articulate with the inferior endplate of the cranial vertebral body. The inventing surgeon implanted this device into ten patients and reported "total failure" after 1-year follow-up radiographs showed spontaneous fusion and resultant absence of motion across the index level in eight of the patients (Pointillart 2001).

There are currently six FDA-approved cervical total disc replacement systems: Prestige (Medtronic), Bryan (Medtronic), Mobi-C (Zimmer-Biomet), ProDisc-C (DePuy Synthes), PCM (NuVasive), and Secure-C (Globus Medical). All of these devices have 2–7-year US FDA IDE prospective randomized controlled trial clinical outcome data showing non-inferiority to anterior cervical decompression and fusion (Sasso et al. 2011; Hisey et al. 2016; Janssen et al. 2015; Phillips et al. 2015; Vaccaro et al. 2013). As with any surgical procedure, particularly in the spine, strict adherence to appropriate criteria of both patient selection and surgical indications is paramount for successful outcomes.

Surgical Techniques: Cervical Disc Replacement

Indications

- Subaxial spinal motion segments between C3 and C7
- One or two-level pathology
- Radiculopathy and/or myelopathy secondary to neural element compression by:
  - Soft disc herniation
  - Osteophyte formation

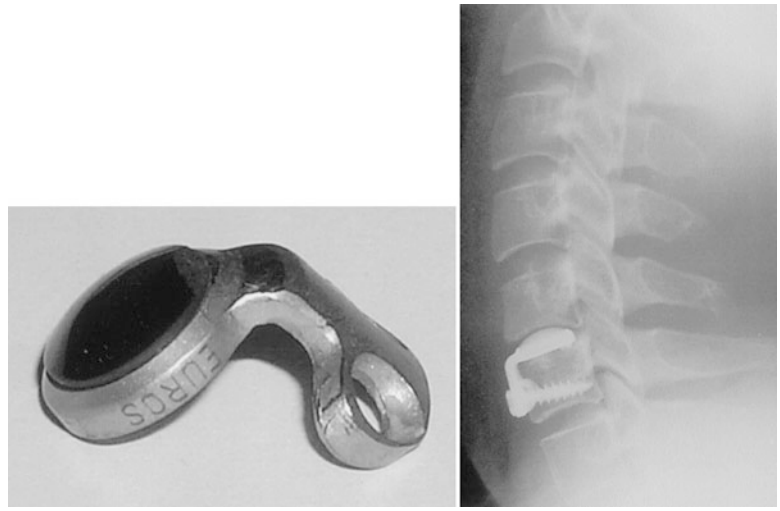

Fig. 4 Pointillart prosthesis. (Reproduced with permission from Pointillart, *Spine* 2001)

Contraindications

- Spondylolisthesis, instability with translation of greater than 3.5 mm
- Deformity
  - Including kyphosis of greater than 11° at the target level
- Trauma (concern for disruption or irregularity of vertebral endplates)
- Prior cervical laminectomy (concern for disruption of posterior stabilizing elements at the level of interest)
- Prior surgery at the level of interest
- Osteoporosis (T-score less than −2.5)
- Other metabolic bone diseases which may result in abnormal bony architecture and/or stability
  - Rheumatoid arthritis, other inflammatory arthropathies
  - Renal disease
  - Cancer
  - Long-term steroid use
- Infection
- Severe facet arthropathy
- Ankylosing disorders
  - Ankylosing spondylitis
  - Diffuse idiopathic skeletal hyperostosis (DISH)
  - Ossification of the posterior longitudinal ligament (OPLL)
- Metal allergy
- Isolated axial neck pain without radiculopathy or myelopathy

Relevant Anatomy

A standard Smith-Robinson approach to the anterior cervical spine is utilized for cervical disc replacement. While this is generally regarded as a common and safe approach, detailed knowledge and understanding of the local anatomy is necessary to minimize inadvertent injury to several important structures:

Nerves

- **Superior laryngeal nerve** is typically encountered for procedures in the upper cervical spine, at or above C3 and C4. It can be identified traversing from the carotid sheath to the larynx at the thyrohyoid membrane along with the superior laryngeal artery. As this nerve contributes to control of a vocal cords, injury to it may result in difficulty with voice control (dysphonia) and swallowing or aspiration (dysphagia).
- **Recurrent laryngeal nerve** is occasionally visualized on its recurrent path in the tracheoesophageal groove. On the left, once the nerve exits the carotid sheath, it

courses inferiorly under the aortic arch prior to returning cephalad in the tracheoesophageal groove. The recurrent laryngeal nerve on the right is beneath the right subclavian artery and is less constant. For this reason, it is sometimes dogmatically believed to be safer to perform the approach on the left side as this course was previously felt to be more predictable; however this has not been demonstrated clinically, and there are many surgeons that perform this approach on the right side without any increased complication rate related to phonation or swallowing. This nerve also contributes to control of vocal cords well as all of the laryngeal muscles and the esophagus. Similar to injury of the superior laryngeal nerve, injury to this nerve can also result in difficulties with dysphonia and or dysphagia.

- **Sympathetic chain** lies on the ventral surface of the longus coli muscles. Because of this, manipulation in this area is generally avoided, with dissection generally limited to the medial aspect of the longus coli. Injury to the sympathetic chain can result in an ipsilateral Horner's syndrome.

Vessels

- **External jugular vein** lies between the platysma and the caudal mastoid. It often is lateral to the operative field; however occasionally the main external jugular or large branches of it can cross the surgical field. Injury to it may not result in significant functional impairment; however it can bleed quite vigorously, adding difficulty and time to the surgery.
- **Carotid artery** travels within the carotid sheath. It can be easily palpated as a pencil-like structure deep to the sternocleidomastoid muscle belly and used as a landmark for the approach as the entirety of the approach should be medial to this structure along with the other contents of the carotid sheath.
- **Vertebral artery** travels within the foramen transversarium of the cervical vertebrae. It typically enters at C6, although can also enter at C7, and travels proximally to supply the brainstem and posterior cranial contents. The longus colli muscle lies ventral to the transverse foramen containing these vessels, and so dissection deep to the longus muscle belly is very limited and cautious to avoid injury to the vertebral arteries. However, should a vertebral artery injury occur elsewhere during the procedure, dissection deep to the longus colli can be utilized to gain access to the vessel and control bleeding. Injury to this blood vessel can result in rapid exsanguination. The overall implications of vertebral artery injury varies widely, from asymptomatic to stroke or even death.

Trachea and Esophagus are midline structures medial to the plane of approach. Further mobilization is often necessary for adequate exposure to the targeted disc site(s). Because of its cartilaginous rings, the trachea is more easily identified. The esophagus lies deep to the trachea. As it is composed of smooth muscle of varying degrees of thickness, it is more prone to inadvertent injury during anterior cervical approaches. Injuries to these structures are often occult and not always identified intraoperatively but can lead to profound morbidity and even mortality if not identified and treated appropriately. For these reasons, a high index of suspicion is mandatory during both the index procedure and follow-up if anything is amiss.

Positioning and Approach

The patient is positioned supine on a radiolucent operating table. The authors prefer to have the patient as caudal on the table as patient's height will allow to provide space for the C-arm rostral to the patient when not in use. The neck is positioned in neutral alignment. The arthroplasty devices are not intended to correct or change alignment, and so native alignment is maintained during positioning so as to avoid improper implant placement. If the shoulders preclude adequate visualization of the targeted surgical level, gentle traction can be gained by either taping the shoulders down caudally to the table or placing wraps about the wrists

that can then be utilized for intermittent traction. If continuous traction is utilized, the surgeon must ensure that excessive traction is not sustained on the brachial plexus for the entirety of the procedure to decrease the chance of root palsies.

A standard Smith-Robinson approach is performed. This is often a left-sided approach, although can be performed on either side depending on surgeon preference. The location of the incision is planned over the targeted disc space based on manual palpation of landmarks and/or fluoroscopy. If possible, the incision is placed within a natural skin crease for cosmesis. Prior to incision, it can be helpful to mark the sternal notch to facilitate orientation to the midline throughout the procedure, as precise alignment is of utmost importance for accurate placement of arthroplasty implants. A 2–3 cm transverse incision is made, extending approximately from midline to the medial border of the sternocleidomastoid muscle. Subcutaneous fat and platysma are then divided. The superficial layer of the deep cervical fascia is divided in the plane visualized between the sternocleidomastoid laterally and the strap muscles medially. The omohyoid can be sacrificed if needed to gain access to the lower cervical levels. Continued blunt dissection in this plane will then lead to the spine, with the carotid sheath the laterally and the larynx and esophagus medially. When the spine is encountered following this plane, a snap is placed on the annulus of the intended surgical level, and localization is confirmed using lateral cross-table fluoroscopy. Adjacent to the target disc level, the longus colli are gently elevated bilaterally to allow adequate access to the disc space out to the uncovertebral joints, however taking care not to dissect too far laterally as the anterior aspect of the vertebral body slopes down and away from the ventral surface to avoid injury to the vertebral arteries. At this point, self-retaining radiolucent retractors can be placed deep to the elevated longus flaps. The annulotomy is performed followed by the discectomy portion of the procedure.

Implant-Specific Instrumentation

Prestige LP (Medtronic Sofamor Danek) (Prestige LP 2009) (Fig. 5)

- *Device type:*
  - Metal-on-metal (titanium alloy)
  - Ball and socket
- *Procedure*

  Caspar pins are placed in the rostral and caudal vertebral bodies, taking care to ensure that placement is midline, parallel to the endplates and with sufficient distance to prevent violation of the endplates during placement or disc space preparation, and parallel to one another so as not to introduce any kyphosis or lordosis during disc space preparation. Fluoroscopic guidance is highly

Fig. 5 Medtronic Prestige LP prosthesis. (Reproduced with permission from Nasto et al. *Cervical Disc Arthroplasty.* In: Cervical Spine. Menchetti P. (eds) Springer, Cham. 2016)

advised when placing these pins. The remainder of the decompression is completed using Kerrison, curettes, and a bur to facilitate complete osteophyte removal for a wide bilateral foraminal decompression. The posterior longitudinal ligament (PLL) is resected. The endplates are gently burred to provide a flat and parallel disc space; however care is taken to limit amount of cortical bone removed to minimize risk of subsidence. The rasp can facilitate fine-tuning of this step after burring. The anterior vertebral bodies are also flattened with the bur so that to the flanges of the prosthesis will lie flush to the anterior aspect of the vertebral body. Periosteum present on the adjacent vertebral bodies is removed with the monopolar cautery, and all bone dust is copiously irrigated and removed to decrease chance of heterotopic ossification formation. The trial is inserted, and sizing is confirmed using lateral fluoroscopy as well as manual assessment of the resistance encountered for insertion and removal. Ensure the tabs on the trial fit flush with the anterior vertebral body. Compare the trial size and space to adjacent healthy disc spaces and facet joints on fluoroscopy. At this point, the Trial Cutter Guide is placed into the prepared disc space. Confirm that the cutter guide is perfectly midline using fluoroscopy because all steps moving forward will now dictate the final positioning of the implant. The Rail Cutter Bit is then used to prepare the rail tracts; the guide is held in place between rail preps with the Temporary Fixation Pins. When all four rails have been cut, all instruments are removed from the disc space. The Rail Punch is tapped into the disc space to complete the rail preparation. The prosthesis is then implanted into the prepared disc space, with the ball endplate rostral. Bone wax can then be applied over the exposed anterior aspect of the implant and over the exposed vertebral bodies to minimize heterotopic ossification. Ensure that the prosthesis remains parallel and the inserter perpendicular to the prepared disc space. Lateral fluoroscopy is used to guide depth of placement, and AP views confirm accurate coronal positioning.

Mobi-C (Zimmer Biomet) (Mobi-C 2016) (Fig. 6)

- *Device type:*
  - Metal on plastic (ultrahigh molecular weight polyethylene)
  - Semiconstrained
- *Procedure*

  Caspar pins are placed in the rostral and caudal vertebral bodies, taking care to ensure that placement is midline, parallel to the endplates and with sufficient distance (5 mm) to prevent violation of the endplates during placement or disc space preparation, and parallel to one another so as not to introduce any kyphosis or lordosis during disc space preparation. The Intervertebral Distractor Device is used to distract the vertebral bodies, and then the distraction is maintained through the Caspar distractor pins. The recommended method of the remainder of the decompression for this device by the manufacture is without

Fig. 6 Mobi-C prosthesis. (Reprinted with permission from Buell, et al. Cervical Arthroplasty: Long-Term Outcomes. In: Handbook of Spine Technology. Cheng B. (eds). Springer, Cham. 2019)

the use of a burr to optimally preserved bony endplate integrity. Bilateral foraminotomies are performed with Kerrison. The PLL is resected to facilitate perpendicular disc space preparation and distraction. The inferior endplate is squared off as wide as possible within the corners of the uncus without complete removal of the uncinates to maximize the width of the footprint of the implant. Next, the Width Gauge is placed into the prepared disc space to determine the width and adequacy of endplate preparation. If this gauge does not lie flat on the endplate, then the uncinates are squared off further using curettes. The Paddle Distractor, Caspar pin, or depth gauge can be used to estimate the depth of the footprint. Do not include anterior osteophytes in this measurement to ensure accuracy of the anterior-posterior footprint measurement. Anterior osteophytes can be removed as needed to create a flat anterior surface; however do not remove the overhang of the superior endplate as this concavity is required to match the shape of the superior endplate of the implant. Place bone wax as needed on exposed or decorticated surfaces of the anterior vertebral body to decrease risk of heterotopic ossification formation. Placed the selected trial with slight distraction on the Caspar pins, and then release the distraction to confirm fit both manually assessing resistances as well as on AP and lateral fluoroscopy. Re-distract the Caspar pins, remove the trial, and place the pre-assembled implant into the prepared disc space, avoiding any rotation during implantation. This can be confirmed using lateral fluoroscopy, ensuring that the Alignment Tabs on the inferior plate remain in line with one another such that only one line is visible without obliquity. The inserter and PEEK cartridge are removed. The implant position can be fine-tuned with the plate impactor and tamp. Prior to removal of the, gently compress through them to seat the prosthesis teeth into the endplates. The Caspar pins are removed and bone wax placed within the defects to control bleeding. Final positioning is confirmed using AP and lateral fluoroscopy.

Bryan Disc (Medtronic Sofamor Danek) (Bryan 2005) (Fig. 7)

- *Device type:*
  - Metal on plastic (soft polyurethane core)
  - Semiconstrained
- *Procedure*

  The remainder of the discectomy is performed with hand instruments, taking care not to remove the uncinates to preserve reference anatomy. The overhanging lip of the anterior superior vertebral body is removed, and the anterior vertebral bodies are smoothed to create a flat surface. The Transverse Centering

Fig. 7 Bryan Disc prosthesis. (Reprinted with permission from Buell, et al. Cervical Arthroplasty: Long-Term Outcomes. In: Handbook of Spine Technology. Cheng B. (eds). Springer, Cham. 2019)

Tool and Centering Level are used to identify and mark the center of the superior vertebral body. This can be confirmed with fluoroscopy if needed. Use the Intradiscal Distractor to distract the disc space to 8.5 mm and maintain this for 60 s to stretch the ligaments. Select the appropriate Alignment Guide, attached it to the Milling Guide, and place it into the prepared disc space over a Steinmann pin which has been placed at the reference point previously marked by the Centering Tool. Place the Stabilizer with the Centering Level on the Alignment Guide. Confirm that the alignment Visualization Slots are parallel to and centered between the endplates using fluoroscopy. The drill pilot holes, place Anchor Posts, distract the disc space, and complete a thorough decompression. Prepare the endplates using provided rasps up to 8.5 mm. Mill the superior and inferior endplates with the included Milling Assembly. Fill the implant with sterile saline. Place the implant into the prepared disc space. Irrigate copiously and place bone wax into screw holes and on exposed cortical surfaces to decrease chance of heterotopic ossification formation. Confirm final placement on lateral and AP fluoroscopy.

Postoperative Protocol

Amount of activity as well as the use of a hard or soft collar is at the discretion of the surgeon. A course of nonsteroidal anti-inflammatories is often utilized to decrease heterotopic ossification. The type, amount, and duration are variable, although a 2-week course is common.

Complications

Adverse events related to the approach such as dysphagia, dysphonia, vascular, or tracheoesophageal injury are possible, but reported rates are not significantly different compared to standard anterior cervical discectomy and fusion procedures (Mummaneni et al. 2007). There are, however, complications unique to total disc arthroplasty. While the goal of cervical disc replacement is maintenance of motion to theoretically protect adjacent levels, heterotopic ossification at these levels of preserve motion has been reported. The rates of heterotopic ossification development very widely; however it is felt to infrequently negatively impact range of motion or postoperative outcome (Lee et al. 2010; Chen et al. 2011). Leung reported 17% incidence of heterotopic ossification with the Bryan total disc arthroplasty device as assessed with radiographs. About 11% of these patients had significant loss of motion; however this was not correlated to clinical outcome such as pain or function (Leung et al. 2005). Similarly, Tu assessed the presence of heterotopic ossification using CT. With this more sensitive method, it was detected in 50% of one- and two-level Bryan total disc arthroplasty recipients, but again without adverse effects on clinical outcomes (Tu et al. 2011). Copious irrigation throughout the procedure including endplate preparation as well as postoperative utilization of nonsteroidal anti-inflammatory medications is often recommended to minimize risk for heterotopic ossification formation.

Subsidence is another complication which is often suggested as a possibility; however it is not often demonstrated or reported in the literature (Hacker et al. 2013). Recommendations for avoidance of this complication are relative contraindication in osteoporotic patients, maximizing the footprint of the implant, avoidance of oversizing the disc space, and preserving the endplate integrity during disc space preparation.

Postoperative kyphosis has been observed following total disc arthroplasty. This is also felt to be multifactorial, with contributions such as excessive anterior superior endplate removal during endplate preparation, incorrect angle of insertion, and amount and direction of distraction during endplate preparation (Sears et al. 2007). Again, outcomes have been evaluated in the setting of postoperative kyphosis. Pickett demonstrated preserved range of motion and no significant difference in outcomes despite focal kyphosis, and overall cervical alignment was maintained (Pickett et al. 2004).

Vertebral body fractures are postulated to be a possible complication, particularly with the keeled implant either during insertion or postoperatively. This is potentially more relevant if multilevel keeled implants are placed, but reports are infrequent to date (Shim et al. 2007; Datta et al. 2007).

In an era of heightened awareness to bearing surface wear with resultant particulate debris and metallosis, this is certainly a concern for the majority of cervical disc replacement implant designs. There is, however, a paucity in the literature regarding clinical examples of this problem. In the cervical spine, Cavanaugh presented a case report of metal ion reactivity resulting in hypertrophic tissue formation posterior to the device and subsequent neural compression. This was addressed with removal of the implant, revision decompression, and anterior fusion with resolution of symptoms (Cavanaugh et al. 2009). More instances of bearing wear-related complications have been presented in the lumbar literature, although true incidence remains unknown (Kurtz et al. 2007; van Ooij et al. 2007; Hallab 2009).

Finally, persistent pain is always a concern following any surgical procedure intended to address pain. As related to cervical disc arthroplasty, ongoing radiculopathy is most often due to incomplete decompression, particularly in a motion sparing technique where osteophytes can progress if not completely removed at the time of the index procedure (Goffin et al. 2002).

Revision Options

While interest in cervical disc arthroplasty continues to grow, the extent of need for revision remains to be seen. There is a paucity in the literature regarding this topic at this time. In general, the revision procedure will largely depend on the underlying problem. Replacement of the device may be considered if the issue is positioning or inadequate decompression after the index procedure. If there is particulate reaction, revision may necessitate conversion to fusion. Corpectomy and anterior column reconstruction may be needed if there is excessive bone loss. Most surgical technique guides recommend simply separating the bone-implant interface with an osteotome or similar device and removing it in a manner similar to which it was placed for implant removal; however in practice this may not always be the case. In the author's experience, some painful cervical arthroplasty devices have been grossly loose and are easily removed during the revision procedure. If radiculopathy is felt to be from recurrent foraminal stenosis secondary to osteophyte formation, some others advocate for posterior foraminotomy to avoid a revision anterior procedure. Likewise, if the pathology dictates, posterior cervical fusion alone is also sometimes a consideration, again to avoid anterior reoperation.

Outcomes

Overall, anterior cervical disc arthroplasty seems to be favorable compared anterior cervical discectomy and fusion in both short- and medium-term studies for both one- and two-level disease (Sasso et al. 2011; Mummaneni et al. 2007; Heller et al. 2009; Murrey et al. 2009; Zou et al. 2017). There is some evidence that two-level cervical arthroplasty procedures may fare better than single-level procedures, perhaps by protection of levels that are already degenerating (Radcliff et al. 2017; Mehren et al. 2018; Sasso et al. 2017). With the technology being available for the better part of two decades at this point, longer-term data are continuing to show favorable outcomes. Some of these longer-term reports are smaller cohorts and without similar rigor as was reported in the original IDE studies that had robust comparisons to traditional anterior cervical fusion, but there is some data suggesting that this option is durable and at least no worse than anterior fusion at these longer intervals. Rates of reoperation for adjacent segment degeneration remain lower than for fusion, although the differences not reach statistical significant (Ghobrial et al. 2018). Sasso and Dejaegher have shown durable outcomes

at 10 years, with favorable results and reoperation profiles compared to anterior cervical fusion. Likewise, Pointillart recently reported excellent outcomes in 80% of their patients 15 years out from cervical disc arthroplasty (Sasso et al. 2017; Dejaegher et al. 2017; Pointillart et al. 2018).

Surgical Techniques: Lumbar Disc Arthroplasty

Indications

- Degenerative disc disease
  - Most often single level, although multilevel use has been reported.
  - Demonstrated on MRI, CT, and/or plain radiographs.
  - Utilization of discography for confirmation of degenerative disc disease being causative for low back pain is suggested in some prior studies and technique guides as some have found it helpful for predicting improved outcome after surgery; however subsequent studies have shown increased rates of degenerative disc disease progression with the use of discography (Colhoun et al. 1988; Carragee et al. 2009). At this time, use of discography remains controversial, although anecdotally seems to have largely fallen out of favor.
- L3-S1 levels
- Failure of conservative measures for at least 6 months

Contraindications

- Instability
  - Spondylolisthesis
  - Spondylolysis
- Deformity
- Severe facet degeneration
  - With or without hypertrophy resulting in lateral recess stenosis
- Herniated nucleus pulposus resulting in radiculopathy
- Osteoporosis or osteopenia (T-score less than −1.5)
  - Metabolic disease resulting in compromised integrity of a bone architecture and/or remodeling
- Infection
- Pregnancy
- Prior trauma or fracture at affected level
  - Large Schmorl's nodes involving endplate at the affected levels
- Vascular calcification
- Metal or materials allergy

Relevant Anatomy

For the lumbar total disc replacements discussed in this section, an anterior approach to the spine is utilized. This can be trans- or retroperitoneal, depending on surgeon preference. Some spine surgeons may utilize an access surgeon to perform the approach.

Vessels

- **Aorta** is the largest artery in the body and courses anterior to the spine, left of and ventral to the inferior vena cava. The bifurcation into the common iliac arteries often occurs near the L5 vertebral body. While injury to the aorta itself is rare, if the great vessels need to be mobilized proximal to the bifurcation, segmental lumbar arteries that come directly off the aorta must be identified, isolated, and ligated to prevent significant blood loss, which can be more difficult to control if the vessels retract when avulsed.
- **Inferior vena cava** (IVC) is rarely encountered as it is predominantly a right-sided structure, and most approaches are left sided to (1) avoid injury to the IVC and (2) because there often is a more favorable plane on the left compared to the right of the great vessels leading to the anterior spine. If the IVC or a direct branch going to it is injured, hemorrhage can be massive and swift.

- **Iliac arteries and veins** – Injury to the left common iliac vein is one of the most commonly reported vascular injuries sustained during this approach and can result in massive hemorrhage in a relatively short amount of time. Often, the vessel can be repaired and the remainder of the procedure completed. Anterior lumbar procedures targeted at the L5-S1 level are typically performed caudal to the bifurcation of the aorta and vena cava and between the common iliac arteries and veins. At more proximal levels rostral to the bifurcations, these vessels need to be mobilized to allow adequate access to the targeted disc spaces.
- **Segmental vessels including the iliolumbar vein** can also cause significant bleeding which can be difficult to control unless these vessels are anticipated, identified, and ligated. Particularly the iliolumbar vein, which can be a large but very thin-walled structure traversing from the posterior aspect of the psoas muscle coursing to the left common iliac or IVC at the L4–5 level. This structure can often be identified on preoperative imaging to facilitate planning; however the surgeon must be aware of this vessel to control a prior to avulsion and retraction into the psoas, which can make it particularly difficult to control.

Ureter is a retroperitoneal structure which is identified by its peristalsis and mobilized medially along with the peritoneal contents during a retroperitoneal approach. One must avoid injuring it.

Sympathetic plexus is a latticework of nerve fibers, the superior hypogastric plexus, that runs anterior to the spine and the great vessels and medial to the iliac vessels. Injury to this structure can result in sexual dysfunction, specifically retrograde ejaculation. Patients must be counseled preoperatively on this potential risk, and younger patients may wish to consider further family planning options prior to undergoing an anterior lumbar procedure. A retroperitoneal approach carries a lower risk of injury to the structure compared to a transperitoneal approach. Additionally, blunt or bipolar dissection is recommended at the level and depth of the vessels to minimize risk of injury to these nerve fibers. Although rare, sympathetic dysfunction may occur resulting in ipsilateral lower extremity vasodilation which can mimic deep vein thrombosis. Subjectively the contralateral leg may feel cool relative to the warm ipsilateral lower extremity. This dysfunction typically resolves with observation.

Positioning and Approach

The patient is positioned supine on a radiolucent operating table with the arms out to the sides or crossed over a pillow on the chest. Some surgeons advocate for placement of a bump beneath the sacrum to bring the lumbar spine into a more accessible position. It should be noted, however, that the bump should not be placed beneath the lordotic portion of the lumbar spine so as not to exaggerated lumbar lordosis which may result in improper implant positioning. If possible, the patient position on the operating table should facilitate storage of the fluoroscopy machine when not in use.

There are several options to gain anterior exposure to the lumbar spine such as trans- or retroperitoneal, midline or paramedian, open, mini open, or laparoscopic assisted. For an open, retroperitoneal approach, the incision is localized over the target disc space using lateral fluoroscopy. Subcutaneous dissection is performed down to fascia, which is also incised. The rectus is mobilized either medially or laterally, depending on the approach and the necessary trajectory. The preperitoneal space is identified and entered, and the peritoneum and its contents are mobilized medially to allow access to the retroperitoneum. The ureter should be identified in this plane and mobilized with the peritoneum. The great vessels are identified and gently mobilized as needed for access to the desired disc space. At L4–5, the iliolumbar vein is identified, ligated, and divided to

avoid inadvertent avulsion and hemorrhage. At L5-S1, the middle sacral artery is isolated and ligated to allow unimpeded access to this disc space. At the level of the vessels and spine, blunt and bipolar dissection is used to minimize risk of injury to the sympathetic plexus. Fixed retractors can then be placed. The targeted disc is confirmed with lateral fluoroscopy, and the midline is marked using AP fluoroscopy. A standard annulotomy and diskectomy are performed, avoiding violation of the endplates.

Implant-Specific Instrumentation

ProDisc-L II (DePuy Synthes) (Prodisc-L 2017) (Fig. 8)

- *Device Type*
  - Metal on plastic (polyethylene)
  - Ball and socket
- *Procedure*

  After a standard discectomy has been performed, the intervertebral space is distracted with the spreader. A trial is placed to assess the implant height, size, and degree of lordosis. The keel tract is prepared with the chisel. During this step, position and trajectory of the keel must be confirmed as this will establish the implant position. The prosthesis is modular such that there are several options for lordosis of each endplate and insert heights to most accurately reconstruct the native disc space. The selected prosthetic endplates are inserted. Disc space is distracted, and the polyethylene inlay is inserted into the caudal endplate. Final position is confirmed using lateral and AP fluoroscopy.

Postoperative Protocol

Much of the postoperative protocol is at the discretion of the surgeon. In general, avoidance of aggressive bending, twisting, or lifting is recommended for 6 weeks followed by gradual return to full activity thereafter. Postoperative bracing is utilized based on surgeon preference, but not required.

Complications

As can be seen with anterior lumbar interbody fusion, approach-related complications do occur. These include injuries to adjacent vasculature, sympathetic plexus, ureter, and rarely lymphatic ducts. The rates of these complications are similar as to what is seen in anterior lumbar interbody fusion (Blumenthal et al. 2005). Heterotopic ossification has been reported in up to 50% of patients; however this often does not result

Fig. 8 Prodisc-L prosthesis. (Reprinted with permission from Atkins, et al. *Lumbar Disc Arthroplasty.* In: Essentials of Spinal Stabilization. Holly L., Anderson P. (eds). Springer, Cham. 2017)

in inferior clinical outcomes (Park et al. 2018). Jackson et al. did report a case in which heterotopic ossification along with implant malposition resulted in a new radiculopathy (Jackson et al. 2015). Symptoms resolved with revision for implant removal, anterior interbody fusion, posterior decompression, and pedicle screw fixation. Implant-related complications such as subsidence, dislocation, or luxation have been reported (Kurtz et al. 2007; Kostuik 2004). Additionally, bearing surfaces do raise the concern abnormal wear, particulate degeneration, and adjacent inflammatory changes. There are case reports and small series of the instances resulting in inflammation and osteolysis. Authors have postulated that suboptimal local biomechanics such as adjacent level fusion, incorrect implant sizes, and impingement may all be contributing factors. Study of removed implants has demonstrated both abrasive and adhesive wear of the polyethylene (Kurtz et al. 2007; van Ooij et al. 2007). Finally, persistent pain postoperatively has been reported. This is also likely multifactorial. It is well-known that there are multiple possible pain generators in the lumbar spine, and disc replacement does not address all of these. Facet degeneration pre- or postoperatively may be may be a major contributor to ongoing pain. Of 91 patients at a single IDE site, 50% of failures were secondary to facet pathology (Pettine et al. 2017).

Revision Options

As is the case with cervical disc arthroplasty revision, the lumbar revision procedure performed ultimately depends on the underlying pathology to be addressed at the time of surgery. Options include revision for replacement of an arthroplasty device, anterior revision for lumbar interbody fusion with or without posterior instrumentation, or posterior lateral instrumented fusion alone without anterior revision. Repeating an anterior exposure may be needed for situations such as arthroplasty device migration but should otherwise be considered with caution as adhesions can be problematic, and there is higher risk of vascular and visceral injury.

Outcomes

The SB Charité lumbar prosthetic was implanted for a period of nearly 20 years. Despite its eventual withdrawal from the market in 2013, this lumbar device has the longest available follow-up data and permits inquiry into the longevity of lumbar total disc replacement systems. Lemaire and colleagues presented 10-year minimum follow-up results in their retrospective case series of 100 patients implanted with the SB Charité III between 1989 and 1993 for the indication of intractable discogenic back pain. The authors used a modified Stauffer-Coventry scoring system which expresses results as relative gain. A relative gain of $\geq$70% indicates an excellent outcome and is defined as no pain, no medication use, and resumption of activity in the same job after 3 months. Ninety percent of patients in their series had an excellent or good outcome at 10 years, and 92% of eligible patients returned to the work force in some capacity. Radiographic analysis at 10 years showed that the Charité maintained normal range of motion in 95% of patients with a mean flexion/extension arc of 10.3°. Five patients underwent secondary arthrodesis at the index level for poor outcomes and the symptomatic adjacent level disease reoperation rate was 2% (Lemaire et al. 2005). David et al. found very similar positive results (82% with excellent or good outcomes) in their 10-year minimum retrospective case series of 106 patients. These authors reported a 10% index level and a 3% adjacent level reoperation rate (David 2007). The longest prospective data reported is the 5-year results from the US FDA IDE randomized controlled trial comparing the Charité to lumbar fusion. Ninety patients randomized to the Charité group between 2000 and 2002 were available for follow-up 5 years later. Guyer et al. found that Oswestry Disability Index (ODI), SF-36, and Visual Analog Scale (VAS) scores maintained clinically significant improvements over baseline. Overall clinical success, defined by the FDA, was achieved in 58% of the Charité patients and 51% of the arthrodesis patients still after 5 years. Seven of 90 cases were reported as "failures" necessitating index level reoperation, and adjacent level disease

Fig. 9 ActivL prosthesis. (Reprinted with permission from Atkins, et al. *Lumbar Disc Arthroplasty.* In: Essentials of Spinal Stabilization. Holly L., Anderson P. (eds). Springer, Cham. 2017)

reoperation rates were 1.1% and 4.7% for the Charité and arthrodesis, respectively (Guyer et al. 2009).

Outcomes of the ProDisc-L (DePuy Synthes) lumbar artificial disc are perhaps the most relevant at this juncture given that it remains commercially available and has the longest track record. Park et al. followed 35 patients for a mean of 6 years. Subjective outcome surveys were quite encouraging as 31 of 35 patients reported being completely or somewhat satisfied with their results. Similarly, 21 of 35 reported that they would definitely or probably undergo lumbar total disc replacement again if represented the option (Park, Spine 2012). Per the FDA-defined clinical success criteria, 71% of the cases qualified (Park, Spine 2012) (Park et al. 2012). In another retrospective case series of 55 patients with an average follow-up of 8.7 years, 75% had excellent or good results (Tropiano et al. 2005). Prospective data also supports lumbar arthroplasty as a reliable alternative to arthrodesis. Siepe and colleagues prospectively reviewed 181 patients after a mean of 7.4 years and found that both VAS and ODI scores were improved with statistical significance compared to baseline preoperative values (Siepe et al. 2014). Eighty-six percent of their patients were highly satisfied or satisfied. They also reported a low adjacent level disease reoperation rate of 2.2% which was comparable to that of the Charité. The most influential data comes from this device's US FDA IDE randomized controlled trial which showed very comparable results at 5 years between the ProDisc-L and circumferential lumbar arthrodesis. FDA-defined clinical success was met by 54% of the lumbar arthroplasty cases and 50% of the fusion cases. Both groups maintained significant improvements in ODI and SF-36 scores compared with baseline values. Restoration of normal lumbar motion, dictated by level, was achieved in 92% of the ProDisc-L cases with a mean flexion-extension arc of 7.2°. The index level reoperation rate was lower in the arthroplasty group (8%) compared to arthrodesis (12%) (Zigler and Delamarter 2012).

There is no long-term follow-up data for the second FDA-approved lumbar total disc replacement system, the ActivL (Aesculap Implant Systems, Fig. 9). It has only been commercially available since 2015. Nonetheless, its 2-year follow-up data appears to show statistically superiority to its predecessors (Garcia et al. 2015).

Conclusion

The theoretical advantage of motion sparing technology for degenerative spinal pathology is appealing. There has been much research and progress on this topic of intervertebral disc replacement over the last several decades, and the future is promising. Despite the advances, an understanding of the failures remains necessary so as not to repeat them. Currently, cervical disc arthroplasty has outpaced lumbar disc arthroplasty. There are more FDA-approved cervical devices than there are lumbar devices, and anecdotally, cervical disc replacement is more

widely favored than lumbar. The greater success of cervical disc replacement may stem from the underlying indications when compared to that of lumbar disc replacement; cervical procedures are indicated for degenerative disc disease resulting in radiculopathy or myelopathy, which are more predictably treatable entities, whereas lumbar disc procedures are often contraindicated in the setting of radiculopathy and predominantly indicated in degenerative disc disease only with axial pain, which is a notoriously difficult entity and patient population to treat successfully and predictably. For both cervical and lumbar disc replacement, early and midrange follow-up are now becoming available up and seemingly favorable, but we will need to continue to follow these technologies for long-term data to show whether it is more definitively a durable alternative to arthrodesis.

Cross-References

- ▶ Adjacent-Level Disease: Fact and Fiction
- ▶ Biological Treatment Approaches for Degenerative Disc Disease: Injectable Biomaterials and Bioartificial Disc Replacement
- ▶ Cervical Arthroplasty: Long-Term Outcomes
- ▶ Cervical Spine Anatomy
- ▶ Cervical Total Disc Replacement: Biomechanics
- ▶ Cervical Total Disc Replacement: Evidence Basis
- ▶ Cervical Total Disc Replacement: Expanded Indications
- ▶ Cervical Total Disc Replacement: FDA-Approved Devices
- ▶ Cervical Total Disc Replacement: Heterotopic Ossification and Complications
- ▶ Cervical Total Disc Replacement: Next-Generation Devices
- ▶ Cervical Total Disc Replacement: Technique – Pitfalls and Pearls
- ▶ Lumbar TDR Revision Strategies
- ▶ Posterior Lumbar Facet Replacement and Interspinous Spacers
- ▶ Thoracic and Lumbar Spinal Anatomy

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Part VI

International Experience: Surgery

The Diagnostic and the Therapeutic Utility of Radiology in Spinal Care

52

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Abstract

Advancements in technology have been a driving force in the development of medical imaging equipment. There are now multiple, varied, and intertwined imaging modalities which visualize the spine in many different formats and positions. This has facilitated an increase in accuracy of diagnosis, and then at the same time allowed medical imaging to be an essential tool, in treatment of spinal conditions. Multiple image-guided therapies are now available to assist physicians/surgeons with treatment regimens and pre- and postoperative surgical planning. This chapter will detail the above.

Keywords

Radiology · Spinal · Neuroradiology · CT · Computed tomography · MRI · Magnetic resonance imaging · Nuclear medicine · EOS · Myelography · Medial branch block · Discography · Intervention · Corticosteroid injection · Aspiration · X-ray · Fluoroscopy

Introduction

Radiology, or medical imaging, has advanced dramatically since the discovery of the X-ray by William Roentgen in 1895. Over the last 120 years, this scientific discovery has evolved from being a novelty nonmedical commercial and social photographic studio tool to a necessity, essential to physicians and surgeons throughout the world (American Society of Radiologic Technologists 2018).

The computer age and advancing technologies allowed the use of X-rays and then other forms of radiation to be progressed into more sophisticated imaging equipment. Thus, medical diagnosis has progressed well beyond the first point of physician-patient contact – history and examination – as the diagnosis or differential diagnoses can be radiologically narrowed or confirmed and the pathology directly viewed within the patient.

The radiology/medical imaging field has taken a dual role of diagnosing and treating. Radiology canbe a primary source of treatment or an adjunctive intervention to both surgical pre- and postoperative care.

Within the field of spine care, radiology has assumed such an important role in the detection, diagnosis, and treatment of spine and spine-related disorders. Thanks to the radiologists, the spine surgeon can deliver a precision diagnosis and with that therapeutic options. When combined with the quantification and prognostication afforded by imaging (e.g., the grade of spondylolisthesis or the amount of sagittal imbalance), this forms an invaluable trinity of diagnosis, quantification, and therapy (see Fig. 1).

The diagnostic and treating armamentarium available to the patient and physician from the radiology specialty is as follows:

- Diagnostic:
  - Noninvasive:
    - *X-ray*
    - *Fluoroscopy*
    - *CT*
    - *MRI*
    - *Nuclear medicine*
  - Invasive:
    - *Myelography*
    - *Medial branch block*
    - *Discography*
- Therapeutic:
  - *Facet joint/medial branch corticosteroid injections*
  - *Epidural/perineural corticosteroid injections*
  - *Synovial cyst puncture and aspiration*
  - *Sacroiliac joint corticosteroid injections*
  - *Coccyx injections*
  - *Facet joint denervations*
  - *Vertebroplasty and kyphoplasty*
  - *Insertion of stimulators*

Comments About Radiation

Plain radiographs, CT, and fluoroscopy all produce ionizing radiation and hence the ability to cause cancer or birth defects, via damage either

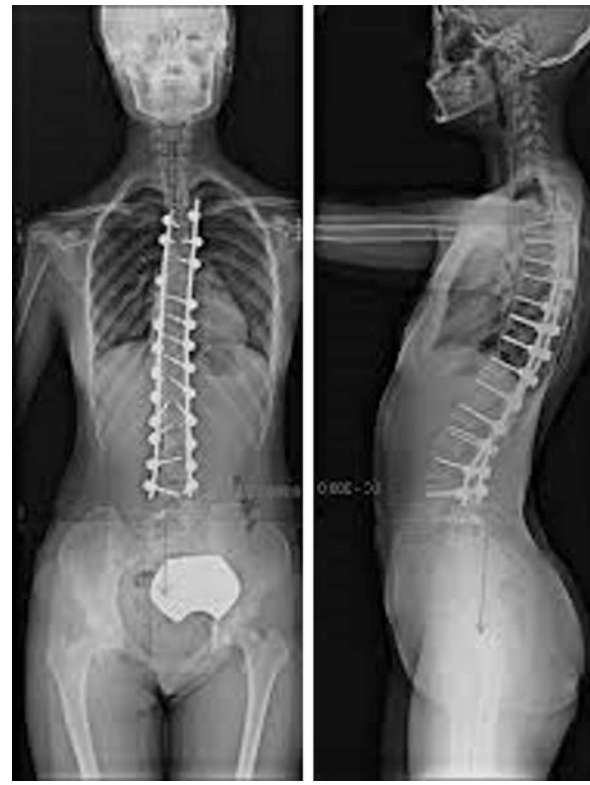

Fig. 1 The unity of diagnosis and treatment clearly shown in verification of deformity correction

to the reproductive organs or to the developing embryo directly. However, the use of radiation from medical imaging procedures when ordered prudently and for the specific benefit of diagnosis or treatment leads to minimal hypothetical risks especially in relation to cancer deaths and estimated cancers produced and even more so when the principles of ALARA (radiation dose as low as possible), ASARA (medical procedures as safe as reasonably achievable), and AHARA (medical benefits as high as reasonably achievable) are followed (Hendee and O'Connor 2012). With technologies improving all the time, the radiation dose from all forms of imaging is becoming less, and the major equipment suppliers make this a standard in design and development and market accordingly. Despite lessening radiation doses from improving technology, the link of abdominal radiation dose with solid organ malignancy mandates careful assessment of risks and benefits from the ordering of tests involving ionizing radiation.

Noninvasive Techniques

X-ray

The humble radiograph. With all the new modalities for imaging now available, the spine radiograph is of less diagnostic importance as CT and MRI provide far more detail. The fact the plain radiograph cannot show soft tissue details of the spine, only bone, and can only image in limited planes is its major drawback, and the radiograph provides a 2D representation of a 3D structure.

However it still does play an essential role in the investigative role of diagnosing spine and spine disorders and as such should not be dismissed as an irrelevant investigation but a useful investigation in the first line of the diagnostic pathway. Despite government detractors that criticize the plain radiograph from the point of view of ionizing radiation and the lack of benefit, the radiograph provides a positive yield in many

situations, clinical and diagnostic, when applied specifically to the clinical situation.

Traditional images are AP and lateral views with oblique or functional views being added depending upon the request of the referrer or individual protocols of the radiology practice. The lateral view plain film will show alignment of the spine – confirming the normal or abnormal lordosis or kyphosis of the cervical, lumbar, and thoracic spines, respectively, and the AP film curvature or more scoliosis. Also disc space narrowing, i.e., degeneration and possibly foraminal stenosis, may also be revealed and of course a bony lesion. Oblique lumbar radiographs may be ordered in the case of spondylolysis to detect pars defects.

For a lumbar spine radiograph, the question of radiation to the reproductive organs is always of some concern. However, like with any radiograph, it must be balanced against its benefit, particularly in the younger person.

An exciting new technology, which has only become available in the last few years, is EOS™. It takes plain film spinal radiography to a new level. Firstly, the radiation dose is about 50% less than for digital radiography; hence the dose is almost negligible. Secondly, the entire skeleton – the chest, upper limbs, entire spine, pelvis, hips, and lower limbs – can be viewed in the weight-bearing position. Both frontal and lateral images are obtained, and from the images, 3D modelling is performed. This allows detailed analysis of the kyphotic and lordotic state of the spine and, of course, scoliosis (see Fig. 2). Hence, the normal distribution of weight, stresses, and angles throughout the axial skeleton can be assessed. Many parameters are measured including the C7 plumb line, kyphosis and lordosis, thoracic and lumbar vertebral and intervertebral rotations, spino-sacral angle, pelvic incidence/version and sacral slope, pelvic obliquity and rotation/tilt, Cobb angle, and scoliosis. Further measurements in relation to lower limb leg lengths and hip and knee angle and alignment parameters can be carried out. With all this additional

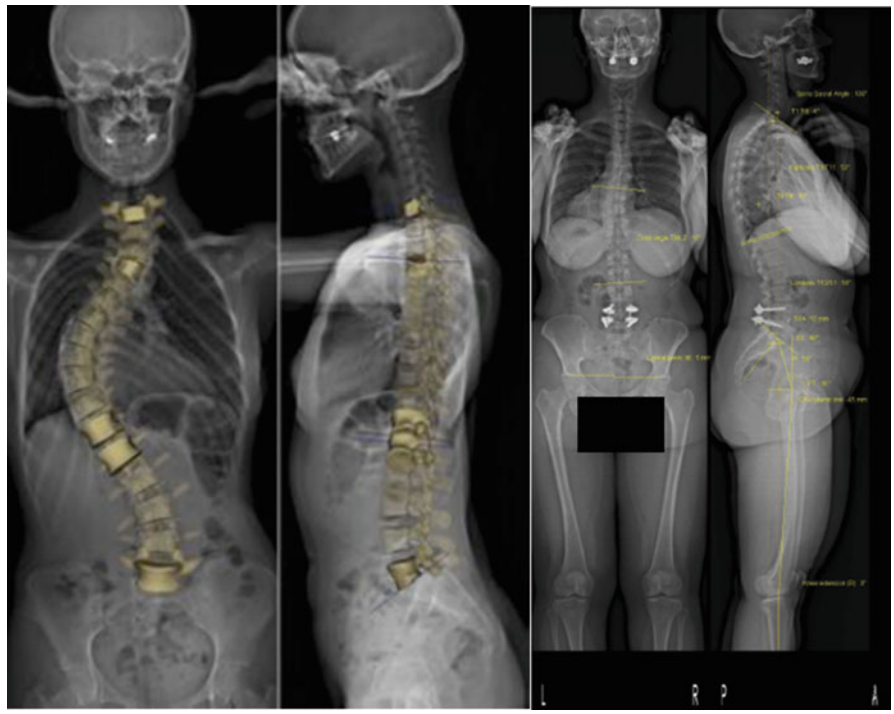

Fig. 2 EOS™ showing images of the whole spine – AP, lateral, and 3D reconstructions – with measurements for assessment of surgical balance as a forerunner to surgical treatment and planning

information, surgical procedures can now be planned (including types and requirements of reconstructions) to take into account the entire axial skeleton rather than solely the symptomatic area in question (Amzallag-Bellenger et al. 2014).

Fluoroscopy

This is using X-rays to allow real-time (i.e., dynamic) imaging. The machinery and technology have developed over time like that of the X-ray machine. It works on a similar principle to the traditional X-ray machine; however it is of low intensity (and hence low radiation) and therefore is coupled with an image intensifier which allows the image to be seen (without the need for a darkened room) (Amzallag-Bellenger et al. 2014).

The fluoroscopy unit has its main use as an adjunct to spinal procedures particularly aiding in needle placement for injections, both for diagnostic, e.g., discography and myelography, and treatment regimens, e.g., corticosteroid – *see below*. It is also used in theater for spinal level checks and aids in planning and confirming spinal surgical hardware placement and position. Such advancements have allowed reduction in malpositioned screws and cages that, if unrecognized, could present problems in the perioperative period for the patient (Amzallag-Bellenger et al. 2014; Goodbody et al. 2017; Deschenes et al. 2010; Laredo et al. 2010).

Computed Tomography

CT was part of the spinal imaging evolution, both diagnostically and therapeutically. The spine could now be imaged in much greater detail than was possible with the plain radiograph and fluoroscopy. The soft tissues, i.e., disc, ligaments, muscle, nerve roots, and CSF, could now be seen as could the size and state of the spinal canal (see Fig. 3). Tumors and fractures were depicted far more clearly. Further benefits were found as CT could image in multiple planes – coronal, sagittal, and axial – as well as oblique planes with rotation and 3D images. Hence, the name changed from computed axial tomography when it originated as a single-slice machine to now just computed tomography with the current cohort being multislice/multidetector up to 640. It remained the most accurate method of neural and soft tissue assessment until advancements in the mid-late 1980s made MRI feasible for routine use. CT remains superior to MRI, however, for assessment of bony structures and is still the gold standard for assessing fusion.

Continued refinements in CT have allowed faster, higher resolution and more accurate scans as well as significant reductions in radiation. CT now has the added benefit of CT fluoroscopy

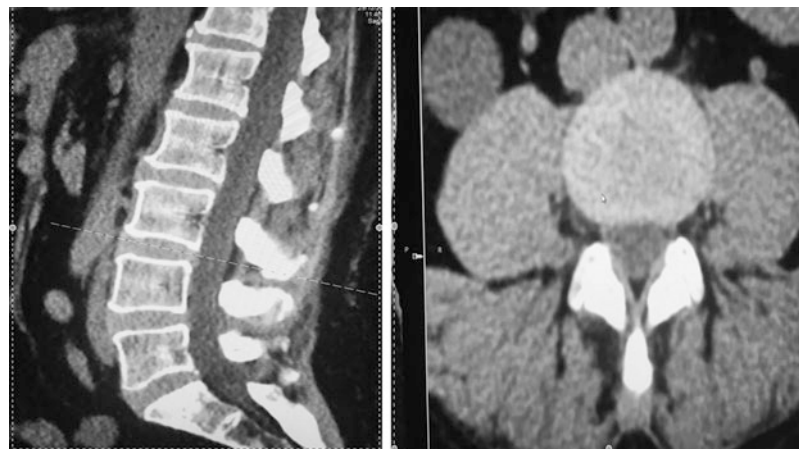

Fig. 3 Sagittal and axial CT of lumbar spine, showing bones, disc, canal, foramina, and nerve roots

– real-time imaging via the CT scanner in procedures.

Diagnostically, CT allows the disc (+/− disc osteophyte complex) to be analyzed, whether or not there is herniation or stenosis and to what degree – both foraminal and central canal. The origin and descending nerve roots can also be seen; hence nerve root compression and displacement becomes available allowing the clinician to diagnose and treat the symptoms with far greater accuracy. This is particularly important in cervical spine surgery where disc osteophytes and uncovertebral complexes need to be cleared to enable unimpeded passage of the nerves. Further diagnostic value is found with discography and myelography, both of which require specific needle tip placement, and this may be done with the use of CT alone or in conjunction with fluoroscopy. All spinal levels – cervical, thoracic, or lumbar – can be analyzed.

Therapeutically, CT (or fluoroscopy alone or CT fluoroscopy) allows the interventionist to perform numerous procedures to treat the patient with spinal pain. Biopsy of perispinal lesions in the case of suspected infection or tumor is an example of a procedure with diagnostic value but also important in planning therapy, e.g., identification of organism or tumor subtype. CT angiogram is particularly useful if an anterior lumbar or high cervical approach is planned and there is concern about vascular anatomy or if there is a thoracic lesion where the spinal cord blood supply is of particular importance when considering embolization of a high vascularity lesion.

MRI

Magnetic resonance imaging is the gold standard for spinal imaging. Like all diagnostic modalities in spinal imaging, it has advanced over time with technology. In particular the availability of high magnetic fields strength systems, increase gradient performance, the use of RF coiler rays and parallel imaging, and increase pulse sequence efficiency allowed for better acquisition speed and improved low signal-to-noise ratio. It provides detailed and conspicuous imaging of the spinal structures, showing greater detail than other modalities (see Figs. 4, 5, 6 and 7). There are categories of MRI available. First is the traditional tunnel lie down 3T MRI (Tesla, the magnetic field strength) which is the most widely used global static imaging tool. The alternative or adjunct to this is the open/upright MRI. The latter provides positional imaging – sitting, standing, flexing, and extending. Different positions can reveal dynamic pathologies that the supine tunnel MRI cannot demonstrate, e.g., instability, herniated discs, and annular tears that may not be detectable when in the unloaded, non-functional position (see Fig. 5a–b).

MRI imaging has the advantage of no ionizing radiation and clearly displays the type and extent of spinal pathology. Additional information can be realized with MR imaging. In particular:

(i) Degenerative state of the disc: It can be clearly characterized by MRI, unlike X-ray or CT where, unless there is a decrease in the disc height or a distinctive disc bulge,

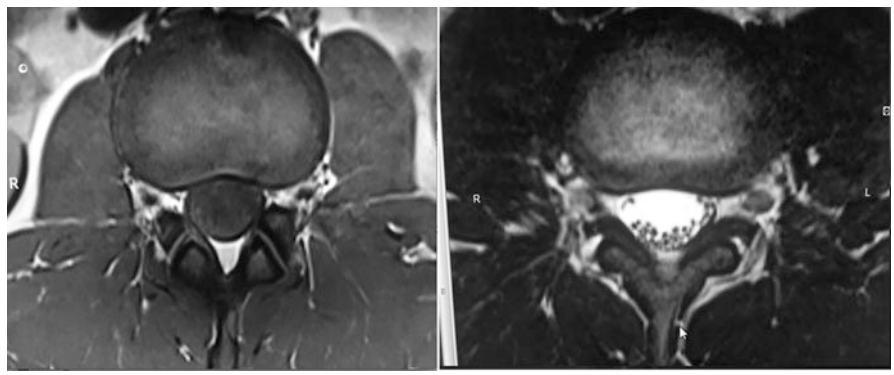

Fig. 4 MRI: note the far clearer delineation of all structures compared to Fig. 3; disc, canal, and nerve roots

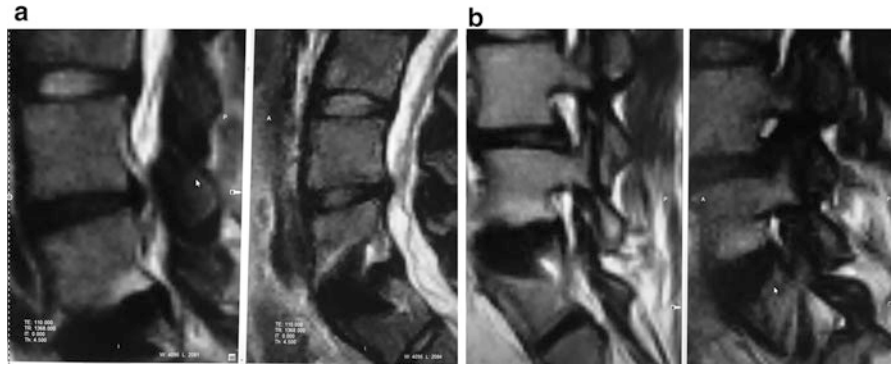

Fig. 5 Note in (**a**) the difference in the degree of herniation and in (**b**) the foraminal stenosis in the weight-bearing position comparing the static lie down images

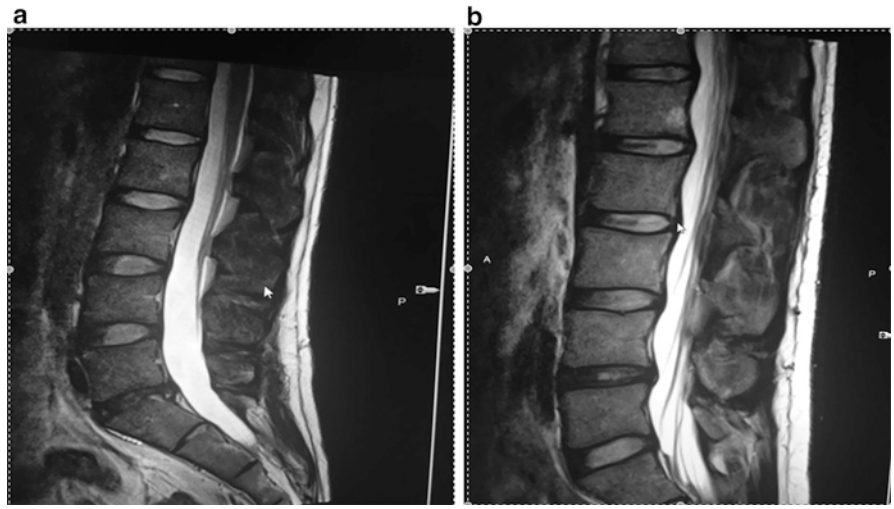

Fig. 6 (**a**) and (**b**) Note also the state of the discs: L1-4/5, all normal; L5/S1, degenerate grade 4, i.e., nucleus no longer white, loss of height, and with the high signal intensity zone/annular tear. a Note in b the degenerate L4/5 disc, grades 3–4

the morphology of the disc is not ascertained. An MRI classification of the disc degeneration has ensued – Pfirrmann grades I–V. The grading is based upon T2-weighted imaging with the low-signal changes to the nucleus pulposus becoming more pronounced and diffuse within the disc as well as loss of disc height as the degenerative process progresses.

(ii) Further markers of intervertebral disc degeneration shown on MRI are:
   (a) High-signal-intensity zone (HIZ) located in the posterior annulus fibrosis, separated from the nucleus pulposus – a relationship between the HIZ and pain has been observed.
   (b) Modic changes (Modic et al. 1988) – signal changes to the vertebral end plate and bone deep to the cartilage; these are graded I–III combining both T1W and T2W images. Type I, also known as the inflammatory phase, is denoted by inflammation of fibrous tissue, low signal intensity on T1W, and high signal intensity on T2W imaging. Type II, known as

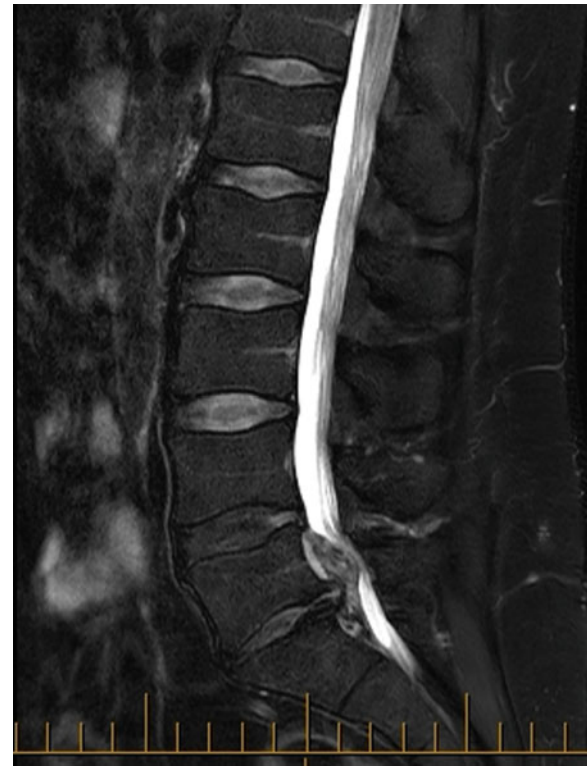

Fig. 7 MRI lumbar spine sagittal slices. Note the detail of the study which enables differentiation of extruded and sequestered disc material in the canal contacting the thecal sac from the broad-based herniation present at L5/S1 and degenerate disc at L4/L5

the fat phase, is marked by a large deposition of fat cells in the end plate and the area underneath it, as well as a high signal intensity on T1W and an equivalent or mildly high signal on T2W imaging. Type III, also known as the bone sclerosis period because the bone becomes hardened in the end plate and the area underneath it, is also characterized by low signal intensity in T1W and T2W imaging (Rahme and Moussa 2008). It has also provided prognostic value for interventions for diagnosed discogenic back pain (Furunes 2018) and has been associated with increased vascular adhesions during anterior lumbar surgery (Malham 2018).

Other value in ordering an MRI includes:

(iii) The exact relation of the herniated disc to the nerve roots and whether or not direct compression is present.

(iv) The status and size of the paraspinal muscles. For example, severe multifidus wasting may suggest radiculopathy and be associated with poorer outcomes for decompression (Zotti et al. 2017) and disc replacement surgery (Le Huec et al. 2005; Storheim et al. 2017).

(v) Vascular pattern: particularly if anterior or oblique or lateral surgery is being considered, then vascular pattern including any anomalies should be studied to anticipate problems.

(vi) Assessment post-surgery for recurrent herniation, stenosis, and/or presence of fusion. This modality can be useful if a patient's leg symptoms recur to the point where intervention would be considered; then MRI with contrast can be of use in assessment to differentiate scar tissue from recurrent disc herniation. Recent studies suggest that MRI is comparable to CT for assessing lumbar spine fusion (Kitchen et al. 2018) (Fig. 7).

MR spectroscopy is an emerging technology whereby differential water and protein contents within the region of interest can be measured

and correlated to the patient's symptoms allowing differentiation of painful from non-painful discs (Zuo 2012). This may in time and with maturity enable diagnosis of discogenic pain without invasive provocative discography. Intraoperative MRI can be performed (more in the setting of craniocervical or spinal cord tumor surgery) but is not routine or widespread.

Nuclear Medicine

Radionuclide bone scanning is a well-accepted and sensitive method for uncovering a variety of bony lesions including abnormalities of vertebral bodies or facet joints that may be contributing to spinal pain. It has a more functional basis than the other imaging modalities as it has the ability to detect the most avid area of "inflammation," seen as increased regional blood flow, as determined by the degree of tracer uptake. Single photon emission computed tomography (SPECT) is especially useful in such an evaluation because it allows for precise localization of a lesion to the vertebral body, disc space, or facet joint. Greater diagnostic accuracy is achieved with this dual technique – using both radionuclide tracer, e.g., technetium 99, and integrated CT – allowing the level and anatomical location of pain generation to be imaged. This anatomic distinction is necessary in order to accurately diagnose the underlying condition detected by the bone scan. Most bony abnormalities result in focal areas of abnormal tracer activity but do not affect all components of a vertebra with equal frequency nor have a random pattern of involvement. Vertebral diseases tend to conform to predictable patterns that can be more readily identified by SPECT scan compared to planar imaging (Gates 1988, 1998). In some applications, such as in symptomatic pars defects, SPECT has sensitivity at least equivalent if not superior to MRI (Fig. 8).

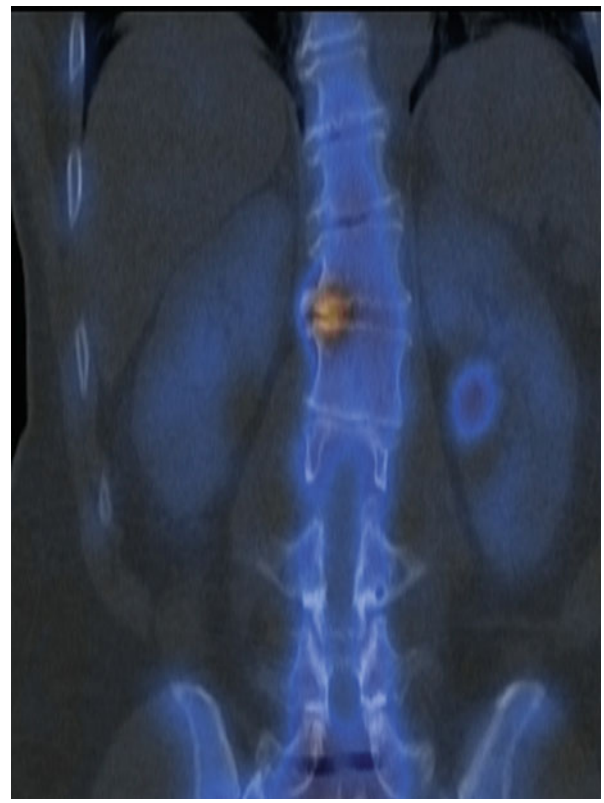

Fig. 8 SPECT scan of the thoracolumbar spine visualized in the coronal plane. Note tracer uptake most pronounced at the T12/L1 end plates asymmetrically which correlated with the patient's pain

Comments About Pain Generators

As with anywhere in the body, the causes and origins of pain are vast and extensive and include referral from extra-spinal regions. In the spine itself, the main pain generators are:

(A) The joints – facet and sacroiliac
(B) The intervertebral disc
(C) The nerve roots
(D) The bones
(E) The muscles

Biomechanical and Chemical Models for Disc and Facet Pain

Intervertebral disc degeneration has been reported to be a source of low back pain in adults. The intervertebral disc consists of the nucleus pulposus, surrounding annulus fibrosus, and the superior and inferior cartilage end plates. Collagen and elastin fibers are present in different orientations lying within a proteoglycan (most prominently aggrecan) and non-cartilaginous protein mixture, forming a complex matrix. Disc degeneration occurs with the breakdown of this matrix with replacement of fibroblasts with chondrocyte-like cells and alteration in the lamellar structure of the annulus and when the nucleus gel becomes fibrous. Annular tears have been strongly associated with the development of degenerative disc disease. In other words as the nucleus can no longer support the load, the annulus can buckle and tear promoting radial and circumferential tears. Neurovascular structures can migrate into these tears. Numerous biomechanical-biochemical studies have shown that following annular tears, the axial load that is normally carried through the center of the disc can shift posteriorly over the nerve concentrated posterior and posterolateral annular fibrosis. Therefore in addition to the painful inflammatory reaction, one can get mechanical irritation of these already inflamed and irritated *nociceptive* fibers in the peripheral annulus. The fundamental basis of this breakdown at the molecular level is the production of an abnormal matrix or an increase in the constituents which cause matrix degradation, e.g., IL-1 and TNF and matrix metalloproteinases (MMPs), and a reduction in the amount of tissue inhibitors of metalloproteinases. The normal disc posteriorly is innervated by branches of the sinuvertebral nerve (from meningeal branches) and sympathetic fibers. Only the outer aspect of the annulus is innervated, and the sensory fibers are primarily nociceptive and proprioceptive (although less so). In a degenerate disc, the number of nerve fibers increases, and nerve nociceptive fibers grow into the normally aneural part of the annulus and nucleus. Many factors may contribute to the degenerative process – genetics, mechanical load, trauma, and nutrition; however, the exact etiology and relationships still require further research.

Studies have linked pathological changes in facet joints with preceding disc degeneration. The intervertebral discs support most of the weight during flexed postures, but the facet joints bear an increasingly greater burden as the lumbar spine is ranged into extension. In addition to stabilizing the spine and guiding segmental motion, facet joints function as weight-bearing structures that support axial loading along with the intervertebral discs. Studies have shown that the facet joints can carry up to 33% of the dynamic axial load. Disc degeneration with associated narrowing of the disc space alters the mechanical load distribution and may result in a degenerative cascade with increased mechanical stress on the facet joint and joint capsule. Within the active range of the lumbar spine, the paraspinal muscles act as the principal contributors to vertebral stability. However, both cyclic and sustained flexion movements decrease the reflexive muscle activity of the paraspinal muscles such as the multifidus muscle. In theory, this may result in increased laxity across the facet joint leading to both decreased stability and increased stress on the facet joint capsule.

The role of the facet joint capsule in stabilizing the motion characteristics of these joints cannot be understated. Studies have suggested that disc degeneration results in increased range of

axial rotation. It has been postulated that the increase in axial rotation and subsequent instability place additional stressors upon the facet joint capsules leading to a molecular response, which results in fibrocartilaginous metaplasia in the capsules of facet joints. Boszczyk et al. (2003) reported hypertrophic and fibrocartilaginous changes in the facet joint capsules of patients who had undergone lumbar fusion for degenerative instability.

The facet joint (or zygapophyseal joint) is innervated by the medial branch of the dorsal ramus of the nerve exiting at the same level and also the medial branch of the nerve one level above. The joint has a strong capsule, and hyaline articular cartilage is present.

Changes in load distributions (from a degenerative disc or from spinal malalignment or pelvic tilting or rotation) can lead to osteoarthrosis, osteophyte formation, and inflammation. The cartilage and synovium of facet joints are sources of inflammatory cytokines. It has been proposed that painful symptoms may arise not only from mechanical stress discussed previously but also from the associated inflammatory response involving cytokines such as tumor necrosis factor alpha, interleukin-6, and interleukin-1 beta, oxygen-free radicals such as nitric oxide and inflammatory mediators such as prostaglandins. Interestingly, some have suggested that inflammatory cytokines originating from inflamed synovium may spread to adjacent nerve roots and produce radicular lower extremity symptoms.

The sacroiliac joint (SIJ) is a true diarthrodial joint with unique characteristics not typically found in other diarthrodial joints. The joint differs with others in that it has fibrocartilage in addition to hyaline cartilage, there is discontinuity of the posterior capsule, and articular surfaces have many ridges and depressions. The sacroiliac joint is well innervated. Histological analysis of the sacroiliac joint has verified the presence of nerve fibers within the joint capsule and adjoining ligaments. It has been variously described that the sacroiliac joint receives its innervation from the ventral rami of L4 and L5, the superior gluteal nerve, and the dorsal rami of L5, S1, and S2. Abnormalities with joint function and mobility – hypo- or hypermobility – are the primary cause of the irritation. Inflammatory systemic disease, e.g., ankylosing spondylitis, is of course another reason for pain generation.

As with other diarthrodial joints, the cartilage of facet joints may also be sex-hormone sensitive. Estrogen has been associated with chondrodestruction, although controversy exists as to its actual role in the development of osteoarthritis. However, Ha and Petscavage-Thomas (2014) have found a statistically significant association between the increased expression of estrogen receptors on the articular cartilage of facet joints and the severity of facet arthritis (Binder and Nampiaparampil 2009).

Invasive Interventions

Myelography – an invasive procedure with contrast media (iodinated) being injected into the subarachnoid space, penetrating the thecal sac, to analyze the spinal canal, including the cord, nerve roots, and foramina. With the introduction of MRI, myelography has diminished in importance as a diagnostic tool. Yet it still can play an important role in diagnosis for those for whom MRI is contraindicated, e.g., those with a pacemaker in situ.

Discography – an invasive provocative procedure to determine whether or not the disc is the cause of the pain. One or a number of needles are placed in the nucleus pulposus (i) of the disc(s) at varying levels and then contrast media injected to attempt to reproduce the patients symptoms. Positive discography is defined as follows: (1) abnormal morphology of the examined disc; (2) consistency of pain by provocation; (3) no pain experienced by provocation of the nearest disc; and (4) less than 3 mL of injected contrast agent.

Discography has been the subject of vigorous debate and controversy with strong advocates for and against this functional test. Many studies have shown it to be valid with high correlation to the person's pain (Walsh et al. 1990; Peng et al.

2006). Other studies have questioned the usefulness of the technique. One of the main points of concern was that pain provocation is a subjective measure dependent on the patient, which despite quantification by the VAS, inevitably yields a high rate of false positives in patients with a psychological fear of pain or hyperesthesia from chronic pain or personality trait scores. Also it can be operator dependent with pressure and flow rates of injection leading to reduced stimulation of pain receptors (Derby et al. 2005; Ohnmeiss et al. 1995).

If used it must be critically examined in association with the patients profile, pain diagnosis, and other image-guided treatments performed, e.g., facet joint injections or nerve root blocks.

The Dallas discogram description grade is the mainstay of reporting (Saboeiro 2009) and is a combination of the interventional procedure followed by a diagnostic CT scan.

The Dallas discogram protocol for performance and reporting (or now more appropriately the modified Dallas classification system) is a widely used and accepted method for describing the CT findings of the test in association with the patient's intra-procedural symptoms (Sachs et al. 1987; Resnick et al. 2005; Carragee and Alamin 2001; Cohen and Hurley 2007; Cohen et al. 2005; Madan et al. 2002). When properly performed, low false-positive rates in the order of 6–10% can be anticipated (Bogduk et al. 2013).

There are six possible categories that describe the severity of the radial annular tear.

The grade 0 is a normal disc, where no contract material leaks from the nucleus.

The grade 1 tear will leak contrast material only into the inner 1/3 of the annulus.

The grade 2 tear will leak contrast through the inner 1/3 and into the middle 1/3 of the disc.

The grade 3 tear will leak contrast through the inner and middle annulus. The contrast spills into the outer 1/3 of the annulus.

The grade 4 tear further describes a grade 3 tear. Not only does the contrast extend into the outer 1/3 of the annulus, but it is seen spreading concentrically around the disc. To qualify as a grade 4 tear, the concentric spread must be greater than 30°. Pathologically, this represents the merging of a full-thickness radial tear with a concentric annular tear.

The grade 5 tear describes either a grade 3 or grade 4 radial tear that has completely ruptured that outer layers of the disc and is leaking contract material out of the disc. This type of tear, which one is most likely to suffer from, can cause a chemical radiculopathy in one or both of the extremities and result in persistent leg pain (Fig. 9).

Irrespective of the controversy, it is currently the only test which can directly link symptoms felt to be significant to the patient to the presumed pathology, and studies have shown that patients selected for intervention in this way have improved outcomes compared to those without precision diagnosis (Colhoun et al. 1988; Margetic et al. 2013; Xi et al. 2016).

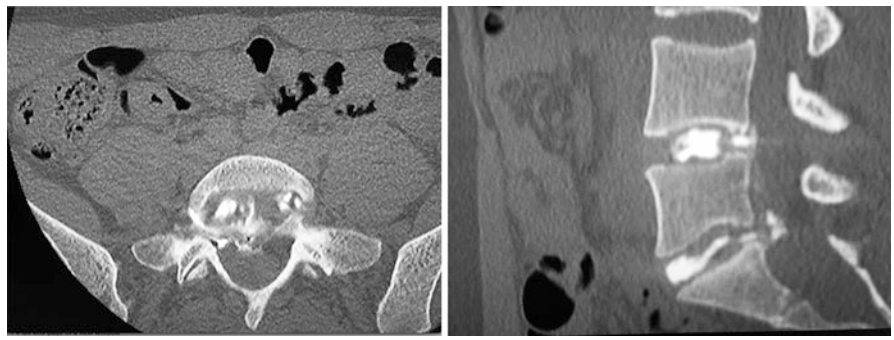

Fig. 9 Note the contrast passing from the nucleus through the outer annulus into the epidural space

Corticosteroid Injections

Which corticosteroid?

- There is great variability in the use of the injected corticosteroid.

Commonly used steroids are:

- Dexamethasone sodium phosphate
- Betamethasone acetate
- Methylprednisolone acetate
- Triamcinolone acetonide

The amount used may also vary considerably and below are examples:

- Dexamethasone sodium phosphate 4–8 mg
- Betamethasone acetate 0.25–1.0 ml
- Methylprednisolone acetate 4–10 mg
- Triamcinolone acetonide 2.5–5 mg

Commonly used local anasthetics and doses:

- Lidocaine hydrochloride (0.25–2 mls)
- Bupivacaine hydrochloride (0.25–2 mls)
- Procaine hydrochloride

Safety

A comprehensive review of the use of injected corticosteroids was undertaken by MacMahon et al. (2009), and this had particular relevance to spinal pain therapy. A number of factors were revealed which previously were not taken into account in terms of safety and protocol. In particular, this related to the particulate composition of steroids. Most corticosteroid preparations contain corticosteroid esters (apart from dexamethasone), which are highly insoluble in water and thus form microcrystalline suspensions. This property cannot only cause adhesions (problematic at subsequent open decompression procedures) but also cause particulate steroid emboli; thus they are likely the primary cause of the reported CNS complications, e.g., paraplegia or stroke. Non-particulate steroid is not known to cause this complication (MacMahon et al. 2009).

Other general complications range from common but minor risks of skin changes or transient hyperglycemia to rare but more significant complications including durotomy causing CSF meningocele and/or arachnoiditis and infection causing osteomyelitis or epidural abscess. Such material risks may be mentioned in discourse if relevant as part of informed consent prior to the injection being performed (Zotti et al. 2012). Cervical injections, particularly, carry the unique risk of vascular injury – particularly radicular artery injury – which can impair spinal cord and brain stem perfusion.

Specific contraindications should be sought and include bleeding diatheses or active use of anticoagulant (for epidural or perineural injections), infection at targeted site (unless for purpose of obtaining a biopsy), immunosuppression, poorly controlled diabetes, and noted contrast or injectable allergy.

Given the above, the alternatives and expected benefits need to be considered for any intervention. In common neurointerventional and spinal surgical practice, corticosteroids when combined with appropriate education and rehabilitation strategies can cure and assist patients with conditions of favorable natural history and who are either unsuitable for or do not wish to undergo formal surgical intervention or, alternatively, palliate patients' conditions.

Mechanism of Action

Corticosteroids predominantly affect the action of cytokines and inflammatory mediators (e.g., substance P, PLA2, arachidonic acid, IL-1, and prostaglandin E2) involved in inflammation. They lead to increased blood flow and down-regulation of immune function, inhibiting cell-mediated immunity, reducing cellular accumulation at inflammatory sites, and decreasing vascular responses. Corticosteroids cause these effects through a mechanism that ultimately involves its active moiety entering cells and combining with receptors to alter messenger RNA production, mainly altering the protein annexin-1 (previously called lipocortin-1) (Barnes 1998; Eymontt et al. 1982; Buckingham et al. 2006; D'Acquisto et al. 2008).

Types of Corticosteroid Injection

Facet joint injection (intra-articular) – the spinal needle is placed into the facet joint cavity and steroid injected along with local anesthetic. Indications include presumed facetogenic lumbar and thoracic or cervical pain. This may include facet-related pain resulting from posterior load-bearing transfer from patients with degenerative disc disease and anterior column pathology where treatment of anterior spinal structures (e.g., intervertebral disc) is thought to be high risk or undesirable. It is important that these patients are counselled that only a portion of their pain will be treated (appropriated to pain relief that may have been experienced from the medial branch block).

There is dispute over the efficacy of these injections, and some of it likely stems from only a limited proportion, perhaps 10–20% of patients having "pure" facetogenic pain. For some, common practice/convention may prevail over scientific evidence as to their efficacy and validity. For greatest accuracy the injection needs to be image controlled. An alternative, which also covers nociceptors from the facet joint but does not violate it, is the medial branch block of the dorsal ramus (Boswell et al. 2007; Sehgal et al. 2007a; Manchikanti et al. 2010; Cohen and Raja 2007; Jackson et al. 1988; Schwarzer et al. 1994, 1997; Sehgal et al. 2007b) (Fig. 10).

Medial branch block – a minimally invasive procedure whereby local anesthetic is injected along the pathway of the medial branch of the dorsal ramus of the spinal nerve, which supplies the facet joints, to determine if the origin of the pain is from the facet joints. It is important to note the innervation of the joint, recognizing that it is not single. The facet joint receives branches from the level above and below. The innervating branch lies with the depression/junction of the transverse process with the body of the vertebra.

Blockade of the medial branch of the posterior ramus nerve is generally preferred over intra-articular facet blocks as it is easy, less traumatic, and less risky than intra-articular injections (including no risk of joint infection) (Dreyfuss et al. 1997). Generally, when facet joint denervation is being considered, it is preferable to assess the patient's response to medial branch blocks given that it allows assessment of analgesic response due to blockade of the anatomic structure to be ablated. A response of 50% or more reduction of pain is an indication for RFD. However, in the presence of inflammation, intra-articular injections may be superior to medial nerve blocks.

Lumbar facet injections and medial branch blocks are both valuable in terms of diagnosis of the patient's pain generator and suitability for other interventions, e.g., radio-frequency neurotomy. However, in themselves there is limited relief of "facetogenic" low back pain. Marks, Houston, and Thulbourne reported limited relief after 3 months with relief of pain diminishing between 1 and 3 months (Marks et al. 1992). Manchikanti and colleagues reported the

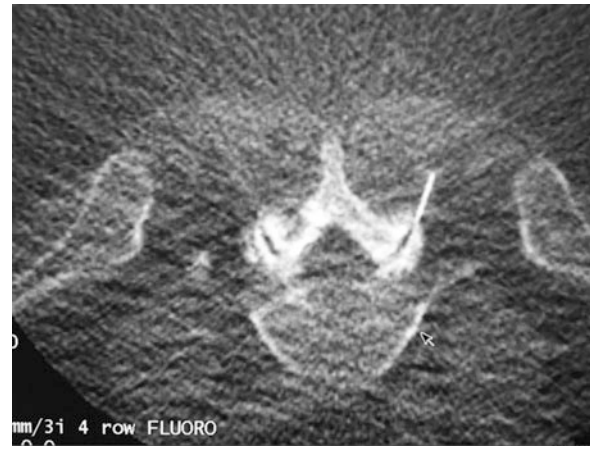

Fig. 10 The needle within the facet joint during an intra-articular injection of L5/S1

majority of patients having improvement in their facet pain at 1 year, however, irrespective of whether treated with local anesthetic alone or with steroid (Manchikanti 2001, 2010).

Most studies report that cervical medial branch facet blocks tend to have longer duration compared to lumbar facets with effect lasting between 3 and 5 months for each injection (Manchikanti 2008). The mean duration of effect for cervical facet block can be up to 8–12 months (Kim 2005), and repeated injections can provide sustained relief at a year and beyond (Manchikanti et al. 2015a). Thoracic facet interventions have not been well studied, and, as such, fair evidence is only available for medial branch blocks in the thoracic spine.

In the lumbar spine, for long-term effectiveness, there is Level II evidence for radio-frequency neurotomy and lumbar facet joint nerve blocks, whereas the evidence is Level III for lumbosacral intra-articular injections. In the cervical spine, for long-term improvement, there is Level II evidence for cervical radio-frequency neurotomy and cervical facet joint nerve blocks and Level IV evidence for cervical intra-articular injections. In the thoracic spine, there is Level II evidence for thoracic facet joint nerve blocks and Level IV evidence for radio-frequency neurotomy for long-term improvement (Manchikanti et al. 2015a). Evidence for diagnosis of cervical facet joint pain with controlled comparative local anesthetic blocks is Level I or II-1. The indicated evidence for therapeutic facet joint interventions is Level II-1 for medial branch blocks and Level II-1 or Level II-2 for radio-frequency neurotomy (Manchikanti et al. 2015a).

Facet joint denervation – this is the "follow on" from a positive medial branch block, which has confirmed that the pain generator is the facet joint. The next step is to denervate the facet joint via radio-frequency ablation or with 90% alcohol. Radio-frequency denervation, involving heating of the targeted nerve typically at 90 °C for 90 s, can provide longer-term relief than the standard facet joint corticosteroid injection. Alcohol denervation also provides significant relief, and some studies show a longer benefit than radio-frequency ablation (Joo et al. 2013).

As a day procedure usually under light sedation and performed with specialized radio-frequency equipment (an addition to standard radiology machine), the medial branches of the dorsal rami are ablated. The technique is very important, and good understanding of anatomy and physical properties of the equipment is paramount. Risks are minimal, but there have been case reports of transient radiculopathy, neural injury, and thermal burns which relate to inappropriate technique and preparation (Barr et al. 2000).

In the cervical spine, the main indication for injections or radio-frequency neurotomy remains facetogenic pain, but facet-pain targeted injections have also been used with varying success for facet pain resulting from herniated nucleus pulposus (load transfer to posterior elements from disc compromise), whiplash, and myofascial pain (Kim et al. 2005).

Like with all forms of thoracolumbar spinal treatment, radio-frequency denervation has been shown in some studies to provide significant pain reduction in patients with chronic low back pain selected with a positive medial branch block for between 6 and 18 months. In addition, this low-morbidity procedure is found to be efficacious on case series when repeated in patients who had a successful prior procedure (Zotti and Osti 2010; Schofferman and Kine 2004; Son et al. 2010) effective in around ~70% of patients for 8–9 months (Zotti and Osti 2010).

Patient selection (i.e., use and quantitative response to intra-articular compared to medial branch blocks) and mode and location of lesioning have been cited for potential inconsistencies in the results of these studies. The majority of patients, in the order of 60–80%, obtain at least 90% relief of pain when selected correctly with a mean effect typically lasting 9–12 months for both cervical and lumbar facet denervation. The evidence for radio-frequency neurotomy for sacroiliac pain is mixed in terms of quality, but sham surgery placebo-controlled trials overall were supportive of this technique (Rupert et al. 2009). However, other studies have shown little benefit to this procedure (Evans et al. 2003; Blasco et al. 2012; Zotti and Osti 2010; Bogduk et al. 2011).

A recent study by Van Tilburg and associates (2016) which was a randomized sham-controlled double-blinded study design was unable to reject the null hypothesis of efficacy for this intervention. However, several studies support the efficacy for this procedure compared to comparative controls (Gallagher et al. 1994; Van Kleef et al. 1999, 2005; Tekin et al. 2007; Kroll 2008).

Synovial cyst puncture and aspiration – a symptomatic synovial cyst from a degenerate facet joint can cause compression upon a descending nerve root and inflammation. The aim of the radiologist to achieve therapeutic relief is to puncture and if possible aspirate the cyst or rupture it, followed by an injection of steroid and local anesthetic. There are two mechanisms for the above:

(i) A direct puncture (which is not always possible due to its position in the canal as access may not be not possible due to the lamina or facet joint covering the anticipated needle pathway).
(ii) An indirect rupture via the facet joint – filling the latter with injectate – steroid and local anesthetic and saline until the cyst ruptures. This technique can be very painful.

Percutaneous treatment for facet cysts has been reported to only fair long-term success, approximately 50–80% of patients in literature reviews, and relief for up to 1 year has been reported (Vad et al. 2002; Carmel et al. 2007). Many of the cysts targeted are gelatinous and not amenable to aspiration, leaving the large residual cyst capsules to continue compressing the neural/dural structures, and cause ongoing neurological dysfunction. Along with the 37.5–50% risk of recurrence is a 45–50% chance of success with repeated cyst rupture attempts (Imai et al. 1998; Rauchwerger et al. 2011; Sabers et al. 2005; Schulz et al. 2011; Shah and Lutz 2003). A further trial can be attempted in refractory cases or recurrence, but a high proportion of these patients (50–60%) will require open spinal surgery. The uncertain efficacy of this intervention has led some authors to advocate for surgical intervention rather than repeated attempts (Epstein and Baisden 2012).

Selective nerve root injections/perineural injections and epidural injections – the spinal needle is placed next to the suspected pain-generating nerve, and a mixture of local anesthetic and steroid (e.g., dexamethasone and bupivacaine being injected) is injected. Again the steroid used varies as does the utilization of the radiology modality and the amount. The technique is most commonly done with fluoroscopy or under CT guidance. There are a number of different techniques/approaches which include transforaminal, interlaminar, and caudal. The most widely used and accepted is the transforaminal approach. The consensus from the literature (and certainly anecdotally) is that epidural steroid injections are effective and of value particularly for limb and girdle pain. However, the degree of efficacy is much and varied. In saying this, the degree of efficacy of the injection is based upon many factors which include the spinal pathology, the severity of the pathology, the expertise and skill of the operator, the exact position of the needle, the patient's mental state, and other systemic or local pathologies. As aforementioned, the mechanism by which the steroid works is manyfold including reducing inflammation/swelling via neutralizing inflammatory mediators, e.g., substance P, PLA2, arachidonic acid, IL-1, and prostaglandin E2. The steroid also increases blood flow and reduces the activity of the immune system (Akuthota et al. 2013; De Smet et al. 2005; Salahadin et al. 2007; Vad et al. 2002; Carmel et al. 2007; Lutz et al. 1998) (Fig. 11).

Many studies report the effectiveness of this intervention, including randomized trials, but large level 1 double-blinded studies with a placebo comparator are lacking. This is particularly so for contained herniated pulposus lesions (MacVicar et al. 2013) with mild neural compression, whereas injections into segments affected by extruded or sequestered disc fragments are thought to be less effective. While the addition of CSI is generally favorable, some studies have suggested that they alter the natural history of the patient and reduce the number of patients who undergo surgery of continued symptoms.

Interestingly, some trials have reported benefit of injection but no additional benefit to

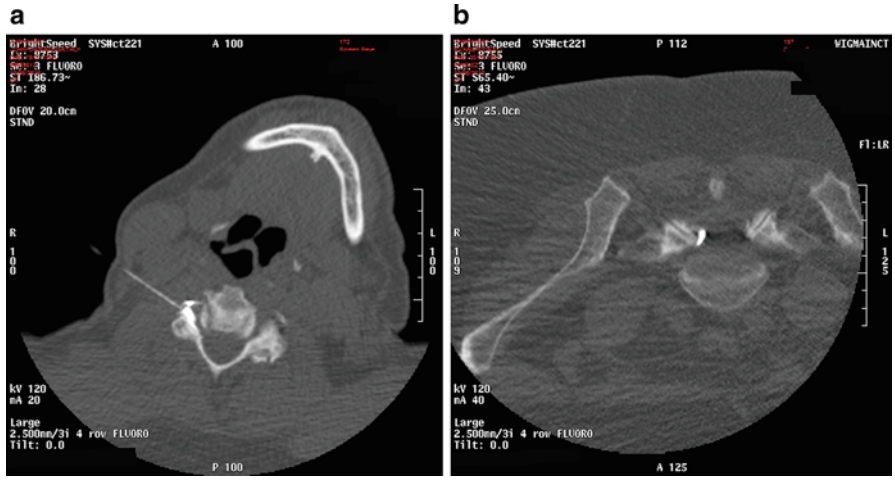

Fig. 11 (**a**) and (**b**) Note the transforaminal approach with contrast (prior to steroid injection) to confirm position around the exiting nerve root and also passing into the epidural space. Note in the next picture the paramedian interlaminar approach noting contrast between the ligamentum flavum and thecal sac in the epidural space

corticosteroids added to local anesthetic (Ng 2005). The majority of patients, in the order of 70–75%, will have significant reduction of their symptoms when they have been presented for less than 3 months. However, patients with symptoms longer than 3 months tend to have more variable success. Furthermore, patients with shorter duration of symptoms can be expected to experience more sustained relief than those with chronic symptoms. When effective, a reduction of at least 50% for 1–2 months can be expected in around 70% of patients and complete resolution in around 30% of patients (Ackerman and Ahmad 2007).

Cervical transforaminal epidural injections are effective for around 70–80% of patients with radiculopathy and have been shown to prevent the need for surgery in around 70% of patients (Costandi 2015; Vallee 2001). While at 3 and 6 months, around 30% of patients have complete resolution of symptoms, this reduces to around 20% at 1 year (Vallee 2001). To achieve sustained and effective relief, repeated injections may be required. For example, Slipman et al. (2000) reported pain reduction, return to full-time work status, reduction or elimination in analgesic use, and satisfaction with treatment in 60% of patients at 12–45 months' follow-up, but treatment on average consisted of 2.2 injections.

Interlaminar injections have good evidence for usage in the setting of herniated discs and radiculitis and fair evidence for axial/discogenic pain without facet joint pain and are technically simpler in the hands of experienced operators. They have been shown to have superior effect for chronic lumbar disc herniation at 2 years compared to caudal and transforaminal injections (Manchikanti 2015b). They have also been shown to be superior to caudal injections for lumbar central spinal stenosis (Manchikanti et al. 2014). In addition, there is Level II and Level II/III evidence for long-term management of cervical disc herniations or stenosis and thoracic disc herniations, respectively. Caudal injections, on the other hand, have good evidence for herniated disc and radiculitis with only fair evidence for axial/discogenic back pain, spinal stenosis, and post-surgery syndrome.

Both interlaminar and caudal injections for axial or discogenic pain are shown to be effective, but interlaminar injections have marginal superiority over caudal injections for this indication (Manchikanti 2015b). Interlaminar and caudal techniques have been reported to be effective for lumbar disc herniation or radiculitis (Kaye et al. 2015); however, some studies have reported them to be less effective than transforaminal injections for radiculopathy due to herniated nucleus

pulposus (Kamble et al. 2016; Ackerman and Ahmad 2007; Lee et al. 2009; Thomas et al. 2003).

Sacroiliac Injections

Sacroiliac joint pain – the great mimicker. One of the greatest challenges in diagnosing the pain from this joint is that the symptoms can imitate other pain-generating conditions, e.g., facet joint arthropathy and discogenic or radicular pain from herniated discs with the malady being both around the sacroiliac joint but also radiating down the lower limb or into the groin. As always, imaging can provide both diagnosis and treatment. The issue the clinician faces is that in many cases, the imaging does not directly confirm the provisional diagnosis. Arthropathy may be present; however the joint may show no signs of pathology on plain X-ray, CT, and MRI. The physical examination is therefore paramount to test the suspicion of SI pain with the location of the patient's symptoms and any worsening with provocative tests. Like with other joint-related conditions, steroid and local anesthetic blocks can aid in both diagnosis and treatment.

Patients are prone and the needle advanced before a sensation of entering the joint which is confirmed on multiple planes to be in the joint. It is performed by imaging guidance due to the highly variable morphometry of pelvises between patients for diagnostic and therapeutic purposes. Smaller doses of LA/steroid focusing on the posterior-inferior hyaline portion of the joint tend to be diagnostic, while larger doses that aim to bathe the entire joint are therapeutic. Some clinicians favor the addition of separating more superior injection into the fibrous component of the joint. The controlled diagnostic blocks utilizing the International Association for the Study of Pain (IASP) criteria demonstrated the prevalence of pain of sacroiliac joint origin in 19–30% of the patients suspected to have sacroiliac joint pain (Forst et al. 2006).

Evidence from meta-analyses (Hansen et al. 2007; McKenzie-Brown et al. 2005), albeit based on low quality data, supports the role of SI injections in treating painful sacroiliac dysfunction and spondyloarthropathy. Maugars et al. (1996) performed a double-blinded placebo assessment of CSI versus placebo and found a statistically and clinically important difference. Eighty-six percent had positive effect at 1 month, while the majority continued to have efficacy of the injection with 58% reporting relief at 6 months (Fig. 12).

Coccyx Injections

Diagnostic and therapeutic injections into the coccygeal region are performed for coccydynia. Ideally, the local infiltration blocks the ganglion

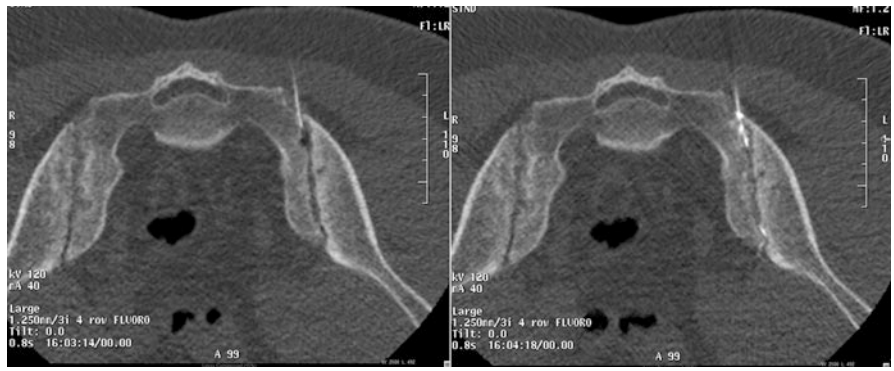

Fig. 12 CT-guided left sacroiliac joint injection. Note the needle confirmed to be within the sacroiliac joint

impar, which is a relay station for nociceptive pain emanating from the sacrococcygeal joint. Indications include coccydynia due to post-traumatic pain/hypermobility or pain from the sacrococcygeal disc. Unique complications to this procedure include rectal laceration and bowel content contamination of the injected field.

The patient is generally prone with sterile preparation and draping and sometimes sedation. Direct percutaneous placement of needle through and proceeding just anterior to the margin of the sacrococcygeal disc with confirmation on lateral and anteroposterior views with dye (if the procedure is done under Xray control rather than CT) followed by injection of LA and CSI to ganglion impar. Occasionally combined with per rectal manipulation in the setting of hyperflexed posture due to trauma or laxity.

Literature for effectiveness is generally limited to smaller cohort studies and case series making it hard to recommend treatments (Howard et al. 2013). Injection alone is effective in around 60–85% of patients with long-term success in around 45–50% with median relief at 6 months (Maigne 2011; Gunduz et al. 2015). Repeated injections were effective in the majority of those presenting with recurrent symptoms (Hodges 2004). Injection combined with manipulation results in around 85% successful outcomes with long-term success in around 60% with the theory for additional manipulation being that abnormally flexed posture of the coccyx leads to increased dural tension.

Other Invasive Forms of Image-Guided Treatment

Vertebroplasty and Kyphoplasty

These are procedures done under image guidance for the treatment of pain due to vertebral compression fractures, usually from osteoporosis. The combination of orthopedic bone cement and direct image guidance of a needle into the vertebra has allowed the past treatments for compression fractures – typically weeks to months of bed rest, analgesia, and sometimes bracing to be replaced or at least supplemented. Kyphoplasty involves partial reduction of fractures by use of an image-guided transpedicular balloon implant prior to cement insertion into the void. These techniques can also be applied to fractures from primary or secondary neoplasia affecting the vertebral body. Success rates vary, but overall significant pain reduction and improvement in the ability to perform ADL have been shown to be statistically significant (Barr et al. 2000; Evans et al. 2003; Blasco et al. 2012). Although felt to be a successful intervention, vertebroplasty for osteoporotic fractures (as distinct from metastases) has been removed from payer coverage in several countries because of equivocal results in sham-controlled procedures.

Spinal Stimulators

Spinal dorsal column stimulators can be inserted either under image guidance or by open techniques in theater with a formal approach and laminectomy. The principle is neuromodulation via electrodes placed onto the spinal cord through interference of emitted frequencies upon pain transmission in the spinal cord. It is believed to take effect through either blockage of pain transmission pathways or upregulation of inhibitory pathways. The patient generally has to meet strict criteria and has a trial period before definitive implantation occurs. The apparatus includes a battery, wires, and an electrode paddle that is applied to the targeted area (depending on pathology).

While the indications are evolving, they are generally indicated for refractory neuropathic pain despite other treatments in patients not amenable to or suitable for any further surgical intervention (low prospect of surgery being able to correct any neuroanatomic abnormality). A classic indication would be arachnoiditis after multiple posterior surgeries but may also include true "failed back surgery syndrome" and complex regional pain syndrome.

Measuring Success of Injections/ Radiology Treatments

There are numerous indicators for pain analysis and benchmarking the premorbid severity and therapeutic impact of interventions and thus providing a means of objectively measuring outcomes and success of treatments. Both statistical and clinical significance of outcomes are both important and measured. More so than other forms of medicine, interventional treatments involving needle injections into joints have undergone extensive analysis against placebo (sham) controls in multiple studies.

Below are listed some of the many available unidimensional assessments relating to pain in such trials but also commonly used in clinical practice (e.g., post-discography or diagnostic injection):

(a) VAS (visual analogue scale)
(b) NRS (numerical rating scale)

Multidimensional scales (looking at both dimensions of pain and effects on life quality):

(c) Brief Pain Inventory Short form
(d) McGill Pain Questionnaire
(e) West Haven Multidimensional Pain Inventory
(f) SF-36 and Oswestry Disability Questionnaire

All of the above have been combined into the Treatment Outcomes of Pain Survey which is a comprehensive and detailed instrument for measuring pain and outcomes (Younger et al. 2009). Future analytic tools should elaborate upon existing ones by assessing indirect and direct effects upon the patient and the economy including changes in need for aids, opioid usage, employment capability, use of healthcare resources (visits/hospitalizations), and need for care in daily living.

Conclusions

Radiology provides a harmonious and encompassing trinity of diagnosis, quantification, and therapy in relation to spinal pathology. Technology has allowed radiology to become an integral part of diagnosis and treatment, both pre- and postoperatively in those with spinal pain. Radiology provides the clinician with numerous adjuncts to the clinical history and examination by allowing direct analysis of the suspected spinal pain generator and the additional means of providing accurate treatment via targeted imaging. Although the success of image-guided therapeutic techniques is open to some contention, two points should always be kept in mind. First, the skill and subspecialization of the operator are paramount, with them having an interest and formal training and education in the field of spinal pathology. This allows safety for the patient and provides the best chance of obtaining a positive result. Secondly, the majority of patients with back and neck pain will be amenable to several minimally invasive therapeutic technique to obtain relief and return to more "normal" lives, hence, the importance of the first point. With all of the above considered, the usefulness of radiology is self-evident in its ability to provide benefits and alter the natural history of painful conditions with a limited risk profile in selected patients.

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Surgical Site Infections in Spine Surgery: Prevention, Diagnosis, and Treatment Using a Multidisciplinary Approach

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Abstract

Surgical site infections (SSIs) after spinal surgery are an important cause of postoperative morbidity and a multidisciplinary approach should focus on prevention. Screening for preoperative and recognition of intraoperative risk factors that increase the incidence of SSIs should be routine practice. Factors shown to influence SSIs include diabetes, obesity, previous SSI, complex multilevel procedures, and excessive surgical time and blood loss.

Multidisciplinary awareness and monitoring for SSIs is required with a high index of suspicion based on a combination of clinical findings including pain in the surgical area, swelling, fever, and wound discharge and diagnostic tests including WCC, CRP, ESR, wound microbiology, and blood cultures. Imaging the area with ultrasound, CT, or MRI and guided needle sampling of any detected collections may be required. Prompt treatment with antibiotics reflecting regional bacterial isolates and their sensitivity patterns should be implemented. Surgical wound wash outs, often performed repeatedly, may be necessary in selected cases.

Keywords

Surgical site infection · Prevention · Risk factors · Diagnosis · Management · Staphylococcus aureus · Implant multidisciplinary · Inflammatory markers · Spinal surgery

Introduction

Surgical site infections (SSIs) represent a significant morbidity after spinal surgery and a multidisciplinary approach is required to minimize their risk and manage them when they occur. They are defined as infections as demonstrated by clinical features with support of ancillary tests and microbial testing in the perioperative area of a spinal intervention. These are subclassified into superficial SSIs, which are localized to the skin and subcutaneous tissue, and deep SSIs, which are deep to the fascia and include either deep incision SSI or organ/space SSI (see Fig. 1). Although rates of SSI in spine surgery are low, recognition of high-risk situations for SSI and knowledge of general and specific measures for prevention is critical for the practicing spinal surgical team. Prompt and appropriate diagnosis and intervention, which may be aggressive, is required to prevent a further complication cascade for the patient. This is particularly so as SSIs are not only associated with potential failure of the intended treatment but are also associated with significant increases in hospital inpatient length of stay, readmission, prolonged antibiotics administration, and, hence, increased health costs (Pull Ter Gunne and Cohen 2009; Van Middendorp et al. 2012) (Table 1).

Epidemiology

In most reports analyzing modern spinal surgery in large cohorts with robustly collected data, the incidence of SSI is typically 1–7% (Van Middendorp et al. 2012). However, this figure has been reported to be as low as 0.5% and as high as 25% (Mistovich et al. 2017). It is difficult to generalize and compare the incidence of SSI between study populations given the large variation in patient factors (including pathology to be treated, comorbidities, risk factors, and regional differences in microbial carriage), surgical factors (including approach and complexity), classification (e.g., Superficial SSI which often presents earlier compared to deep), and methods

Table 1. Criteria for Defining a Surgical Site Infection (SSI)*

Superficial Incisional SSI

Infection occurs within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:

1. Purulent drainage, with or without laboratory confirmation, from the superficial incision.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision.
3. At least one of the following signs or symptoms of infection: pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative.
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician.

Do *not* report the following conditions as SSI:

1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration).
2. Infection of an episiotomy or newborn circumcision site.
3. Infected burn wound.
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI).

Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds.[433]

Deep incisional SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision *and* at least *one* of the following:

1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site.
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: fever (>38°C), localized pain, or tenderness, unless site is culture-negative.
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician.

Notes:

1. Report infection that involves both superficial and deep incision sites as deep incisional SSI.
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI.

Organ/space SSI

Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:

1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space.
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space.
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination.
4. Diagnosis of an organ/space SSI by a surgeon or attending physician.

Fig. 1 Classification and criteria for spinal SSI according to the National Noscomial Infections Surveillance System Criteria. (Reprinted with permission from Mangram et al. 1999). (Copyright 1999 by Elsevier)

of diagnosis with variable identification of less virulent organisms (Collins et al. 2008; Schoenfeld et al. 2011). A good example of the variation in incidence and the role of pathology and complexity is within the pediatric scoliosis population – the incidence of SSI for routine AIS correction is in the order of 0.5%, while correction of complex syndromic and neuromuscular scoliosis has a far higher incidence in the order of 20–25% (Mistovich et al. 2017).

Etiology

The understanding of SSI in the spine continues to evolve and the differences in pathophysiology between organisms and processes likely accounts for some of the different presentations observed in the patient clinically. It must be stressed that the etiology is different to that observed in primary spinal infection. Surgical site infections can be sub grouped into temporal (i.e., acute < 3 weeks, subacute 3 weeks–3 months, and chronic > 3 months) and physical characteristics (superficial and deep). The most common organism isolated is *staph. aureus* followed by *coagulase negative staphylococci* with *staph. Epidermidis, Pseudomonas aeruginosa, E. Coli, Proteus,* and *P. Acnes* all relatively common (Abdul-Jabbar et al. 2013).

Superficial infection (superficial to fascia) as in other areas of the body relates to the favorability of the healing environment at the level of the superficial integument: the genetics and immune system of the host, physical tension, wound oxygen tension, vascularity, dead space, apposition of layers, amount of foreign material, and local bacteria all have a role here. Assuming a truly no fascial breach, either local wound care and antibiotics or simple drainage/aspiration of any abscess with antibiotics may resolve the situation.

Deep infection, however, is a different entity not dissimilar to that seen in deep infection of extremity orthopedic implants. Unlike primary spinal infections, SSI is more commonly a result

Table 1 Criteria for Defining a Surgical Site Infection (SSI)*

Superficial incisional SSI
Infection occurs within 30 days after the operation *and* infection involves only skin or subcutaneous tissue of the incision *and* at least *one* of the following:
1. Purulent drainage, with or without laboratory confirmation, from the superficial incision
2. Organisms isolated from an aseptically obtained culture of fluid or tissue from the superficial incision
3. At least one of the following signs or symptoms of infection: Pain or tenderness, localized swelling, redness, or heat *and* superficial incision is deliberately opened by surgeon, *unless* incision is culture-negative
4. Diagnosis of superficial incisional SSI by the surgeon or attending physician
Do *not* report the following conditions as SSI:
1. Stitch abscess (minimal inflammation and discharge confined to the points of suture penetration)
2. Infection of an episiotomy or newborn circumcision site
3. Infected burn wound
4. Incisional SSI that extends into the fascial and muscle layers (see deep incisional SSI)
Note: Specific criteria are used for identifying infected episiotomy and circumcision sites and burn wounds[433]
Deep Incisional SSI
Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves deep soft tissues (e.g., fascial and muscle layers) of the incision *and* at least *one* of the following:
1. Purulent drainage from the deep incision but not from the organ/space component of the surgical site
2. A deep incision spontaneously dehisces or is deliberately opened by a surgeon when the patient has at least one of the following signs or symptoms: Fever (>38 °C), localized pain, or tenderness, unless site is culture-negative
3. An abscess or other evidence of infection involving the deep incision is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of a deep incisional SSI by a surgeon or attending physician
Notes:
1. Report infection that involves both superficial and deep incision sites as deep incisional SSI
2. Report an organ/space SSI that drains through the incision as a deep incisional SSI
Organ/Space SSI
Infection occurs within 30 days after the operation if no implant† is left in place or within 1 year if implant is in place and the infection appears to be related to the operation *and* infection involves any part of the anatomy (e.g., organs or spaces), other than the incision, which was opened or manipulated during an operation *and* at least *one* of the following:
1. Purulent drainage from a drain that is placed through a stab wound‡ into the organ/space
2. Organisms isolated from an aseptically obtained culture of fluid or tissue in the organ/space
3. An abscess or other evidence of infection involving the organ/space that is found on direct examination, during reoperation, or by histopathologic or radiologic examination
4. Diagnosis of an organ/space SSI by a surgeon or attending physician

∗ Horan TC et al.

† National Nosocomial Infection Surveillance definition: a nonhuman-derived implantable foreign body (e.g., prosthetic heart valve, nonhuman vascular graft, mechanical heart, or hip prosthesis) that is permanently placed in a patient during surgery.

‡ If the area around a stab wound becomes infected, it is not an SSI. It is considered a skin or soft tissue infection, depending on its depth.

of direct inoculation during the surgical procedure, although early postoperative contamination (e.g., getting early postoperative wound wet) and hematogenous spread remains a possibility; this is particularly so if gram-negative organisms are isolated (Chahoud et al. 2014). Whatever the cause, the concern in deep infection is biofilm, which is difficult to control without metal removal. There is then the difficult balance and so-called race between fusion and progression of infection where the natural history is unpredictable. Bacteria embedded in biofilms have been shown to develop and colonize on inert surfaces of many spinal implants and

electron microscopy of samples taken from implant surfaces have shown biofilms to be the foci of device-related infection for "typical" biofilm forming bacteria such as staphylococci and streptococci (Tofuku et al. 2012). The bacteria within biofilms are protected against host defense mechanisms as there is no native blood supply and antibiotic therapy alone is ineffective because activated phagocytes cannot kill bacteria in biofilms. This is as antibodies released from sessile bacterial cells and antibiotics fail to penetrate biofilms and phagocytosis cannot be achieved (Tofuku et al. 2012). Interestingly, stainless steel implants are particularly vulnerable to biofilm compared to titanium implants. Further development of the use of materials or coatings that release antibiotics in concentrations that kill planktonic bacterial cells around the implant may have a role here. Until then, the only reliable way to disrupt the biofilm is surgical (Chahoud et al. 2014).

There is emerging interest in the atypical presentation of spinal infection, particularly in association with *propionibacterium acnes.* This organism, previously thought to be a contaminant, often causes no fever and a low-grade response with indolent failure of the implant construct. It is notoriously difficult to isolate and culture and, as such, should be sought for with PCR and extended cultures when implant constructs fail without a clear pyogenic presentation (Chahoud et al. 2014; Collins et al. 2008).

Risk Factors

Several papers, including those from large databases, have assessed the risk factors for spinal SSI but are limited in their identification of risk factors by methodology (Van Middendorp et al. 2012). From this viewpoint, several risk factors have been repeatedly identified and should be regarded as established while others have associated conflicting data and should be regarded as relative. Established risk factors include the comorbidities of type II diabetes mellitus, obesity, multiple spinal operations, and previous SSI with surgical factors being length of open operation $\geq$ 5 h, $\geq$ one liter blood loss and multilevel constructs. Subpopulations identified as high risk of spinal SSIs compared to population norms include oncology patients, syndromic or neuromuscular deformity patients, patients with inflammatory arthritis, and immunosuppressed patients, e.g., HIV/AIDS (Chahoud et al. 2014; Pull Ter Gunne and Cohen 2009).

Relative risk factors which have been variably reported or not robustly studied include several patient and surgical factors. Patient factors include female gender, advanced age, fecal or bladder incontinence, atherosclerotic vascular disease, hypertension, smoking, alcohol, malnutrition, corticosteroids, and multiple operations. Comorbidities such as the above are thought to be compounding and additional to the risk inherent in any spinal procedure (Chan et al. 2014; Oichi et al. 2015; Quan et al. 2011; Walid and Robinson 2011). MRSA carriage is a controversial risk factor in its implications for screening, prevention, and treatment (Catanzano et al. 2014; Mehta et al. 2013; Molinari et al. 2012).

Relative surgical risk factors that have limited or conflicting data include the approach (higher prevalence with posterior and non-same day staged 360° fusions), "invasiveness" of the approach (higher in open compared to minimally invasive for multilevel procedures) (McGirt et al. 2011; Smith et al. 2011), visceral injury (e.g., bowel for lumbar; esophageal for cervical) (Kang et al. 2009; Pichelmann and Dekutoski 2011), thoracic procedures (Smith et al. 2011), instrumented procedures (Smith et al. 2011) particularly stainless steel, transfusion use intraoperatively and use of surgical drains (Kawabata et al. 2017).

The implication of identifying situations of high SSI risk is to optimize the situation for the patient so as to minimize the risk of infection and also to counsel the patient regarding their relative risk for planned surgery. It is self-evident that the relative risk discussion with a

patient with minimal comorbidities undergoing a single-level procedure would be different to an elderly, obese, diabetic patient planned for a multilevel reconstruction. Optimizing the patient may then also have benefits with regard to minimizing anesthesia-related comorbidity and reaching the therapeutic goal (e.g., increasing likelihood of fusion of a painful motion segment). Several comorbidity-derived calculators may be useful for this purpose, including screening with the Charlson comorbidity index calculator (Walid and Robinson 2011). At present, while infection risk calculators such as the standardized infected ratio exist, no validated long-term data is available for any spinal specific scoring system (Fukuda et al. 2013).

Prevention of Spinal SSIs

Prevention and treatment of spinal SSIs must be viewed through a truly multifaceted manner. To regard prevention of infections with a narrow focus such as concentrating on patient selection, on which prophylactic antibiotic to administer or on which surgical skin preparation to use misses the very broad range of factors that can be successfully addressed with a holistic approach and a multidisciplinary team. In identifying SSIs postoperatively, a search for factors that have led to the SSI and how they can be prevented in future should be prompted, ideally, in a collaborative audit setting. Involvement of physicians, infection control personnel, and specialty nurses may uncover previously unrecognized factors in the patient care that, if unabated, could lead to continued high incidence of SSIs. These include changes which may seem trivial or banal in patient preoperative skin care, theatre equipment sterilizsation, theatre environment such as laminar flow and cleaning, and in ward care such as showering and wound dressing protocols. However, these are changes which the surgeon may not immediately consider or be aware of in their busy routine of daily practice. With the insight and knowledge of other key allied health personnel involved in the hospital facility and the patient's perioperative journey, such factors are imminently amenable to prevention of further infection episodes. From this viewpoint, below are points considered important and best practice to avoid SSI in our practice.

Preoperative

Prehospital

Patient

- Assess and manage patient-related risk factors as detailed above including diabetic, blood pressure and weight control, cessation of smoking and alcoholism, and optimizing nutrition.
- Educate the patient regarding optimal nutrition and hygiene in planned surgical sites. For example, topical benzoyl peroxide may be useful in decolonizing adolescent patients prior to posterior spinal surgery who would otherwise be at risk of *p. acnes* infection.
- Ensure the patient is free of any intercurrent treatable infections. Although controversial, screening the urine for asymptomatic infection may be appropriate in selected populations.
- Depending on regional prevalence of MRSA and VRE coverage, consider adoption of a screening and eradication program, e.g., Nasal screening, washes, and intranasal mupirocin.
- Referral to or involvement of a dermatologist preoperatively should be considered in selected cases. For example, adolescent patients with widespread dorsal acne planned for scoliosis correction or patients with eczema/dermatitis that may require treatment.
- Involvement of an infectious diseases physician in selected cases. For example in patients with immunodeficiency due to HIV/AIDS or tuberculosis.
- For oncology patients, close collaboration with oncology colleagues regarding the patient's immune status and any radiotherapy or chemotherapy interventions perioperatively.
- Liaison with rheumatologist regarding antirheumatic and immune modulating drugs for patients with inflammatory arthritis and whether they should be discontinued perioperatively.

In Hospital

Theatre

- Robust infection control protocols and procedures including audit of theatre and ward cleanliness and sterilization effectiveness.
- Meticulous hand hygiene of all those in contact with the patient.
- Ensure access to large and clean theatres with laminar flow or clean filters (Gruenberg et al. 2004).
- Properly sterilized equipment available.
- Trays, staff, personnel, and theatre traffic managed by team in a way that minimizes potential for contamination and particulate agitation. Signage that open surgery is in progress to minimize traffic.
- Insist on mask donning and appropriate hair coverage at time of tray opening for all personnel and minimize unnecessary equipment movement, e.g., II.
- Meticulous draping technique and patient warming.
- There are mixed reports regarding efficacy of surgical isolation hoods and ultraviolet light (Cheng et al. 2005).

Patient

- Preincision antibiotics, most commonly cephalosporins in the low-risk population, with appropriate cover of skin organisms (Petignat et al. 2008)
- Clipping of excess hair at the surgical site
- Pre-incision cleaning and scrubbing
- Sterile insertion of any drains or invasive monitoring

Intraoperative, in Hospital

- Minimize soft tissue trauma and retraction times where possible. Where surgery is prolonged, consider release of retraction momentarily to prevent prolonged ischemia. Consider use of minimally invasive muscle sparing techniques if appropriate for pathology and adequate training/skillset.
- Utilization of a "no touch" technique where possible and regular glove changes after heavy soiling.
- Adequate hemostasis given that residual hematoma likely to be nidus for infection.
- Minimizing the repetition of steps and adhering to efficient completion of the operative case to minimize any unnecessary delays in achieving sterile wound closure.
- Intermittent saline bathing of tissues to prevent desiccation and lavage of wounds prior to closure (Brown et al. 2004). Diluted betadine has also been shown to be effective for prevention of infection but its effects on tissue fibroblasts need to also be considered (Cheng et al. 2005).
- Consider use of topical vancomycin powder. Some authors advocate for routine usage in spinal surgery as has been shown in some literature reviews to be effective for prevention of deep SSI (Devin et al. 2015; Godil et al. 2013; Schroeder et al. 2016).
- Apposition of skin edges without excessive tension. Dressings that allow removal of excess moisture on the wound and vapor exchange.

Postoperative, in Hospital

- Prophylactic antibiotics according to local guidelines
- Meticulous hand hygiene and environmental cleaning of the patient's surrounds. Adequate signage and control of visitors if the patient has additional resistant organisms or visitors are found to be unwell.
- Mobilization of the patient with physiotherapy and regular positioning and appropriate mattress selection to offload pressure from skin. Regular pulmonary toilet to prevent respiratory collapse and infection.
- Optimal nutrition with diet on ward having adequate protein, vitamins, and minerals to support healing.
- Regular aperients and encouraging elimination to minimize risk of bowel stasis and urinary tract infection.

- Maintaining adequate perfusion with good hydration and consideration for transfusion if levels critically low, e.g., ≤9 g/dL. Perioperative physician care to support the patient in the postoperative period is valuable.
- Preference for mechanical deep vein thrombosis prophylaxis over chemical, where possible, to reduce risk of wound ooze
- Wound changes to be kept to a minimum and performed only where necessary (contaminated wound or excessive fluid).
- Removal of any drains and indwelling devices as soon as practicable to prevent device-related infections

Postoperative, Following Hospital Admission

Patient

- Education and provision of appropriate wound care and hygiene instructions, including washing.
- Maintenance of optimal health and avoiding toxins, e.g., excessive alcohol and tobacco.
- Early review of wound as outpatient and early and aggressive management if infection diagnosed.

Hospital and Surgical Unit

- Hospital infection control and regional infectious disease monitoring to assess local organisms and antibiotic sensitivities.
- Regular auditing and surveillance to correct any unexpected infections or unusual organisms and change practice accordingly. For example, contaminated theatres or malfunctioning sterilization machines.
- Participation in morbidity and mortality meetings and self-reflection on own practice SSI incidence.

Diagnosis of SSI

The diagnosis of SSI can be challenging and a low index of suspicion for infection must be held. With this mentality, neither the "obvious" pyogenic infections heralded by febrile patients with painful and purulent wounds nor the patients who present in an insidious way with persistent low-grade pain and malaise should be missed. This is particularly important with emerging evidence of previously difficult to diagnose organisms affecting instrumented spinal cases (Collins et al. 2008). Figure 1 shown previously provides objective criteria for superficial, deep, and organ space SSIs.

Clinical Presentation

A presentation of a wound issue, such as a discharging, swollen, purulent, erythematous, or discharging wound, should always be a cause for concern for surgeons and staff alike of a SSI. Systemic symptoms such as lethargy, malaise, loss of appetite, and, in more severe cases, fevers, rigors, and sweats should alarm staff that there is not only a local issue in the spine and its surroundings but potentially a systemic response that, if unabated, could lead to a septic syndrome. The sequelae of this can be heralded by hemodynamic dysfunction and metabolic dysfunction before multiorgan failure ensues.

In fact, the most common presenting complaint of patients later diagnosed with infection is less dramatic in the form of back pain. This presents a quandary for the clinician, where postoperative back pain may have a myriad of causes including residual pathology and "normal" postoperative tissue response in the first month. The onset tends to be insidious and persistent (Collins et al. 2008). The usual duration between procedure and discernible features of infection ranges from 2–30 days and varies depending on the behavior of the organism (Chahoud et al. 2014).

The more dramatic presentation of the unwell patient who is septic is becoming increasingly concerning with different resistant strains of staphylococci identified that have the potential to incite a violent systemic response. However, as an increasingly aging and comorbid population come to spinal surgery, there must be an index of suspicion for hematogenous seeding of implants with

the increased incidence of intercurrent infections that can mask an implant infection.

Ancillary investigations that support this diagnosis include blood serology testing, microbiology, and imaging. This also includes evaluation of other potential sites of infection such as the urine, heart, abdomen, and chest with urinalysis, echocardiogram, and radiographs, if the history and physical examination indicates it. Elevated CRP is nonspecific postoperatively but very high levels and levels that do not come down after the early postoperative period is concerning. Likewise, WCC has fair sensitivity for spinal infection only but lacks specificity. ESR can be useful when adjusted for age and sex in the subacute and chronic settings and is concerning if raised but is, again, nonspecific. Novel technologies that are emerging include serology such as serum amyloid and synovial procalcitonin and alpha defensin but these require further validation in the spinal setting (Chen et al. 2017).

Microbiological identification of the causative organism with accurate and careful handling and preparation of sample tissues is critical. It is important, if possible, to avoid the temptation to treat the patient with antibiotics prior to microbiological identification of an organism empirically (unless they are septic) in the cases where a specimen can be obtained. Correct organism identification is paramount to appropriately targeting and tailoring antibiotics to the organism and understanding its behavior. In the case of the septic patient who is progressing to extremis or the patient with probable epidural abscess-related neurological deterioration, blood cultures should at least be obtained prior to commencing empirical antibiotics. Should the patient have inadvertently been given antibiotics then delaying an aspiration for 1 week may be advisable to increase yield. Wound swabs are of mixed value, particularly as they are hard to interpret in the presence of skin colonized by commensals and their often polymicrobial growths. Histopathological examination as an adjunct is useful in assessing for typical pyogenic changes as opposed to granulomatous change or unexpected neoplasm. DNA microarrays and PCR molecular amplification techniques are likely to become the standard of care and offer high sensitivity and specificity (Chahoud et al. 2014).

Imaging can help define and localize the infection and helps to exclude other causes for the patient's presentation. Nuclear medicine, unlike in primary spine infections, have a limited role in SSI given the extent of uptake expected from surgical intervention albeit that continued improvements in technology may make this a more specific and reliable tool in identifying SSI accurately (Cornett et al. 2016). Specimens obtained under sterile conditions either operatively or under image guidance (ultrasound, fluoroscopy or CT) will likely yield the causative organism. In the setting of a spinal SSI, it is important to assess whether there is a collection or any clearly pathological tissue which to target for culture before proceeding with the intervention and it is also important to use a wide-bore cutting needle to maximize tissue yield through a core biopsy (Garg et al. 2016). Imaging here either with MRI, CT (with metal suppression if implants present), or a combination can allow evaluation of the bony and soft tissues in the surgical site and evaluate for evidence of infection as opposed to postoperative edema, hematoma, or pseudomeningocele. For example, if the MRI diagnoses pyomositis and deep soft tissue abscesses around the surgical site, then these present a clear target for diagnostic yield sonographically and likewise suspected vertebral osteomyelitis can be identified readily with CT guided biopsy. While this technique may be useful in trying to avoid the morbidity of addressing a deep SSI, image guided biopsy does not have such a strong indication for superficial infections and when compared to open sampling their diagnostic yield is inferior in the order of 40–60% (Chahoud et al. 2014).

However, there are situations where suspected infected areas are not safely or easily amenable to percutaneous techniques for a diagnostic sample. An example of this is an infection following a decompression procedure that involves an epidural abscess. While some situations allow for safe percutaneous sampling of the abscess, a surgeon must be prepared to perform open sampling with or without drainage of the abscess, depending on

the presence of phlegmon and dural adhesions. Infection around pedicle screws and cross links in the absence of a discernible abscess may have limited yield with percutaneous techniques due to difficulty sampling around the metal and fusion mass. In this setting, where the diagnosis of infection is strongly suspected from the patient history, clinical presentation, and supportive serology, the surgeon must consider the role of an open operative biopsy with or without metal exchange. The advantage of metal exchange, other than to reduce the potential for a nidus and debride the involved spinal tissue is to allow sonification of the spinal implants which can greatly improve yield. Again, one should consider PCR and extended cultures for *p. acnes* or staining for fungi or *mycobacterium* if there is an atypical presentation.

Management

Once the diagnosis of a spinal SSI is made, the approach should generally be aggressive. The exception to this is a cellulitis or suture abscess where a more conservative approach with dressings and antibiotics may be advisable. Where the potential for clinical deterioration, instability, and neurological compromise exists that will likely be difficult to control with medical therapy, early and judicious intervention is recommended (Cornett et al. 2016).

Superficial infections should be managed surgically with either wound excision or incision and drainage depending on its size and localization, followed by debridement and lavage of the area. An assessment should then be made on suitability for primary versus delayed primary closure depending on the patient and the extent of wound infection. This can then reverse a potentially catastrophic complication of deep-space involvement with the relatively simple measure of rapid superficial wound treatment. The difficulty in this scenario is often knowing when to intervene when the patient is systemically well, and markers of infection are equivocal but there is a slow-to-settle or oozing wound. Judgment is required here to ensure that wounds progress towards healing and, if this is not the case, then a return to theatre to achieve a clean and sealed wound is advisable (Cornett et al. 2016).

Deep infections present difficulty not just diagnostically but in deciding on the amount of treatment that should be offered to the individual patient. In an ideal world, infection should be treated in accordance with oncological principles achieving wide local clearance and adequate systemic therapy; however, this is not always possible due to the frailty of the patient or the locale of the infection, e.g., on the spinal cord. The intervention also varies depending on which approach the previous operation used and whether it involved instrumentation. In certain circumstances, where there has been very complex surgery, neurological injury, the need for reuse of potentially dangerous approach (e.g., anterior lumbar) or in a physiologically vulnerable patient then nonoperative treatment with suppression may be reasonable if the patient is stable systemically and neurologically. If there is clear infection and the patient is suitable for an intervention, then the surgeon must decide if it is a situation where the natural history will allow for likely resolution of the infection. The un-instrumented patient with a deep infection may be suitable for antibiotics only or in the instrumented complex multilevel posterior case for temporary suppression and later removal of implants (e.g., when arthrodesis or fracture united).

We favor a more aggressive approach for management of SSI when feasible and safe:

- For posterior instrumentation, this would typically involve exchange of any posterior metalwork, washout, grafting, and vancomycin powder application.
- For posterior abscesses in uninstrumented cases, then drainage and washout is recommended provided there is no direct infection with phlegmon on the neural elements, where careful partial de-bulking may be more appropriate.
- For anterior cervical cases (rare), utmost care must be taken given difficulty in reestablishing planes in the revision setting. Assessment for any esophageal breach should be undertaken as a deep cervical infection anteriorly is unusual.

Again, removal of implants and replacement with graft and vancomycin is advisable.

- For posterior cervical and thoracic decompression cases, care must be taken with washout and debridement due to risk to the spinal cord. Gentle lavage and partial de-bulking only along with vancomycin powder is advised for an epidural collection.
- Anterior column infection complicating interbody cage or disc prosthesis insertion requires a considered approach as to whether an anterior or lateral approach is feasible and, generally, either a vertebrectomy or revision with graft and a titanium cage would be preferable depending on the extent of osteomyelitis and post-debridement bony defect.
- In the rare case of exposed metal or large areas of devitalized soft tissue (usually after posterior wound debridement), then a plastic surgeon may be consulted to provide vascularized coverage to the implants.
- In the rare case of an "open space" SSI related to anterior cervical or lumbar fusion, it is advisable to provisionally diagnose the organ (s) which the infection involves and enlist the assistance of a relevant surgical colleague, for example, otorhinolaryngologist for organ involvement in the anterior neck and a vascular or general surgeon for assistance with organ or vessel infection in the abdomen.

Once a sample is taken or the organism is identified, we commence empirical antibiotics transitioning to tailored antibiotics as soon as practicable. Again, the patient should be optimized and cared for in the standard postoperative manner as detailed above. However, the length and course of the antibiotics will be different and should be discussed with a physician so that consensus over the most effective course for eradicating the infection can be achieved. Close follow-up must then be instituted to confirm successful remission and eradication of infection, including in the medium term. This should be undertaken clinically as well as with serology and imaging, such as CT scans, to verify the absence of any implant loosening or compromise.

Conclusions

SSIs represent a significant morbidity associated with spinal surgery and warrant a multidisciplinary approach to management. Early and aggressive treatment can lead to macroscopic eradication and salvage of the situation. A holistic and considered approach to prevention, diagnosis, management, and follow-up is likely to yield a lower incidence of SSI and improve patient outcomes.

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Lumbar Interbody Fusion Devices and Approaches: When to Use What

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Abstract

Lumbar interbody fusion is an established surgical technique for a variety of conditions affecting the lumbar spine. A large number of interbody fusion devices made of differing materials are now available for use. Approaches for interbody fusion include anterior lumbar interbody fusion, oblique lumbar interbody fusion, lateral lumbar interbody fusion, axial lumbar interbody fusion, transforaminal lumbar interbody fusion, and posterior lumbar interbody fusion. This chapter discusses the biomechanics of lumbar interbody fusion devices and approaches and the clinical rationale and the clinical results of each approach. The advantages and disadvantages of each approach are compared and contrasted. The importance of an appropriate preoperative assessment to determine the best approach for interbody fusion is emphasized, taking into account the condition being treated, sagittal balance, bone quality, and contraindications to a specific approach. The best approach to lumbar interbody fusion by indication and surgical level(s) is discussed.

Keywords

Lumbar interbody fusion · ALIF · OLIF · LLIF · AxiaLIF · TLIF · PLIF · Sagittal balance

Introduction

As with any operation in spinal surgery, the ultimate goal of interbody fusion is to decrease pain and increase function in the patients we treat. The specific technical goals of interbody fusion are to achieve a solid, stable arthrodesis of spinal segments that is able to sustain physiological loads while maintaining disc height and maintaining or restoring sagittal alignment. Any associated neural compression should be addressed as part of the fusion procedure. Maintenance of disc height and lordosis is necessary to preserve the natural alignment of the spine and the dimensions of the neural foramen, thus avoiding compression of the exiting nerve roots.

Spinal fusion has been used for many decades to treat a variety of spinal disorders. Instrumented spinal fusion was introduced to allow surgeons to alter the position of the spine, increase the rate of successful fusion, and allow earlier patient mobilization and recovery. To decrease failure rates of posterior instrumentation, the concept of anterior column interbody support was introduced.

Interbody fusion was originally performed using autograft iliac crest or allograft bone alone (Cloward 1953). The donor site morbidity associated with harvesting large amounts of iliac crest autograft and the inferior mechanical and biological properties of allograft bone were of concern. A significant incidence of collapse and pseudarthrosis was observed. Therefore interbody fusion devices were developed to provide mechanical support, while fusion takes place, thus increasing the rate of successful fusion and maintaining disc height and sagittal alignment while the fusion process occurs.

There are now many devices available for interbody fusion that vary in their material properties and route of implantation. In the lumbar spine, options include anterior lumbar interbody fusion (ALIF), oblique lumbar interbody fusion (OLIF), lateral lumbar interbody fusion (LLIF), posterior lumbar interbody fusion (PLIF), transforaminal lumbar interbody fusion (TLIF), and axial interbody fusion (AxiaLIF).

In determining which approach and device to use for interbody fusion, the surgeon must take into account the specific aims of the surgery in each individual patient. The interbody fusion

device itself is only one of many factors in achieving clinical success for the patient. Appropriate patient selection for surgery and technical expertise in performing the surgery are of vital importance. This chapter will discuss the biomechanics of interbody fusion, the various approaches and devices available, the clinical results of interbody fusion, and "when to use what" in various clinical scenarios.

Historical Perspective

Early techniques of interbody fusion using autograft or allograft without instrumentation were associated with a high rate of clinical failure and pseudarthrosis. Stauffer and Coventry (1972) reported a 44% rate of poor clinical outcomes and a 44% rate of pseudarthrosis in 83 patients who underwent anterior interbody arthrodesis. A number of other studies reported similar results. The need for interbody devices to provide mechanical support while fusion occurs was thus established.

Bagby (1988) developed the first interbody fusion cage, "the Bagby basket," a stainless steel basket that was packed with local autograft bone and used in horses undergoing ACDF for wobbler syndrome, a type of spondylytic myelopathy. Bagby and Kuslich developed the first stand-alone threaded intervertebral cages which were a modified version of the Bagby basket made of titanium alloy and FDA approved in 1996 (Kuslich et al. 1998) (see Figs. 1 and 2). The BAK cage (Sulzer Spine-Tech, Minneapolis, Minnesota) was closely followed by the Ray threaded fusion cage (US Surgical, Norwalk, Connecticut), the threaded interbody fusion device (TIBFD, Medtronic Sofamor-Danek Group, Memphis, Tennessee), the Harms titanium mesh cage (DePuy-Acromed, Cleveland, Ohio), and the Brantigan rectangular and rounded cages (DePuy-Acromed). The cages were designed to stabilize a segment through distraction and tensioning of the annular and ligamentous structures; by partially reaming the end plates, cancellous bone would be exposed for arthrodesis.

Second-generation lumbar cages such as the LT cage (Medtronic, Minneapolis, Minnesota) were designed to be end plate sparing and able to obtain lordosis by threading a wedge-shaped device into the disc space. Since the design of these original devices, the field of interbody fusion technology has advanced significantly with multiple designs now available. The majority of interbody fusion devices are currently made from titanium alloy or polyetheretherketone (PEEK). Other materials include tantalum, carbon fiber, carbon fiber reinforced PEEK (CFRP), and more recently hybrid cages such as those made of titanium-coated PEEK. Emerging technologies include expandable cage technology and 3-D printed cages.

Biomechanics of Interbody Fusion

Interbody fusion offers several biomechanical advantages over posterolateral fusion. The interbody space offers a relatively large area for grafting with excellent vascularity, and the graft is placed under compression further enhancing

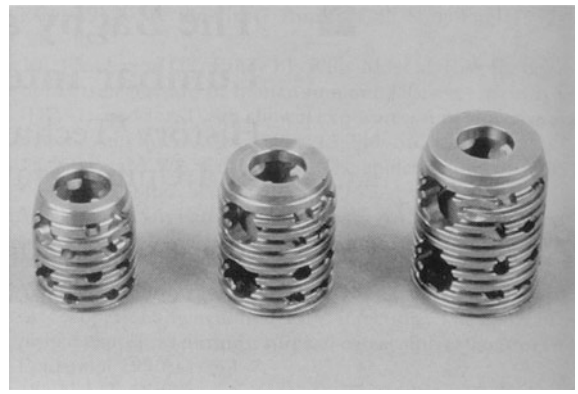

Fig. 1 The Bagby and Kuslich Implant (BAK cage). (Reprinted with permission from The Bagby and Kuslich Method of Lumbar Interbody Fusion: History, Techniques, and 2-Year Follow-up Results of a United States Prospective, Multicenter Trial. by Kuslich S. et al.; *Spine* 1998; 23(11); pp. 1267–1279. Copyright 2018 by Elsevier)

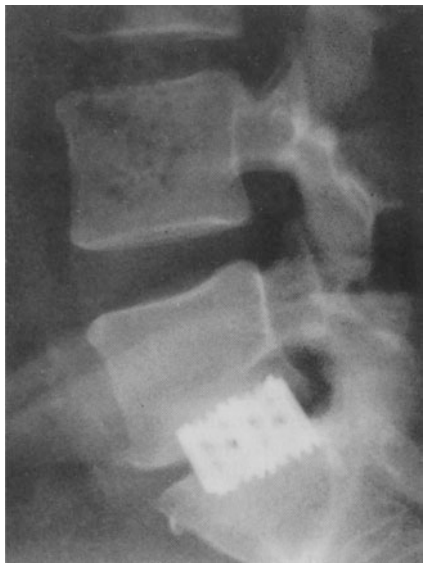

Fig. 2 BAK cage employed for L5–S1 ALIF. (Reprinted with permission from The Bagby and Kuslich Method of Lumbar Interbody Fusion: History, Techniques, and 2-Year Follow-up Results of a United States Prospective, Multicenter Trial. by Kuslich S. et al.; *Spine* 1998; 23(11); pp. 1267–1279. Copyright 2018 by Elsevier)

fusion. As 80% of axial compression forces are transferred through the anterior spinal column, the resulting arthrodesis is biomechanically superior to posterolateral fusion (Cunningham and Polly 2002). Interbody fusion also allows better maintenance or restoration of disc height and segmental lordosis and overall sagittal balance when compared to posterolateral fusion. This is associated with improved outcomes and a reduced rate of adjacent segment degeneration and disease (Rothenfluh et al. 2015).

When choosing a fusion device, the surgeon must consider the biomechanical properties of the device, in particular the implant stiffness which is determined by the material modulus of elasticity (Young's modulus) and the implant design (see Fig. 3). The implant design is in turn determined by the strength of the material used; a stronger material can have a more open architecture for bone graft and vascularization. An implant with a stiffness close to that of bone will allow load sharing between the device and the graft material, thus optimizing the biomechanics for fusion. An implant with a stiffness much higher than bone will load bear, therefore, stress shielding the graft material which can lead to resorption and pseudarthrosis.

When performing interbody fusion, the surgeon must consider the biomechanics of the vertebral end plates. Grant et al. (2002) conducted a biomechanical study assessing regional differences in end plate rigidity and found the posterior part was stronger than the anterior and that the periphery was stronger than the center. The strongest part was the posterolateral area, just in front of the pedicles. The superior end plate was much weaker than the inferior end plate. These findings have implications for implant design and placement when performing interbody fusion. A large footprint cage sitting on the peripheral end plate will be less likely to subside.

Early biomechanical studies suggested that threaded lumbar intervertebral cages were potentially stable enough to be used as stand-alone devices. Brodke et al. (1997) showed that two threaded BAK cages placed from a posterior approach resulted in greater stability in a bovine spine motion segment than a PLIF bone graft alone and equivalent stability to a PLIF bone graft and pedicle screw construct. Kettler et al. (2000) found that posteriorly placed intervertebral cages stabilized the spine in flexion and lateral bending but not extension and rotation and reduced stability under cyclical loading conditions was observed. Similarly, Oxland et al. (2000) found that anteriorly placed threaded cylindrical cages enhanced motion segment stability in all directions except extension and that supplementary translaminar facet screw fixation provided additional stability in extension. Rathonyi et al. (1998) also found that translaminar facet screw fixation greatly improved the stability of anterior threaded cylindrical cages in extension and rotation.

Kanayama et al. (2000) investigated the stability and stress-shielding effect of various lumbar interbody fusion devices; 11 different cages were tested, either threaded cages, non-threaded cages or allograft. No statistical differences were observed in construct stiffness among threaded and non-threaded devices in most of the testing modalities. Threaded cages demonstrated significantly lower intra-cage pressures compared with non-threaded cages and structural

Material	Young Modulus (GPa)	Poisson Ratio
Cortical bone	13.7[51]	0.30[51]
Cancellous bone	1.37[51]	0.30[51]
Titanium implant	110[51]	0.35[51]
Titanium base abutment	110[51]	0.35[51]
Zirconia customized abutment	210[52]	0.30[52]
PEEK customized abutment	3.5*	0.36*
Polymer infiltrated hybrid ceramic	30*	0.23[53]
Translucent zirconia	210*	0.26[54]
Lithium disilicate glass ceramic	95*	0.20[54]
Dual polymerized resin cement	18.6[55]	0.28[55]

PEEK, polyetheretherketone. *Values provided by manufacturer.

Fig. 3 Elastic modulus of materials used in interbody fusion devices. Note near identical elastic modulus of PEEK and cancellous bone. (Reprinted with permission from Effect of different restorative crown and customized abutment materials on stress distribution in single implants and peripheral bone: A three-dimensional finite element analysis study, by Kaleli N et al.; *The Journal of Prosthetic Dentistry* 2018; 119(3); pp. 437–445. Copyright 2018 by Elsevier)

allograft, suggesting a stress shielding effect with threaded cages.

Initial threaded cage stability is dependent on achieving adequate disc space distraction with resultant annular tensioning and is also dependent on compressive preload generated by muscle forces across the disc space. Phillips et al. (2004) found that under low preload conditions such as supine posture, BAK cages were less effective at stabilizing the motion segment in extension, whereas higher compressive preloads such as in sitting or standing led to stability of the motion segment in all motion planes. Supplementary translaminar facet screws provided a significant stabilizing advantage during low preload conditions.

ALIF

Further biomechanical testing of ALIF constructs has defined the relative stability of various stand-alone configurations (usually with integrated fixation) and anterior cage-plate constructs compared to the "gold standard" of ALIF with supplementary bilateral pedicle screw fixation.

Tsantrizos et al. (2000) compared the biomechanical stability of five stand-alone ALIF cages and found that all cage constructs reduced range of motion (ROM) but no cage construct managed to reduce the neutral zone (NZ), in fact the NZ was seen to increase with all constructs suggesting an initial segmental instability. Anteroposterior and mediolateral cage dimensions, cage height, and cage angle all influenced initial stability. Cages with teeth had higher pullout strength. They concluded that stand-alone cages reduced ROM effectively, but the residual ROM present indicated micromotion at the cage-end plate interface which may influence fusion.

Gerber et al. (2006) conducted a human cadaveric biomechanical assessment of ALIF with an anterior plate and screws compared to ALIF with supplementary pedicle screw fixation. ALIF was performed with two INTER FIX cages (Medtronic Sofamor Danek, Memphis Tennessee). Compared to stand-alone cages, supplementary anterior plate and screws reduced ROM by a mean of 41%, and compared to stand-alone cages, supplementary pedicle screw fixation reduced ROM by 61%. Similarly, Beaubien et al. (2005) in another human cadaveric study found that, although not as rigid as pedicle screws or translaminar screws, anterior lumbar plating does add significant stability to an ALIF construct.

A biomechanical evaluation of a stand-alone PEEK ALIF cage (Brigade NuVasive, Inc., San Diego, California) found that the cage alone was significantly more rigid than the intact

state in flexion-extension and lateral bending. The addition of three integrated screws was significantly more rigid than the cage alone in all loading directions. The addition of a fourth screw did not significantly increase stability over three screws. The cage with integrated screws allowed more flexion-extension motion than the cage with anterior plate fixation or pedicle screw fixation. Adding a spinous process plate to the 3-screw cage provided the most rigid construct in flexion-extension, providing more stability than the anterior plate and equivalent stability to the pedicle screw construct. Pedicle screw fixation provided the most rigidity in lateral bending and axial rotation although the later was not significant (Kornblum et al. 2013).

Similarly, a comparative biomechanical analysis of a PEEK ALIF cage with integrated fixation anchors (Solus, Alphatec Spine, Carlsbad, California) compared to a standard PEEK cage (ALS, Alphatec Spine), combined with various posterior fixation constructs found that the Solus cage in combination with all posterior constructs provided significant fixation compared to the intact spine. The ALS cage combined with screw-based posterior constructs also provided significant fixation, but the ALS cage combined with an interspinous process clamp showed a significant reduction in stability for lateral bending and axial torsion (Yeager et al. 2015).

Chen et al. (2013) conducted a biomechanical comparison of three different designs of stand-alone ALIF cages using three-dimensional finite element analysis. The cages differed in their method of integrated fixation. All three designs were compared to the "gold standard" of ALIF cage (SynCageOpen, Synthes Spine, Inc., Pennsylvania) with bilateral pedicle screw fixation. The three cages tested were the Latero system (Latero, A-Spine Asia, Taipei, Taiwan) (trapezoidal cage with integrated lateral plate), the Synfix system (Synfix, Synthes Spine Inc., Pennsylvania) (four integrated screws), and the Stabilis system (Stabilis, Stryker, Michigan) (a central threaded cylinder). At the surgical level, the SynCageOpen with bilateral pedicle screws decreased ROM (>76%) in all directions. The Synfix and Latero systems also decreased ROM in all motions compared to the intact model. However, the Stabilis model only decreased ROM slightly in extension, lateral bending, and axial rotation. At the adjacent levels, there was no obvious differences in ROM or annulus stress among all instrumented models. The authors concluded that the Synfix and Latero systems provided adequate stability for clinical use without additional posterior fixation, but the Stabilis cage would require additional fixation. This highlights the importance of biomechanical testing of different cage designs to determine relative stability.

In summary, biomechanical testing suggests that the use of stand-alone ALIF devices without integrated fixation may not offer enough stability to allow fusion to reliably occur. In patients with good bone quality, if an appropriately sized ALIF cage can be placed, then a stand-alone construct with integrated fixation or a cage-plate construct appears to provide adequate stability (see Fig. 4). In a biomechanically challenging environment such as patients with poor bone quality and multilevel surgery or in the setting of sagittal imbalance, the addition of supplementary screw-based posterior fixation provides the most robust biomechanical construct.

OLIF and ATP

First described by Mayer in 1997, there is a paucity of published biomechanical data on OLIF and ATP constructs although in clinical studies the vast majority of OLIF procedures are supplemented with posterior pedicle screw-rod fixation (Sorian-Baron et al. 2017).

The biomechanics of OLIF can be considered similar to LLIF between L1–L2 and L4–L5. At L5–S1 with release of the ALL, the biomechanics are likely more similar to ALIF.

LLIF

The lateral transpsoas approach was developed as a minimally invasive alternative to access the anterior column and places a large surface area interbody device without mobilization of the great

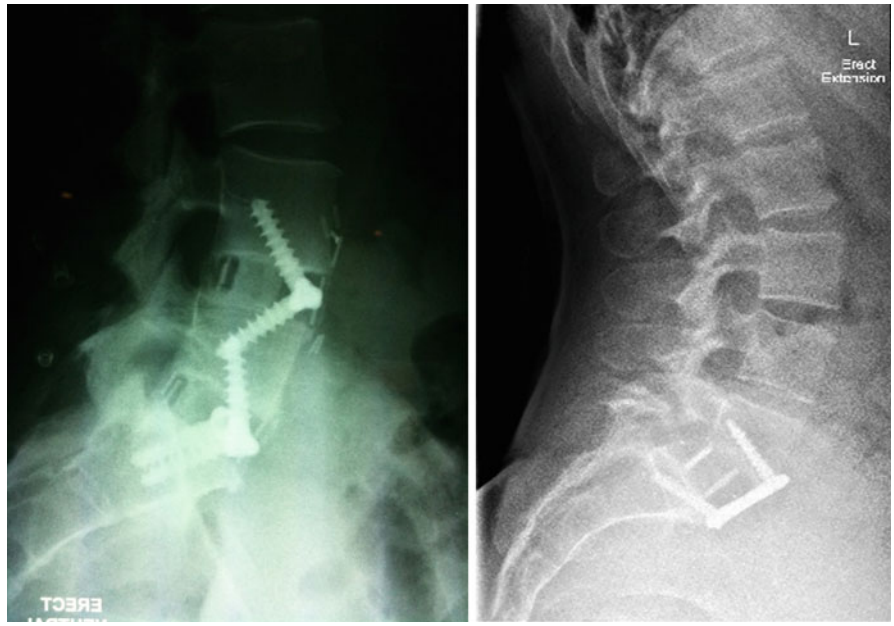

Fig. 4 Examples of stand-alone ALIF cage with integrated fixation, left, and a stand-alone ALIF cage-plate construct, right

vessels. Early biomechanical studies of LLIF have investigated the stability of LLIF compared to ALIF as well as the stability of stand-alone LLIF constructs to the stability of constructs with supplementary lateral plate or posterior fixation.

Laws et al. (2012) performed a human cadaveric biomechanical study to determine the biomechanical differences between ALIF and LLIF with and without supplementary instrumentation. Testing was performed in the intact state, with ALIF or LLIF cage, with cage plus stabilizing plate, with cage plus unilateral pedicle screw fixation, and with cage plus bilateral pedicle screw fixation. The cages used were PEEK cages (Cougar, De Puy Spine, Raynham, Massachusetts). Compared to the intact state, stand-alone LLIF significantly reduced ROM in flexion, extension, and lateral bending, which was not seen with stand-alone ALIF. Addition of a plate increased ALIF group stiffness by 211% in extension and 256% in axial rotation. Compared with stand-alone cages, supplementing with bilateral pedicle screws increased ALIF motion segmental stiffness significantly in flexion (455%) and lateral bending (317%) and LLIF stiffness significantly in flexion (350%) and extension (222%). When bilateral pedicle screws supplemented fusion, ALIF and LLIF were biomechanically equivalent.

Fogel et al. (2014) investigated the biomechanics of lateral lumbar interbody fusion constructs with lateral and interspinous plate fixation and compared these constructs with supplementary bilateral pedicle screw fixation. They found that a stand-alone lateral cage significantly reduced ROM with respect to the intact state in flexion-extension, lateral bending, and axial rotation. Addition of a lateral plate did not alter flexion-extension ROM but significantly reduced lateral bending and axial rotation. Cage with lateral plate was not statistically different from bilateral pedicle screws in lateral bending. Supplementary fixation with a spinous process plate was not statistically different from bilateral pedicle screws in flexion-extension. A combination of lateral plate and spinous process plate was not statistically different from cage with bilateral pedicle screws in all loading modes.

Similarly Reis et al. (2016) found that a stand-alone lateral cage significantly decreased ROM in

all directions, with the addition of a lateral plate improving stability in lateral bending, and the addition of an interspinous plate improved stability in flexion-extension; a combination of lateral cage, lateral plate, and interspinous plate was biomechanically equivalent to a lateral cage with bilateral pedicle screws.

One potential disadvantage of LLIF is that, without release of the anterior longitudinal ligament (ALL), there is limited ability to restore segmental lordosis. Thus the LLIF technique has evolved to sometimes include release of the ALL if correction of lordosis is required; this has been termed anterior column realignment (ACR) (Saigal et al. 2016; Berjano et al. 2015).

Melikian et al. (2016) examined the effect of cage angle and surgical technique on segmental lordosis achieved during lateral interbody fusion. They found that insertion of a parallel or 10 ° cage had little effect on lordosis and even insertion of a 30 ° cage with ALL release only led to a modest increase in lordosis (10.5 °s). The addition of spinous process resection and facetectomy was needed to obtain a larger amount of correction (26 °s). None of the cages, including the hyperlordotic cage, caused a decrease in posterior disc height, suggesting hyperlordotic cages do not cause foraminal stenosis.

A cadaveric biomechanical study examining the effect of anterior longitudinal ligament resection on lordosis correction during LLIF found that an 8 mm parallel spacer with an intact ALL provided the greatest stability relative to the intact state but did little to restore lordosis (1.44 ° increase). Conversely, ALL release led to significant improvement in lordosis correction (6.4 ° increase with 8 mm cage and 11 ° increase with 13 mm cage) but significantly destabilized the spine relative to the intact state. Addition of integrated screws to the fusion cage following ALL resection improved stability back to the level of the intact spine (Kim et al. 2017).

There does not appear to be any biomechanical advantage of expandable lateral cages over static lateral cages. Human cadaveric biomechanical testing showed comparable stability between static and expandable lateral stand-alone cages with the most stable construct being a static cage with bilateral pedicle screws. The authors cautioned that there was minimal feedback when expanding the expandable cage which may lead to over-distraction of the disc space and end plate failure (Gonzalez-Blohm et al. 2014).

In summary, a purely stand-alone LLIF cage appears to have more inherent stability than a stand-alone ALIF cage due to preservation of the ALL; however this is at the expense of the ability to effectively restore lordosis. Addition of supplementary lateral or posterior fixation adds further to stability. Release of the ALL significantly destabilizes the motion segment, and much like ALIF, supplementary fixation with integrated screws, lateral plate, or posterior constructs is required to restore stability.

PLIF and TLIF

The biomechanical considerations of posteriorly placed interbody fusion cages differ significantly from ALIF and LLIF. As the ALL is not resected, a ° of inherent stability is retained; however restoration of anterior disc height and lordosis may be somewhat limited. Lordosis can be achieved with compression across a pedicle screw-rod construct with or without osteotomy of the facet joints. This is feasible with an open PLIF or TLIF procedure but difficult to achieve with a MIS-TLIF procedure due to the limited exposure. The interbody fusion devices placed with PLIF or TLIF are typically a lot smaller than those placed for ALIF or LLIF as exposure of the disc space is limited by the neural elements. End plate coverage by the interbody cages is therefore limited and subsidence much more likely if used in a stand-alone fashion. Therefore, in general, PLIF and TLIF cages are supplemented with posterior screw-rod constructs to increase stability and reduce the chances of subsidence.

Brodke et al. (1997) used a calf lumbar spine model to compare PLIF using structural autograft to BAK cages with or without supplementary pedicle screw fixation. PLIF with bone graft alone was the least stiff construct, less stiff than the normal spine. BAK cages alone were similar in stiffness to bone graft with pedicle screw

fixation which were both significantly stiffer than the normal spine. BAK cages with pedicle screw fixation were significantly stiffer than all other constructs.

In regard to device material, Xiao et al. (2012) used finite element analysis to compare the biomechanics of PLIF with autogenous iliac bone, PEEK cages, and titanium cages. The lowest stresses on the bone graft and the highest stresses on the end plates were seen with titanium cages, whereas the PEEK cages showed significant stresses on the bone graft and less stresses on surrounding ligaments. The authors concluded that the titanium cage was inferior to the other two models with potentially an increased risk of subsidence due to high end plate stresses and increased risk of pseudarthrosis due to stress shielding of the bone graft.

Vadapalli et al. (2006) also investigated the biomechanics of PEEK and titanium PLIF cages with supplementary pedicle screw fixation. Stresses through the bone graft increased by at least ninefold with the PEEK spacers compared to the titanium spacers. Conversely, end plate stresses increased by at least 2.4-fold with titanium spacers compared to PEEK spacers. There was no difference in stability between the two constructs. Again they concluded that PEEK was superior to titanium in a PLIF construct with similar stability but more graft loading and less chance of subsidence into the end plates.

Slucky et al. (2006) investigated the biomechanics of TLIF with either unilateral or bilateral pedicle screw fixation or unilateral pedicle screws with a contralateral facet screw construct. After TLIF, the unilateral pedicle screw construct provided only half of the improvement in stiffness compared with the other two constructs and allowed for significant off-axis rotational motions.

Similarly, Chen et al. (2012) performed a finite element analysis of unilateral and bilateral pedicle screw fixation for TLIF after decompressive surgery. Finite element analysis was performed for TLIF with a single moon-shaped PEEK cage in the anterior or middle portion of the vertebral bodies and TLIF with a left diagonally placed oval-shaped PEEK cage, all with both unilateral and bilateral pedicle screw fixation. All TLIFs with bilateral pedicle screws appeared biomechanically stable; however TLIF cages with unilateral pedicle screws on the same side showed increased ROM and annular stress in extension, contralateral lateral bending, and contralateral axial rotation. This was particularly pronounced with the diagonal TLIF cage. The authors cautioned against performing TLIF with unilateral pedicle screws, especially if a diagonal cage is used.

Ames et al. (2005) performed a biomechanical comparison of PLIF and TLIF performed at one and two levels. There was no statistically significant difference in flexion-extension, axial rotation, or lateral bending after either PLIF or TLIF at one level compared to the intact condition. The addition of pedicle screws significantly increased the rigidity for both PLIF and TLIF. Similar findings were seen in the two-level constructs. They concluded that posterior fixation with a pedicle screw-rod construct is suggested for single-level PLIF or TLIF and is necessary to achieve stability with a two-level PLIF or TLIF.

In summary, there is biomechanical evidence supporting the use of PEEK over titanium cages when performing PLIF/TLIF surgery. There is also good evidence suggesting that all PLIF/TLIF constructs should be supplemented with a posterior bilateral screw-rod construct to enhance stability.

AxiaLIF

Biomechanical studies with single-level and two-level AxiaLIF constructs have been performed. In a cadaveric study looking at single-level constructs, ROM was reduced by 40% with a stand-alone trans-sacral rod. Augmentation with facet or pedicle screws reduced ROM between 70% and 90% (Akesen et al. 2008). In two-level stand-alone constructs, ROM decreased by greater than 42% at L4–L5 and 66% at L5–S1. Supplementary pedicle or facet screws further reduced motion (Erkan et al. 2009). Both studies recommended supplementary posterior fixation to provide greater construct stability. In ROM studies, single-level AxiaLIF was shown to be comparable to other fusion types (Ledet et al. 2005).

Clinical Rationale

Anterior Lumbar Interbody Fusion (ALIF)

ALIF is indicated for the treatment of degenerative disc disease (DDD), spondylolisthesis, recurrent disc herniation, and pseudarthrosis, for deformity correction including long fusions to the sacrum/pelvis, and for treatment of adjacent segment degeneration above a previous posterior fusion. It can also be used for debridement and stabilization in cases of infective discitis.

ALIF can be performed via either a retroperitoneal or transperitoneal approach with subsequent mobilization of the great vessels to expose the anterior aspect of the disc. The approach is predominantly used to approach L4–L5 and L5–S1. Access to higher lumbar levels is possible, often involving a transperitoneal approach and the assistance of a vascular surgeon. Renal vein anatomy may preclude accessing L1–L2 and L2–L3 and should be assessed preoperatively if access to the higher lumbar levels is contemplated.

The approach provides extensive exposure of the disc space allowing release of the ALL, thorough discectomy and release of the posterior annulus, excellent end plate preparation, appropriate restoration of disc height and lordosis, and insertion of a large footprint implant. ALIF avoids injury to the paraspinal muscles and direct mobilization of the neural elements.

ALIF is a preferred approach for the treatment of discogenic pain as it allows thorough removal of the pain generator and excellent stabilization of the motion segment. Several studies have shown ALIF to be superior to PLF for the treatment of discogenic pain (Derby et al. 1999; Weatherley et al. 1986).

ALIF is particularly advantageous in patients with severe disc space collapse and spondylolisthesis as it allows a direct and thorough release of the disc space, restoration of disc height and lordosis, and reduction of spondylolisthesis. Restoration of disc height and spondylolisthesis reduction indirectly decompresses the neural foramen.

The biggest driver of disability in adult spinal deformity is loss of lumbar lordosis and sagittal balance. In these patients ALIF is an effective way to release the disc space and correct disc height and lordosis. ALIF is also useful in correcting large coronal plane deformities, especially in rigid curves. In cases where two or more levels are involved, ALIF may be a more efficient strategy than multilevel PLIF or TLIF. In long fusions to the sacrum (L1 or above), ALIF at L4–L5 and L5–S1 has been shown to lower pseudarthrosis rates (Farcy et al. 1992; Kostuik and Hall 1983).

ALIF is the technique of choice in patients who are at high risk of pseudarthrosis such as smokers and in patients with established pseudarthrosis or ongoing discogenic pain after previous posterolateral fusion.

ALIF is also useful in the management of adjacent segment disease after previous posterior fusion as it avoids reoperating through previous scarring, reinjury to the paraspinal muscles, as well as the need for removal and extension of previously placed posterior instrumentation.

ALIF has several potential disadvantages. Many surgeons are unfamiliar with the anterior approach to the lumbar spine, and a volume performance threshold likely exists. Direct decompression and visualization of the neural elements are not possible, and stenosis due to facet joint and ligamentum flavum hypertrophy is not directly addressed.

Anterior approach-related complications can occur. These include vascular and visceral injury, ileus, sympathetic dysfunction, and, in male patients, retrograde ejaculation. Relative contraindications to ALIF include significant obesity, multiple previous abdominal surgeries, significant vascular calcification, and vascular anatomy precluding safe exposure of the disc space.

Oblique Lumbar Interbody Fusion (OLIF)

The OLIF or anterior to psoas approach (ATP) is designed to access the disc space anterior to the psoas muscle (thus avoiding potential injury to the lumbar plexus) without the requirement

for mobilization of the great vessels. The indications for OLIF are the same as for ALIF, excepting cases of high-grade spondylolisthesis.

The surgery is performed with the patient in the lateral position either left or right side up, depending on surgeon preference and the pathology being treated. The spine can be accessed from L1–S1 using this technique. Like ALIF, OLIF allows good restoration of disc height and lordosis, although, similar to lateral interbody fusion, adequate release of the ALL is required to achieve significant lordosis correction.

Advantages of OLIF include the minimally invasive approach, facilitating faster patient recovery, and the ability to perform extensive disc space clearance and insert a large interbody implant, thus promoting high fusion rates. The approach is useful in obese patients as the lateral positioning allows the abdomen to fall forward out of the operative field.

As with any minimally invasive retroperitoneal approach, the potential disadvantage is major vascular injury that cannot be easily controlled due to lack of a wide exposure. Sympathetic dysfunction is also a potential complication.

Lateral Lumbar Interbody Fusion (LLIF)

The LLIF technique was pioneered by Pimenta who subsequently first published the technique in the literature with Ozgur et al. (2006). The disc space is accessed via a retroperitoneal transpsoas corridor where no direct mobilization of the vessels is undertaken. The technique allows access from T12–L1 to L4–L5. The L5–S1 level cannot be accessed due to the iliac crest obstructing access.

The patient is positioned laterally either left or right side up depending on surgeon preference and the pathology being treated. A small lateral incision is made followed by placement of a guide wire through the psoas under image intensifier guidance. Serial dilation through the muscle is then undertaken before retractor blades are placed flush on the lateral annulus. Neuromonitoring is essential to avoid injury to the lumbar plexus which courses through the psoas muscle. The plexus is more at risk at the lower lumbar levels where it courses more anteriorly in the psoas muscle.

LLIF allows good restoration of disc height via a minimally invasive approach. If significant lordosis restoration is required, ALL release can be performed before insertion of a hyperlordotic cage. LLIF also allows excellent correction of coronal plane deformity (Arnold et al. 2012) and is a useful approach in obese patents as the abdomen falls forward "out of the way."

LLIF has limited ability to decompress severe central and lateral recess stenosis, and the approach is difficult in high-grade spondylolisthesis (Malham et al. 2015). In general supplementary posterior instrumentation is used, especially in cases with instability and deformity, adjacent to a previous fusion, multiple-level LLIF, and in patients with osteoporosis.

LLIF is contraindicated in patients with prior retroperitoneal surgery and abnormal vascular anatomy. "Flying" or "Mickey Mouse ears" psoas muscles are also a relative contraindication as the lumbar plexus is put at significant risk due to anterior position. The axial MRI should be reviewed preoperatively to assess this.

Complications of LLIF include bowel injury, lumbar plexus injury (particularly at L4–L5), and postoperative lower limb dysesthesia on the side of the approach which is quite common and may last for many months. Quadriceps palsy is a rarer complication but devastating functionally for the patient. Like OLIF, if vascular or bowel injury occurs, it may be difficult to control due to lack of a wide exposure for repair.

Transforaminal Lumbar Interbody Fusion (TLIF)

TLIF allows access to the disc space unilaterally via the neural foramen and can be performed via an open procedure or MIS technique. Indications for TLIF include degenerative disc disease, spondylolisthesis, recurrent disc herniation, spinal stenosis, and degenerative scoliosis. It is useful in patients requiring an interbody fusion who have had previous anterior surgery or who have

contraindications to an anterior or lateral approach. In young male patients, it avoids the potential complication of retrograde ejaculation which can occur with an anterior approach. The approach requires less neural retraction than a PLIF procedure.

The patient is positioned prone and a midline or bilateral paramedian incisions used. The disc space is accessed via a unilateral laminectomy and facetectomy. The approach can be used for all lumbar levels.

Advantages of TLIF include direct access and decompression of the neural elements unilaterally and the ability to perform a "circumferential" fusion via a posterior only approach. The approach-related complications of anterior and lateral approaches are avoided. The midline ligamentous structures are preserved due to use of muscle-splitting approaches, thus aiding postoperative stability (Park et al. 2005).

Disadvantages include iatrogenic injury to the paraspinal muscles and limited ability to restore disc height, lordosis, and coronal balance (especially with MIS procedures) (Sakeb and Ahsan 2013; McAfee et al. 2005). If significant lordosis correction is required, then a bilateral open TLIF with complete facetectomies and posterior compression across a pedicle screw-rod construct is an option.

Complications include dural tear/CSF leak, nerve injury, epidural fibrosis, end plate damage with cage subsidence, pseudarthrosis, and iatrogenic injury to the supradjacent facet joint.

Contraindications include severe segmental kyphosis, epidural scarring, conjoined nerve roots, and osteoporosis where a fusion device with a larger footprint (ALIF, OLIF, LLIF) is preferred.

Posterior Lumbar Interbody Fusion (PLIF)

In the PLIF technique, the disc space is accessed posteriorly after laminectomy, facetectomy, and contralateral retraction of the neural elements; traditionally it is performed as a bilateral procedure with supplementary pedicle screw stabilization. The patient is positioned prone, and the procedure performed via an open midline approach or in an MIS fashion via paramedian muscle-splitting incisions. The indications for PLIF are the same as for TLIF.

PLIF has several advantages including direct visualization and decompression of the neural elements and restoration of disc height with preservation of the facet joints, thus aiding in postoperative stability (Lestini et al. 1994). PLIF allows bilateral circumferential fusion through a single incision. Like TLIF, PLIF is useful in patients with contraindications to an anterior or lateral approach. In young males, the risk of retrograde ejaculation is eliminated.

Disadvantages of PLIF include iatrogenic injury to the paraspinal muscles from prolonged retraction (Fan et al. 2010). It may be difficultly to correct coronal imbalance and restore lordosis. The procedure requires significant retraction of the nerve roots which may lead to fibrosis and chronic radiculopathy (Zhang et al. 2014). Other potential complications include dural tear or nerve root injury risking arachnoiditis.

Contraindications include previous posterior surgery, extensive epidural scarring, and arachnoiditis. PLIF is not recommended above L2–L3 as retraction of the conus medullaris can lead to paralysis.

Axial Lumbar Interbody Fusion (AxiaLIF)

Introduced in 2004 and described by Marotta et al. (2006), the AxiaLIF approach was designed to allow distraction and fusion of the L5–S1 disc space through a minimally invasive trans-sacral approach that preserves the anterior and posterior longitudinal ligaments. It is also possible to extend the fusion construct up to include the L4–L5 disc space. AxiaLIF is indicated for degenerative disc disease, low-grade spondylolisthesis, and pseudarthrosis at L5–S1 or L4–L5 and L5–S1.

The patient is positioned prone with care taken to maintain lumbar lordosis. A 2 cm incision is made midline or just left of the paracoccygeal

notch, and blunt finger dissection is used to displace the rectum away from the sacrum. The presacral space is developed using blunt dissection followed by docking of a guide pin at the S1–S2 level. The guide pin is advanced into the L5–S1 disc space, followed by over-reaming to create a 10 mm channel and preparation of the disc space using rotating shavers. The disc space is then packed with local autograft +/− other grafting materials. A channel is then drilled into L5, and an interbody screw with a differential thread is then inserted that allows distraction of the disc space as it is inserted.

The advantages of AxiaLIF include its minimally invasive nature using an avascular and aneural corridor, with preservation of the ALL and PLL, thus aiding in initial stability of the construct. AxiaLIF avoids the approach-related complications of anterior, lateral, and posterior interbody fusion techniques.

Although AxiaLIF has some ability to restore disc height, there is little ability to restore lordosis if required, as the ALL is not released. As the disc space is not directly visualized, the quality and quantity of discectomy may be suboptimal. No direct decompression of neural elements is possible. Only the L5–S1 +/− the L4–L5 levels can be accessed. In some patients the procedure is not possible due to the sacrococcygeal morphology. Complications of AxiaLIF include infection, rectal injury, pseudarthrosis, retroperitoneal hematoma, and subsidence/loss of distraction across the disc space.

Clinical Results

ALIF

Early Studies

In one of the first studies comparing fusion to non-operative treatment for DDD, Fritzell et al. (2002) conducted a prospective multicenter randomized trial comparing three lumbar fusion techniques and non-operative treatment in patients with DDD. Two hundred ninety-four patients were randomized; in the interbody fusion group, 56 patients received ALIF using autologous tricortical bone blocks (19 patients received a PLIF) with additional PLF using pedicle screws and plates. The mean age in this group was 42 years. VAS back pain improved from 65.6 pre-op to 45.7 at 2 years, and ODI improved from 47.3 pre-op to 38.5 at 2 years. The fusion rate was 91% at 2 years. As the biomechanical advantages of graft packed interbody cages over graft alone became apparent, multiple early studies confirmed the clinical effectiveness of the ALIF technique utilizing these devices.

Burkus et al. (2003) reported on 254 patients treated with ALIF using the LT cage device with rhBMP-2 (Medtronic Sofamor Danek, Memphis, Tennessee) and noted a mean 29.3-point improvement in ODI and a 13.5-point improvement in SF-36 PCS. Further follow-up of 146 patients at 6 years (Burkus et al. 2009) was undertaken. The fusion rate was 98%. The ODI improved from 52 pre-op to 20.7 at 6 years. Back pain (using a 20-point scale) improved from 15.4 to 6.9, leg pain improved from 11.6 to 4.8, and SF-36 PCS improved from 27.9 to 43.1 at 6-year follow-up.

Madan and Boeree (2003) conducted a prospective study comparing ALIF, with circumferential fusion through a posterior approach (PLIF and PLF) in patients with degenerative disc disease (DDD). There were 39 patients (47 fusion levels) in the ALIF group. The ALIF procedure was performed using the Hartshill horseshoe cage along with tricortical and cancellous iliac crest autograft. Minimum follow-up was 2 years. Using the subjective score assessment, there was a satisfactory outcome in 71.8% of patients in the ALIF group, and assessment of ODI showed a satisfactory outcome in 79.5% of patients. 64% of patients saw an improvement in their working ability.

Sasso et al. (2004) conducted a prospective randomized controlled trial comparing a cylindrical threaded titanium cage (INTER FIX device, Medtronic Sofamor Danek) to a control group using femoral ring allograft for ALIF. There were 78 patients in the cage group; all had autogenous iliac crest inserted in the cage and had a single-level stand-alone ALIF performed at L4–L5 or L5–S1 for DDD. The fusion rate in the cage group was 97% at 12 months (40% in the

control group). ODI improved from 51.1 pre-op to 23.7 at 48 months. SF-36 PCS improved from 28.3 pre-op to 39.8 at 24 months.

Glassman et al. (2006) conducted a multicenter retrospective review of prospectively collected data analyzing clinical outcomes after single-level and two-level lumbar fusion. A total of 497 patients were included in the study; 125 patients underwent ALIF. The ALIF group had a mean age of 42 years. At 2 years post-op, SF-36 improved 13.8 points. Mean improvement in ODI was 27 points at 2 years.

The results of these four relatively early studies of ALIF fusion devices are very similar, with high fusion rates and clinically and statistically significant improvements in ODI and SF-36 scores.

ALIF Using Femoral Ring Allograft

With the advent of rhBMP-2 and other biologics to enhance fusion, a number of studies revisited the use of femoral ring allograft for use in ALIF. Freudenberger et al. (2009) conducted a retrospective review of 59 patients with single-level or two-level lumbar DDD who underwent ALIF with anterior tension band plating or PLIF with pedicle screw instrumentation. ALIF (29 patients) was performed with an allograft bone spacer, BMP, and an anterior tension band plate. In the ALIF group, median estimated blood loss was 112.5 ml and median surgical time 104 min. At 6–9 months post-op, partial to solid fusion was seen in 92% of patients. ODI improved from 24.3 pre-op to 16.0 at 12–18 months post-op. Complications occurred in four patients in the ALIF group (two intra-op common iliac vein injuries, one post-op thrombosis, and one ileus). Compared to the PLIF group, the ALIF group had similar clinical outcomes but with significantly shorter surgical time and decreased blood loss.

Anderson et al. (2011) retrospectively reviewed 50 patients who underwent ALIF using femoral ring allograft and rhBMP-2 with supplementary percutaneous pedicle screws for degenerative lumbar pathology. Twenty-four patients had a single-level fusion and 26 a two-level fusion. Operating time was 131 min anteriorly and 102 min posteriorly. Mean EBL was 288 ml. Follow-up was 12 months. 61% were "definitely fused" and 31% "probably fused." VAS back pain improved from 8 to 3, VAS leg pain improved from 6 to 2. ODI improved from 47 to 28. The overall complication rate was 12%. No intraoperative complications occurred.

ALIF can also be combined with open posterolateral fusion in a true circumferential fusion construct. Zigler and Delamarter (2013) investigated 75 patients treated with 360 ° lumbar fusion as the control group in a prospective randomized FDA IDE trial of the pro-disc lumbar disc arthroplasty. The fusion patients were treated with femoral ring allograft and DBM for the interbody fusion and open posterolateral fusion. The follow-up rate was 75% at 5 years. VAS improved from 74.9 preoperatively to 40 at 5 years. ODI improved from a mean of 62.7 preoperatively to 36.2, and SF-36 improved from 30.9 preoperatively to 40.1. The fusion rate was 95.6%.

Degenerative Disc Disease

Further studies have examined the role of stand-alone ALIF cages with rhBMP-2 or other biologics in the management of DDD. Gornet et al. (2011) investigated 172 patients undergoing stand-alone ALIF as the control group in a randomized controlled multicenter IDE study of lumbar disc arthroplasty (Maverick). Follow-up was to 24 months. ALIF was performed with tapered fusion cages and rhBMP-2. Mean patient age was 40.2 years. Operative time was 1.4 h and blood loss 95.2 ml. ODI improved from 54.5 pre-op to 24.8 at 24 months. Mean improvement in low back pain was 49 points and mean improvement in leg pain was 23.1 points. The fusion rate was 100%.

Lammli et al. (2014) conducted a retrospective chart review of a consecutive series of patients with DDD treated with single-level or two-level stand-alone ALIF using either a cage and anterior plate or an integrated cage/plate device packed with autograft and rhBMP-2. One hundred eighteen patients were included in the study. The average patient age was 43 years; follow-up was 2 years. VAS score improved from 6.35 to 3.02. Average improvement in ODI was 17%.

Allain et al. (2014) conducted a prospective study involving 65 patients who underwent ALIF using a PEEK cage with integrated intracorporeal anchoring plates (ROI-A, LDR Medical, Troyes, France) in the treatment of lumbar DDD. The average age was 57 years. In 91% of patients, autologous bone and rhBMP-2 were used within the cage. The mean duration of surgery was 133 min and the mean blood loss was 205.8 ml. At 12-month follow-up, the fusion rate was 96.3%. Statistically significant improvements in back and leg pain were seen by 6 weeks and maintained at 12 months. ODI improved by 26.6 points at 12 months post-op. 88.7% of patients were very satisfied or satisfied with their outcome.

Siepe et al. (2015) reported on 71 patients who underwent stand-alone ALIF at L5–S1 for DDD. ALIF was performed using the Synfix-LR cage (DePuy Synthes, Wet Chester, PA) and rhBMP-2 in the vast majority. The mean follow-up was 35.1 months. Statistically significant and clinically relevant improvements in VAS and ODI were seen at all time points from 3 months postoperatively. The fusion rate was 97.3% at a mean of 27.7 months. Segmental lordosis increased from 16.1 °s to 26.7 °s.

Mobbs et al. (2014) reported on 110 patients who underwent single-level or multilevel ALIF for DDD. Surgery was performed using a stand-alone PEEK cage (Synfix, Synthes) packed with i-FACTOR. Mean follow-up was 24 months. The fusion rate was 93.6% for the whole cohort (98% for single-level fusion and 82% for two-level fusion). SF-12 improved from 68.57 to 92.99. ODI improved from 61.02 to 28.42, and VAS score improved from 7.38 to 2.65. 85.3% of patients reported good to excellent outcomes. They concluded that stand-alone ALIF with i-FACTOR was a viable treatment option for DDD with clinical and radiographic results comparable to ALIF with autograft or rhBMP-2.

Giang et al. (2017) conducted a systematic review of outcomes of stand-alone ALIF. Seventeen studies were included. Mean age of all included patients was 48.5 years. ODI improved by a mean of 26.7 points, VAS back pain improved by 4.1, VAS leg pain improved by 3.3, and SF-36 PCS improved by 12.7. The pooled fusion rate was 79.8%. These studies highlight that in the treatment of DDD, stand-alone ALIF can be expected to give clinically significant improvements in both pain and function with a high fusion rate and patient satisfaction.

Ohtori et al. (2011) also provided level I evidence for ALIF in the treatment of confirmed discogenic low back pain patients without leg pain in a small randomized study of 41 patients. Compared to the non-operative treatment patients, patients who underwent ALIF had reduced ODI and VAS scores.

Spondylolisthesis

ALIF can also be used successfully in the treatment of single-level or multilevel spondylolisthesis.

Kim et al. (2010) compared ALIF and percutaneous pedicle screws with circumferential fusion (ALIF with open instrumented PSF) for adult low-grade isthmic spondylolisthesis. Forty-three patients underwent ALIF and 32 circumferential fusion. ALIF was performed with a stand-alone cage with integrated screws packed with allograft chips. Percutaneous pedicle screws were then inserted. Operative time averaged 189.9 min and blood loss averaged 300 ml. The mean follow-up in the ALIF group was 41.1 months. Significant improvements in segmental lordosis, whole lumbar lordosis, and percentage listhesis were seen. Fusion was seen in 42/43 patients. VAS back pain improved from 7.6 to 2.1, VAS leg pain improved from 7.5 to 2.0, and ODI improved from 49.3 to 13.7.

Hsieh et al. (2017) reported on 23 consecutive patients who underwent ALIF with supplementary percutaneous pedicle screws for multilevel isthmic spondylolisthesis. Twenty-one patients had two-level spondylolisthesis and two patients had three-level slips. The mean follow-up was 22.26 months. Mean operating time was 251.1 min and mean estimated blood loss 346.8 ml. ODI improved from 56.2 to 14.9, VAS back from 8 to 1.7, and VAS leg 7.6 to 1.1. Segmental lordosis improved from 22.7 to 32.7, and total lumbar lordosis improved from 45.8 to 53.1. Successful fusion was seen in all patients.

Adult Spinal Deformity

ALIF has also been used successfully in the treatment of spinal deformity and sagittal imbalance and is an effective way to restore lumbar lordosis (see Fig. 5). Saville et al. (2016) assessed the segmental correction obtained using 20 ° and 30 ° hyperlordotic cages for ALIF in staged anterior-posterior fusions in adults with degenerative pathology and spinal deformity. The authors assessed 69 levels in 41 patients with a mean age 55 years. The average follow-up was 10 months. The cages used were made of either PEEK or carbon fiber reinforced polymer. For 30 ° cages, the mean segmental lordosis achieved was 29 °s; in the presence of spondylolisthesis, this reduced to 19 °s. For 20 ° cages, the mean segmental lordosis achieved was 19 °s. The mean lumbar lordosis increased from 39 °s to 59 °s. The mean SVA reduced from 113 mm to 43 mm. Six cages (9%) displayed a loss of segmental lordosis during follow-up, on average 4.5 °s.

Rao et al. (2015) in a prospective study of 125 patients compared the clinical and radiological outcomes of ALIF based on surgical indication. The mean follow-up was 20 months. Patients with DDD (with or without radiculopathy), spondylolisthesis, and scoliosis had the best clinical response to ALIF with statistically and clinically significant improvement in SF-12, ODI, and VAS scores. The favorable results can be partly explained by the powerful ability of ALIF to obtain lordosis which is vital to at least maintain in the aforementioned indications, where mild deformities can coexist. Failed posterior fusion and adjacent segment disease also showed significant improvement although the mean changes were lower. The overall radiological fusion rate was 94.4%.

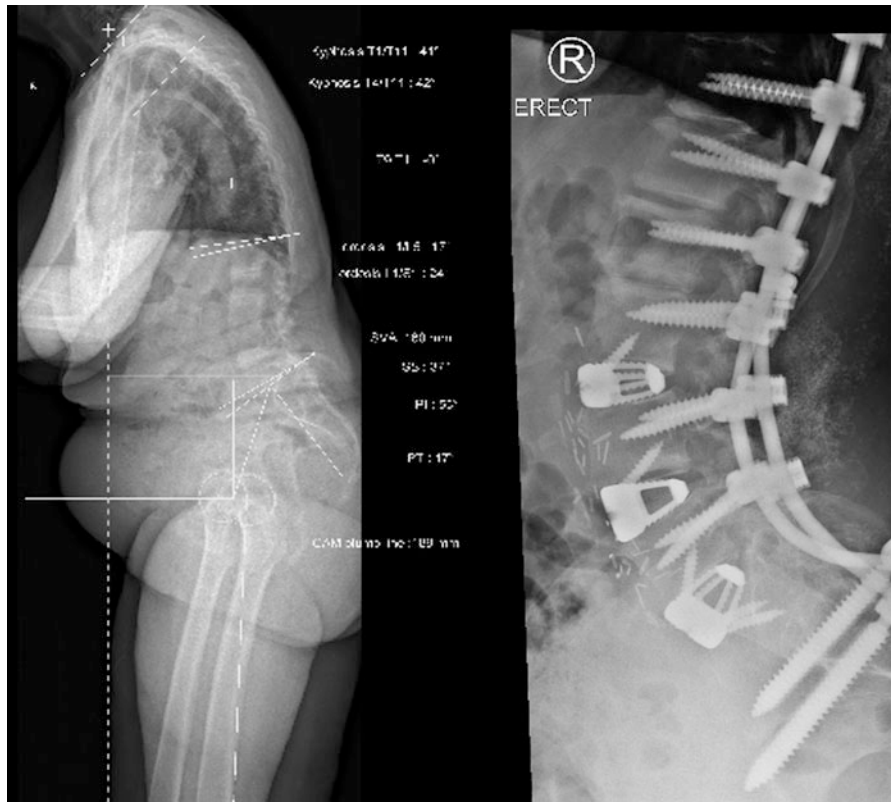

Fig. 5 Preoperative (EOS™) and postoperative standing lateral radiographs of a combined anterior-posterior correction for severe unbalanced kyphoscoliosis utilizing multiple ALIF for anterior column support

In summary, ALIF is an established approach for interbody fusion that can be used successfully to treat DDD, spondylolisthesis, and deformity. ALIF leads to clinically significant improvements in pain and function in appropriately selected patients. The technique is particularly effective at restoring disc height and lordosis, thus maintaining or restoring sagittal balance. Good clinical outcomes are reported for femoral allograft, stand-alone devices with integrated fixation, cage-plate constructs, and circumferential instrumentation.

OLIF

Mayer (1997) were the first to describe the modern OLIF approach in 20/25 patients with DDD, degenerative spondylolisthesis, isthmic spondylolisthesis, or failed back surgery syndrome.

Segments between L2–L3 and L4–L5 were accessed through a retroperitoneal "OLIF" approach and L5–S1 through a traditional transperitoneal ALIF approach. Patients had undergone posterior decompression and pedicle screw fixation 1–2 weeks prior. OLIF was performed using autologous iliac bone graft. The mean follow-up was 10.6 months. For the OLIF approach, mean operating time was 111 min; mean blood loss was 67.8 ml. The fusion rate was 100%.

Lin et al. (2010) presented the results of a prospective clinical study of single-level or two-level OLIF in 46 patients with DDD, low-grade spondylolisthesis, or pseudarthrosis. The mean follow-up was 15 months. OLIF was performed using a titanium cage and plate and autograft bone. The fusion rate was 94.2%. VAS improved from 9.13 to 2.33 and RMDQ improved from 18.58 to 5.43. Good to excellent outcomes were reported in 87% of patients.

Mehren et al. (2016) conducted a chart review of patients who had undergone OLIF over a 12-year period at a single center, specifically focussing on complications. Eight hundred twelve patients with a median age of 63 years were investigated. Patients predominantly suffered from DDD or spondylolisthesis. OLIF was performed using tricortical iliac crest bone graft early in the series, and titanium or PEEK cages filled with autograft, tricalcium phosphate, or rhBMP-2 later in the series. 98% of cases were combined with posterior instrumentation. 62% of patients underwent single-level surgery. The average operating time for OLIF was 110 min. An inhospital complication occurred in 3.7% of patients. The superficial infection rate was 0.24% and deep infection rate 0.37%. There were three intraoperative vascular injuries (0.37%). Nine patients experienced a neurologic injury (1.1%), six of these were meralgia paresthetica due to iliac crest bone harvesting.

Molloy et al. (2016) conducted a prospective cohort study of 64 patients who underwent OLIF using porous tantalum cages for degenerative spine pathology. All patients had additional pedicle screw fixation. The mean follow-up was 1.8 years. VAS back pain improved from 7.5 preoperatively to 1.4, and ODI improved from 64.3 preoperatively to 6.7 at 12 months postoperatively. Radiographic analysis confirmed improvement in multiple lumbopelvic parameters (including pelvic tilt, sacral slope, lumbar lordosis) and the SVA.

Li et al. (2017) conducted a systemic search of the literature to assess operative outcomes and complications of the OLIF procedure. Sixteen studies were included for review, representing 2364 operated levels in 1571 patients. The average follow-up was 22.3 months. The mean blood loss was 109.9 ml, operating time 95.2 min, and postoperative hospital stay 6.3 days. Fusion was achieved in 93% of operated levels. Intraoperative complications occurred in 1.5% and postoperative complications in 9.9% of patients.

In summary, OLIF is a relatively new approach to lumbar interbody fusion that is currently gaining popularity. Initial clinical studies suggest that OLIF is a relatively safe technique that can be used effectively in the treatment of DDD and spondylolisthesis. High fusion rates and the ability to restore lordosis and sagittal balance have been reported in the literature.

LLIF

Ozgur et al. (2006) reported on the first described cases of LLIF, termed XLIF in their series. All procedures were supplemented with percutaneous pedicle screw fixation. Thirteen patients were reported on at short-term follow-up with no early complications noted.

Youssef et al. (2010) conducted a retrospective review of patients treated with LLIF for multiple clinical indications. Single-level, two-level, and three-level procedures were performed using the CoRoent implant (NuVasive, Inc., San Diego, CA). A total of 84 patients were included in the study (15 stand-alone LLIF, 31 with addition of a lateral plate, 38 with supplemental PSF). The mean operating time was 199 min, mean estimated blood loss was 155 ml, and length of hospital stay averaged 2.6 days. The perioperative complication rate was 2.4% and the postoperative complication rate 6.1%. The mean follow-up was 15.7 months. Solid fusion was seen in 68/84 patients (81%). At 1 year postoperatively, VAS improved from 58.9 to 13.7 and ODI improved from 39.7 to 17.3.

Ahmadian et al. (2015) also reported their experience with stand-alone LLIF for the treatment of DDD, spondylolisthesis, and adult degenerative scoliosis. Follow-up was up to 12 months. Fifty-nine patients were included in the study: average age 60 years. Diagnoses were DDD in 63%, degenerative spondylolisthesis in 7%, and ADS in 30%. Surgery was performed using a 10 ° lordotic, 8–12 mm height PEEK cage packed with allograft (and BMP in 19 patients). The fusion rate was 93% at 12 months. VAS improved from 69.1 to 37.8. ODI improved from 51.8 to 31.8. Grade I–II subsidence was seen in 30% of patients. The authors advised that to consider a stand-alone construct, patients should be sagittally balanced, have a coronal Cobb angle less than 30 °s, and be evaluated for osteoporosis preoperatively.

Spondylolisthesis

Ahmadian et al. (2013) reported on the results of LLIF for treatment of L4–L5 spondylolisthesis. Thirty-one patients were included in the study. All patients were treated with LLIF and supplementary percutaneous pedicle screw fixation. The mean follow-up was 18.2 months. Average age of the patients was 61.5 years. Mean blood loss was 94 ml. ODI improved from 50.4 to 30.9, VAS improved from 69.9 to 38.7, and SF-36 improved from 38.1 to 59.5 at latest follow-up. No motor weakness or permanent deficits were noted. Transient anterior thigh numbness was reported in 22.5% of patients. All patients had improvement in spondylolisthesis classification.

Adult Spinal Deformity

Phillips et al. (2013) conducted a prospective multicenter study to evaluate the clinical and radiographic results of patients undergoing LLIF for the treatment of degenerative scoliosis. A total of 107 patients were included in the study. Follow-up was at 24 months. The mean patient age was 68 years. An average of three levels were treated with LLIF at surgery (range: 1–6). ODI, VAS back, VAS leg, and SF-36 PCS scores all improved significantly. Patient satisfaction was 85%. In hypolordotic patients, lumbar lordosis was corrected from a mean of 27.7 °s pre-op to 33.6 °s at 24 months.

Anand et al. (2013) conducted a retrospective review of 2- to 5-year clinical and functional outcomes of minimally invasive surgery for adult scoliosis. Seventy-one patients were included in the study. All underwent a combination of LLIF, AxiaLIF, and posterior instrumentation. LLIF was performed using a PEEK cage filled with rhBMP-2 and Grafton putty. The mean patient age was 64 years and average follow-up was 39 months. On average, patients were sagittally balanced preoperatively and remained that way at latest follow-up. VAS improved from 6.43 to 2.35 and ODI improved from 50.3 to 41 at latest follow-up.

Tempel et al. (2014) reported on 26 patients who underwent combined LLIF and open PSF for the treatment of adult degenerative scoliosis. Patients were aged between 40 and 77 years. LLIF was performed with a 10 ° lordotic PEEK cage 10–12 mm in height packed with DBM. One-year follow-up results were reported. Statistically significant improvement in regional coronal angles

and segmental coronal angulation at all operative levels was seen. Coronal Cobb angle improved from a mean of 41.1 °s to 12 °s at latest follow-up. Mean PI-LL mismatch improved from 15 °s to 6.92 °s, and SVA improved from 59.5 mm preoperatively to 34.2 mm at latest follow-up. Significant improvements in clinical outcomes were also observed. VAS back pain improved from 7.5 to 4.3, VAS leg pain improved from 5.8 to 3.1, ODI from 48 to 38, and SF-36 PCS from 27.5 to 35. Three major and 10 minor complications were reported.

Costanzo et al. (2014) conducted a literature review focussing on sagittal balance restoration in adult degenerative scoliosis with the LLIF approach. Fourteen studies were identified representing 476 patients and 1266 operated levels. Only two studies measured global sagittal alignment. They concluded that LLIF was particularly effective when the lumbar lordosis correction goal was less than 10 °s and the sagittal balance correction goal was less than 5 cm.

Phan et al. (2015b) conducted a systematic review to assess the safety and clinical and radiological outcomes of LLIF for the treatment of degenerative spinal deformity. Twenty-one studies were included for review (948 patients, 1920 levels). The median follow-up was 14 months. Mean VAS improved from 6.8 to 2.9 and mean ODI improved from 44.5 to 20.5. Regional lumbar lordosis significantly improved from 35.8 °s to 43.3 °s. Sagittal alignment was unchanged (SVA 34 mm vs. 35.1 mm).

Saigal et al. (2016) performed a literature review of the anterior column realignment (ACR) procedure for sagittal deformity correction. ACR generally involves a LLIF with sectioning of the anterior longitudinal ligament (ALL) and placement of a hyperlordotic cage. ACR usually also involves a second stage posterior column osteotomy. Twelve papers met the inclusion criteria. Segmental lordosis between 10 and 27 °s was reported with use of hyperlordotic cages. A 19 ° increase in mean intradiscal angle was reported when ACR was combined with posterior column osteotomy, 13 °s more than is reported for LLIF alone without a hyperlordotic implant. Complication rates ranged between 18% and 47%. Transient hip flexion weakness was reported in 9.3% and transient paresthesia/dysesthesia in 12%. Motor deficit was reported in 11/75 cases, lower than typically reported for three-column osteotomy procedures.

Berjano et al. (2015) assessed the use of the LLIF-based anterior column reconstruction technique for correcting major sagittal deformity in 11 patients. A mean value of 27 °s lordosis was restored at a single ACR level but two major complications occurred, being a bowel perforation and a postoperative infection requiring posterior debridement. Nevertheless, the authors stated that the ACR technique could provide similar correction to a pedicle subtraction osteotomy with comparable complication profile.°

Complications

Rodgers et al. (2010) reported a prospective analysis of 600 LLIF cases; the paper focussed on intraoperative and perioperative complications. Seven hundred forty-one levels were treated; 99.2% included supplementary internal fixation. The overall incidence of perioperative complications (intraoperative out to 6 weeks postoperative) was 6.2%. Complications were statistically more common at the L4–L5 level. VAS improved from 8.82 preoperatively to 3.12 at 1 year post-op. The patient satisfaction rate was 86.7%.

Lykissas et al. (2014) performed a retrospective analysis of 919 LLIF procedures to identify risk factors for lumbosacral plexus injuries. Four hundred fifty-one patients were included in the study (919 levels). Immediately postoperatively 38.5% of patients reported anterior thigh/groin pain. Sensory deficits were recorded in 38% and motor deficits in 23.9%. At last follow-up, 4.8% of patients reported anterior thigh/groin pain, whereas sensory and motor deficits were recorded in 24.1% and 17.3% of patients, respectively. When patients with preoperative neural deficits were excluded, persistent surgery-related sensory and motor deficits were noted in 9.3% and 3.2% of the patients, respectively. Increased risk of neurological deficit was associated with surgery at the more caudal lumbar levels. The use of rhBMP-2 was associated with persistent motor deficits.

In summary, LLIF is now an established interbody fusion technique with good results reported in the treatment of DDD, spondylolisthesis, and deformity. Supplementary pedicle screw instrumentation is recommended in the majority of cases. To achieve significant lordosis correction, additional release of the ALL is required as part of the procedure. A high incidence of temporary postoperative lower limb neurological symptoms is expected due to the transpsoas approach, particularly at the L4–L5 level. The rate of permanent neurological deficit is low.

TLIF

Despite the popularity of the TLIF procedure, there is a relative paucity of robust published literature regarding the clinical outcomes of the technique. Lowe and Tahernia (2002) conducted a prospective analysis of 40 patients treated with TLIF for degenerative disease of the lumbar spine. TLIF was performed using autograft bone and titanium mesh cages. Bilateral posterolateral fusion and contralateral facet fusion were also performed. The mean follow-up was 3.4 years. The fusion rate was 90% and segmental lordosis was increased in all patients. VAS improved from a mean of 8.3 pre-op to 3.2 at latest follow-up. 85% of patients reported a good to excellent result.

Spondylolisthesis

Rosenberg and Mummaneni (2001) described their early experience with TLIF for the treatment of grade I or II spondylolisthesis. They retrospectively reviewed 22 patients, all presenting with low back pain, the majority with associated radiculopathy. TLIF was performed using Pyramesh titanium cages and iliac crest autograft with supplementary pedicle screw fixation. At a mean follow-up of 5.3 months, low back pain was completely resolved in 16 patients, moderate relief was achieved in 5 patients, and pain was unchanged in 1 patient. One intraoperative durotomy occurred, two postoperative wound infections developed, and one patient had a mild postoperative L5 motor palsy that resolved quickly.

Hackenberg et al. (2005) reported their minimum 3-year follow-up of 52 consecutive patients treated with TLIF for isthmic spondylolisthesis (22 patients) and lumbar degenerative disorders (30 patients). Thirty-nine cases were single-level, 11 cases were two-level, and 2 cases were three-level fusions. Operating time averaged 173 min for single-level cases and 238 min for multiple-level fusions. TLIF was performed using a curved titanium cage and autograft iliac crest. Four major complications occurred: one deep wound infection, one persistent radiculopathy, one contralateral disc herniation, and one pseudarthrosis. The fusion rate was 89%. VAS and ODI both improved significantly by 3 months postoperatively and remained significantly better than preoperative scores through follow-up.

Lauber et al. (2006) conducted a prospective clinical study evaluating the 2–4-year clinical and radiographic results of TLIF for the treatment of grade I–II degenerative and isthmic spondylolisthesis. Nineteen degenerative, 19 isthmic, and 1 dysplastic spondylolisthesis were treated. Fusion was performed using a curved titanium cage (Micomed Ortho AG, Switzerland) and autograft bone. Minimum follow-up was 24 months, with a mean clinical follow-up of 50 months and mean radiographic follow-up of 35 months. Mean ODI suggested mild to moderate disability preoperatively, but significant improvements were seen postoperatively (23.5 pre-op to 13.5 postoperatively). Significant improvements in VAS were also observed postoperatively. Both VAS and ODI scores began to deteriorate at the 4-year postoperative follow-up. Better results for both VAS and ODI were seen in the isthmic patients compared to degenerative patients, possibly due to the patients being significantly younger. The radiographic fusion rate was 94.8%. There were three serious postoperative complications requiring a return to theatre.

Open Versus Minimally Invasive TLIF

Since these early reports of the open TLIF procedure (O-TLIF), the technique has been modified into the now widely used minimally invasive

TLIF procedure (MI-TLIF). A number of systemic reviews and meta-analyses have been performed comparing the open and minimally invasive procedures.

Khan et al. (2015) performed a systemic review and meta-analysis to investigate early and late outcomes of MI-TLIF in comparison with O-TLIF. Thirty studies were included in the meta-analysis. MI-TLIF was associated with reduced blood loss, length of stay, and complications but increased radiation exposure. Fusion rates and operative times were comparable between the two groups. There were no differences in early and late ODI or early VAS back pain scores, but a (statistically significant but clinically insignificant) decrease in late VAS back pain scores was noted in the MI-TLIF group.

Goldstein et al. (2016) conducted a systematic review and meta-analysis to compare the clinical effectiveness and adverse event rates of MI-TLIF versus O-TLIF. Twenty-six studies met the inclusion criteria; of note, all were of low to very low quality. Overall, there were 856 patients in the MI-TLIF cohort and 806 patients in the O-TLIF cohort. Estimated blood loss, time to ambulation, and length of stay were all in favor of MI-TLIF. Operative times did not differ significantly. There was no difference found in surgical adverse events, but medical adverse events were significantly less likely in the MI-TLIF group. No differences in non-union or reoperation rates were observed. Mean ODI scores were slightly better in the MI-TLIF group at a median follow-up time of 24 months (3.32-point difference). There was no difference observed in VAS back and leg pain scores at 24-month follow-up.

Phan et al. (2015a) conducted a systemic review and meta-analysis of the relative benefits and risks of MI-TLIF and O-TLIF. Twenty-one studies were included in the analysis, representing 966 patients undergoing MI-TLIF and 863 patients undergoing O-TLIF. No significant difference in operating time was noted between the two groups. The median intraoperative blood loss was significantly less in the MI-TLIF group (177 vs. 461 ml). Length of hospital stay was shorter in the MI-TLIF group (4.7 days vs. 8 days). Infection rates were significantly lower in the MI-TLIF cohort (1.2% vs. 4.6%). There was no difference between the groups in overall complication and reoperation rates. VAS back pain scores and ODI were also slightly lower in the MI-TLIF group, reaching statistical significance but likely not clinically relevant.

Bevevino et al. (2014) conducted a systematic review and meta-analysis to investigate fusion rates of MI-TLIF performed without posterolateral bone grafting. Seven studies with a total of 408 patients were assessed. Average radiographic follow-up was 15.6 months. TLIF was performed using PEEK cages or allograft interbody cages with local autograft bone. In four studies, rhBMP-2 was also used. The overall fusion rate was 94.7% on CT scan, suggesting MI-TLIF without posterolateral bone grafting has similar fusion rates to O-TLIF or MI-TLIF with posterolateral grafting.

In summary, the available literature reports good results for open TLIF in the treatment of degenerative disease of the lumbar spine including spondylolisthesis. Clinically significant improvements in pain and function and a high fusion rate can be expected. In comparison to O-TLIF, MI-TLIF reduces blood loss and hospital stay but does not appear to improve the fusion rate or the clinical outcomes beyond the immediate postoperative period. Restoration of lordosis is possible with O-TLIF but limited with MI-TLIF.

PLIF

In one of the earliest published studies of posterior lumbar interbody fusion, Steffee and Sitkowski (1988) described their experience with PLIF in conjunction with pedicle screws and segmental spine plates. Allograft was used for the PLIF procedure. Thirty-six patients were included in the study with follow-up of 6–12 months. 33/36 had significant improvement in their pain. The fusion rate was reported as 100%.

Degenerative Disc Disease

Barnes et al. (2001) reported their experience with the PLIF procedure for DDD using allograft threaded cortical bone dowels for interbody

fusion. Thirty-five patients with a mean age of 46 years were included in the study. Twenty-three patients underwent a PLIF procedure and 12 patients underwent ALIF. All PLIFs except one were backed up with pedicle screws and rods without posterolateral grafting. ALIFs were performed as a stand-alone procedure. Twenty-eight patients were followed up at a mean of 12.3 months. Satisfactory outcomes were reported in 70% of the PLIF patients. The fusion rate in the PLIF group was 95%. Barnes et al. (2002) also conducted a study comparing the use of allograft cylindrical threaded dowels and allograft impacted wedges for PLIF. There was a 13.6% rate of permanent nerve injury in the threaded dowel group versus 0% in the impacted wedge group. There was no significant difference in fusion rate (95.4% vs. 88.9%). There was a significantly higher rate of satisfactory outcomes in the impacted wedge group.

Chitnavis et al. (2001) reported their experience of PLIF using carbon fiber cages for revision of previous disc surgery. Surgery was performed on patients who had undergone previous discectomy surgery and had ongoing or recurrent low back pain and sciatica with compatible MRI findings. Fifty patients were included in the study; in 40 patients (80%), supplementary pedicle screws were not used. PLIF was performed using paired carbon fiber Brantigan cages packed with autograft bone (iliac crest or spinous process). Symptoms improved in 46 patients (92%) after surgery. Two thirds of patients experienced good to excellent outcomes at early and late follow-up. There was no difference in clinical outcome between those in whom pedicle screws were used or were not used. The fusion rate at 2 years postoperatively was 95%.

Molinari and Gerlinger (2001) reported the functional outcomes of instrumented PLIF in active duty US serviceman and compared these with non-operative management in a non-randomized study. Twenty-nine consecutive patients with single-level lumbar disc degeneration were treated; 15 were treated with instrumented PLIF, and 14 refused surgery and were treated with spinal extensor muscle strengthening, medications, and restricted duty. PLIF was performed using Brantigan or Harms cages, autogenous iliac crest, and pedicle screw-rod fixation. Average follow-up time was 14 months. Only 5/14 soldiers in the non-operative group returned to full unrestricted military duty. In the PLIF group, 12/15 soldiers were able to return to full duty. Outcomes with respect to posttreatment pain, function, and satisfaction were higher in patients treated with instrumented PLIF.

Haid et al. (2004) published their results of PLIF using rhBMP-2 with cylindrical interbody cages in patients with single-level lumbar DDD. The study was a prospective randomized multicenter study comparing iliac crest autograft and rhBMP-2 in paired cylindrical threaded titanium fusion cages (INTER FIX cages). No supplementary pedicle screw fixation was used. Sixty-seven patients were assigned to one of the two groups. There was no significant difference in operative time or blood loss. The fusion rate at 24 months was 92.3% in the rhBMP-2 group and 77.8% in the autograft group. At all postoperative intervals, mean ODI, VAS back and leg pain, and SF-36 PCS improved in both groups compared to preoperative scores.

Hioki et al. (2005) conducted a retrospective review of 19 patients who underwent two-level PLIF for DDD. PLIF was performed using various interbody cage devices and local autograft bone, with supplementary pedicle screw instrumentation. The mean follow-up was 3.6 years. Lumbar lordosis improved from 25.2 °s preoperatively to 36.6 °s at 6 months postoperatively. Segmental lordosis at the fused levels increased from 12.5 °s preoperatively to 18.7 °s at final follow-up. The fusion rate was 100%. Mean JOA score increased from 12.9 preoperatively to 21.3 at final follow-up. There was a positive correlation between increase in lordotic angle and increase in JOA score. Dural tear occurred intraoperatively in two cases. Postoperatively there were one case of displacement of an interbody spacer, two cases of L3 radiculopathy, and one case of pulmonary embolism.

Spondylolisthesis

Wang et al. (2017) conducted a retrospective analysis of the outcomes of autograft alone versus

PEEK + autograft PLIF in the treatment of adult isthmic spondylolisthesis. Eighty-four patients were included in the study: 44 patients had interbody fusion performed with local autograft alone and 40 patients with autograft + 2 PEEK cages. All cases had supplementary pedicle screw instrumentation. The minimum follow-up was 24 months. At last follow-up, there was no difference between the two groups in clinical outcomes (VAS back and leg pain, ODI, and patient satisfaction). The PEEK + autograft group showed better maintenance of disc height, but this did not reach statistical significance. The fusion rate was 90.9% in the autograft alone group and 92.5% in the autograft + PEEK group.

Sears (2005a) published results of PLIF for lytic spondylolisthesis using insert-and-rotate interbody spacers. The study was a prospective observational study of 18 consecutive patients with lytic spondylolisthesis grades I to IV. The mean age of patients was 50.2 years; the majority of patients presented with predominant radicular symptoms. The mean follow-up was 17.3 months. Intervertebral disc space spreaders and pedicle screw instrumentation were used to reduce the spondylolisthesis. PLIF was then performed using carbon fiber, titanium mesh or PEEK fusion cages, and local and iliac crest autograft bone. VAS improved from 5.0 preoperatively to 2.9 postoperatively. Good to excellent results were reported in 83.3% of patients. Mean preoperative slip reduced from 30.2% to 6.2%. Mean focal lordosis improved from 10.6 °s to 18.1 °s. Total lumbar lordosis did not change, but the lordosis over the lumbar segments above the fusion reduced from 46.8 °s to 34.9 °s.

Sears (2005b) also published results of the same PLIF technique for degenerative spondylolisthesis. Thirty-four patients, mean age 65.1 years, were assessed with the majority presenting with predominantly radicular pain. The mean follow-up was 21.2 months. VAS improved from 5.3 pre-op to 2.2 at last follow-up. 31/34 patients rated their outcome as good to excellent. The mean preoperative slip reduced from 20.2% to 1.7%. The mean focal lordosis increased from 13.1 °s to 16.1 °s.

In summary, PLIF is also a well-established technique for interbody fusion, with good clinical results reported for the treatment of DDD and spondylolisthesis. With appropriate surgical technique, appropriate restoration of segmental lordosis is achievable. A high fusion rate is expected with the procedure.

AxiaLIF

Bohinski et al. (2010) reported on the clinical outcomes, complications, and fusion rate of the AxiaLIF procedure at L5–S1 and L4–S1 in 50 patients presenting with low back pain and radiculopathy due to DDD (37 patients) and spondylolisthesis (6 patients) and in 7 patients with ongoing or recurrent symptoms after previous discectomy. Follow-up was out to 1 year. The procedure was performed at L5–S1 in 35 patients and L4–S1 in 15 patients. Supplementary pedicle screw fixation was used in 45 patients. At 1-year follow-up, VAS score improved by 49% (77 to 39) and ODI by 50% (56 to 28). Fusion was assessed by CT scan and was seen in 44 (88%) patients. One case of bowel perforation occurred.

Bradley et al. (2012) conducted a retrospective review of 41 patients who underwent AxiaLIF at L5–S1 for DDD, the majority combined with posterior fusion. Mean follow-up was 22.2 months. VAS back pain improved from 7.1 to 4.2 and VAS leg pain improved from 6.0 to 3.0. ODI improved from 45.5 to 32.6. Fusion was seen in 26/41 (63.4%) patients. There were four (9.7%) reoperations directly related to the AxiaLIF procedure.

Zeilstra et al. (2017) evaluated the mid- and long-term results of AxiaLIF performed for DDD in 164 patients. Additional facet screw fixation was used in 95 patients. Average follow-up was 54 months with longest follow-up out to 10 years. No intraoperative or perioperative complications were reported. VAS back pain improved from 80 to 34, and VAS leg pain improved from 43 to 24. ODI decreased from 46 to 19. The fusion rate was 89.4%. Female sex, work status (still working), lower BMI, and absence of Modic type II changes were correlated with a good result.

Melgar et al. (2014) measured changes in segmental and global lordosis in patients treated with L4–S1 AxiaLIF and posterior instrumentation. A retrospective multicenter review of 58 patients was performed. The majority of patients suffered from DDD. Mean follow-up was 29 months. VAS back pain improved from 7.8 to 3.3. ODI improved from 60 to 34. Fusion was seen in 96% of treated levels. Maintenance of lordosis was identified in 84% of patients at L4–S1 and 81% of patients at L1–S1. Spino-pelvic parameters and sagittal balance were not assessed.

Schroeder et al. (2015) conducted a systemic review investigating the fusion rate and safety profile of L5–S1 AxiaLIF. Fifteen studies were included in the review. The overall pseudarthrosis rate was 6.9% and the rate of all other complications was 12.9%. The reoperation rate was 14.4% and the infection rate was 5.4%. Deformity studies reported a significantly higher rate of complications (46.3%).

In summary, the published literature suggests that AxiaLIF is a relatively safe procedure with good clinical outcomes in the treatment of DDD (predominantly at L5–S1). The fusion rate of AxiaLIF is comparable with other interbody fusion approaches. However it has a limited role in the treatment of spondylolisthesis and deformity, as fusion is performed "in situ" with little in the way of restoration of disc height or lordosis.

Comparative Studies

Humphreys et al. (2001) conducted a prospective study comparing their early experiences with TLIF to the already established PLIF procedure. Forty TLIFs were compared to 34 PLIFs. TLIF was performed using a Harm's titanium mesh cage packed with iliac crest autograft. Of the 40 TLIF procedures, 17 were single-level, 23 were two-level, and 1 was a three-level fusion. For the single-level fusions, no significant difference in blood loss, operative time, and hospital stay was seen between the TLIF and PLIF groups. Significantly less blood loss occurred in the two-level TLIF group compared to the two-level PLIF group. No complications were seen with the TLIF approach, whereas multiple complications were seen in the PLIF group (four cases of radiculitis, one case of broken hardware, one screw loosening, two cases of screw removal, one superficial infection, and one pseudarthrosis).

Lee et al. (2017b) compared the outcomes of ALIF, PLIF, and TLIF at L5–S1 for the treatment of lumbar degenerative spinal disease in 77 patients. Thirty-four patients were diagnosed with isthmic spondylolisthesis at L5–S1 and the rest with degenerative lumbar spinal stenosis at L5–S1. Specific indications for surgery differed between groups. ALIF was associated with better restoration of segmental lordosis. The fusion rate based on X-ray and CT scan did not differ between the three groups. TLIF was associated with a better postoperative VAS back pain score. PLIF showed the lowest cage subsidence rate.

Lee et al. (2017a) investigated which approach (ALIF, LLIF, or PLIF) is advantageous in preventing development of adjacent segment disease after fusion for L4–L5 spondylolisthesis. Eighty-two patients were included in the study. The mean follow-up was 25 months. ASD was seen in 37% of the ALIF group, 41.7% of the LLIF group, and 64.5% of the PLIF group. The ALIF and LLIF group had significantly increased disc height and foraminal height compared to the PLIF group. The ALIF group had significantly improved lordosis compared to the PLIF and LLIF groups. There was no difference in clinical outcomes (VAS and ODI). This suggests that sagittal profile and avoidance of damage to the posterior spinal structures may help prevent adjacent segment disease.

Phan et al. (2015c) conducted a systematic review and meta-analysis of ALIF versus TLIF. Twelve articles were included in the meta-analysis with a total of 609 ALIF and 631 TLIF patients. Fusion rates and clinical outcomes were comparable between ALIF and TLIF. ALIF was associated with better restoration of disc height, segmental lordosis, and total lumbar lordosis. ALIF was associated with longer hospitalization and, as expected, a lower rate of dural injury and a higher rate of vascular injury.

Dorward et al. (2013) conducted a matched cohort analysis of ALIF versus TLIF in long deformity constructs. There were 42 patients in each group. The average age was 54 years and the number of instrumented vertebrae averaged 13.6 levels. TLIF was associated with less operative time but greater blood loss. Overall complications and neurological complications did not differ. The ALIF group had greater improvement in SRS scores. ODI scores improved similarly in both groups. Segmental lordosis at L4–L5 and L5–S1 as well as regional lordosis (L3–S1) was greater in the ALIF group. TLIF allowed greater correction of coronal plane deformity.

Jiang et al. (2012) conducted a systematic review comparing ALIF and TLIF in the treatment of lumbar spondylosis. Nine studies were included in the review, all retrospective comparative studies. Blood loss and operative time were greater in the ALIF cohort. There was no significant difference in complication rates between ALIF and TLIF. The restoration of disc height, segmental lordosis, and total lumbar lordosis in ALIF was superior to TLIF. Clinical outcomes and fusion rate were not significantly different, but radiological alignment and adjacent segment disease were not outcomes uniformly assessed.

Similarly, Hsieh et al. (2007) compared ALIF and TLIF in regard to restoration of foraminal height, disc angle, lumbar lordosis, and sagittal balance. A retrospective radiographic and clinical analysis was completed, with 32 patients in the ALIF group and 25 patients in the TLIF group. There was no difference in improvement in VAS scores. ALIF was superior to TLIF in its capacity to restore foraminal height, local disc angle, and lumbar lordosis. ALIF increased foraminal height by 18.5%, whereas TLIF decreased it by 0.4%. ALIF increased the local disc angle by 8.3 °s and lumbar lordosis by 6.2 °s, whereas TLIF decreased local disc angle by 0.1 °s and lumbar lordosis by 2.1 °s. They concluded that ALIF may lead to better long-term outcomes compared to TLIF due to better restoration of sagittal balance.

Hoff et al. (2016) conducted a prospective randomized trial comparing the lumbar hybrid procedure (stand-alone ALIF L5–S1 and total disc replacement L4–L5) with two-level TLIF for the treatment of two-level DDD. Sixty-two patients were enrolled, 31 in each arm. TLIF was performed using a PEEK cage, local autograft bone, and pedicle screws. ALIF was performed using a stand-alone PEEK cage with integrated screws. The TDR used was the Maverick™. The mean follow-up was 37 months. Hybrid patients had significantly lower VAS scores immediately postoperatively and at final follow-up compared to fusion patients. There was also a trend for lower ODI scores in the hybrid group although this did not reach statistical significance. Complication rates were low and similar between groups. Lumbar lordosis increased at the operative levels in the hybrid group but not in the TLIF group with a compensatory increase in lordosis at the supradjacent levels. ROM at L3–L4 was significantly higher in fusion patients compared to hybrid patients at final follow-up.

Joseph et al. (2015) conducted a systematic review comparing and contrasting the complication rates of MI-TLIF and LLIF. Fifty-four studies were included for analysis of MI-TLIF, and 42 studies were included for analysis of LLIF. In total 9714 (5454 MI-TLIF and 4260 LLIF) patients were assessed with 13,230 levels fused (6040 MI-TLIF and 7190 LLIF). The total complication rate per patient was 19.2% in the MI-TLIF group and 31.4% in the LLIF group. The rate of sensory deficits, temporary neurological deficits, and permanent neurological deficits in the MI-TLIF group was 20.16%, 2.22%, and 1.01%, respectively. In the LLIF group, the rates were 27.08%, 9.4%, and 2.46%, respectively. Rates of intraoperative and wound complications were 3.57% and 1.63% in the MI-TLIF group compared to 1.93% and 0.8% for the LLIF group, respectively. No significant differences were noted for medical complications or reoperations.

In summary, comparing posterior interbody fusion procedures, TLIF is associated with a lower complication rate than PLIF. ALIF achieves better restoration of disc height and lordosis than TLIF and LLIF (without ALL release). Anterior interbody fusion procedures (ALIF and LLIF) are associated with a lower rate of adjacent segment disease than posterior interbody fusion

procedures (PLIF and TLIF). The short-term to midterm clinical outcomes and overall complication rates are similar between anterior and posterior interbody fusion approaches.

Lumbar Interbody Fusion: When to Use What?

When deciding which interbody fusion approach and device to use in each individual patient, the specific goals of lumbar interbody fusion must be kept in mind. These are:

1. Decompression of neural elements, if required
2. Appropriate maintenance or restoration of segmental disc height and lordosis
3. Placement of an interbody fusion device that is able to stabilize the motion segment in the correct position while fusion occurs
4. The use of bone graft and/or other biologic agents to enhance and achieve fusion
5. Avoidance of complications and "collateral damage" from the approach

Decompression of the neural elements can often be achieved indirectly. Restoration of posterior disc height increases foraminal volume allowing decompression of the exiting nerve roots. Restoration of posterior disc height also achieves a ° of central and lateral recess decompression by uncoupling the facet joints and reversing buckling of the ligamentum flavum and posterior disc bulging. In cases of severe lateral recess and central stenosis due to facet arthropathy and ligamentum flavum hypertrophy or a disc protrusion/extrusion, a direct decompressive procedure may still be required. Direct decompression occurs as part of the procedure during PLIF and TLIF procedures. It is also possible to remove disc protrusions/extrusions during an ALIF or LLIF procedure by utilizing rents in the posterior longitudinal ligament to remove the disc fragments. ALIF and LLIF procedures can be combined with a laminectomy if direct decompression is required in addition to the indirect decompression achieved with the procedure.

Increasingly, the importance of maintaining or restoring disc height and lordosis at the time of interbody fusion is being recognized. Fusion of the lumbar spine in appropriate segmental lordosis and sagittal balance leads to a reduced rate of adjacent segment degeneration and disease and therefore a lower incidence of reoperation and superior long-term clinical outcomes (Rothenfluh et al. 2015). With the advent of modern spinal instrumentation and biologics such as rhBMP-2, achieving fusion is no longer a significant issue. Fusion rates for all the approaches to lumbar interbody fusion are high, and as a result the short-term clinical outcomes are fairly similar between the approaches. A high fusion rate and good short-term clinical outcomes should not necessarily be considered a "success" in modern spine surgery, if appropriate segmental lordosis and sagittal balance are not achieved.

As discussed earlier in this chapter, modern interbody device constructs (combined with supplementary pedicle screw-rod fixation when appropriate) are able to achieve a biomechanically stable environment for fusion to occur. In general, a device with a larger footprint is preferred as it provides a larger surface area for fusion to occur and avoids "point loading" and "fish mouthing" through the vertebral end plates, thus reducing the risk of end plate failure and device subsidence. This is of particular importance in osteoporotic bone. The appropriate interbody fusion device combined with bone graft and/or a biologic agent such as rhBMP-2 can be expected to give a high fusion rate, of $>90\%$ in most recent published studies.

Avoiding complications and reducing approach-related "collateral damage" rely on appropriate preoperative planning and meticulous surgical technique. Anticipation of approach-related complications preoperatively is vital as it allows modification of the approach or the selection of a different approach for interbody fusion. For example, significant obesity or aortoiliac vascular calcification may preclude performing ALIF. A "flying" or "Mickey Mouse" psoas pattern or large iliolumbar vein at L4–L5 may prevent LLIF at that level. Multiple previous posterior decompressive procedures with epidural

scarring may prevent PLIF or TLIF being performed safely. Intraoperatively, each approach for lumbar interbody fusion is associated with its own unique set of approach-related complications which have been discussed earlier in this chapter. Meticulous technique at the time of surgery is required to minimize "collateral damage."

With the above goals of lumbar interbody fusion kept in mind, a number of important factors must be considered preoperatively when planning an interbody fusion.

1. **Are there any absolute or relative contraindications to interbody fusion via a particular approach?**

   An appropriate history, physical examination, and review of imaging studies will determine which approaches are feasible in each individual patient. Contraindications to the various approaches for lumbar interbody fusion have been discussed earlier in the chapter.

2. **What are the patient's lumbopelvic parameters? Is there loss of lumbar lordosis segmentally and globally? Is there sagittal imbalance?**

   In the authors' opinion, every patient who is being worked up for a lumbar interbody fusion should have a preoperative standing full spine X-ray including the pelvis and hips or an EOS scan to assess pelvic parameters (pelvic incidence, sacral slope, pelvic tilt), lumbar lordosis (including where in the lumbar spine it is occurring), and sagittal balance. This is not only appropriate for cases of spondylolisthesis or adult spinal deformity but also in all cases of degenerative disc disease where subtle loss of lumbar lordosis and sagittal balance can occur. When assessing preoperative lumbar lordosis, it is important to assess the relative contribution of each segment to total lumbar lordosis.

   Two thirds of lumbar lordosis occurs between L4 and S1, and it is these levels that are most commonly affected by DDD and spondylolisthesis. A lack of lordosis through the lower lumbar segments can be compensated for by increased lordosis through the upper lumbar segments. Therefore although total lumbar lordosis and sagittal balance may be normal in a patient about to undergo an interbody fusion, it should not be assumed that no increase in lordosis is required as part of the interbody fusion procedure. It is well accepted that fusion of a segment of the lumbar spine in kyphosis increases stresses on the adjacent levels and leads to an accelerated rate of adjacent segment degeneration and disease, even if total lumbar lordosis is normal.

   In general, three patterns are seen when assessing these preoperative images.

(A) Total lumbar lordosis, segmental lordosis, and sagittal balance are all normal.

   This pattern is usually seen in patients with internal disc disruption or early-stage DDD where disc height and lordosis at the involved segment(s) are still relatively well preserved. Interbody fusion must maintain the lordosis of the operative segment(s) to minimize the rate of adjacent segment disease and thus improve long-term outcomes.

(B) Total lumbar lordosis and sagittal balance are normal, but there is loss of segmental lordosis at the operative level(s).

   This pattern is usually seen in the more advanced stages of DDD where loss of disc height and lordosis occurs. It is also commonly seen in low-grade spondylolisthesis. A compensatory increase in lordosis of the unaffected levels normalizes total lumbar lordosis. In these patients the lack of segmental lordosis should be corrected at the time of interbody fusion to minimize the rate of later adjacent segment disease. While the patent may have a good short-term clinical outcome from successful fusion of a segment in kyphosis, the long-term clinical outcome is dubious.

(C) There is loss of both segmental and total lumbar lordosis. Sagittal balance may be maintained by compensatory pelvic retroversion or knee flexion, or there may be loss of sagittal balance.

This pattern is seen in the advanced stages of DDD, spondylolisthesis, and adult spinal deformity. Surgery should plan to correct segmental and global lumbar lordosis and restore sagittal balance. Failure to restore lumbar lordosis and sagittal balance is associated with poor clinical outcomes in both the short and long term.

3. **Does the patient have osteoporosis?**

As osteoporosis affects cancellous bone more than cortical bone, the vertebral bodies are more affected by this disease than the posterior elements. Therefore the presence of osteoporosis is important to consider when planning interbody fusion. Assessment of osteoporosis in the spine can be difficult. DEXA scans through the lumbar spine are performed in cross section and therefore give an "average" of the often osteoporotic vertebral body cancellous bone and the more sclerotic bone of the posterior elements which can give false "normal" readings. The bone density of the femoral neck is a more accurate predictor of vertebral body bone density. Other factors predictive of spinal osteoporosis include a history of osteoporotic fracture elsewhere in the body (femoral neck or distal radius), a family history of osteoporosis and vitamin D deficiency, and a prolonged period of relative inactivity due to the spinal condition or other conditions. Postmenopausal women should be assumed to have spinal osteoporosis until proven otherwise.

Especially in the setting of adult spinal deformity/sagittal imbalance, confirmation of osteoporosis should prompt referral to an endocrinologist for assessment and treatment preoperatively to optimize bone quality which often takes months.

At the time of surgery, patients with osteoporosis are at increased risk of vertebral body end plate failure and subsidence of the interbody device. This can occur either intraoperatively or postoperatively as the patient begins to mobilize and weight bear through the spine. The consequences of subsidence include pseudarthrosis, recurrent foraminal nerve compression, and loss of correction of segmental lordosis. The combination of significant osteoporosis and a very collapsed disc space is especially problematic at the time of surgery as an attempt to increase disc height and place interbody fusion devices without appropriate release of the anterior and posterior longitudinal ligaments will likely result in acute end plate failure.

Strategies to combat osteoporosis at the time of interbody fusion include appropriate (usually circumferential) release of the disc space as noted above and placement of an interbody fusion device with a large surface area that sits on the harder bone of the peripheral end plate ring apophyses. In this regard, ALIF and LLIF are favored over PLIF and TLIF constructs. A device with a relatively low modulus of elasticity (see Fig. 3) is also less likely to subside; therefore PEEK cages are theoretically more appropriate than titanium cages in the setting of osteoporosis. Supplementary pedicle screw-rod fixation is advisable in the setting of osteoporosis. If osteoporosis is severe, cement augmentation of the pedicle screws or vertebroplasty (either delivered directly from an anterior approach into the body or transpedicular) can be used.

4. **Can neural decompression be achieved indirectly or is direct decompression required?**

As discussed above, neural decompression can often be achieved indirectly via anterior interbody fusion approaches (ALIF/OLIF/LLIF). If a direct decompression is required, a posterior interbody fusion approach may be preferred (TLIF/PLIF); however if segmental lordosis needs to be restored also, an anterior approach with supplementary laminectomy will likely achieve this more effectively.

5. **Will supplementary fixation be required?**

Supplementary fixation is often required in biomechanically challenging environments such as in patients with osteoporotic bone, multilevel fusions, large corrections of sagittal imbalance, and spondylolisthesis. In general, due to the smaller footprint of the interbody device used, PLIF and TLIF are supplemented with pedicle screw fixation. Depending on the

patient's bone quality and the condition being treated, anterior interbody fusions (ALIF, OLIF, LLIF) may also require supplementary fixation.

Approach by Indication and Level(s) Requiring Interbody Fusion

The decision about which approach to use for interbody fusion is multifactorial and depends on the patient and the condition being treated, the relative advantages and disadvantages of each approach, and the training and experience of the treating surgeon. However based on the biomechanical and clinical literature available, some general recommendations can be made.

Degenerative Disc Disease

ALIF is the preferred approach for management of DDD. The approach avoids iatrogenic injury to the paraspinal muscles and psoas muscles and retraction of the neural elements. With ALIF the pain generator can be almost entirely removed, and the approach allows appropriate restoration of disc height and lordosis with a high fusion rate achieved. DDD typically affects L5–S1 and L4–L5. LLIF cannot be performed at L5–S1 and has a higher complication rate at L4–L5. TLIF and PLIF are options for treatment of DDD with good results published in the literature; however some ° of iatrogenic injury to the paraspinal muscles is expected, and it may be hard to restore disc height and lordosis appropriately. Both these factors likely lead to a higher rate of adjacent segment disease.

Isthmic Spondylolisthesis

Both ALIF and TLIF/PLIF are reasonable treatment options for isthmic spondylolisthesis. Again, this condition is usually seen in the caudal two lumbar levels, limiting the use of LLIF in this condition. ALIF achieves better restoration of disc height and lordosis than TLIF/PLIF.

Supplementary percutaneous pedicle screws of posterior spinal fusion are often required. Care must be taken when performing ALIF for a high-grade L5–S1 spondylolisthesis as L5 nerve injury can occur. Posterior decompression and a pedicle screw-based reduction can be performed prior to ALIF in this setting.

Degenerative Spondylolisthesis

Degenerative spondylolisthesis is often accompanied by some ° of lateral recess stenosis due to facet joint and ligamentum flavum hypertrophy; therefore a posterior approach (TLIF/PLIF) is attractive as it allows both direct and indirect neural decompression and fusion through the one approach. However anterior approaches (ALIF/LLIF) are able to better achieve restoration of disc height and lordosis and as a result achieve significant indirect neural decompression. Each patient should be assessed individually regarding the benefits and risks of an anterior versus posterior approach. If both significant correction of disc height/lordosis and direct neural decompression are required, then ALIF/LLIF can be combined with laminectomy.

Adult Spinal Deformity

ALIF, LLIF/ACR, and TLIF/PLIF are all reasonable options for interbody fusion in the setting of adult spinal deformity, and different approaches can be combined in the same operation if required. ASD is almost always characterized by some ° of sagittal imbalance, and ALIF/ACR are favored over LLIF without ALL release or TLIF/PLIF for correction of sagittal balance. Effective anterior interbody fusion may avoid the need for posterior three-column osteotomy to restore sagittal balance, a procedure associated with a high complication rate, often in elderly comorbid patients. Surgical treatment of ASD generally involves interbody and posterolateral fusion, often up into the thoracic spine. TLIF/PLIF avoids the need for a staged anterior-posterior procedure and allows direct decompression of any associated nerve compression. Each patient should be assessed individually regarding the relative merits of each approach.

Adjacent Segment Disease

There is a paucity of literature to define the best approach for treatment of adjacent segment

disease after lumbar fusion. Intuitively, choosing a different interbody approach for the treatment of adjacent segment disease will avoid scarring from the initial surgery and lower the rate of approach-related complications. For example, after a previous L5–S1 ALIF, adjacent segment disease at L4–L5 may be approached using LLIF or TLIF to avoid mobilization of the great vessels in an area of scarring. Conversely, after a previous L5–S1 TLIF, L4–L5 ALIF is a good choice as operating in an area of potential epidural scarring is avoided. Sagittal balance and segment lordosis should be assessed carefully preoperatively, as, if the original fusion was performed in kyphosis, more lordosis will be required when treating the adjacent level.

Pseudarthrosis

Pseudarthrosis after PSF or PLIF/TLIF is best managed with an ALIF as this avoids reinjury to the paraspinal muscles and operating through epidural scarring. Interbody cages previously placed posteriorly can be removed during the ALIF procedure. Previously placed pedicle screws may have to be removed prior to the ALIF if further restoration of disc height/lordosis is required. Pseudarthrosis after a previous ALIF or LLIF procedure is best managed with an open PSF. Re-exposure anteriorly in an attempt to remove the interbody device carries a high risk of vascular, bowel or ureteric injury.

L5–S1

ALIF is the preferred method of interbody fusion for DDD at L5–S1. It allows excellent release of the disc space, restoration of disc height and lordosis, and placement of a large footprint interbody device for fusion (Lee et al. 2016). Male patients who still plan to have children should be warned of the small risk of retrograde ejaculation, and sperm banking can be performed preoperatively or an alternate approach used if deemed an unacceptable risk by the patient. OLIF is also a reasonable option at this level. LLIF is not possible at L5–S1. Open PLIF and TLIF can be considered especially in the setting of associated lateral recess stenosis or recurrent disc herniation; however iatrogenic injury to the paraspinal muscles is of concern, and restoration of segmental lordosis may be limited. MI-TLIF has no ability to effectively restore segmental lordosis and may not even maintain preoperative lordosis and, therefore, is not a good option at L5–S1 where at least maintaining segmental lordosis is critical for overall lumbar lordosis. AxiaLIF similarly has limited to no ability to restore segmental lordosis.

ALIF can also be used effectively in the treatment of degenerative and low-grade lytic spondylolisthesis, usually combined with supplementary pedicle screw fixation. It can also be used in high-grade lytic spondylolisthesis although a posterior decompression may be required first to avoid L5 nerve injury as the slip is reduced. In these cases, open PLIF/TLIF also is a reasonable treatment option as direct decompression, reduction, and stabilization can all be performed through the one approach. Placement of the interbody cages anteriorly within the disc space, and compression across a posterior pedicle screw-rod construct can help achieve segmental lordosis.

L4–L5

ALIF or OLIF are excellent treatment options for DDD, as disc height and lordosis can be restored effectively and iatrogenic injury to the paraspinal muscles is avoided. The favorability of the vascular anatomy around the bifurcation will dictate which of these two approaches is preferable. LLIF is also a reasonable treatment option for DDD; however a higher rate of lumbar plexus injury is seen with LLIF at L4–L5 compared to higher lumbar levels. PLIF/TLIF can also be considered at L4–L5; however if significant restoration of segmental lordosis is required, ALIF, OLIF, and LLIF with or without ALL release are preferred.

Both anterior interbody approaches (ALIF, OLIF, and LLIF) and posterior interbody approaches (TLIF/LLIF) can also be used effectively to treat L4–L5 spondylolisthesis. If associated spinal stenosis requires direct decompression, then PLIF/TLIF may be preferred. If lordosis restoration is required, then anterior approaches are preferred.

L3–L4 and L2–L3

Exposure for ALIF becomes difficult above L4–L5, and in general, requirement for restoration of segmental lordosis is not as great in the higher lumbar levels. OLIF or LLIF and TLIF/PLIF are therefore good options for DDD and spondylolisthesis of the higher lumbar levels.

L1–L2 and T12–L1

ALIF is not feasible and TLIF/PLIF risk retraction injury to the conus, while OLIF/ATP risks injury to renal vessels and higher retroperitoneal structures. LLIF is, therefore, a good option at these levels.

Multilevel/Deformity Correction

A combination of anterior/lateral and posterior techniques can be used depending on the specific goals of the surgery. Anterior/lateral approaches are preferred if significant correction of sagittal alignment is required, but usually supplementary posterior instrumentation is required necessitating a staged procedure (either same day or delayed).

Conclusion

Interbody fusion is a well-established technique in the treatment of various lumbar pathologies including degenerative disc disease, spondylolisthesis, adult spinal deformity, adjacent segment disease, and pseudarthrosis. Multiple approaches to lumbar interbody fusion exist including ALIF, OLIF, LLIF, TLIF, PLIF, and AxiaLIF with biomechanical and clinical data supporting their use in various contexts. In deciding which approach for interbody fusion is most appropriate in each individual patient, the surgeon must take into account their own skill and experience, the pathology being treated, sagittal balance parameters, bone quality, associated neural compression, and any specific contraindications that may preclude a particular approach. With comprehensive preoperative assessment, appropriate surgical decision-making, and strict surgical technique, lumbar interbody fusion can be expected to yield good to excellent clinical outcomes in both the short-term and long-term with a low complication rate and a high rate of fusion.

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Stand-Alone Interbody Devices: Static Versus Dynamic

55

Ata G. Kasis

Contents

Abstract

Disc degeneration in the lumbar spine accounts for the vast majority of non-acute spine pathology. Progressive loss of disc height leads to a cascade of biomechanical and morphological changes locally in the functional spinal unit (FSU), which in turn may affect the adjacent segments. Loss of disc height may lead to neural compression, facet joint arthropathy, and progressive instability. Multilevel disc degeneration may affect the global spinal biomechanics and alignment resulting in degenerative kyphoscoliosis.

Treatment of degenerative disc disease (DDD) aims to remove the pain generator (degenerative disc), restore disc height and lordosis, and decompress the neural elements (directly or indirectly). The treatment should take into account the alignment (lordosis) of the FSU and also the global alignment of the spine.

Restoring the disc height is achieved by inserting an interbody device to restore the disc height and lordosis. The interbody device could be static which aims at fusing the spinal segment and stopping the painful movement of the disc and the facets, or dynamic, which maintains full or partial controlled movement of the spinal segment as close as possible to the physiological movement (close to the axis of rotation of the disc). The aim of this chapter is to explore the methods of restoring the disc height with either static or dynamic devices and also by combining the two methods depending on the stage of disc degeneration.

The ideal treatment of DDD is to match the pathology with the technology, taking

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into account patient needs, expectations, comorbidities, and the surgeon's skills and training.

Keywords

Degenerative disc · Interbody fusion · Disc replacement · Disc height · Static interbody · Dynamic interbody

Introduction

Degeneration of the lumbar intervertebral disc is multifactorial and includes genetic and environmental factors. Disc degeneration is associated with changes in the concentration and fragmentation of the matrix molecules (Singh et al. 2009). Also loss of water content within the nucleus leads to progressive changes in the viscoelastic behavior of the disc (Panagiotacopulos et al. 1987a, b). Similarly, changes in the ratio of collagen contents affect the biomechanical properties of the disc (Melrose and Ghosh 1988; Roberts et al. 1989). Loss of the structural properties of the disc leads to a change in the center of rotation of the disc and instantaneous centers of rotations change from a tightly clustered zone to a long random shape (Gertzbein et al. 1985). Progressive loss of disc height and lordosis leads to a cascade of changes of segmental and global spine biomechanics and alignment. The cascade starts with an internal disc disruption (IDD) and may progress to degenerative kyphoscoliosis affecting the global coronal and sagittal balance.

IDD is the first stage of disc degeneration, and patients usually present with discogenic back pain with a "normal" magnetic resonance imaging (MRI) scan. IDD is diagnosed by performing a provocative discogram, followed by a computed tomography (CT) discogram to confirm the diagnosis. Progression of disc degeneration leads to progressive loss of lumbar disc height resulting in neuroforaminal stenosis in addition to central canal stenosis. At this stage, patients usually present with back and/or leg pain. An MRI scan confirms the degeneration and neural compression. Further disc degeneration results in facet joint arthropathy and further neural compression. Fritzell et al. (2001) showed that surgical treatment for DDD is superior to nonsurgical treatment. The surgical group had a 33% reduction in back pain score and a 25% decrease in disability, measured using the Oswestry Disability Index (ODI), whereas the nonsurgical group had 7% and 6% reductions, respectively.

The art of treating DDD involves obtaining a precision diagnosis, then removal of the pain generator (degenerative disc and the sinuvertebral nerve), and restoration of the disc height, by replacing the disc with a device which either prohibits movement (fusion or static) or maintains it (dynamic or total disc replacement, TDR). Restoring the disc height indirectly decompresses the neuroforamen and the spinal canal. Complete removal of the disc is best achieved by an anterior approach to the lumbar or cervical spine as this allows complete removal of the nucleus pulposus and the cartilaginous end plate. The anterior approach to the spine allows a stand-alone device to be used to replace the disc without the necessary requirement of supplementation with posterior pedicle screws, which would be required if removal of the disc was performed using posterior (or transforaminal) lumbar interbody fusion, for example.

The indications and contraindications for TDR and fusion are discussed in this chapter, as well as the advantages and disadvantages.

Anterior Lumbar Interbody Fusion

Stand-alone anterior lumbar interbody fusion (ALIF) has been performed for many decades in the treatment of DDD with good outcomes (Greenough et al. 1994). It is performed through an anterior approach to the lumbar spine at L2-S1 levels. Anterior approach to the lumbar spine is most commonly performed through a retroperitoneal approach (left or right) to the lumbar spine or transperitoneal approach. Using an appropriate retractor that the surgeon is familiar with is crucial. An example of an anterior retractor is shown in Fig. 1.

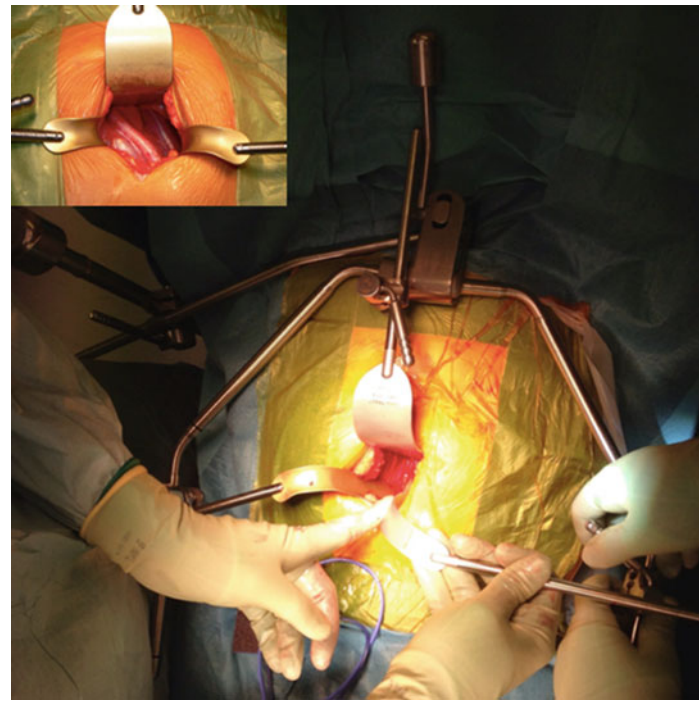

Fig. 1 The Integra Omni-Tract® retractor used during an anterior approach to the lumbar spine

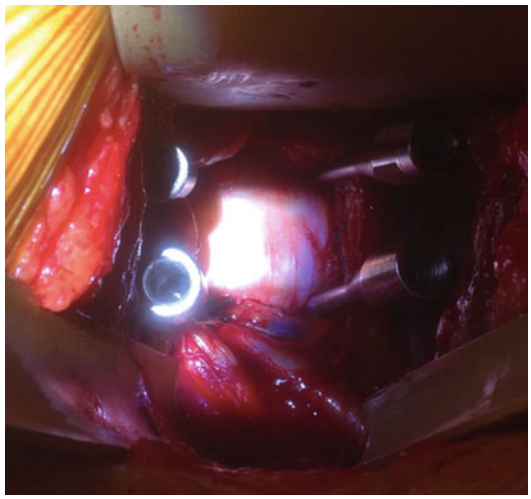

Fig. 2 Modified Steinman pins (OZ pins) are used to hold the vessels while performing the ALIF

Additional retractors are useful during ALIF procedures. In our units (Wansbeck General Hospital and Nuffield Hospital, Newcastle-upon-Tyne, UK), we have adopted the same technique used by Associate Professor Matthew Scott-Young in the Gold Coast Spine practice in Queensland, Australia. Steinman pin retractors are used to hold the vessels after mobilization while performing the ALIF (Fig. 2). Maintaining the anterior annulus and using it as a retractor allows a safe corridor to the disc space and is useful in protecting the surrounding soft tissues and the vessels. This is achieved by performing an H-shaped incision in the annulus and using a stay suture for each arm of the H-shape. This also allows closure of the annulus by suturing the two stay sutures together (Fig. 3).

Anterior approach allows a radical discectomy, removal of the cartilaginous end plate, and the insertion of the interbody cage which contains a bone graft. This allows restoration of the disc height and also restoration of the sagittal and coronal balance (Siepe et al. 2015). Fusion is performed by inserting a cage with or without a bone graft. Cages of various footprint sizes, height, and lordotic angles are available to permit restoration of the appropriate disc height and alignment. Sound interbody fusion is obtained by achieving stability, viability, and proximity of the bone graft to both end plates. This is achieved through meticulous surgical preparation of the end plates, internal fixation, and a good quality

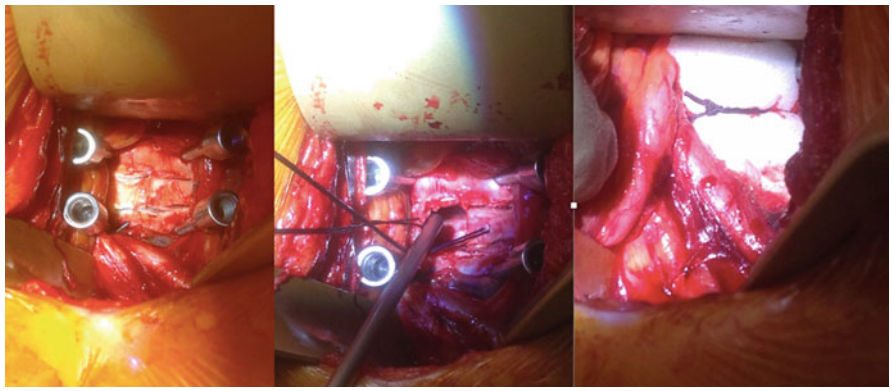

Fig. 3 H-shaped incision in the annulus and suturing the stay sutures to close the annulus on a Spongostan™ as a barrier between the plate and vessels at the end of the procedure

Fig. 4 Comparison between anterior cages (black) of different sizes (small, medium, and large) and a large cage inserted through a posterior approach (white)

bone graft. Inserting the interbody device through an anterior approach places the graft under compression with a large surface area for bony union and with a uniform load transfer. The footprint of an anterior cage is much larger than that of a cage inserted through a posterior approach and allows cross-sectional support on the peripheral ring apophysis (Fig. 4).

Bone graft choice is vital in achieving fusion. The choices for bone graft include autograft, allograft, and synthetic bone graft (Lechner et al. 2017). Combining bone grafts is also an option to improve the fusion rate. Bone morphogenetic protein (BMP-2) has become more popular in recent years (Burkus et al. 2002). Combining allograft (cancellous bone obtained from a femoral head) with BMP-2 INFUSE® is a technique used in Gold Coast Spine, which allows containment of an osteo-inductive bone graft (BMP-2) inside an osteo-conductive allograft-cage construct by drilling holes inside the allograft to host the BMP-2 (Fig. 5). We modified the technique in our unit by inserting a core of autograft (obtained through a vertebral biopsy 10 gauge needle from the iliac crest) inside the allograft. This was used due to the shortage of BMP-2 in Europe in 2016 (Fig. 6).

In our unit, we retrospectively reviewed and compared 50 consecutive patients who underwent ALIF using the bone graft technique described in Fig. 5 with 50 consecutive patient using the technique in Fig. 6. All patients had a CT scan at 5–6 months postoperatively, and the CT scans were reviewed by an independent consultant radiologist. The fusion rate in both groups was identical at 98%.

Fixation of a stand-alone cage is performed either through screws integrated into the cage or through the application of a plate with screws in both vertebral bodies. The aim of the fixation is to stabilize the cage especially in extension which might cause anterior kickout of the cage. Also, fixation limits rotation and flexion. When axial loading is applied through the cage/plate construct, the construct resists axial loading by virtue of its intrinsic cantilever beam with fixed moment arm characteristics.

Gerber et al. (2006) showed that a stand-alone anterior interbody device supplemented by anterior fixation using a plate carries similar stability to a stand-alone cage supplemented by posterior

Fig. 5 Combining BMP-2 and femoral head allograft

Fig. 6 Combining autograft with allograft

screw fixation. Both were more stable in all ranges of movement compared to a stand-alone cage with no fixation (Fig. 7).

Treating loss of disc height using the ALIF procedure obtains indirect decompression by increasing the neuroforaminal height and indirectly decompressing the neural elements (Fig. 8). This was proven by an MRI study by Choi et al. (2014).

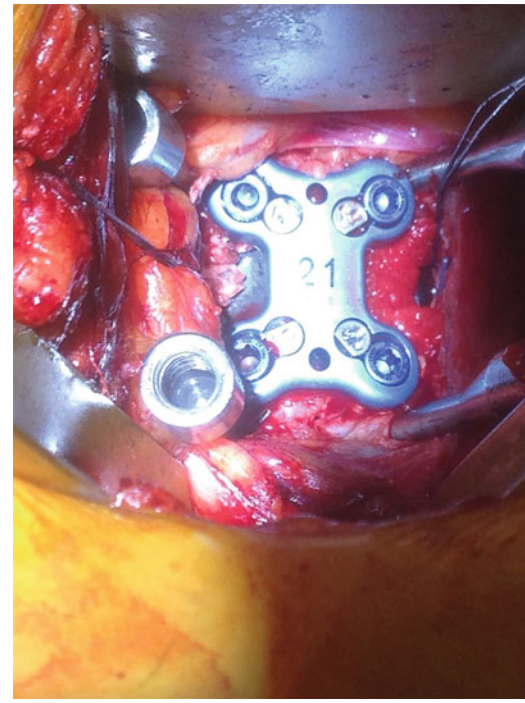

Fig. 7 AEGIS® (DePuy Synthes, Raynham, MA, USA) Anterior Lumbar Plate System. Example of anterior fixation using a plate and four screws with a cam locking mechanism

The indications for ALIF include symptomatic disc pathology which varies from IDD (Blumenthal et al. 1988), DDD, spondylolisthesis, failed prior posterior spine surgery (recurrence/residual disc prolapse (Choi et al. 2005; Vishteh and Dickman 2001) and non-union of posterior fusion (Lee et al. 2006)), and spine deformity. In the absence of spinal instability and deformity, disc degeneration could be treated with stand-alone ALIF. We recommend obtaining a standing lateral and flexion/extension radiograph of the lumbar spine to rule out instability before considering an ALIF procedure (Fig. 9).

Specific complications following an ALIF procedure could be approach-related complications (vascular injury (Fantini et al. 2007; Rajaraman et al. 1999), bowel and ureteric injury, and retrograde ejaculation) or long-term complications such as non-union, metalware complications, and adjacent segment degeneration. Venous thromboembolic (VTE) events are a recognized

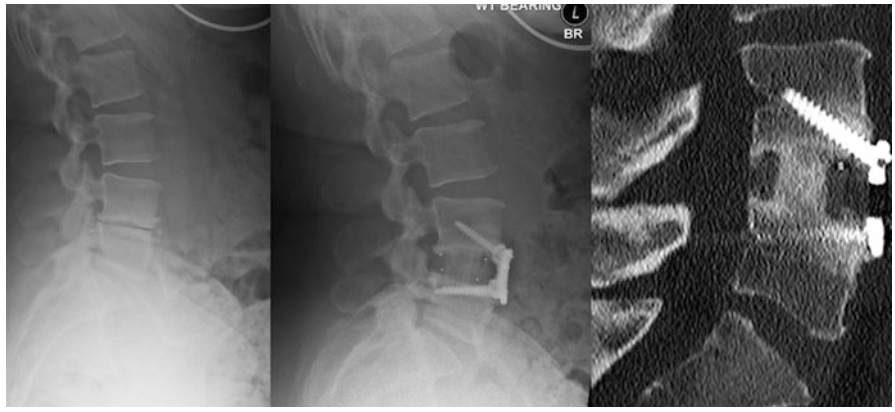

Fig. 8 An example of indirect neuroforaminal decompression obtained by restoring the disc height and a CT scan showing solid fusion at 4 months

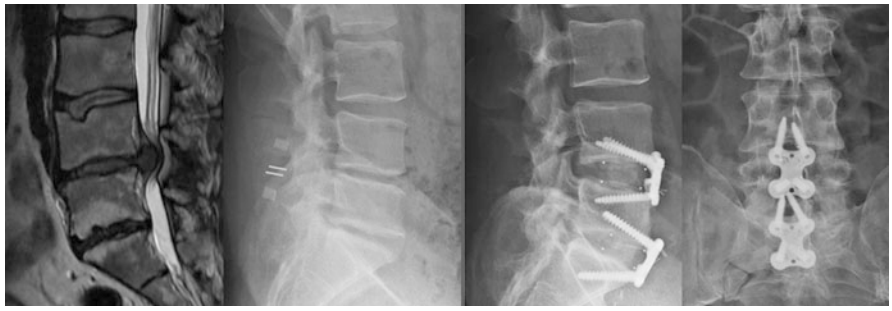

Fig. 9 An example of treating failed posterior surgery using ALIF. A 45-year-old patient who had two-level discectomy at L4/5 and L5/S1 with the insertion of an interspinous spacer. Patient had a two-level ALIF to remove the recurrent disc at L4/5, indirectly decompressing the foramen of L5/S1 and restoring the lordosis

complication after abdominal surgery, and ALIF is no exception since it is done through a mini-laparotomy approach with vessel mobilization. Our unit has adopted a thromboprophylactic regime utilizing physical and chemical prophylactic techniques. This entails TED stockings and compressive calf pumps during surgery and the 24 hours following. The calf pumps are then removed and the TED stockings maintained on the patient for 3 weeks until outpatient review. Postoperatively we use low molecular weight heparin (tinzaparin) 4500 units subcutaneously on the evening before surgery and then daily for 3 to 5 days (while an inpatient) and then Aspirin orally 150 mg daily for 4 weeks after surgery with proton pump inhibitor (PPI) cover. Our unit conducted a study on 160 consecutive patients who underwent ALIF by reviewing their records and also by contacting the patients. There were no symptomatic VTE events in any of the 160 patients. There was no incidence of wound hematomas or bleeding and no symptomatic retroperitoneal hematomas requiring intervention.

Graft migration is often related to the surgical technique and is a difficult management problem in that it involves revision anterior surgery. This is challenging in inexperienced hands and associated with high complication rates. Ideally a CT angiogram and insertion of a ureteric stent should be performed before revision of an anterior approach. Non-union due to patient factors, poor bone quality, or lack of meticulous surgical

preparation is also challenging and could be treated through a revision anterior approach or through a posterior approach.

Failure of an ALIF procedure is often due to failure of indication and/or failure of technique. Volume performance threshold and fellowship training is of great importance in performing anterior approach to the lumbar spine in order to reduce the complication rate and improve patient outcomes (Regan et al. 2006).

The aim of ALIF in addition to restoring the disc height is to fuse the spinal segment and eliminate any movement between the two vertebrae. This may change the biomechanics of the adjacent segments resulting in a theoretical increase in the load of the adjacent segment and accelerated degeneration. The effects of post-fusion biomechanics upon adjacent segment disease (ASD) and the role of different approaches remain controversial.

Tang and Meng (2011) showed that restoring disc space height and spinal segmental lordosis is important for preventing ASD by using an anterior cage with appropriate height and lordotic angle. Horsting et al. (2012) followed up 25 patients (minimum 10 year follow-up) who underwent ALIF and posterior fixation for chronic low back pain. The incidence of ASD was 12% above and 20% below the index level. There was significant improvement in patient pain and function up to 2 years with some deterioration at 4 years which was stable at 10 years, but this was not related to the ASD. Kanamori et al. (2012) followed up 20 patients for a minimum of 10 years who had ALIF procedure for degenerative spondylolisthesis and showed progressive ASD. Choi et al. (2014) followed up 49 patients (minimum 10 years) who underwent ALIF for isthmic spondylolisthesis with CT and MRI at 5 and 10 years. The incidence of radiographic ASD was 38.8%, symptomatic ASD was 12.2%, and 4.1% of the patients underwent revision surgery. Also, patients with ASD had more advanced pre-existing facet degeneration compared to those without ASD ($p = 0.01$). They concluded that radiographic ASD is common, while revision for symptomatic ASD is rare, with a risk factor being pre-existing facet joint arthropathy. However, despite the reported incidence of ASD after ALIF procedures, it is reported to be comparatively much less than the incidence of ASD following posterior surgery (Tsuji et al. 2016).

Lumbar TDR

Preventing (or reducing) the incidence of ASD is challenging and has been a subject of debate between surgeons aiming at neural decompression and surgeons aiming at spinal reconstruction. This debate goes back to ASD following knee and hip fusion, which led to the innovation of total hip and total knee replacements and later, ankle and other joint replacements. Similarly in spine, the concept of movement preservation was first introduced in 1966 by Fernström (1966); however the long-term results were disappointing. It was not until 1984 that Schellnack and Buttner-Janz updated this concept by introducing the SB Charité total disc replacement (Buttner-Janz and Schellnack 1990; Buttner-Janz et al. 1987, 1989). Since then the TDR has undergone various modifications in its biomechanics and design.

Based on its biomechanics, the lumbar TDR is classified either as an unconstrained device (Charité III® and In-motion®), as a semi-constrained device (Prodisc®, Maverick®, and Flexicore®), or as a constrained device (the visco-elastic lumbar disc prosthesis-elastic spine pad, LP-ESP®). A mobile core prosthesis (In-motion®) allows uncoupled rotation/translation, while a fixed core prosthesis allows coupled rotation/translation (Fig. 10).

The learning curve of performing lumbar TDR is a steeper curve than that of ALIF (Regan et al. 2006). Inserting the TDR in the midline in the coronal plane is essential, especially when using an unconstrained device. In the sagittal plane, the center of rotation should be at the middle of the end plate or posterior to it (1–3 mm). Correct patient selection for TDR is vital. The condition of the facet joints should be investigated before considering TDR and the type of TDR used. Advanced facet joint arthropathy is a contraindication for performing TDR. Similarly, instability is a contraindication for using unconstrained

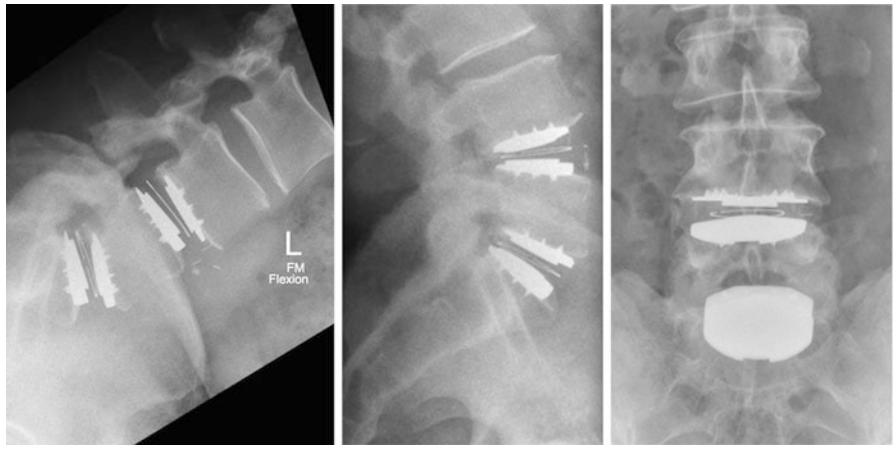

Fig. 10 An example of two-level In-motion TDR for a patient with two-level DDD. (Courtesy of Associate Professor Scott-Young, Gold Coast Spine, Queensland)

Fig. 11 Using the Charité retractor in the intervertebral space to clear the posterior part of the nucleus and the disc allowing assessment of the disc space

TDR. One key factor when performing lumbar TDR is the way the posterior annulus is handled. Ensuring that the posterior annulus is mobile and assessing the symmetry of disc movement is important during preparation of the disc space. This can be achieved by using a Charité or David retractor, for example, which allows symmetrical distraction of both end plates, and the surgeon can then assess the movement of the disc and its suitability for a TDR (Fig. 11).

Great care should be taken when performing multilevel lumbar TDR as it is essential to obtain near perfect alignment in the coronal and sagittal planes. Eccentric positioning of the TDR leads to

suboptimal biomechanical restoration and increased incidence of subsidence and may increase the wear rate. The surgeon should strive to insert the prosthesis with the largest footprint possible to reduce the risk of subsidence. Scott-Young et al. (2012) presented their results, reporting good outcomes of two-level TDR with a minimum follow-up of 4 years.

Lumbar TDR maintains movements of the spinal segment allowing controlled dynamic stability while maintaining near normal disc biomechanics. Maintaining near physiological range of movement reduces the stress on the adjacent segments, and this in turn reduces (and may prevent) ASD and the reoperation rate. Scott-Young et al. (2016) showed a significant reduction of ASD following TDR. In a systematic review, Hiratzka et al. (2015) demonstrated a relative risk of reoperation of 1.7 in the fusion group compared with lumbar TDR, although this risk decreased to 1.1 at 5-year follow-up.

Lumbar TDR is indicated in patients with proven discogenic back pain due to IDD or DDD (with or without disc herniation). Contraindications to lumbar TDR include infection, osteoporosis, scoliosis greater than 20°, spondylolisthesis, failed back surgery syndrome, inflammatory arthropathy, advanced facet joint degeneration, and pregnancy. Adherence to the indication is essential for a good outcome after TDR. Bertagnoli and Kumar (2002) defined criteria for TDR enabling classification of patients as prime, good, borderline, and poor candidates for the procedure. Holt et al. (2007) showed that the incidence of perioperative and postoperative complications for lumbar TDR was similar to that of ALIF, and they recommended that vigilance is necessary with respect to patient indications, training, and correct surgical technique to maintain TDR complications at the levels experienced in the investigational device exemption (IDE) study.

There is robust evidence from class one Food and Drug Administration (FDA) studies of good results achieved using TDR to treat DDD in improvement of both leg and back pain (Delamarter et al. 2011; Gornet et al. 2011; Zigler et al. 2007; Blumenthal et al. 2005). Jacobs et al. (2012) in a systematic literature review found that the TDR had a statistically significant clinical improvement over other methods of treating DDD including fusion; however, they suggested that the differences in clinical improvement were not beyond generally accepted boundaries for clinical relevance.

Combining TDR and Fusion (the Lumbar Hybrid Procedure)

Surgical management of patients presenting with multilevel DDD in various stages of degeneration is challenging. Fusion of multilevel segments increases the risk of ASD (Hiratzka et al. 2015). A good outcome is achieved by matching the technology with the pathology. ALIF could be performed at the symptomatic level if there is significant loss of disc height, facet joint arthropathy, or instability. This allows stabilization of the level, restoring the disc height and treating the facet joint arthropathy. In the level with early stages of DDD, TDR could be performed to maintain movement and reduce the stress on the adjacent segment (Fig. 12).

Aunoble et al. (2010) reported on 42 patients who underwent hybrid lumbar reconstruction with a median follow-up of 26.3 months. The mean improvement of ODI was 53% at 2 years. The visual analogue score improvement for the back pain was 64.6%. Scott-Young et al. (2017) reported that improvements in both back and leg pain and function can be achieved using the hybrid lumbar reconstructive technique and the improvements were maintained at 96 months postoperatively. They reported the largest series in the literature (617 patients) and showed that both statistically and clinically significant ($p < 0.005$) reductions were seen in back and leg pain, which were sustained for at least 8 years post-surgery. In addition, significant improvements ($p < 0.001$) in self-rated disability and function were also maintained for at least 8 years. Patient satisfaction was rated as good or excellent in >90% of cases. Hoff et al. (2016) showed good results of the hybrid procedure in 23 patients in a prospective randomized trial

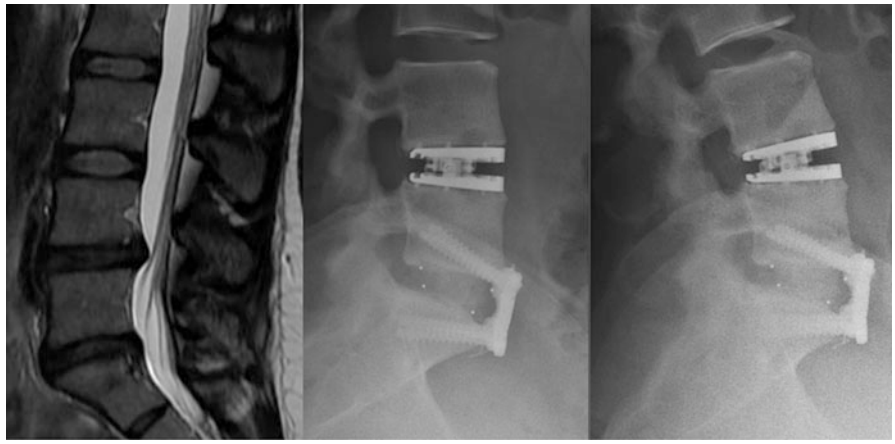

Fig. 12 A 47-year-old patient with two-level DDD, disc prolapse at L4/5 (mobile level) and L5/S1 DDD with facet joint arthropathy who underwent TDR at L4/5 and ALIF at L5/S1

compared with two-level transforaminal lumbar interbody fusion. Yue and Bertagnoli (2006) also showed good results using the hybrid procedure. Chen et al. (2016) showed that hybrid fusion is a valid and viable alternative to ALIF, with at least equal if not better clinical outcomes in terms of survivorship, back pain, and disability scores.

Conclusions

Obtaining a precision diagnosis is paramount to good clinical outcomes in spine surgery. Both ALIF and TDR are valid options in treating DDD; however strict criteria should be met before considering TDR. These include patient factors, surgical training, and also the degree of degeneration. Matching the technology with the pathology is where the art of spine surgery lies.

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Allograft Use in Modern Spinal Surgery

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Matthew N. Scott-Young and Mario G. T. Zotti

Contents

Abstract

Allograft use continues to be important in modern spinal surgery due to its abundant supply, ability to customize to shape, and avoidance of donor site morbidity. However, surgeons must be aware of the limitations of the grafts when used in isolation and how to obtain bony healing. These limitations include subsidence from altered mechanical properties, a lack of osteoinduction and risk of

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immunogenicity. Optimal healing can be achieved through optimizing the host, selecting the correct graft for the bony environment where the healing is required, and optimizing local graft site biology and stability. Tissue engineering in arthrodesis through obtaining a stable mechanical construct, use of an appropriate structural allograft, and placement of a biologic component (e.g., BMP-2) has shown to be a reliable means to obtain union and achieved satisfactory outcomes. Novel biological agents show promise and will continue to mature in their clinical application.

Keywords

Allograft · Bone banking · Corticocancellous · Femoral ring · Demineralized bone matrix · Bone morphogenetic protein (BMP) · Union · Arthrodesis · Outcomes

Introduction

It is estimated that the number of people aged 65 and older globally will grow from an estimated 524 million in 2010 to nearly 1.5 billion in 2050 with most of the increase occurring in developed countries. Many individuals will suffer from chronic conditions such as hypertension, hypercholesterolemia, osteoarthritis, diabetes, heart disease, cancer, dementia, and congestive cardiac failure. It is thought that heart disease, stroke, and cancer will be the leading chronic conditions that have the greatest impact on the ageing population. However, also to be considered is that a significant number of these individuals will require oncologic surgery, corrective surgery for trauma, revision arthroplasty surgery, and spinal reconstructive surgery which all require bone grafting. At present, it is estimated that there are over two million bone graft procedures performed in the world in a given year. Bone grafting is indeed the second most frequent tissue transplantation worldwide, after blood transfusion. It is estimated that the global bone graft and substitute market accounts for $3.02 billion in 2014 and, it is expected to rise in excess of $4 billion by 2022, growing at a rate of approximately 5% per year.

The use of bone graft and substitutes in the spinal market has increased significantly in conjunction with the aging population and the demand for better standards of health care outcomes. North America is sharing the largest market revenue but Asia-Pacific accounts for the highest growth rate led by the vast ageing population. As a result of the change in demographics, there has been a surge in bone- and joint-related disorders and diseases. Because of this demand, a wide range of products have become available in the market place. These include allograft-based bone graft substitutes, factor-based bone graft substitutes, cell-based bone graft substitutes, ceramic-based bone graft substitutes, and polymer bone graft substitutes. Combining this with the fact that there are limitations associated with autograft, the use of bone graft substitutes has dramatically increased over the last decade. This is due to their ease of use and handling, improved safety profiles, intraoperative cost and time advantages, and adaptability to a variety of clinical challenges.

There are currently over 200 different bone grafts available for surgeons to choose from. This number continues to grow year on year; representing an ever-changing overabundance of options with respect to bone grafting options. Currently, over 90% of reconstructive spinal procedures still utilize autograft and allograft tissue. The current *gold standard* is autogenously sourced bone harvested for reconstructive surgery from the patient. This usually requires an additional surgery from the donor site (usually the pelvis) and has complications such as inflammation, blood loss, infection, and chronic site pain. However, the autogenous bone graft possesses all the necessary characteristics for new bone growth: osteoconductivity, osteogenicity, and osteoinductivity. The ideal synthetic bone graft substitute material would be osteoinductive, osteoconductive, able to bear weight, be resorbable and biologically acceptable, and have a proven safety profile with no adverse local or systemic effects. As yet, the perfect material does not exist, although many materials address one or more of these features.

Basic Process of Bone Formation and Union

In order to achieve solid arthrodesis in the spine, it is a prerequisite to understand the process of bone formation and healing.

Bone is a regenerative organ and maintains this capability in adult life. There is periodic remodeling of the skeleton throughout life and this unique quality allows for fractures to heal and bone grafts to incorporate. The complex and coordinated pathway of bone healing requires an understanding of biomechanical principles, physiological mechanisms, molecular factors, and genetic expression that involves spatial and temporal events. This provides solutions to improve fracture healing or bone grafting and subsequent regeneration. Much of the basic science related to bony union comes from the study of extremity fractures and, as such, the following section talks of union in a spinal (e.g., vertebral body fracture or interbody arthrodesis) as well as an extremity fracture context.

During bone repair, the osteogenic process (under the influence of bone-derived bioactive factors) commences after the inflammatory phase and is initiated by precursor cells from the periosteum adjacent to the fracture site. This generates hard callus by intramembranous bone formation. An autologous bone graft or bone substitute is often required to assist in the healing of an extensive traumatic or postsurgical bone defect and of osseous congenital deformities. The majority of bone formation, however, is by endochondral ossification of the soft callus that appears after infiltrated mesenchyme cells are induced to chondrogenesis. This improved understanding of repair and regeneration has helped with the development of orthopedic tissue engineering.

Understanding the complicated process of bone healing is essential knowledge for a spine surgeon. The primary goal of achieving a successful fusion requires extensive knowledge of bone generation and union and implies a thorough understanding of molecular, physiological, and biomechanical principles. Selection of graft material depends on its properties, the biological status of the patient, comorbidities, mechanical environment, supplemental fixation, availability, cost, efficacy, and the patient's expectations. Inserting materials expecting union or arthrodesis without appreciation of what the role of that material is in bony healing in that particular patient will likely lead to suboptimal results.

Selection of a graft is complex and the three important biological prerequisites need to be considered: osteogenicity, osteoinduction, and osteoconduction. This triangular shaped complex has been extensively studied; however, a fourth element (see Fig. 1 below) should be given the same recognition in terms of significance: mechanical stability. Mechanical stability is a critical factor for bone healing. Progressive maturation of the callus from woven to lamellar bone requires stability. The AO group popularized open reduction and internal fixation techniques to improve union rates. They recognized the role parameters such as fracture rigidity, fracture contact and gap healing, inter-fragmentary strain, and significant role of the soft tissue envelope and vascular environment at the fracture site and coined "The Diamond Concept" (see Fig. 1) (Giannoudis et al. 2007).

To understand new concepts and strategies to enhance the healing of a spinal arthrodesis, a basic summary of the current knowledge on the repair process is required. There are several pathways in which bone can repair, and these are discussed below. One needs to consider that achieving a spinal arthrodesis is a form of tissue regeneration and if fibrous scars form instead then a pseudoarthrosis has developed.

Direct Bony Healing

Direct healing does not commonly occur in the natural process of bone healing. It refers to a direct attempt of the cortical cells to reestablish structural continuity, which requires anatomical reduction of the fragment ends without any gap formation and a stable fixation. This is the primary goal of open reduction and internal fixation surgery. It is also an important type of healing process that occurs when structural allografts are placed under compression in the anterior spine.

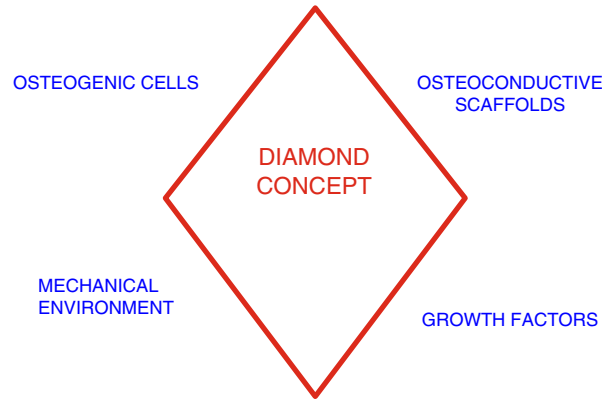

Fig. 1 The diamond concept of bony healing. Reprinted with permission from Fracture healing: The diamond concept, by P. V. Giannoudis; *Injury* 2007 (supp 4; S3–6). (Copyright 2007 by Elsevier)

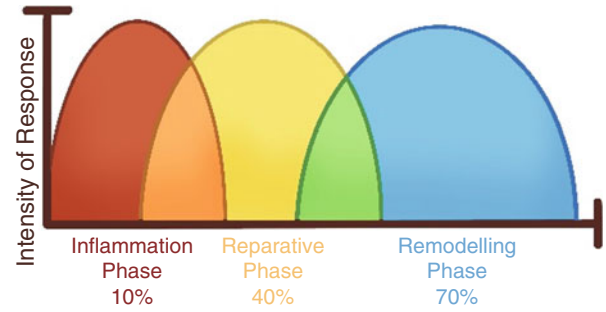

Fig. 2 The overlapping phases of bone healing and relative intensities of response over different time points with display of the relative contribution of the three phases to the overall time taken to heal

Table 1 Phases of bone formation

The acute inflammatory response	Necrotic debris stimulates release of signaling molecules
MSC recruitment	Multipotent mesenchymal stem cells are recruited and transformation to osteoblasts occurs
Vasculogenesis and neoangiogenesis	Stimulation of osteoblast and osteoclast function
Cartilage reabsorption and mineralization	Bone forms around the new scaffold
Remodeling	Continual process occurs for years

Direct bone healing can now occur by direct remodeling of lamellar bone, the Haversian canals, and blood vessels. Complete healing takes several months to a year and progresses through overlapping phases (see Fig. 2 and Table 1). Although time honored, the old dogmatic mnemonic of "coapt coplanar large cross-sectional cancellous surfaces under compression" still holds wisdom.

Contact Healing

To directly reestablish an anatomically correct and biomechanically competent lamellar bone structure, primary healing can occur through contact or gap healing. If bone on one side of the interface is to unite with bone on the other side of the interface there must be anatomic restoration of the bone fragment surfaces and rigid fixation. This will result in a favorable biomechanical environment that will reduce the inter-fragmentary strain (Shapiro 1988). With gaps less than 0.01 mm, the inter-fragmentary strain is less than 2%, thus the vertebral bodies will unite by contact healing (Rahn 2002). Cutting cones consisting of osteoclasts cross the fracture at a rate of 50–100 μm/day. Osteoblasts then occupy the cavity at the end of the cutting cones (Einhorn 2005). This results in simultaneous generation of a bony union and

the restoration of Haversian systems formed in an axial direction (Bais et al. 2009). The reestablished Haversian systems allow for penetration of blood vessels carrying osteoblastic precursors and, with that, complete remodeling ensues in an axial direction (Einhorn 2005).

Gap Healing

If conditions are stable, an anatomical reduction is achieved and the gap is less than 800 μm to 1 mm, gap healing can occur. This differs from contact healing in that the bony union and Haversian remodeling do not occur simultaneously. In this process, the fracture site is primarily filled by lamellar bone oriented perpendicular to the long axis (Dimitriou et al. 2005). This is then replaced by longitudinal revascularized osteons carrying undifferentiated multipotent mesenchyme stem cells (MSC). These MSC differentiate into osteoblasts and produce lamellar bone on each surface of the gap (Shapiro 1988). This lamellar bone, however, is laid down perpendicular to the long axis and is mechanically weak. A secondary remodeling resembling the contact-healing cascade with cutting cones now takes place.

Indirect Fracture Healing

Secondary or indirect fracture healing is the most common form of fracture healing. It involves intramembranous and endochondral ossification leading to callus formation and bone healing (Gerstenfeld et al. 2006). Anatomical reduction or rigid stability is not required. Micro-motion and load bearing enhance the healing process. Excessive load and motion can result in delayed healing or even non-union (Green et al. 2005). Secondary bone healing occurs in the fracture site in non-operative fracture treatment and in operative treatments such as intramedullary nailing, external fixation, or internal fixation of comminuted fractures.

The Acute Inflammatory Response

When a fracture occurs, there is formation of a hematoma and an associated inflammatory response. This consists of cells from both peripheral and intramedullary blood as well as bone marrow cells. The injury initiates an inflammatory response, causing the hematoma to coagulate in between and around the fracture ends as well as within the medulla, forming a template for callus formation (Gerstenfeld et al. 2003). Many local and systemic regulatory factors, hormones, and cytokines work in conjunction with the extracellular osteoconductive matrix producing various cell types and are the first step in the repair process (Gerstenfeld et al. 2003). The acute inflammatory response peaks within the first 24 h and is complete after 7 days. This fracture hematoma produces signaling molecules such as tumor necrosis factor-α (TNF-α); interleukin-1 (IL-1), IL-6, IL-11, and IL-18; fibroblastic growth factor (FGF); insulin-like growth factor(IGF); vascular endothelial growth factor (VEGF); and transforming growth factor-beta (TGFB) that induce a cascade of cellular events that initiate healing (Gerstenfeld et al. 2003). These factors recruit inflammatory cells and promote angiogenesis (Sfeir et al. 2005). The TNF-α concentration has been shown to peak at 24 h and to return to baseline within 72 h post trauma. These factors are secreted by macrophages, MSCs, platelets, chondrocytes, osteoblasts, and other inflammatory cells, and it is believed to mediate an effect by inducing secondary inflammatory signals and act as a chemotactic agent to recruit the necessary cells (Lee and Lorenzo 2006). Differentiation of MSCs down the osteoblastic line is induced by TNF-α. These effects are mediated by activation of the two receptors TNFR1 and TNFR2, which are expressed on both osteoblasts and osteoclasts (Balga et al. 2006).

Interleukins, IL-1 and IL-6, are believed to be most important for fracture healing. There is an overlapping biphasic mode of expression of IL-6 and TNF-α. IL-1 is produced by macrophages in the acute phase of inflammation and induces production of IL-6 in osteoblasts, facilitating the production of the primary cartilaginous callus and angiogenesis at the injured site. IL-6 is produced during the acute phase and stimulates angiogenesis, VEGF production, and the differentiation of osteoblasts and osteoclasts (Lee et al. 2006).

MSC Recruitment

Bone regeneration requires mesenchyme stem cells (MSCs) to be recruited, proliferate, and differentiate into osteogenic cells. MSCs are derived from surrounding soft tissues and bone marrow; there is evidence that a systemic recruitment of circulating MSCs to the injured site might be of great importance for an optimal healing response (Granero-Molto et al. 2009). Which molecular events mediate this recruitment is still under debate. BMP-2 has an important role in this recruitment, but other BMPs such as BMP-7 may play a more important role in the recruitment of progenitor cells (Rahn 2002).

Vasculogenesis and Angiogenesis

There is a greater understanding of the molecular mechanisms controlling callus vascularization. Bony healing requires a blood supply to the healing site, and revascularization is essential. New blood vessels form most commonly, by angiogenesis as well as by vasculogenesis (endothelial progenitor cells, EGC). The vascularization process is mainly regulated by two molecular pathways, an angiopoietin-dependent pathway, and a vascular endothelial growth factor (VEGF)-dependent pathway (Tsiridis et al. 2007). The primarily angiopoetin-1 and 2 are vascular morphogenetic proteins. They are induced early in the healing cascade, promoting vascular in-growth from existing vessels in the periosteal tissues. The VEGF pathway is considered to be the key regulator of vascular regeneration. High levels of VEGF are expressed by chondrocytes and osteoblasts, promoting the penetration of blood vessels and transforming the avascular cartilaginous matrix into a vascularized osseous tissue. VEGF plays a critical role in the neoangiogenesis and revascularization by promoting vasculogenesis (aggregation and proliferation of EGC) and angiogenesis (growth of new vessels from already existing ones). It has been observed that blocking VEGF signaling with antibodies demonstrates that intramembranous bone formation during distraction osteogenesis is dependent on VEGF signaling. The blocking of VEGF-receptors inhibits vascular in-growth and delays or disrupts the regenerative process (Keramaris et al. 2008). Other factors promote neoangiogenesis and vasculogenesis such as the synergistic interactions of the BMPs with VEGF.

Cartilage Resorption and Mineralization

Bony healing is a combination of cellular proliferation and differentiation, increasing cellular volume, and increasing matrix deposition. As fracture callus chondrocytes proliferate, they become hypertrophic and the extracellular matrix becomes calcified (Breur et al. 1991). The primary soft cartilaginous callus needs to be resorbed and replaced by a hard bony callus. Resorption of this mineralized cartilage is initiated by osteoprotegerin (OPG) and TNF-α, macrophage colony stimulating factor (M-CSF), and receptor activator of nuclear kappa factor ligand (RANKL) also known as the RANKL-OPG pathway (Gerstenfeld et al. 2003). These molecules mediate and recruit bone cells and osteoclasts to form woven bone. TNF-α further promotes the recruitment of MSCs and has an important role in initiating chondrocyte apoptosis. The mitochondria accumulate calcium-containing granules, which are transported into the extracellular matrix where they precipitate with phosphate. This becomes a nidus for the formation of apatite crystals. The hard callus formation progresses and the calcified cartilage is replaced with woven bone, the callus becomes more solid and mechanically rigid.

Remodeling of Bone

Hard callus provides biomechanical stability but does not fully restore the biomechanical properties of normal bone. The fracture-healing cascade initiates a second resorptive phase, remodeling hard callus into a lamellar bone structure with a central medullary cavity. This phase is characterized by temporal changes in signaling molecules. IL-1 and TNF-α show high expression levels during this stage, as opposed to most members of the TGF-β family, which has diminished in expression (Ai-Aql et al. 2008). BMP2 is also involved in this phase with reasonably high expression levels (Marsell and Einhorn 2009).

The remodeling process occurs through a combination of resorption by osteoclasts, and lamellar

bone deposition by osteoblasts. The remodeling may take years to be completed to achieve a fully regenerated bone structure. There are many factors which affect the speed and efficiency of the healing process, such as the production of electrical polarity created when pressure is applied in a crystalline environment. This in turn affects the bone modeling. The creation of one electropositive convex surface, and one electronegative concave surface, caused by axial loading, activates osteoclastic and osteoblastic activity. The external callus is gradually replaced by a lamellar bone structure, whereas the internal callus remodeling reestablishes the medullary cavity.

The process of bone healing involves osteogenesis, osteoinduction, and osteoconduction. For bone remodeling to be successful, an adequate blood supply and a gradual increase in mechanical stability is crucial (Gerstenfeld et al. 2003). This is clearly demonstrated in cases where neither is achieved, resulting in the development of an atrophic fibrous non-union. However, in cases where there is good vascularity but unstable fixation, the healing process progresses to form a cartilaginous callus resulting in a hypertrophic non-union or a pseudoarthrosis.

Bone Graft Classification System

Autologous bone represents the *gold standard* source whenever a skeletal deficiency needs to be grafted. It is osteoconductive, osteoinductive, and osteogenic. It has the passive ability of a scaffold to be progressively substituted by viable bone; the capacity to stimulate the osteoblastic differentiation of local and systemic mesenchymal stem cells through specific growth factors, such as bone morphogenetic proteins (BMPs); and the ability to form new bone from the living osteoblasts and MSCs present within the graft material.

Autograft is non-immunogenic and cannot transmit infectious agents unless contaminated during donor site harvesting. It represents the first choice in several procedures such as fracture non-union surgery, spinal fusion, and orthopedic reconstructive surgery (Kannan et al. 2015). Autografts provide the best replacement tissue to a defect site. However, autografts from the donor site require an additional surgery. This can result in complications such as inflammation, lengthening of surgical time, infection, blood loss, hematoma formation, and chronic local pain, especially in older patients who are common candidates for primary and revision spine surgery. This donor-site morbidity occurs in approximately 20% of all cases (Perry 1999). In addition, the volumetric supply limitations reduce its desirability. The quality of the bone in the elderly as a source for grafting is questionable in many cases and the osteoinductive potential may be variable in patients.

As a consequence of the donor issues, market forces have developed scaffolds as bone graft **extenders** (or expanders), which are mixed with the bone graft to augment its volume; bone graft **substitutes**, that may be used alone in place of the bone graft; and bone graft **enhancers**, that are adjuvant therapies aimed at improving the biological performance of the bone grafts by adding cells or growth factors.

There are several categories of bone graft substitutes encompassing varied materials, material sources, and origin (natural vs. synthetic). A bone graft classification system has been developed that describes these groups based on their material makeup (Laurencin and Khan 2013) (see Table 2).

A brief discussion on each group is appropriate on the basis it will provide a basic understanding of each group, advantages and disadvantages, as well as knowledge of when, where, and which product to apply to achieve stability and, ultimately, a solid fusion mass.

Allograft-Based Grafts

Allograft bone refers to bone that is harvested from cadavers and donors. Initially, it was primarily used as a substitute for autografts in large defect sites. Its use has expanded as a result of the absence of autograft donor morbidity, the expansion of bone grafting procedures, and the evolution of bone banks. The coordination of bone bank regulations resulted in donor

Table 2 Different classes of bone graft substitutes

Class	Description
Allograft-based	Allograft bone used alone or with other materials
Factor-based	Natural and recombinant growth factors used alone or in combination with other materials
Cell-based	Cells used to generate new tissue alone or seeded into a support matrix
Ceramic-based	Includes calcium phosphate, calcium sulfate, and bioactive glasses used alone or in combination
Polymer-based	Degradable and nondegradable polymers used alone or combined

screening, tissue processing techniques, and reduction in the risk of disease transmission. This resulted in the acceptance of allographic tissues as a source of grafting and an emergence of allographic materials. A variety of allograft forms are available, including osteochondral, cortical, cancellous, and processed bone derivatives such as demineralized bone matrix (DBM). The processing of allograft ensures there are no viable cells, and consequently, these grafts themselves are not osteogenic. Allograft is osteoconductive and, sometimes, mildly osteoinductive.

Factor-Based Grafts

Growth factors have been extensively researched and have been proven to regulate cellular activity. Proteins and/or growth factors bind to cell receptor sites and stimulate the transcription of messenger RNA that leads to formation of proteins that regulate intra- and extracellular homeostasis. These factors include platelet-derived growth factors (PDGFs), IL-1, IL-3, IL-6, macrophage colony-stimulating factors, the transforming growth factor-β family (TGF-β), BMPs, insulin-like growth factors (IGFs), and vascular endothelial growth factor (VEGF). These factors act in a coordinated manner and influence inflammation, cellular migration and differentiation, angiogenesis, and cellular proliferation. They have both paracrine and autocrine capabilities. Recent approaches have focused on using a combination of factors so as to evoke a synergistic response in the healing of non-union fractures (Kempen et al. 2010). These combinations are delivered in a manner such that they artificially recreate the native microenvironment of healing bone. The use of single factors requires supraphysiological doses to obtain desirable effects. Such high dosages have led to complications such as ectopic bone, osteolysis, and immunological reactions. Multiple growth factor delivery is advantageous because of its ability to promote two or more diverse functions such as mineralization and angiogenesis. This approach requires study on growth factor combinations dosage, temporal events, and release kinetics. Few studies have been performed in this direction, and the delivery or scaffolds to house and release these factors at the appropriate time have yet to be proven.

Cell-Based Grafts

In significant breakthrough in 2006, Takahashi and Yamanaka discovered how mature cells treated with the right factors could be engineered back to a pluripotent stem cell state capable of producing any cell in the body (Takahashi and Yamanaka 2006). Various stem cells are now available for use in conjunction with bone graft substitutes including mesenchymal stem cells (MSCs), adipose-derived stem cells (ADSCs), induced pluripotent stem cells (iPSCs), and embryonic stem cells (ESC).

MSCs are more primitive than ESCs, consequently in the presence of TGF-b and BMP-2, −4, and −7 to culture media can be differentiated down the osteogenic line. ESCs' somatic cell differentiation requires more steps. ESCs are characterized by their unlimited proliferation and ability to differentiate to any somatic cell type, which makes them a great cell source for tissue regeneration.

ADSCs are an attractive source of stem cells because supply limitations and ease of harvesting is less of a problem given the ready access of adipose tissue deposits found under the dermal layers. These cells induced back to an earlier lineage became known as iPSCs. Stem cell technological advances lead to a greater understanding

about the interaction between stem cells and their potential use in bone graft substitutes for clinically relevant applications.

Ceramic-Based Grafts

Ceramics are highly crystalline structures formed by heating non-metallic mineral salts to high temperatures in a process known as sintering. Many ceramics are used in various orthopedic applications (White and Shors 1986). There are resorbable ceramics such as tricalcium phosphate (TCP) and ceramics with highly reactive surfaces such as bioactive glasses and calcium phosphates. The least reactive ceramics are in use in hip arthroplasty (zirconia).

Currently available bone graft substitutes contain ceramics, including calcium sulfate, bioactive glass, and calcium phosphates. Ceramics contain calcium hydroxyapatite (HA), a subset of the calcium phosphate group, which is the primary inorganic component of bone. Calcium phosphates can come close to mimicking the natural matrix of bones, depending on the porosity and structure hence the widespread use of bone graft substitutes that contain HA-based biomaterials.

Calcium phosphates are also osteoconductive, osteointegrative, and, in some instances, can be osteoinductive by the addition of MSCs (Urist and Strates 1970). The structure and crystallinity can influence osteoblastic proliferation and differentiation when in contact with calcium phosphate. The crystallinity of the HA can vary the spatiotemporal proliferation of osteoblasts, and therefore the biological repair activity. The manufacturing of ceramics requires exposure to high temperatures. This complicates the addition of biological molecules. They also tend to be brittle, making them challenging in certain bone graft applications. They are frequently combined with other materials to form a composite.

Polymer-Based Grafts

Polymers are chemical compounds or mixtures of compounds formed by polymerization and consist of repeating structural units. They are classified into natural polymers and synthetic polymers, which can be divided further into degradable and nondegradable. Natural polymers, such collagen, are derived from living sources, whereas synthetic polymers are manufactured.

Synthetic polymers can be used in a wide variety of medical applications. The polymerization process can achieve an extraordinary range of physical and chemical properties. They can be utilized because of their structural and mechanical properties that allow for complex shapes. Polylactideco-glycolide (PLGA) is an example of a synthetic, degradable polymer for bone graft applications. With the addition of water, it can break down to lactic acid and glycolic acid, which are natural human metabolites.

Natural polymers, such as collagen hydrogels, are used in scaffolds in tissue engineering as cells adhere and grow on the collagen fibers within the hydrogel.

Due to their carbon-based chemistry, polymers are closer to biological tissue than inorganic materials. This can be used for targeted interaction between the material and the body. As with ceramics, the functionality of polymers can be enhanced if used in combination with other materials, such as ceramics, to form composites.

Allografts

Introduction

Bone grafting is an essential component of spinal surgery. The need commonly arises in spinal fusion (Takaso et al. 2011) and is utilized in trauma, infection, and tumor resection (Finkemeier 2002), where bony defects can arise. These defects can be filled with autograft, which is generally preferred as it is osteoconductive and osteoinductive. However, harvesting for autograft creates donor morbidity, extended operating time, and may be contaminated by systemic processes (e.g., sepsis, metastases) (Aro and Aho 1993). In addition, autografts are limited in number, shape, size, and volume to which allografts are not constrained.

Consequently, the need for bone banks arose. Currently bone is a commonly transplanted tissue, second only to blood.

Therefore allografts supplied by a bone bank are commonly used instead of autografts because of their immediate availability and unlimited volume. The use of allograft bone eliminates the operative time required for harvesting and associated donor morbidity. Virtually any shape or size can be fashioned and are often combined with other enhancers, extenders, and substitutes to achieve union. Allogenic bone has osteoconductive activity; it serves as an acellular mineralized frame against which newly formed bone gets deposited. It is, however, variably and weakly osteoinductive (depending on source and processing) and is not osteogenic.

The obvious disadvantages of allografts are the potential for disease transmission, host incompatibility, and infection from contaminated tissue.

The Food and Drug Administration (FDA) has established guidelines that all bone and tissue banks must adhere to. The American Association of Tissue Banks (AATB) established guidelines that accredited banks must follow, which have set the industry standards. These guidelines include training and certification of employees as well as regular inspections of the facility through to assessing documentation and auditing.

The AATB is a not for profit organization that regulates and monitors the safety, consistency and availability of allografts across the United States. The AATB ensures and accreditates tissue banks to ensure their compliance with the FDA guidelines. Governments have imposed the standardization of bone bank operations to ensure the safety of transplanted tissues. The performance of a bone bank depends on its organization, donor selection and procurement, documentation, storage and processing, and implementation.

There are two types of donor of homologous tissues: live donors, consisting mainly of donations of femoral heads after fractures and total hip arthroplasty and cadaver donors, from which much greater quantities of tissues can be harvested, from any segment of the skeleton. Cadaveric donors are usually younger and have better bone quality.

Allograft Safety

The aggregate risk of disease transmission with allograft is a reflection of the rigor of the screening and testing of donors and the type of allogenic tissue that is transplanted. The risk of transmission of viral diseases (human immunodeficiency virus (HIV), hepatitis B (HBV), hepatitis C (HCV)) depends on the product type and its preparation. Regulatory guidelines in Europe, the United States, and Australia have developed critical pathways for manufacturers of biological products to follow. Simply stated, these involve screening tissues for infectious agents (viral/bacterial), processing techniques to ensure sterilization (ethylene oxide/radiation), and follow up mechanisms to track the patient and product. By AATB standards, serologic testing is used including for hepatitis B surface antigen, hepatitis B core antibody, hepatitis C antibody, syphilis, human T-lymphotrophic virus-1 antibody, HIV 1 and 11 antibodies, and HIV P24 antigen. All tissue and blood samples are tested for infectious diseases, including for AIDS with Nucleic Acid Testing (NAT by TMA), HCV, HIV-1, HIV-2, HTLV-1, HTLV-11, HB Core, RPR, HCV-Ab, HBs Ag, HIV-1 NAT, and HCV-NAT.

Mroz et al. (2009) performed a retrospective review of data analyzing 54,476 allograft specimens recalled by the FDA. They found that despite the large number of allograft recalls in the USA, there was only one documented case of disease transmission (HIV) in spine surgery. The review found no reports of bacterial transmission from the use of allograft. They admitted that the precise incidence of disease transmission linked to tissue allografts was unknown. They concluded that there appears to be no overt risk associated with the use of allograft bone in spine surgery.

Bone Banking Overview

The presence of microorganisms on processed tissues is inevitable and unavoidable. In order to prevent disease transmission the appropriate donor selection process, proper tissue processing,

and adequate sterilization is of paramount importance.

The most valuable method for determination of suitability is the donor's medical history. In general, there should no history of infectious, malignant, neurological, and autoimmune diseases. In addition, there should be no metabolic bone disease, drug abuse, or exposures to radiation and toxic substances present in the history. Essentially, any condition in which there is the possibility of disease transmission or where the quality of the bone may be compromised could warrant exclusion from donation.

The procurement and processing of allograft has to be performed with a sterile and hygienic technique. Grafts may be harvested from two sources. Bone is procured aseptically or cleanly. The first is from live donors where femoral heads are typically collected aseptically in the operating room by a surgeon in the course of a hip replacement. The second source is cadaver bone which can also be procured under aseptic conditions in the operating room. Removal of bone should take place within 12 h of death or within 24 h if the body has been refrigerated at 4 °C to reduce bacterial growth and bone autolysis. Standard sterile draping of the cadaver and sterile gowning of all trained procurement personnel are essential.

A sterilization process that has a high inactivation process prevents the transmission of diseases from donor to recipient. Various techniques are utilized such as ethylene oxide (Dziedzic-Goclawska 2005), irradiation (Nguyen et al. 2007), thermo disinfection (Folsch et al. 2015), and other techniques such as antibiotic soaks. Ethylene oxide sterilization is of limited use because of limited tissue penetration and can cause an inflammatory reaction to ethylene chlorohydrin, a by-product formed from ethylene oxide. Gamma irradiation has bactericidal and viricidal properties and has been proven to be successful in sterilizing medical products. The concept of sterility assurance level (SAL) is derived from studies on bacteria, fungi, and spores where a sterilization dose is high enough that the probability of an organism surviving is no greater than one in one million units tested. The dosage of 25 kGy has been the recommended for terminal sterilization of allograft tissues. This is 40% above the minimum dose required to kill resistant microorganisms. Research has shown dose-dependent reductions in biomechanical properties of allografts at high levels of gamma irradiation (>30 kGy). This prompted bone banks to employ lower doses that are efficient at deactivating microorganisms, while protecting the biomechanical properties of bone allograft. Several bone and tissue banks around the world utilize minimum doses to achieve sterility with dosages as low as 11 kGy. The radiation process is a cold sterilization process and therefore preserves the properties and characteristics of tissues (Singh et al. 2016).

Gamma irradiation of allografts is a safe and highly effective sterilization method and offers a clear advantage in terms of safety compared with other sterilization techniques. There is no substitute for donor screening and rigorous tissue processing procurement techniques and, when combined with gamma irradiation, the sterile product is safe for clinical use.

Types of Bone Allograft

There are three commonly used forms: fresh frozen allograft, freeze dried allograft and demineralized bone matrix (DBM).

Allografts are either fresh or processed. Fresh allografts are sometimes utilized because they are alive. However the immunologic reaction and the risk of disease transmission has led to most allografts being processed.

Fresh frozen allograft has improved osteoinductive and biomechanical properties relative to irradiated materials. After harvest, the allograft is cleaned by a high-pressure lavage and antibiotic solutions. The removal of marrow elements removes a significant antigenic cell population. After cleaning, the tissue is cultured and if sterile the graft is then frozen and released for implantation in due course. The grafts are packaged without solution and frozen to −70 °C to −80 °C. The stored life of sterile fresh frozen allograft is 3–5 years. Fresh frozen graft has the greatest strength of any type of structural allograft, however carries the risk of disease

transmission, which can be reduced by donor screening and sterile harvesting techniques. Any grafts that have positive cultures after processing are secondarily sterilized. This secondary sterilization process occurs with either gamma irradiation or ethylene oxide.

Freeze-dried allograft is prepared by tissue water being replaced with alcohol to a moisture level of 5% with the alcohol, then being removed under vacuum. Freeze-dried grafts can be stored at room temperature for 3–5 years and are therefore easier to maintain. The graft requires a 30 min period of rehydration prior to implantation. The risk of disease transmission is also reduced with no cases of HIV transmission being reported. It is estimated the risk is 1 in 2.8 billion compared to fresh frozen allograft risk of 1 in 1.6 million (Costain et al. 2000). Freeze drying does not eliminate the HIV virus, however it does reduce the immunogenicity. The effect of freeze-drying on the mechanical characteristics of the graft is dependent on the method and rate of rehydration. Compared with fresh frozen bone, it has been found that the process results in a small but significant reduction in stress (18%) and stiffness (20.2%) (Cornu et al. 2000). A study comparing the compressive strengths of fresh frozen, freeze dried and ethylene oxide treated allograft showed no significant differences (Brantigan et al. 1993). The effect of irradiation on freeze-dried allograft has been shown to reduce graft strength further (Hamer et al. 1996). As well as the mechanical stability reduction, irradiation results in the denaturing of endogenous BMPs eliminating much of its osteoinductive capacity.

The discovery of osteoinductive proteins within demineralized bone matrix has resulted in the widespread use of DBM in grafting procedures (Urist et al. 1967). The production of DBM is a multistep process commencing with cortical bone being cleaned followed by machining into small particles. Acid is then applied to reduce the calcium content while maintaining the organic matrix and growth factors. The demineralization process releases these cytokines that participate in the complex cascade of events leading to bone repair. This renders DBM weakly osteoinductive. Approximately 93% is collagen and 5% are growth factors, a portion of which is BMPs. There is variability in the osteoinductivity depending on the donor, the site of the harvest and the method of processing. This variability resulted in different osteoinductive capabilities between different manufacturers and within a single manufacturer's product (Wang et al. 2007). The end product is a powder and therefore the handling characteristics were problematic. If placed in a cavity the product could be easily displaced from its desired location by blood and other fluids. Hence, most DBMs are placed in carriers such as putty or glycerol. DBMs have been found to be useful as graft extenders for both local bone and iliac crest bone graft (Schizas et al. 2008). The literature supports the utility of DBMs as enhancers and extenders but not as bone substitutes in isolation.

It is important to select an allograft product that is applicable to the clinical situation. In addition, surgeons should be familiar with the bone bank and its regulations, the products and their preparation, the biologic activity and biomechanical characteristics, as well as cost, safety, and efficacy of the product.

Allograft Use in Spine Surgery

It is clear that there are four essential elements of bone grafts for successful bone regeneration. Osteoconductivity, osteoinductivity, osteogenicity, and the mechanical environment is the diamond concept and all aspects need to be considered when selecting an allograft in a particular operation to fulfill a particular role.

Osteoconductivity is the ability of a material to provide a three-dimensional structure for the ingrowth of host capillaries, perivascular tissue, and osteoprogenitor cells.

Osteoinductivity is defined as the ability of a material to stimulate primitive, undifferentiated, and pluripotent cells to develop into the bone-forming cell lineage with the capacity to form new bone.

Osteogenicity implies that a bone grafting material has the intrinsic capacity to stimulate

bone healing by the presence of mesenchymal stem cells (MSCs) or osteoprogenitors cells.

The mechanical environment in which the allograft is placed is critical to the success: the construct needs to be rigid, the graft under compression and the recipient vascular bed viable.

The choice of bone graft for achieving an arthrodesis or reconstruction in the spine should be made on the evidence available from the literature and not from a salesman in a suit or a glossy brochure. The primary goal is to achieve an interbody arthrodesis, therefore, many factors need to be taken into account. Less commonly, graft is used to recreate and restore anatomy in the case of spinal deformities. For example, remodeled endplates can be recreated in cases of high grade dysplastic spondylolisthesis to support an interbody cage/graft and anterior fixation. The recipient's biological status, age, comorbidities, graft harvest site, the vascularity and local tissue viability, the mechanical environment and the use of supplemental fixation influences the environment for bone healing to occur. In selecting a graft, one needs to take into account the diamond concept: osteoinductivity, osteoconductivity, osteogenicity and the mechanical environment.

Although iliac crest bone graft is the gold standard, there are numerous reports on the success of alternate approaches, especially in combinations. For example, with large or segmental bone defects, the healing process is impaired; thus the use of tissue engineering techniques becomes a necessity. To mimic the natural bone healing process, three major components are required: a mechanically stable graft, a suitable cell source and the presence of chemical and biological factors. Extensive research has been done in all three components mentioned above; however, we are still at the laboratory bench stage, in which biomaterials, growth factors, and cell sources are being examined and optimized for the regeneration of bone. In addition new efforts by several major orthopedic companies have expanded the role of allografts by tailoring them for specific surgical procedures. For example, dowels and wedges can be utilized in spinal fusions and DBMs with carriers to provide better handling and performance characteristics.

Allografts are now manufactured in a variety of forms and consequently offer versatility to meet the requirements of an ideal graft. They can be processed to offer mechanical support in load bearing environments, provide the ability to incorporate and remodel, to be biocompatible, to be osteoinductive when demineralized and to provide a high level of safety. As mentioned earlier factor, cellular, ceramic and polymer based bone enhancers, extenders and substitutes are used singularly or in combinations to enhance the role of allografts in spinal fusion. As new technologies are developed, tissue engineering and gene therapies are likely to add to the biological characteristics already available with allografts.

Allograft in the Anterior Column

Multiple studies on the radiographic success of allograft in the anterior column of the cervical spine have been reported. Few studies have studied the clinical efficacy. Generally, the use of allografts is supported for use in anterior column support (level I-IV evidence). The utilization of supplemental fixation, such as cages and plates, has resulted in a substantial increase in fusion rate as well as maintenance of lordosis, which in turn appears to reduce adjacent motion segment degeneration (AMSD) and improves the clinical efficacy. Many options exist for the usage of allograft in the anterior column: these include cortical or cortico-cancellous allograft, with or without supplemental cage or plate fixation, and DBM, which always requires supplemental fixation. It should be noted that allograft alone with BMP-2 leads to high union rates but is prone to subsidence (Vaidya et al. 2007) and, as such, additional measures to improve the biomechanical environment such as cage support and/or plate/posterior fixation is important (Slosar et al. 2007).

The Cervical Spine

Allograft has been shown to be at least equivalent to autograft when used for anterior cervical procedures with the exception of multilevel constructs. Tuchman et al. (2017), in a systemic review compared the effectiveness and safety

between iliac crest bone graft (ICBG), non-ICBG autologous bone, and allograft in cervical spine fusion. The review identified 13 comparative studies: 2 prospective cohort and 11 retrospective cohort studies. Twelve cohort studies compared allograft with ICBG autograft during anterior cervical fusion and demonstrated with a low evidence level of support that there are no differences in fusion percentages, pain scores, or functional results. There was insufficient evidence comparing patients receiving allograft with non-ICBG autograft for fusion, pain, revision, and functional and safety outcomes.

The FDA IDE studies on disc replacement have provided information on allograft fusion in the anterior cervical spine (Coric et al. 2018; Gornet et al. 2017). These studies have provided valuable information on the control group in regards to the incidence of fusion, reoperation, non-union and data on the patient-reported outcome measures (PROM) and have generally found high fusion rates and acceptable outcomes. These, along with other studies with single level allograft constructs supported with internal fixation show that meticulous surgical technique could result in fusion and improvement in PROMs irrespective of graft choice (Yeh et al. 2017; Fraser and Härtl 2007).

ACDF using allografts have in general shown clinical and radiological success. Muzević et al. (2018) investigated clinical parameters of ACDF treatment and outcomes using osseous allografts in different age groups, studying the postoperative results of restoration of lordosis and evaluating the utility of bone allografts for ACDF, including graft subsidence. Fifty-two patients had disc herniation and 102 had spondylosis. Surgery was performed on a total of 313 levels. The median duration of follow-up was 24 months, and no patients were lost to follow-up. Human cortical allografts were used in 51 segments (16.3%), and corticocancellous allografts were used in 262 segments (83.7%). Solid fusion was achieved in 97.92% of patients and 98.37% of levels at a mean follow-up of 5.97 $\pm$ 2.86 months. Graft sizes ranged from 8 mm to 15 mm. The most frequently used graft size for fusion was 11 mm (119 levels; 38%), followed by 10 mm (72 levels; 23%) and 12 mm (70 levels; 22.4%). Anterior cervical plates and screws were used in all patients. The importance of a plate in load sharing is recognized, especially in patients with a kyphotic cervical spine. Treatment outcomes achieved excellent or good outcomes in more than 80% of patients, regardless of age. Yeh et al. (2017) retrospectively collected preoperative and postoperative radiographic and clinical data of 50 patients from 2005 to 2009, with a diagnosis of multilevel cervical spondolytic myelopathy (MCSM), who received 2-level anterior cervical corpectomy and fusion (ACCF) with a fresh frozen cortical strut allograft (FFCSA) fibular shaft and an anterior dynamic plate (see Fig. 3). The cervical curvature lordosis improved and the neurogenic function recovered well postoperatively. The VAS-neck and NDI scores both decreased after 12 and 48 months following surgery. The Japanese Orthopaedic Association score recovery rate at postoperative 4 years was 87.5%. Fusion rates achieved were 100% at 12 months. They stated the results were satisfying and the complication rate was low. The authors emphasized meticulous graft preparation on both the donor bone ends and the recipient endplates so the graft could be inserted with a press fit technique.

Evidence for the efficacy regarding the use of allograft in multi-level anterior cases is mixed. A study by Park et al. (2017) demonstrated similar clinical and radiologic outcomes between patients treated with corticocancellous composite allograft or autograft for ACDF, with a decreased subsidence rate in the corticocancellous composite allograft group. They utilized freeze dried, fully machined corticocancellous composite allograft cages. APS was utilized for primary fixation. Corticocancellous composite allograft is composed of cortical lateral walls with a cancellous centre. The cortical portion provides structural support for the disc space, while the cancellous portion provides a scaffold for bone in-growth that can minimize graft subsidence with an enhanced fusion rate. The authors stated the allograft group took longer to fuse and in multi level cases, may result in hardware failure. Peppers et al. (2017) reported on the results of a prospective multicentre clinical trial assessing the safety

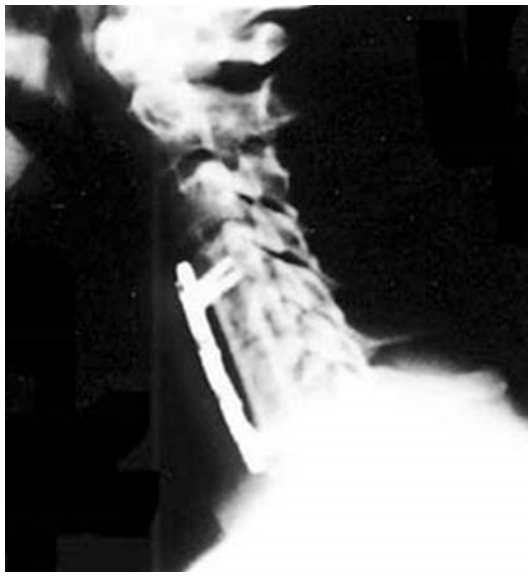

Fig. 3 Example of corpectomy and fibular strut allograft with plate/screw stabilization for reconstruction of the anterior column

and effectiveness of the viable cellular bone allograft in combination with a polyetheretherketone (PEEK) interbody spacer in two-level ACDF using patient reported and radiological outcome measures. The per subject fusion rate increased over time and was determined to be 65.7% of subjects fused at 6 months and 89.4% at 12 months. This study did not have a control group and thus treatment was not directly compared to autograft or non-cellular allograft treatments. Samartzis et al. (2003) however found equivalent and high rates of fusion (in the order of 97–98%) with rigid plating emphasizing that mechanical stability may be a factor influencing the difference between autograft and allograft in older studies without rigid fixation.

A near 100% union rate is achievable with the addition of BMP to allograft but the side effects related to dosage require caution. Burkus et al. (2017) reported on a prospective study evaluating the safety and efficacy of BMP-2 with allograft for ACDF in single level degenerative disc disease (DDD). The investigational group had 0.6 mg of BMP-2 inside a PEEK cage/APS with a fusion rate of 99.4% versus a control group treated with allograft spacer/APS with a fusion rate of 87.2%. A higher rate of adverse events such as swelling, dysphagia and oropharyngeal pain was noted. Butterman (2008) similarly found high rates of union but increased incidence of neck swelling and higher cost of allograft with BMP-2 compared to iliac crest autograft for ACDF. Higher dosage has also been linked with increased osteoclastic activity via the RANKL-OPG pathway and osteolysis (Gerstenfeld et al. 2003) that can lead to subsidence of implants.

While allograft and autograft showed near equivalence in the literature for the cervical spine, the same cannot be said for synthetic bone graft. Buser et al. (2016) reviewed the efficacy and safety of synthetic bone graft substitutes versus autograft or allograft for the treatment of cervical degenerative disc disease. Data from 8 comparative studies were included: 4 RCTs and 4 cohort studies (1 prospective and 3 retrospective studies). Synthetic grafts included HA, β-TCP/HA, PMMA, and biocompatible osteoconductive polymer (BOP). The PMMA and BOP grafts led to lower fusion rates, and PMMA, HA, and BOP had greater risks of graft fragmentation, settling, and instrumentation problems compared with iliac crest bone graft. The authors stated that conclusions regarding the efficacy and effectiveness of these products are low and insufficient. Most of these studies were sponsored and the sample size inadequate, therefore with the potential for bias. The use of bone substitutes, extenders and enhancers has escalated rapidly and of course buyers are being charged a premium without clinical evidence to support the use of such products. In this review, synthetic grafts performed similarly or worse than autologous grafts in achieving fusion. A detailed review of the level of evidence, safety, and efficacy is required.

It should be discussed briefly also that allografts play a role in providing structural integrity or bridging significant bone loss in certain circumstances in the anterior cervical spine. This includes structural allograft for vertebrectomy cases anteriorly in the setting of metastatic tumor or systemic infection or significant traumatic bony comminution in a burst fracture where the patient's autograft may be less

desirable for reasons of contamination, healing problems or increased morbidity.

In summary, the evidence suggests that ICBG and allograft demonstrated clinical equipoise in terms of fusion rates, pain scores, and functional outcomes following anterior cervical fusion. Recognition about patient factors and surgical techniques play a significant role in the outcome of anterior cervical fusion surgery. Age, osteoporosis, the number of levels and tobacco use can affect the fusion rate. In addition, surgeon factors such as graft doweling, endplate preparation and the use of supplemental fixation can also affect fusion rates.

Allograft utilization removes donor site complications. While the preparation and sterilization reduce or eliminate transmission of disease, it also reduces or eliminates osteoinductive capabilities and can mechanically alter the graft and the ability to withstand compressive and torsional loads. This can result in longer fusion times, subsidence, and loss of correction.

The Lumbar Spine

A large variety of devices have been developed and used for structural support of the spine in the anterior and middle columns. These structural deficits arise from anterior discectomies, trauma, tumor resections and following osteotomies for correction of deformity. The anterior lumbar spine is similar to the cervical spine in that, following disc resection or vertebrectomy, the graft is placed under compression. An additional advantage is the larger cross sectional area of the lumbar spine vertebral body on which to seat the allograft. The loads are mainly axial compression, although some rotational stresses are also applied. The two most commonly used allografts in the anterior spine are femoral ring allografts (FRA) and tricortical iliac crest. Mechanical testing of the vertebral body and FRAs has revealed compressive strength of 8000n and 25000n, respectively (Voor et al. 1998). These biomechanical tests revealed the importance of placement, surface area coverage, and the importance of endplate preservation.

Clinically, studies of allograft use in the lumbar spine for degenerative disc disease and deformity have reported favorable outcomes in use with an anterior approach (ALIF). Burkus et al., in a randomized controlled trial of 131 patients used ALIF threaded cortical allograft dowels and BMP equivalent rates to autograft without additional morbidity (Burkus et al. 2005). In fact, some other multicenter studies have even reported superior results compared with allograft (Burkus et al. 2003).

Regarding tumor and deformity, allograft has been a useful tool in the surgeon's armamentarium. Bridwell et al. (1995) reported in a prospective study of 24 patients with kyphosis or anterior column defects treated with fresh frozen allograft and posterior instrumentation and autogenous grafting. Only two patients showed some subsidence and the other 22 maintained the correction. Bridwell (Bridwell et al. 1995) also found that deformity correction using anterior allograft support was effective on the proviso it was combined with rigid posterior fixation and autograft. Janssen et al. (2005) reported on the clinical and radiographic outcomes of 137 patients who were treated with a FRA allograft packed with ICBG ($n = 117$) and DBM ($n = 13$) and supplemental posterior fixation. They were able to achieve a 94% fusion rate.

Systemic review and consensus of expert opinion in the setting of reconstructions following en bloc tumor resection have recommended cages packed with morcelized allograft and suitable autograft for single level vertebrectomies with strut bone grafting used in the thoracic spine (Glennie et al. 2016).

Other interbody approaches have had variable success. Generally, PLIF studies have reported inferior outcomes from the use of allograft compared with autograft alone (Jorgenson et al. 1994), be it with or without instrumentation (Brantigan 1994). Anand et al. (2006) in a study of allograft laden TLIF cages have been more favorable with regard to fusion at 99% and satisfaction 96%. The literature on interbody fusion via lateral and oblique approaches utilizing allograft is limited so an inference as to their efficacy cannot currently be drawn.

It is important that one is aware of the potential for allograft resorption when used in isolation with BMP-2 (Pradhan et al. 2006). An anterior cage-allograft-BMP-2 combination may provide the best synergy in terms of initial support,

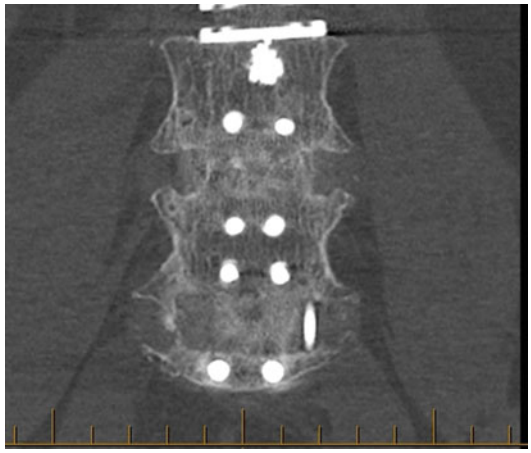

Fig. 4 Solid arthrodesis achieved in the lumbar anterior column as demonstrated across a coronal CT plane through a tissue engineering construct of plate-PEEK cage-femoral allograft and BMP-2

scaffolding and growth factor stimulus combining to support effective arthrodesis. The cage (usually with supplemental screw fixation within or extraneous to the cage) provides the mechanical stability, the cancellous structural graft the osteoconductive matrix and the BMP-2 the osteoinductive protein (see Fig. 4). This is effectively tissue engineering. There is good evidence for the utility of spinal allografts for structural reconstruction in the anterior spine. They have the advantage of immediate strength, are under compression and have comparable fusion rates with autograft if combined with anterior and/or posterior instrumentation.

Posterior Elements

Cervical

There is limited literature on use of allograft for fusion of the posterior elements of the cervical spine as most studies relate to anterior cervical reconstructions. However, studies do highlight their utility with regard to availability of shape and size in more complex anatomy. For example, posterior interventions including occipitocervical and C1–2 posterior based fusions can benefit from access to spanning shaped segmental support (Nockers et al. 2007; Aryan et al. 2008).

Thoracolumbar

Posterior correction of scoliosis is a particularly important clinical situation requiring large amounts and surface area of bone graft to achieve a solid posterior fusion. In the most common cases of either adolescent idiopathic or pediatric neuromuscular scoliosis, adequate quantity and quality of autograft bone may not result from simple local bone grafting alone. In this instance, the choice of graft(s) is important in minimizing further blood loss and morbidity from an already invasive procedure for the child. To this end, freeze-dried allograft chips have been employed with high success in some literature with the advantage of reduced blood loss and morbidity (Blanco et al. 1997; Montgomery et al. 1990) but some studies have reported inferior outcomes when compared to autograft only or composite autograft-demineralized bone matrix combinations (Price et al. 2003).

Regarding fusion of the posterior elements in posterolateral fusion (PLF), studies are mixed on the efficacy of allograft bone making it difficult to recommend for or against for posterior fusion, e.g., in a 360° fusion strategy. An and colleagues reported inferior clinical and radiological results of allografts compared to autografts in PLF (An et al. 1995). However, in a randomized controlled trial instrumented allograft use in PLF without BMP has been found to have equivalent fusion rates and outcomes scores to autograft (Gibson et al. 2002). In general, there is little or no evidence for any utilization of structural allograft in the posterior spine except at the occipital-cervical junction. There is some evidence for cancellous allograft chips being used as an extender in PLF. There is evidence for the use of DBM as an extender and possibly as an enhancer in the posterior spine.

Conclusions

There is a wide range of osseous allografts available for use in spinal surgery. Allograft has gained popularity because of its abundant supply and absence of donor site morbidity. The goal is to produce comparable or superior outcomes when

used as a substitute for autograft. The surgeon needs to take into account the type of procedure and therefore the graft best suited for that environment.

The ideal bone replacement material should be osteoinductive or conductive, non-pathogenic, minimally antigenic and mechanically stable. Compared with autografts, allografts show delayed vascularization and remodeling of the fusion mass. Allogenous bone has limited osteoinductive properties and carries the risk of subsidence due to delayed union or non-union. Currently, several modified allograft cages have been introduced to enhance union rate and structural stability, including corticocancellous composite allograft. Despite these facts, allografts are in plentiful supply, have a proven track record, and are an effective adjunct when used in the correct clinical situation.

There are many patients who may not have enough available bone for the prescribed procedure and any additional surgery may result in added blood loss, pain, infection, contamination and an increased hospital stay. Therefore, allogeneic bone from cadaver donors or live donors has been used successfully for a number of procedures and has several advantages including long-term storage, large available quantities, and specific types and sizes of bone.

Regenerative engineering is emerging at a rapid rate. More is now understood about material science, stem cells, signaling molecules, growth factors, and the strategies available to integrate these components to produce the functional biological system we regard as bone. One can envisage a time when structural allografts will be composites of minerals and signaling molecules with growth factors in their structure that will facilitate bone union.

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Posterior Approaches to the Thoracolumbar Spine: Open Versus MISS

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Abstract

The traditional open approach to the thoracolumbar spine remains one of the most powerful and widely practiced approaches in all of spine surgery. Over the past 2 decades or so, minimally invasive options have gained increasing traction and have been associated with reduced blood loss, paraspinal musculature disruption, infection rates, and length of stay, as well as hospitalization costs, without compromising clinical outcomes or radiographic fusion rates. The minimally invasive approach is not necessarily appropriate for all patients and pathologies, and the two approaches are not mutually exclusive. Currently an array of open and minimally invasive options exist for posterior thoracolumbar fusion, including midline and paramedian approaches, conventional and tubular retractors, posterior and transforaminal interbody as well as posterolateral fusion options, static and expandable cages, and various fixation systems, including pedicle (both open and percutaneous) and cortical bone trajectory screws. More recently, endoscopic spine surgery has garnered growing attention as an ultra minimally invasive alternative and may yet play a significant role in neural decompression and spinal fusion. Furthermore, advances in navigation, robotics, osteobiologics, and perioperative protocols will hopefully translate into increased safety, efficacy, and reproducibility for posterior thoracolumbar fusion procedures.

Keywords

Thoracolumbar fusion · Open · Minimally invasive · Posterior lumbar interbody fusion · Transforaminal lumbar interbody fusion · Tubular retractor · Percutaneous pedicle screw · Cortical bone trajectory screw · Endoscopy

Introduction

The posterior approach to the thoracolumbar spine is one of the most powerful tools in the spine surgeon's armamentarium. This approach is the oldest, and most widely practiced and accepted technique in all spinal surgery (Knoeller and Seifried 2000). It affords the surgeon access to all three columns of the spine through a single stand-alone approach, obviating the need for patient repositioning and staged procedures. It enables direct decompression of the common thecal sac and nerve roots and provides an avenue for fixation and fusion and therefore correction of instability and deformity.

Despite these advantages, the traditional open approach to the thoracolumbar spine is associated with significant iatrogenic disruption of normal surrounding tissue, in particular collateral damage to the paraspinal musculature, leading to devascularization, pain, atrophy, and disability (Fan et al. 2010; Kim et al. 2005). Minimally invasive spine surgery (MISS) has gained much popularity in recent years owing to the reductions

in patient morbidity, length of hospital stay, and costs. This has been supported by advances in technology, including access, instrumentation, neuromonitoring, biologics, navigation, and robotics (Yoon and Wang 2019).

In this chapter, we will address the history of lumbar instrumentation and fusion, and the increasing adoption of minimally invasive techniques. We will also address current trends in spinal procedures performed in Australia and outline the common indications for lumbar fusion, including reviewing the most contemporaneous literature on the subject. Rather than exhaustively detailing each step involved in common thoracolumbar fusion operations, we will endeavor to share with our reader specific nuances accumulated through our surgical experience.

Brief History of Open and Minimally Invasive Spinal Fusion

Harrington in the 1950s is credited with the birth of spinal instrumentation (Harrington 1962). He revolutionized the treatment of pediatric scoliosis with his stainless-steel rod construct. While these were effective in correcting coronal deformities, it created a generation of patients with flat back deformities. The next major revolution in instrumentation came in the form of segmental transpedicular screw fixation, and while described a few decades earlier (Knoeller and Seifried 2000), Roy Camille is often credited with their popularization in the 1970s (Roy-Camille et al. 1976). While Hibbs had harvested iliac crest bone graft in the 1910s for posterolateral graft (Hibbs 1911), Cloward in the 1940s was the first to describe its placement in the interbody space (Cloward 1952), now considered the first iteration of the posterior lumbar interbody fusion (PLIF). To mitigate the forceful retraction applied to the traversing nerve root and thecal sac, Harms (Harms and Rolinger 1982) modified this technique in the 1980s to a more lateral approach, now termed transforaminal lumbar interbody fusion (TLIF) involving total facetectomy and entrance through a corridor referred to as Kambin's triangle (Kambin and Zhou 1996), formed by the obliquely oriented exiting nerve as its hypotenuse, the longitudinally oriented traversing nerve root medially, and the transversely oriented disc space and vertebral endplates inferiorly. Following the lead of our general surgical colleagues and their widespread adoption of laparoscopic techniques over traditional open laparotomies, the search for less invasive approaches to the spine had started to gain momentum. Magerl's percutaneous adaptation of the pedicle screw in the 1980s (Magerl 1982) and Foley's introduction of the tubular retractor[7] a decade later are often considered two of the most significant landmarks in MISS. Kambin, in addition to his eponymous anatomical triangle, is also credited with the development of percutaneous and later endoscopic approaches to the intervertebral space (Kambin and Zhou 1996), and thus spinal endoscopy was born.

Regional and Global Trends in Spinal Fusion

The World Health Organization estimated that low back pain (LBP) affects approximately two-thirds of people in industrialized countries at some point in their lives (Duthey 2013). Epidemiological studies have ranked LBP as the second commonest cause of disability in adults (Prevalence and most common causes 2009), and number one in Years Lived with Disability (Hoy et al. 2014). In parallel to the growing disability incurred by spinal pathology, the number of spinal surgeries performed has also increased, particularly fusion procedures. In Australia, where we practice, the number of simple spinal fusion procedures doubled between 2003 and 2013, while complex fusion procedures quadrupled (Machado et al. 2017). Similar trends have been demonstrated in the United States, with the fastest increases seen in the over 65 age group (Martin et al. 2019). Over a similar epoch, MISS has also gained increasing traction. According to a recent global survey of nearly 300 spinal surgeons, most respondents (71%) regarded MISS as mainstream, while the majority (86%) practiced some form of

MISS (Lewandrowski et al. 2020). In parallel with this trend, based on patient surveys, most patients (80%) prefer MIS over open surgery, provided that long-term outcomes and complication risk are comparable (Narain et al. 2018).

Selected Indications and Evidence for Spinal Fusion

Most spine surgeons would support the addition of fixation and fusion in patients with evidence of instability, classically manifesting as spondylolisthesis with abnormal movement on dynamic radiographs, although indirect signs such as sagittally oriented facets, intra-articular effusions, and synovial cysts may sway a surgeon toward fusion out of concern for creating iatrogenic instability following decompression (Blumenthal et al. 2013). Furthermore, the predominance of mechanical LBP in patients with neurogenic claudication or radiculopathy significantly reduces probability of improvement following decompression alone and may provide further impetus to fusion (Pearson et al. 2011). More recently, our growing understanding of spinal deformity and the negative impact of sagittal imbalance and spinopelvic mismatch on outcomes following spine surgery (Glassman et al. 2005; Schwab et al. 2013) has contemporized our understanding of the longitudinal impact of segmental fusion upon regional and global spinal alignment, as well as the potential benefits and pitfalls of long segment fusion, strategic placement of interbody devices and osteotomies, and deformity correction.

Spondylolisthesis

The rate of *fusions* around the world has more than doubled from the start of the twenty-first century and is only continuing to *increase* from *year* to *year* (Makanji et al. 2018). Despite this, evidence from large randomized controlled trials remains either lacking or conflicting. Certainly, the as-treated results from the spondylolisthesis arm of the Spine Patient Outcomes Research Trial (SPORT) supported surgery over conservative management for patients with degenerative spondylolisthesis (Abdu et al. 2018). However, the significant crossover rate mitigated the benefits of randomization, and the heterogeneity in surgical methods prevented any firm conclusions regarding whether fusion afforded additional benefit to decompression alone.

The two recent randomized controlled trials published in the New England Journal of Medicine addressing whether the addition of fusion to decompression in patients with low-grade degenerative spondylolisthesis raised more questions than they answered. The Swedish study (SSSS) randomized more patients (Försth et al. 2016), around 250, but only half had spondylolisthesis, and important patient characteristics such as dynamic instability and relative contributions of mechanical LBP versus leg pain were not addressed. They concluded that fusion was no better than laminectomy alone in all outcome measures and resulted in longer length of stay and higher costs. The North American study (SLIP) compared the addition of fusion to laminectomy alone in approximately 60 patients (Ghogawala et al. 2016). Patients with mechanical LBP and dynamic instability, generally considered relative indications for fusion, were excluded, potentially reducing the applicability of their patient population to real-world practice. Their results suggested a small but statistically significant improvement in the physical component of the 36-item Short Form Health Survey (SF-36). Neither trial was able to explore the nuances in decision-making spine surgeons face every day in this diverse patient population, and both largely used a surgical strategy, instrumented posterolateral fusion with autologous iliac crest bone graft without interbody that some would consider outdated today. Certainly, no minimally invasive techniques were utilized. Some evidence does also exist supporting the use of interbody over posterolateral fusion with respect to fusion and reoperation rates (Liu et al. 2014). Furthermore, interbody graft provides additional potential benefits of anterior column support and load sharing, fusion under compression and over a shorter distance, as well as indirect foraminal

decompression and restoration of segmental lordosis.

Axial Back Pain

Fusion specifically for LBP has remained a subject of contention for many years. The reduced efficacy of surgery in patients with back-pain predominant symptomatology (Pearson et al. 2011), coupled with difficulties in localizing a specific pain generator in these patients (Brusko et al. 2019), who often possess significant psychological overlay and covert secondary gain, has made this field one of the most controversial in all of spine surgery. The initially positive Swedish trial (Fritzell et al. 2001) on fusion for intractable LBP was later rebutted by the Norwegian trial (Brox et al. 2003), which showed no benefit for fusion over rehabilitation with a cognitive behavioral component. True structured rehabilitation is, however, a scarce commodity in a lot of countries, including Australia, often with lengthy wait times. The latest American Association of Neurological Surgeons (AANS) and Congress of Neurological Surgeons (CNS) guidelines support at least consideration for fusion surgery in the setting of persistent mechanical LBP once all reasonable conservative alternatives have been exhausted (Eck et al. 2014).

Thoracolumbar Burst Fractures

Trials on surgery versus nonoperative management for thoracolumbar burst fractures in neurologically intact patients have shown similarly conflicting results (Abudou et al. 2013), although contemporary minimally invasive methods have not yet been rigorously studied. Certainly, patients with unstable thoracolumbar fractures without need for direct decompression may serve as an ideal cohort for percutaneous fixation to facilitate pain control, mobilization, and fracture union, with minimal collateral soft tissue disruption (Court and Vincent 2012). The instrumentation can often be removed following fracture union to remobilize the involved segment of the spine and prevent long-term adjacent segment issues (Court and Vincent 2012). Similarly, percutaneous instrumentation has an established role in providing supplemental fixation in the context of interbody fusion approached via a lateral route (Alvi et al. 2018) and holds promise in the realm of spinal infection (Deininger et al. 2009), with minimization of communication with infected tissue, and preservation of paraspinal musculovasculature and viability.

MISS Fusion

With an aging population and associated frailty, coupled with increasing emphasis on healthcare economics, there is growing demand for less invasive surgical options. The benefits of MISS have been clearly demonstrated in other subspecialties, such as laparoscopic abdominal surgery and endovascular neurosurgery. There is now a growing body of evidence that MISS fusion provides similar outcomes and fusion rates as traditional open methods. Our meta-analysis on MISS TLIF versus open TLIF showed less blood loss and lower incidence of infection with at least comparable clinical outcomes with regard to axial pain and disability (Phan et al. 2015a). Other studies have consistently shown shorter length of stay (Goldstein et al. 2014), reduced complications (Khan et al. 2015), less disruption of paraspinal musculature (Fan et al. 2010; Kim et al. 2005), less postoperative narcotic use, and earlier return to work (Adogwa et al. 2011), as well as decreased overall costs (Wang et al. 2012). Concerns around increased fluoroscopic exposure to the surgical team (Khan et al. 2015) have been counteracted by advances in navigation and robotic technology, which have also resulted in improved fixation accuracy (Kosmopoulos and Schizas 2007). The initial steep learning curve has been overcome to some extent by widespread dissemination of techniques, and opportunities to learn and practice at cadaveric workshops. The unique challenges raised by patients at risk for nonunion, including osteoporosis (Benglis et al. 2008), have led to strategies such as augmenting pedicle screws with cement to increase pull-out strength, and bone morphogenetic protein (BMP) to improve

fusion (Mccoy et al. 2019). Understanding the dose-dependent properties of BMP, and risks of radiculitis, heterotopic ossification, and osteolysis (Fu et al. 2013), has led to more controlled application of smaller doses in carefully selected patients without malignancy to areas without exposed dura or nerve root, or endplate violation.

The classic tenets of MISS involving small incisions and tubular retractors have shifted toward an overarching paradigm of minimizing collateral tissue disruption to reduce disability, and a greater appreciation for the importance of multidisciplinary teams in enhancing recovery after surgery (ERAS). (Dietz et al. 2019) Patient selection remains key, and while indications for minimally invasive approaches have expanded, there remain pathologies, including but not limited to severe adult spinal deformity, especially if concomitantly rigid, which may be better suited to an open approach (Mummaneni et al. 2019).

Open Lumbar Fusion

There are several variations on the traditional open PLIF technique. We prefer to decompress then instrument to allow us to palpate and visualize the pedicular walls, although the opposite sequence is equally valid. This guides our pedicle screw trajectory both in the craniocaudal as well as medio-lateral planes, thereby minimizing risk of breaching. We also remove most if not the entire facet, comparable to a traditional Ponte osteotomy or Schwab grade 2 osteotomy (Schwab et al. 2014) and affording a similar lateral trajectory as TLIF. Not only does this minimize the amount of nerve root retraction necessary, it also increases the amount of autologous bone available for fusion, and mobilizes the spine to facilitate interbody insertion, foraminal height restoration, spondylolisthesis reduction, and deformity correction. Topical hemostatic agents such as thrombin and gelatin are essential to minimize blood loss, and cell saver technology should be considered if available. Retractors are intermittently released throughout the case to minimize muscle ischemic time. In closing, the muscle is approximated to obliterate dead space, but not so tightly as to risk ischemia. The fascia is closed tightly, particularly if there has been incidental durotomy. We prefer to do this is in an interrupted fashion so that suture line integrity is not reliant on a single knot at each end. We often place an epidural catheter for narcotic infusion (Klatt et al. 2013) postoperatively in addition to a wound drain. There is also some evidence to suggest that topical vancomycin placed in the wound may reduce the incidence of postoperative infection, particularly following instrumentation (Khan et al. 2014). Loupe magnification with headlight illumination is used to enhance visualization.

Positioning

Following appropriate timeout, intravenous antibiosis, and application of mechanical lower limb antithrombotic devices, the patient is positioned prone on the operating table. Particular emphasis is paid to the position of the arms to avoid undue traction on the brachial plexus, padding of all potential pressure areas, sufficient room for the abdomen so as to not impede venous return, and slight reverse Trendelenburg position and avoidance of any direct pressure on the globes to prevent ischemic optic neuropathy.

Laminectomy

In exposing the spine, it is critical to avoid, if possible, violating the capsules of the facet joints of uninvolved levels, particularly at the upper-instrumented vertebra, to minimize acceleration of adjacent segment disease (ASD). Furthermore, clear delineation of bone and bony edges is paramount and facilitates surgeon orientation, particularly in revision cases where the anatomy may be distorted. Laminectomy is performed with a combination of Leksell bone nibblers, high-speed drill, and Kerrison punches. There is usually a deficiency in the midline where ligamentum flavum attaches to the undersurface of the lamina, where epidural fat is encountered, heralding entrance into the spinal canal. The thinner the bone is egg-shelled, the easier it is to enter the

canal with rongeurs. Significant dural adhesions may be encountered, especially in revision cases, which require careful separation with blunt dissectors such as curettes. Not all epidural adhesions or scar tissue require excision, provided the necessary neural elements have been detethered and decompressed.

Facetectomy

Following laminectomy, attention is turned to the facetectomy. The inferior articular process (IAP) is disarticulated by drilling or osteotomizing across the pars interarticularis, allowing it to be removed en bloc and saved as graft. Care must be taken to avoid violating the superior pedicle. The naked articular surface of the superior articular process (SAP) is then exposed. The SAP can be similarly removed en bloc by first palpating the superior border of the inferior pedicle with a blunt dissecting instrument such as the Woodson elevator. This defines the inferior limit of drilling or osteotomy (Fig. 1). The pars artery (Macnab and Dall 1971) is often encountered during these maneuvers and must be secured for hemostasis. In excising both the IAP and SAP en bloc, it is important that bony leverage occurs in the upward direction to avoid neural injury. Alternatively, Kerrison punches can be used to skeletonize the medial and superior borders of the inferior pedicle until sufficient space is created for interbody insertion. Care is taken superiorly and laterally in the foramen to avoid injury to the exiting nerve root. Foraminal ligament can be preserved as a protective barrier over the exiting nerve root if satisfactory direct and indirect decompression has otherwise been achieved.

Interbody

The epidural veins are cauterized with the bipolar tips parallel to the traversing nerve root to avoid inadvertent thermal injury, and divided to avoid neural traction. In cases where the disc is severely collapsed, it may be difficult to gain entrance into the disc space with traditional interbody instruments. It may be effective in these situations to enter the space with a smaller blunt tipped instrument, such as a pedicle probe, under lateral fluoroscopic guidance. Gradual distraction can then be achieved by sequentially upsizing spacers placed contralateral to the side that discectomy and endplate preparation is occurring if bilateral interbody devices are planned. Alternatively, laminar spreaders or ones anchored to pedicle screw heads can be used. Aggressive distraction must be avoided in the latter instance to avoid pedicular fracture, particularly in patients with osteoporosis.

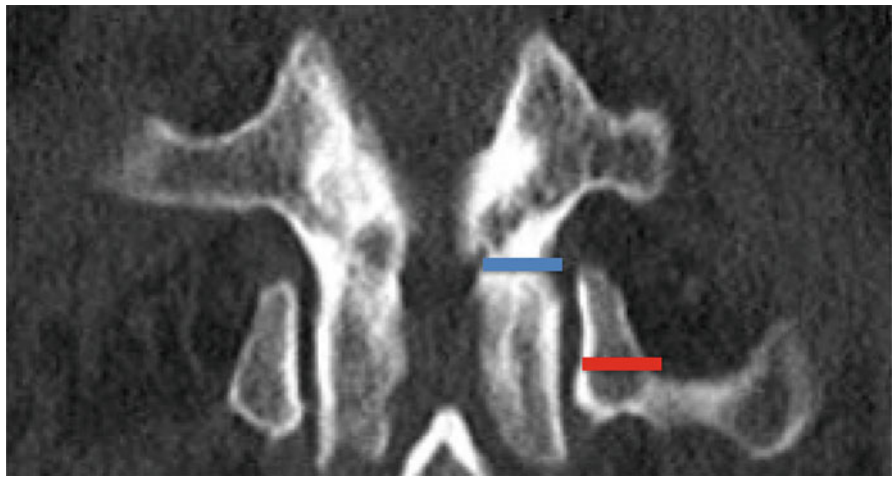

Fig. 1 Coronal lumbar spine computed tomography (CT) demonstrating the relationship of the IAP and SAP. The osteotomies performed are indicated by the blue (IAP) and red (SAP) lines, taking care not to violate the cranial and caudal pedicles

Similarly, care must be taken to avoid violating the bony endplate with forceful use of oversized shavers. The final implant is then inserted and impacted as ventrally as possible to take advantage of the strong apophyseal ring as well as maximize segmental lordosis. However, care must be taken to avoid breaching the anterior longitudinal ligament, as ventrally displaced cages are notoriously difficult to retrieve (Murase et al. 2017). Autogenous bone, supplemental allograft and BMP, if necessary, is packed into the disc space to enhance fusion (ventral to the implant in the case of BMP to prevent predural seroma and radiculitis), as implants themselves often contain very little space to accommodate graft. Traditionally, polyetheretherketone (PEEK) cages have been used, although titanium technologies are gaining popularity due to their osteo-integrative potential (Rao et al. 2014), at the cost of possibly increased risk of subsidence due to higher modulus of elasticity (Seaman et al. 2017), radio-opacity, and difficulties visualizing fusion mass. Insert and rotate devices (Sears 2005), as well as expandable cages (Fig. 2), offer further options in disc height and segmental lordosis restoration (Boktor et al. 2018). Autologous iliac crest bone graft, the gold standard to which other interbody devices and biologics have historically been compared, has been used with decreasing frequency due to the morbidity associated with its procurement (Banwart et al. 1995).

Pedicle Screw Placement

There are several methods for placing pedicle screws, including free hand and fluoroscopic techniques. Advances in navigation and robotics have improved placement accuracy (Kosmopoulos and Schizas 2007). We do not routinely use neuromonitoring due to its expense, lack of availability at our institution, and lack of substantive evidence demonstrating efficacy in preventing neurological harm outside of deformity, lateral transpsoas, and intramedullary tumor surgery (Fehlings et al. 2010). The safety of the freehand method is enhanced by intimate understanding of anatomy, visualization and palpation of the pedicular walls, tactile feedback, and subtle adjustments made based on detailed study of

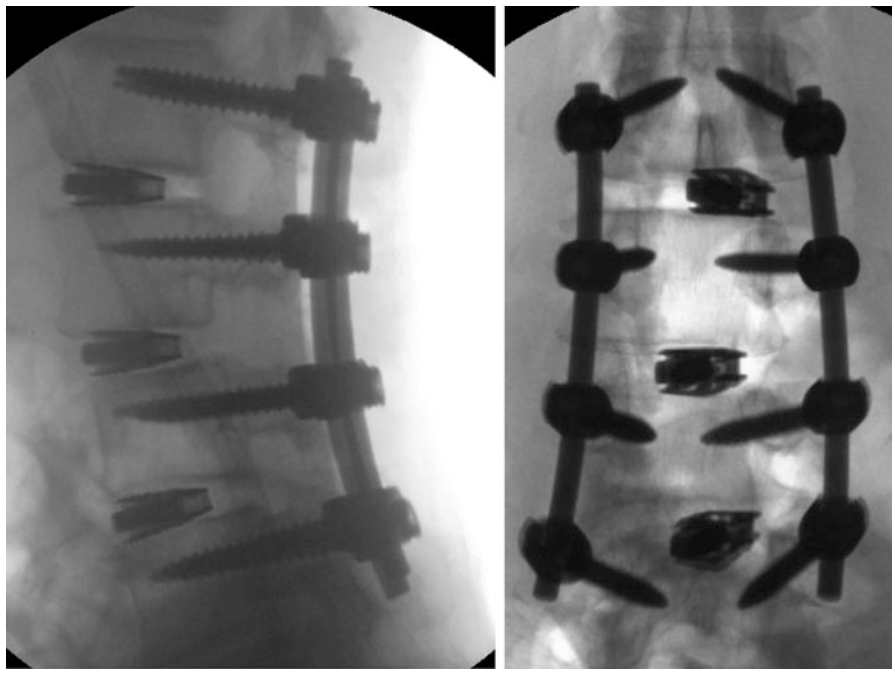

Fig. 2 Intraoperative lateral and AP x-rays demonstrating open L2–5 pedicle screw fixation and interbody fusion with expandable cages to restore foraminal height as well as segmental lordosis

preoperative imaging. Aiming perpendicularly toward the floor in the craniocaudal plane at L4 and adding approximately 5° of medialization per level to a baseline of 10° at L1 serve as useful additional guides.

The entry point is at the junction between the SAP and the bisected transverse process, where the mammillary process may be visualized (Fig. 3). To identify the entry point, it is often necessary to remove the lateral overhang of hypertrophic facets. This also serves to create sufficient room to house the head of the screw. Entry points can be customized to facilitate easier rod passage, particularly if multiple levels are instrumented. Furthermore, the trajectory of open pedicle screws is usually less medialized than their percutaneous counterparts due to the significantly increased amount of tissue dissection necessary in order to achieve a sufficiently lateral starting point, and the hindrance of both paraspinal musculature and retractors to medialization.

In probing the pedicle, tactile feedback is provided by the crunchiness of cancellous bone (in contrast to the hardness of cortical bone), and visual feedback by the marrow blush of the cancellous bone. It is critical that the screw goes down the same tapped hole, and can be aided by marking the trajectory on the skin edge, and to avoid forcefully tightening the screw against the facet, losing its poly-axiality and potentially stripping the screw. Screw symmetry can be achieved by leaving the handle on the contralateral screw as a guide or using fluoroscopic control. Pull-out strength is improved by using the longest screw possible with the widest diameter and augmenting with cement in osteoporotic patients. Given the largely cancellous nature of S1, it may be desirable to achieve bicortical purchase through the sacral promontory (the most corticated part of the vertebra) at this level. Compression and reduction are achieved against a final tightened screw if necessary, aided by extension tabs on the screw head, lordotically contoured rods, and cantilever maneuvers, although a significant degree of reduction is often already accomplished through the interbody work.

One must also be adept at managing breaches of the pedicular wall. While medial and inferior breaches have classically been associated with injury to the traversing and exiting nerve roots, respectively, lateral breaches can be equally undesirable, with potential injury to the adjacent intrapsoas lumbar plexus, as well as lumbosacral trunk at the caudalmost levels. While existing pilot holes can sometimes be rescued by redirecting the pedicle probe, including using ones with curved tips, it is often easier to fashion

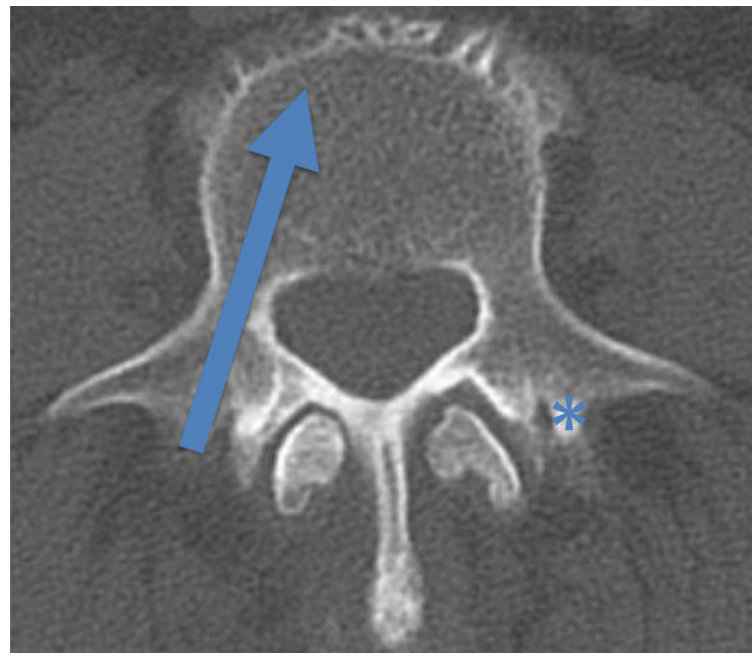

Fig. 3 Axial CT demonstrating the typical latero-medial trajectory of a lumbar pedicle screw (asterisk represents the mammillary process, an ideal entry point)

new entry points in order to avoid existing tracts. Careful examination of preoperative imaging can aide in preventing pedicular breach, including accounting for rotational deformities, as well as accounting for narrow, dysmorphic, or sclerotic pedicles, particularly on the concavity of a scoliotic curve in the latter.

Selected Variations in Open Lumbar Fusion

Posterolateral Fusion

We place interbody grafts routinely due to the aforementioned benefits. However, there may be clinical scenarios such as significant disc space collapse, weakened osteoporotic endplates, or minimal neuro-foraminal stenosis, in which interbody fusion may be difficult, inappropriate, or unnecessary. In these cases, posterolateral fusion serves as a reasonable alternative. Equally, posterolateral fusion may serve as a useful adjunct to interbody fusion in patients at risk for nonunion and in revision cases for pseudoarthrosis. It is critical that meticulous decortication of the transverse processes down to bleeding cancellous bone is performed to create an ideal fusion environment, a process that is often neglected. The remaining facet joint may also be decorticated. A cottonoid may be temporarily placed over the thecal sac as a barrier against bone graft inadvertently placed epidurally, preventing iatrogenic stenosis.

Pedicle Screws Via a Wiltse Approach

One of the criticisms of open pedicle screws is the difficulty in achieving the desired medialization due to hindrance by paraspinal muscles and retractors. Idealized exposures often require extensive lateral dissection and lengthy incisions. To mitigate this, bilateral incisions can be made in the lumbodorsal fascia through a single midline skin incision. Dissection is then carried down between the multifidus and longissimus muscles, often through a natural avascular cleavage plane, landing directly onto the junction between the facet joint and transverse process (Wiltse et al. 1968). This plane between the two muscles is measurable from the midline on preoperative imaging (Fig. 4), and often palpable and visible

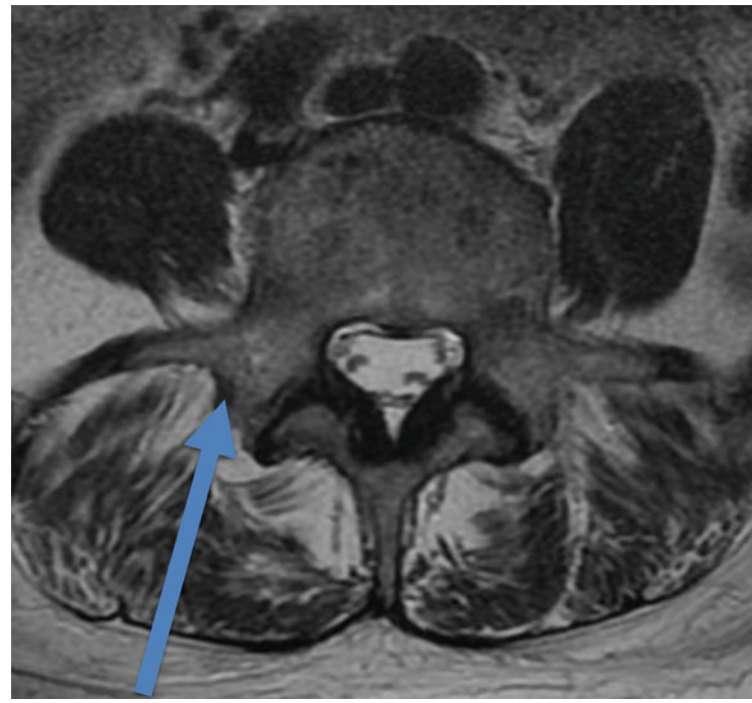

Fig. 4 Axial T2-weighted magnetic resonance imaging (MRI) illustrating the Wiltse paraspinal plane between medial multifidus and lateral longissimus, with a muscle-sparing approach (arrow) landing directly onto the facet-transverse process junction

intraoperatively. Pedicle screw insertion then proceeds in the aforementioned fashion. However, the extensive suprafascial undermining required creates significant dead space, which must be obliterated to prevent postoperative seroma and potential infection.

Cortical Bone Trajectory Screws

Some of the other criticisms of the open approach to pedicle screw placement are the amount of lateral muscular dissection required and the propensity to violate the facet capsule at the upper-instrumented level, thus potentially accelerating adjacent segment degeneration (Sakaura et al. 2019). Furthermore, pedicle screws reside mostly in cancellous bone, which is significantly weaker than cortical bone, an issue accentuated in osteoporotic patients. Within the last decade, a medial to lateral and inferior to superior screw trajectory has been proposed to address these issues, including maximizing purchase into cortical bone (Santoni et al. 2009). The entry point is in the pars, and the upward and outward trajectory is analogous to lateral mass screws in the cervical spine (Fig. 5). The poorer definition on fluoroscopy of the pars on fluoroscopy and the lack of tactile feedback due to the cortical nature of the traversed bone can be mitigated by use of intraoperative navigation. The spinous process navigation clamp, if used, should be placed at the cranial end of the exposure (rather than caudal end in navigated pedicle screws) to ensure that it remains between the surgeon and navigation camera, as well as maximizing the amount of

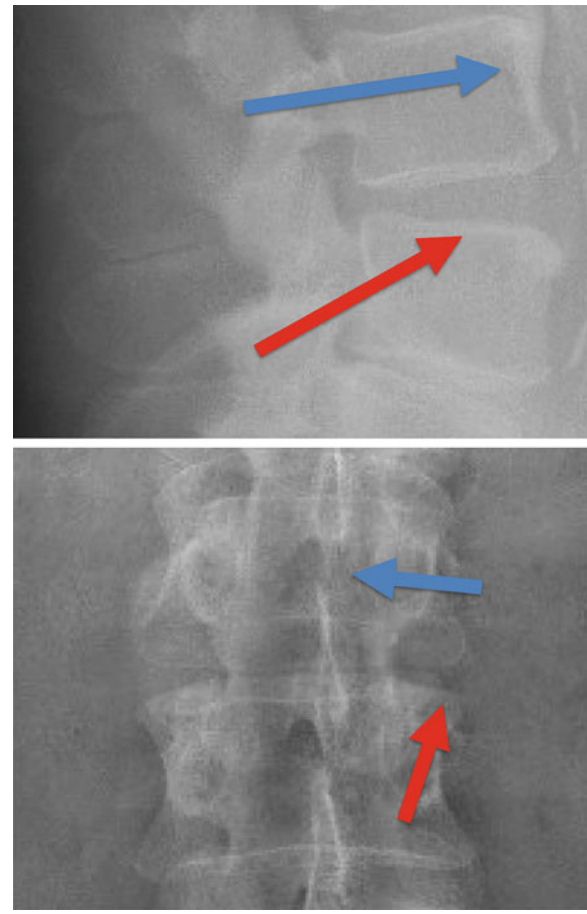

Fig. 5 Lateral and AP radiographs contrasting the latero-medial trajectory of traditional pedicle screws (blue arrows) versus the infero-superior and medio-lateral trajectories of CBT screws (red arrows)

working space given the caudo-cranial trajectory of these screws. The diameter and length of cortical bone trajectory (CBT) screws are typically narrower and shorter. While laboratory studies have demonstrated comparable biomechanical strength and some evidence exists to support similar short-term clinical and radiographic outcomes compared to traditional pedicle screws, long-term follow-up data remains pending (Phan et al. 2015b). The CBT screw certainly represents a less invasive open alternative to traditional pedicle screws, with a potential specific role in osteoporotic patients, although its efficacy in multilevel constructs, high-grade spondylolistheses, and deformity remains unknown.

Hybrid Percutaneous Screws with Miniopen Interbody

A minimally invasive variation on the traditional open PLIF combines percutaneous pedicle screw fixation, described later, with a miniopen midline incision for laminectomy and interbody work (Mobbs et al. 2012). This reduces the amount of lateral muscular dissection required and shortens the midline incision. In these hybrid cases, we prefer transversely oriented stab incisions for pedicle screw placement to longitudinal ones to minimize devascularization of overlying skin and soft tissues. A further variation involves paramedian stab incisions in the fascia through a single midline incision to avoid multiple unsightly skin incisions. The same percutaneous instrumentation can then be used through the fascial incisions. However, this often necessitates a longer incision, such as a traditional open approach, as well as extensive undermining of the skin alluded to previously.

Minimally Invasive Lumbar Fusion

An MISS TLIF is the archetypal MISS fusion procedure. It is often synonymous with tubular retractors and percutaneous pedicle screws, (Foley et al. 2003) although several variations exist. We prefer the miniopen paramedian Wiltse approach on the side of interbody, dissecting between the multifidus and longissimus muscles as this represents a natural cleavage plane, landing the surgeon directly onto the junction between the SAP and transverse process. Critics of the unilateral transforaminal approach cite poor disc clearance and endplate preparation for fusion, comparative biomechanical weakness in lateral bending compared to bilateral PLIF constructs (Sim et al. 2010), and inability to induce significant segmental lordosis (Carlson et al. 2019) as justification against minimally invasive TLIF. However, in cases of immobile facets, or where significant segmental lordosis induction (Jagannathan et al. 2009) or spondylolisthesis reduction is desirable, we often perform bilateral facetectomies for complete segmental mobilization through short bilateral paramedian incisions and muscle splitting Wiltse approaches. Expandable cages can further facilitate induction of segmental lordosis without compromising disc and foraminal height. Percutaneous pedicle screws are inserted through the Wiltse incision on the side of the interbody and small contralateral stab incisions. The MISS transforaminal approach also naturally lends itself to revision cases where florid epidural scar makes reapproaching through the midline technically challenging and potentially hazardous, with heightened risks of durotomy and cerebrospinal fluid leak.

Fluoroscopy Nuances

Once the patient is positioned, prepped, and draped, the C-arm is positioned in the anteroposterior (AP) plane. Kirschner wires are used to identify the desired level, as well as mark out the lateral border of the pedicle in the vertical plane and the bisected pedicle in the transverse plane. It is imperative that a true AP image of the desired vertebra is obtained, with a clearly defined superior endplate without any elliptical shadow, and midline spinous processes (Fig. 6). The C-arm should be locked in this position and any adjustments from the orthogonal plane recorded to ensure ease of return to the same desired position.

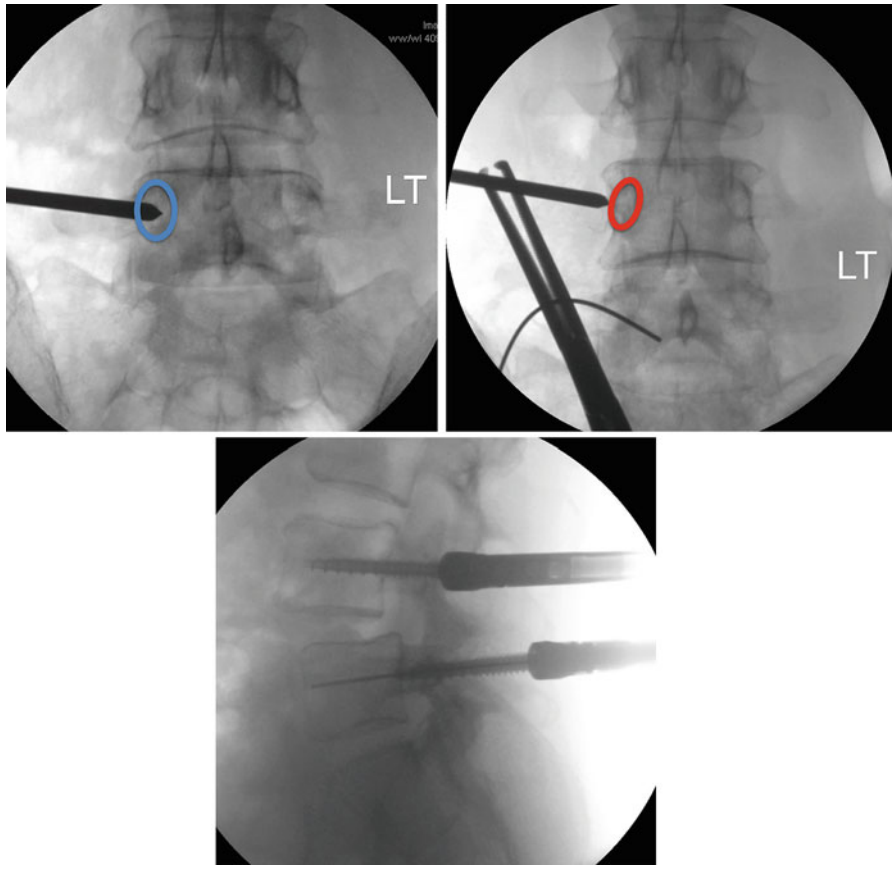

Fig. 6 True AP fluoroscopy with crisp L5 superior endplate (top image) and midline spinous process, demonstrating passage of Jamshidi needle and K-wire through the right L5 pedicle (blue circle, top image), followed by L4 (red circle, middle image), starting at 9 o'clock. At an approximate depth of 2 cm (usually heralding the junction between pedicle and vertebral body), the tip of the needle should not transgress the medial border of the pedicle. Screws are subsequently placed under lateral fluoroscopy (bottom images)

The importance of having a skilled radiographer experienced in the percutaneous workflow cannot be overemphasized. Draping of the C-arm and absolute attention to sterility are also of paramount importance, as any adjustments to the C-arm, particularly switching between AP and lateral views, can desterilize the drape and endanger the operative field.

Jamshidi Needle Advancement

Stab incisions are made approximately 1–2 cm lateral to the outer border of the pedicle, depending on the body habitus of the patient and the depth of intervening soft tissue. The bull's eye technique is used for pedicle cannulation (Fig. 6). The Jamshidi needle is docked at the junction of the SAP and the transverse process. It is often useful to walk the tip of the needle along the superior and inferior borders of the transverse process and the lateral wall of the facet joint for secondary anatomical confirmation. Close examination of preoperative imaging is crucial, as a severely hypertrophied facet joint can significantly alter the desired entry point as well as increase the depth the Jamshidi needle needs to be advanced in order to traverse the pedicle, traditionally considered to be 2 cm in patients without distorted anatomy. Failure to account for this

can lead to complications, including medial pedicular breach, and injury to the traversing nerve root and common thecal sac. The craniocaudal trajectory of the Jamshidi needle should match the degree of tilt or Ferguson on the C-arm.

While fluoroscopic control is critical, a degree of both tactile and aural feedback, similar to traditional open pedicle screw probing, remains possible and serves as secondary confirmation. Tactilely, advancement through crunchy cancellous bone should be relatively unhindered. Resistance often heralds proximity to cortical bone and forewarns against imminent pedicular breach. Similarly, the sound the Jamshidi needle makes against cortical bone when using the mallet is usually lower in frequency and duller in quality. There is often a small amount of toggle within the cancellous part of the pedicle to allow subtle redirections of the Jamshidi needle. Excessive force should, however, be avoided as the needle may bend, making passage of the Kirschner wire and subsequent needle removal from the vertebra difficult. It is critical to be constantly cognizant and wary of the length of the needle that has been advanced. Sclerotic pedicles pose a specific challenge to Jamshidi needle advancement and may necessitate gentle coring out of the pedicle with a high-speed drill to facilitate Kirschner wire passage, both carefully performed under fluoroscopic control but nonetheless often still achievable percutaneously.

Kirshner Wire Management and Screw Placement

The Kirschner wire can often be manually advanced up to 1 cm further into the cancellous bone through the Jamshidi needle without need for the mallet. Tip position within the vertebral body is confirmed if a bottom is palpable, analogous to using the ball tip feeler in open cases. At all stages, including Jamshidi needle removal, tissue dilation, tapping, and screw insertion, care must be taken to avoid inadvertent loss of wire position, including pullout or advancement, and undue twisting and bending. This is achieved both manually with judicious control with the noninstrumenting hand as well as constant attention to fluoroscopy.

Pedicle screws are inserted down the Kirschner wire through the tapped hole under lateral fluoroscopy (Fig. 6). When advancing the pedicle screw, resistance is met once the screw head meets the facet capsule. Further forceful advancement may cause stripping of the screw and loss of poly-axiality of its head. Systems incorporating a sharp-tipped stylet into a self-tapping screw now exist and further streamline the percutaneous workflow (Huang et al. 2020), although possibly at the cost of reduced tactile feedback. Navigation and robotic technologies that marry percutaneous pedicle screw systems also exist, reducing radiation exposure for the surgeon and other operating room staff, while maintaining high rates of placement accuracy (Kochanski et al. 2019).

Interbody

Once the contralateral pedicle screws and ipsilateral Kirschner wires have been placed, the ipsilateral skin and fascial incision are connected, and the facet landed upon by dissecting down through the natural cleavage plane between multifidus and longissimus. This is often accomplishable by spreading the tips of the bipolar forceps, coagulation and division of any small bridging fibers, and gradual retractor advancement. Blunt finger dissection is also often effective. Upon landing on the facet joint, we use a bladed retractor system such as the McCullough, with the short blade medial and long lateral, to maintain exposure. Kirschner wires can often be engaged into the teeth of the retractor blades and kept out of instruments' way. Further medial dissection with electrocautery is carried out, partially exposing the lamina. The steps that follow are like the interbody portion of the open approach detailed earlier, performed either under loupe magnification and headlight illumination, or microscopic visualization. A laminotomy is performed, followed by facetectomy, discectomy, and endplate preparation. Disc removal and fusion bed preparation can be optimized by gradual medialization of interbody instruments and

deployment of forward angled rongeurs. Distraction on the contralateral screws can be performed if necessary, to facilitate entrance into the disc space and maintenance of working corridor. Several interbody options exist, including banana-shaped devices, initially inserted vertically then gradually horizontalized to optimize ventral and medial positioning, maximizing cortical apophyseal ring contact, and potentially inducing lordosis, as well as bulleted and the expandable technologies previously described.

Rod Passage

After interbody and once the pedicle screws have been inserted bilaterally, attention is turned to rod placement. The incision through which the rod is placed may need to be extended to facilitate passage to avoid excessive skin tension. The tip of the rod is inserted initially vertically to engage the screw head and then advanced through each successive tower. This not only ensures subfascial placement, but also minimizes the amount of paraspinal muscle captured, preventing possible compartment syndrome. The rod is maneuvered with subtle movements to engage each tower, including medially or laterally rotating the rod holder. Screw engagement is confirmed if the overlying tower no longer rotates, by dropping a specialized measuring tool down the tower, by direct visualization, or by fluoroscopy. Placing the set screw into the tulip closest to the rod holder first brings the rod beyond the screw head, ensuring sufficient rod proximally. Reduction can be achieved through a variety of means, including rod contouring, extension, and cantilever maneuvers, as well as specialized reduction tools.

Selected Variations in Minimally Invasive Lumbar Fusion

Tubular Retractors

Traditionally, MIS lumbar fusions have been associated with the tubular retractor (Foley and Smith 1997). This requires gradual dilation through the paraspinal musculature and docking of the final tube on the facet joint prior to securement onto a table-mounted arm. Despite gradual dilation, a small amount of muscle is invariably encountered at the depth of the retractor, which then requires excision for exposure. If the tubular system is used, we advise against the use of the initial Kirschner wire due to the risk of inadvertent dural puncture and neural injury. The retractor should be docked onto the facet joint with sufficient exposure of the adjacent lamina, and ideally orthogonal to both the desired disc space as well as the floor to optimize disc access and surgical ergonomics. Given the narrow working corridor, specialized angled and bayonetted instruments are necessary. Similarly, the protected portion of the conventionally straight monopolar tip can be manually bent to facilitate use. Various other retractor systems, including bladed and screw-based assemblies, are also available.

Cross over the Top Decompression for Bilateral Stenosis

If decompression of the contralateral subarticular zone is desired, the retractor can be wanded medially (Fig. 7) or the bed rotated to facilitate over-the-top decompression. In this method, also known as unilateral laminotomy for bilateral decompression (ULBD) or ipsilateral-contralateral approach, the ligamentum is left intact while the base of the spinous process and under surface of the contralateral lamina are drilled to protect the underlying dura. Flavum and contralateral medial facet can subsequently be removed till the hump of the thecal sac drops away and the contralateral traversing nerve root visualized. The dura is at greatest risk of injury when rongeuring medially due to the upward slope of the thecal sac, though the risk of overt cerebrospinal fluid leak is low as the paraspinal muscles remain largely intact and reapproximate following retractor removal, obliterating any dead space. Use of upward angled Kerrison punches can also be useful in this approach to achieve contralateral decompression. The results of this approach are comparable to the traditional midline laminectomy, while largely

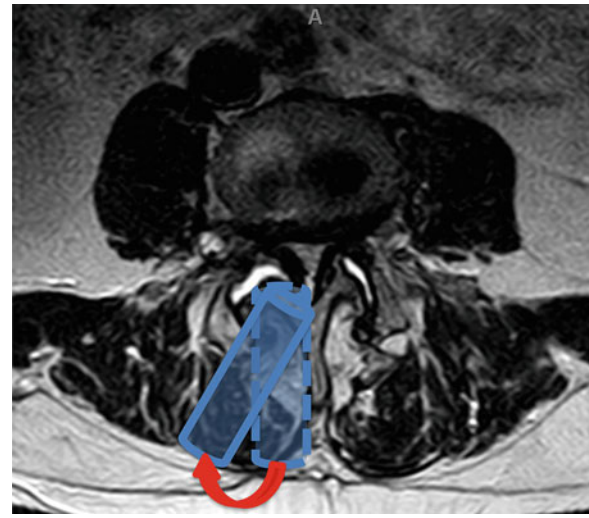

Fig. 7 Axial MRI simulating wanding (red arrow) of the tubular retractor (blue cylinders) to facilitate decompression of the contralateral lateral recess from a unilateral approach

preserving the posterior tension band (Mobbs et al. 2014).

Endoscopy

More recently, endoscopic techniques have been applied to minimally invasive TLIFs, permitting even smaller incisions and less tissue destruction. This has been combined with awake anesthetic techniques, application of long-acting liposomal local anesthetic agents, expandable technologies, biologic materials, and ERAS protocols to treat a range of lumbar spondylotic conditions (Kolcun et al. 2019). The intervertebral disc is accessed via percutaneous transforaminal route through Kambin's triangle using a spinal needle, followed by nitinol wire insertion and sequential dilation and docking of an endoscopic channel, all under constant fluoroscopic control (Fig. 8). Discectomy and endplate preparation are accomplished using specialized endoscopic rongeurs and curettes, and percutaneous reamers, shavers, and stainless-steel brushes, followed by sizing and insertion of an expandable interbody device. The procedure is completed by standard insertion of percutaneous pedicle screws. While long-term and comparative data are eagerly awaited, this technique, representing the least anatomically and physiologically disruptive of all MIS fusion methods, holds promise for elderly and infirm patients who may not otherwise tolerate lengthy prone general anaesthetics (Kolcun et al. 2019).

Thoracic Instrumentation and Selected Variations

A comprehensive description of the multitude of approaches to the thoracic spine is beyond the scope of this chapter. We will, however, endeavor to describe the various options for posterior thoracic instrumentation, both open and minimally invasive. MIS thoracic instrumentation naturally lends itself to scenarios in which direct decompression or fusion is unnecessary, such as burst fractures in patients without neurological compromise, while traditional open methods remain valid, particularly if concomitant direct decompression, fusion, or anterior column reconstruction is required, such as in oncologic pathologies.

The traditional entry point for thoracic pedicle screws is immediately inferior to the intersection between the superior border of the transverse process and the lateral border of the SAP, classically

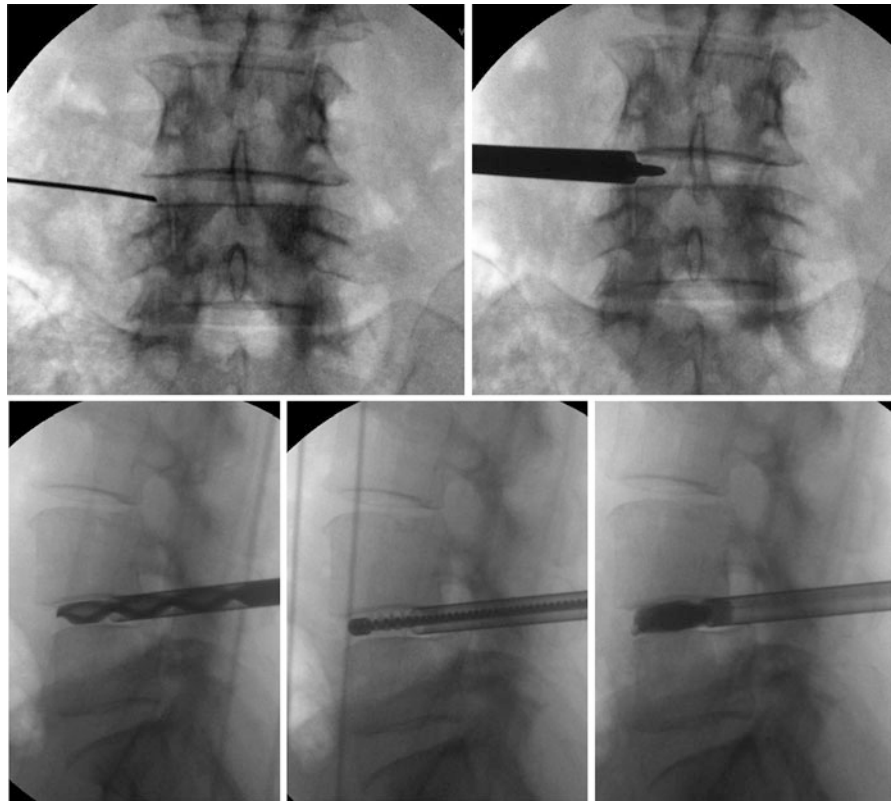

Fig. 8 Intraoperative fluoroscopy demonstrating transforaminal entrance into the L4–5 intervertebral space via Kambin's triangle using a spinal needle (**a**), followed by sequential dilation (**b**), introduction of percutaneous reamer and stainless steel brush (**c** and **d**), and measurement of extent of discectomy and sizing of interbody graft size by inflation of a balloon with radio-opaque contrast (**e**)

described as the junction between the medial two-thirds and lateral one-third of the base of the SAP (Fig. 9) (Chung et al. 2008). The ideal entry point moves slightly laterally and inferiorly as one progresses toward the cranial and caudal ends of the thoracic spine (Kim et al. 2004). Adjustments to the entry point in the axial plane can also be made based on the patient's unique anatomy on preoperative CT. Furthermore, bleeding cancellous pedicular bone can often be exposed by removing the tip of the transverse process, particularly at T12 (Fig. 10). Medialization increases at the superior-most segments of the thoracic spine, while both straight forward and the more caudally directed anatomical trajectories (Fig. 9) in the sagittal plane are acceptable (Puvanesarajah et al. 2014). The in-out-in technique (Fig. 9) with a more lateral entry point along the superior edge of the transverse process to minimize risk of medial breach has also been advocated and may be especially useful in patients with narrow pedicles, particularly in the mid-thoracic spine, enabling the insertion of wider and longer screws with tri-cortical purchase (Jeswani et al. 2014).

Percutaneous thoracic pedicle screw insertion follows the same principles described previously for the lumbar spine. We adopt a strategy of erring on the side of less medialization of the Jamshidi until the pedicle-vertebral body junction is reached to minimize risk of medial breach, followed by subtle toggling of the needle to

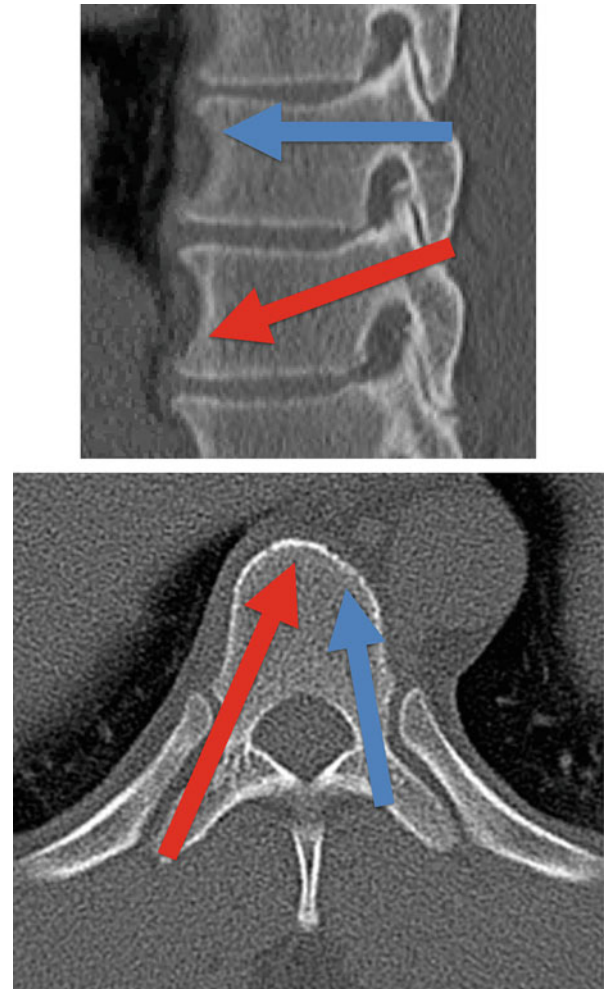

Fig. 9 CT comparing the straight forward (blue arrow) trajectory, parallel to the endplates, with anatomical (red arrow), parallel with the superior and inferior pedicular borders, in the sagittal plane (top image), and traditional intrapedicular (blue arrow) and in-out-in (red arrow) techniques in the axial plane (bottom image)

achieve more medialization to ensure that it remains within the vertebral body. Navigation and robotics may also improve accuracy of thoracic pedicle screw insertion, both open and percutaneous, especially in cases with narrow pedicles or significant deformity (Kochanski et al. 2019).

Conclusion

In summary, the posterior approach to the thoracolumbar spine is a versatile workhorse for the spine surgeon, affording access to all three columns of the spine and enabling the trinity of decompression, instrumentation, and interbody through a single approach. Both open and minimally invasive approaches present valid options, and the modern spine surgeon should be adept at both in order to cater to the needs of different patient populations with contrasting pathologies. Advances in navigation and robotics, biologics, access, instrumentation, and expandable technologies have improved the safety and efficacy of minimally invasive thoracolumbar fusions. These advances, coupled with progress in perioperative protocols and multidisciplinary care, will continue to deliver improvements in posterior thoracolumbar surgery.

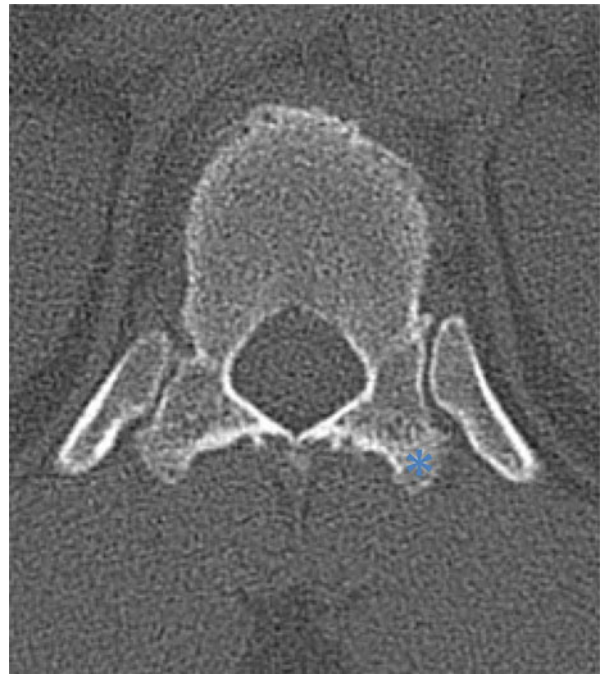

Fig. 10 Removing the tip of the T12 transverse process (asterisk) can aide in the exposure of the underlying cancellous pedicular bone

Cross-References

- ▶ Lumbar Interbody Fusion Devices and Approaches: When to Use What
- ▶ Minimally Invasive Spine Surgery
- ▶ Pedicle Screw Fixation

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Lateral Approach to the Thoracolumbar Junction: Open and MIS Techniques

58

Mario G. T. Zotti, Laurence P. McEntee, John Ferguson, and Matthew N. Scott-Young

Contents

Abstract

The thoracolumbar junction is a site less commonly affected by degenerative disease but disproportionately affected by unstable spinal pathologies such as fractures, infections, and neoplasms. Varying approaches for the treatment of these pathologies have been historically described, but there has been a shift toward more pathology being treated by minimally invasive approaches. While a working knowledge of the open approach and its advantages and disadvantages is important, the MIS approach is favored where feasible due to being less disruptive with reduced cardiovascular, respiratory, muscular, and cosmetic morbidity. The unique anatomy of the thoracolumbar junction is discussed with respect to the separation of and structures relevant to the abdominal and thoracic cavities. Evaluation of and preparation for surgery

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of patients with thoracolumbar junction pathologies are also discussed. With considered techniques, an expansion of the safe treatment of spinal pathologies has been made possible.

Keywords

Thoracolumbar junction · High lumbar · Lower thoracic · Lateral approach · Lateral interbody fusion · Minimally invasive (MIS) · Open

Introduction

The thoracolumbar junction (TLJ) is a transitional zone between the rigid thoracic spine and relatively mobile lumbar spine, making it a common site for spinal fractures, as well as being afflicted by other diseases including infectious, neoplastic, and degenerative lesions. With the advent of modern instrumentation, pathology and deformity involving the thoracic spine are being increasingly treated via posterior techniques in isolation. However, the sensitivity of the spinal cord to any manipulation, high rates of durotomy, and the limited access afforded by other posterior-based approaches such as costotransversectomy limit the safe and complete treatment of anterior column-based pathology with posterior approaches (Arnold et al. 2012; Malham and Parker 2015). Concurrently, there has been a significant advancement of surgical approaches and techniques to approach the thoracolumbar and lower thoracic vertebrae safely causing a paradigm shift from open thoracotomy-based techniques to thoracoscopic and lateral minimally invasive surgery (MIS) exposures. This development has led to expanding indications for the lateral and anterolateral approaches to treating pathology of the thoracolumbar region such as disc herniation, vertebral body/pedicle tumor, and infection as well as allowing efficient and safe intervertebral space access for interbody anterior column support.

Patient Presentation

Pathology of the TLJ such as tumor, trauma, and infection of the thoracolumbar anterior column will generally present with significant pain with or without radiculopathy or myelopathy. Trauma or systemic malaise in these cases will cause the patient to present for medical investigation where further imaging may reveal a TLJ lesion. Deformity, where utilization of the anterior column of the TLJ may form part of the surgical strategy, may include coronal or sagittal plane deformities and may be idiopathic or syndromic in nature. While many of these deformities will present in childhood, there is an increasing burden of ageing patients presenting for treatment with de novo deformities in middle age and beyond due to pain or deformity.

The degenerate or herniated thoracic disc presents variably. While many thoracic disc lesions are asymptomatic, significantly symptomatic thoracic herniations account for around 1% of disc-related presentations. Anand and Regan (2002) developed a classification system for different presentations of symptomatic thoracic disc herniations and their outcome. These include presentations of axial pain only (28%), thoracic radicular only (5%), axial pain and thoracic radiculopathy (38%), axial pain and lower leg pain (19%), myelopathy (8%), and paralysis (2%). Unlike symptomatic lumbar disc disruption, symptomatic thoracic disc disruption does not tend to respond favorably to nonsurgical measures, and surgery is generally recommended. Arce and Dohrmann (1985) in their series of 280 thoracic discs found that 75% are in the lower thoracic segments (T8–T12).

Indications and Comparison of Approaches

Indications for thoracolumbar spinal surgery include treatment of anterior- and middle column-based tumors or infections (Kawahara et al. 1997; Uribe et al. 2010; Pimenta 2015), as an adjunct in a deformity correction strategy for short segment fusion of focal coronal malalignment

or focal kyphosis (usually with posterior instrumentation) (Good et al. 2010; Min et al. 2012), in the trauma setting for vertebrectomy of burst fractures, and treatment of pseudarthrosis and degenerative lesions. Regarding the latter, disc pathology either herniated nucleus pulposus causing ventral cord compression or significant degenerative disc disease can be treated with microdiscectomy or interbody fusion, respectively. While microdiscectomy has been published with favorable results (Malone and Ogden 2013; Nacar et al. 2013; Oskouian et al. 2002; Otani et al. 1982; Berjano et al. 2014; Roelz et al. 2016), the desire to avoid further approach involving the pleura for the patient in the form of a revision fusion has led some authors to advocate for primary fusion, with satisfactory results (Berjano et al. 2012, 2015; Malham and Parker 2015; Meredith et al. 2013). Posterior-based approaches can be considered for dorsal cord compression, but treatment of anterior-based pathology from a posterior-only approach historically yielded unsatisfactory results, and an example of this is shown in Fig. 1 (Love and Kiefer 1950; Logue 1952; Benson and Byrnes 1975; Perot and Munro 1969).

Complications, regardless of mode of approach, remain significant and include pleural effusion, pneumothorax, intercostal neuralgia, vascular injury, pain associated with chest tube (if required), and diaphragmatic paresis or herniations (if affected) (Boriani et al. 2010). Open procedures, despite being considered "gold standard," were particularly affected by intercostal neuralgia and incisional pain and required a thoracic access surgeon. Open approaches have more classically been either the transthoracic retroperitoneal or lateral retropleural approaches and, more recently, a lateral extensile extracavitary approach. There is significant patient discomfort and pulmonary complications that stem from need for resection of a rib, deflation of ipsilateral lung, and insertion of a chest tube which can all contribute to postoperative pain, atelectasis, and pneumonia (see Fig. 2). Thoracotomy-associated major complications occur in 11% to 11.5% of patients, tend to extend hospitalizations, and augment medical resource use (Faciszewski et al. 1995).

Treatment of thoracolumbar lesions that was once marked by significant morbidity and patient risk that resulted from traditional open techniques has become feasible and technically simpler due

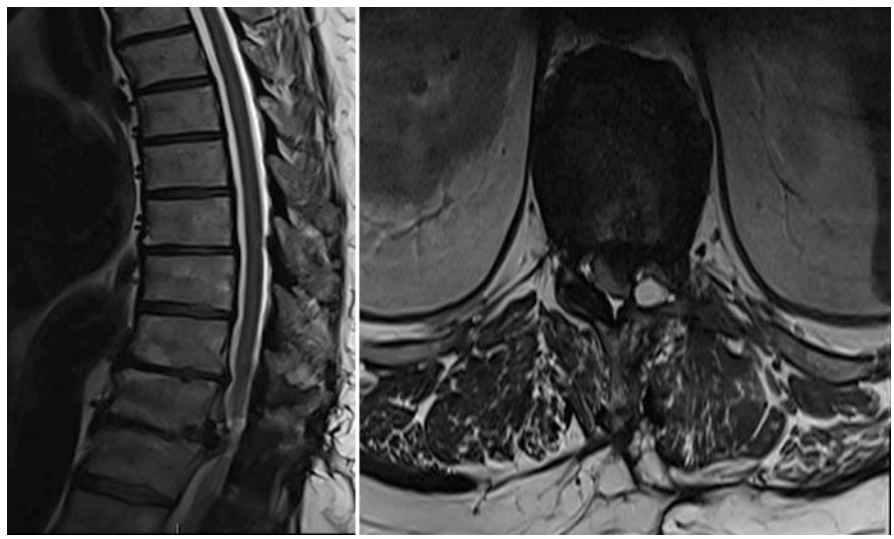

Fig. 1 Ventral cord compression from T11/12 degenerative disc-osteophyte complex causing clinical myelopathy. Posterior decompression failed to improve the patient's symptoms and residual compression and cord signal change is demonstrated

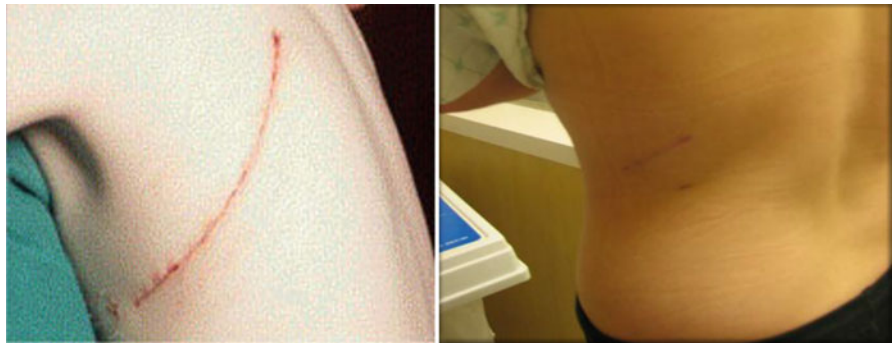

Fig. 2 Significant scar and morbidity from traditional open transthoracic approaches to the thoracic spine (left); MIS incision required to approach limited TLJ levels (right). (Copyright 2009, used with permission from NuVasive. All rights reserved)

to the evolution of surgical techniques stemming from development of MIS approaches to the thoracic spine (Smith and Fessler 2012). The advantage of thoracoscopic and MIS techniques is that they are minimally disruptive (not usually requiring rib resection), deflation of the lung is not routinely required, and there is minimal blood loss, direct visualization, less risk of aortic injury, and typically no requirement for any chest tube. However, circumstances may dictate that such approaches may not be appropriate for the patient despite indicating pathology, e.g., significant thoracic pulmonary injury and hemothorax involving the operative segments for trauma vertebrectomy or a primary bone tumor in the anterior column necessitation open approach to minimize contamination and safely perform spondylectomy (Gandhoke et al. 2015).

Limitations of the thoracoscopic (also known as video-assisted thoracic surgery (VATS) or thoracic endoscopic) technique include a high learning curve, limited visualization compared to direct stereoscopic assessment, and need for lung deflation. VATS had been first reported in 1993 for spinal disease by Mack et al. (1993) VATS allows a significant reduction in chest wall morbidity related to the traditional thoracotomy (Cunningham et al. 1998; Newton et al. 2003). These included a reduction of the postoperative incisional pain and intercostal neuralgia. While thoracoscopy is capable of producing the same exposure as the transthoracic route without the need for a large incision or rib resection, there is, however, still a significant decrease in vital capacity by up to 30% (Faro et al. 2005). This technique provides a greater access to more vertebral levels through smaller incisions, when compared to transthoracic approach, but still presents some complications, such as intercostal neuralgia (7.7%), symptomatic atelectasis (6.4%), excessive (>2000 cc) intraoperative blood loss (2.5–5.5%), pneumonia (1–3%), wound infections (1–3%), chylothorax (1%), tension pneumothorax, long thoracic nerve injury, and pulmonary embolism (Pimenta Journal of Spine 2015). Although this is an effective technique in specialized practices that have sufficient experience and expertise with this skill set, MIS techniques are technically simpler, without a steep learning curve, and arguably safer for spine surgeons not trained in endoscopic surgery, and, as such, we will focus on open and MIS TLJ approaches.

The MIS approach referred to herein is either a direct or extreme lateral approach depending on the proprietary company and is either in the form of a coelomic (transthoracic) or extracoelomic (retropleural) approach, while the lumbar spine requires a retroperitoneal approach (Uribe et al. 2010). Because this approach remains in the retroperitoneal/retropleural space, it can be performed from the right or left side depending on surgeon preference or location of the pathology without interference by the liver, spleen, or other peritoneal structures and theoretically can access from T4 to L5 blocked superiorly by the axilla and inferiorly by the iliac crest (Malham and Parker

2015). Because the approach remains in the extracoelomic space and the diaphragm is not incised, there is no need for any repair of the diaphragm (Pimenta 2015). The MIS approach also can traverse the diaphragm with care, enabling the surgeon to treat low thoracic and high lumbar levels either side of the TLJ by coming from pleural to retroperitoneal through a diaphragmatic incision. Above T12–L1 there is typically no need for dividing the diaphragm. Diaphragmatic incisions need to be biased toward the chest wall and periphery to minimize diaphragmatic innervation disruption and enable a tendinous repair, and regarding incisions, there is evidence that incision <4 cm of the diaphragm heal without suture.

With regard to pitfalls and contraindications to the MIS approach, it is important to understand that there is a long working distance in a relatively narrow working space, and as such, the operative tools typically used may not be long enough to perform the procedure in some patients. Further, retropleural and retroperitoneal dissection may not be feasible after a previous ipsilateral thoracotomy or retroperitoneal approach such as patients who have had osteomyelitis of the spine and spinal metastases, where marked paraspinal pleural reactions with adhesive thickening of the parietal pleura and infiltration of the pleura by tumor or inflamed fibrous tissue can occur (Uribe et al. 2010).

Relevant Anatomy of Thoracolumbar Junction

The complex relationship between the diaphragm, ribs, pleura, and peritoneum poses a notable challenge when surgically approaching the lower thoracic and upper lumbar vertebrae (Pimenta 2015), and the relevant structures at risk to be aware of must be studied and anticipated.

The basic path of MIS approaches is through the rib cage laterally onto the targeted disc space. After incision through the skin and fat, the palpable targeted rib is sought and a plane developed above the rib. This is as the intercostal neurovascular bundle lies directly inferior and deep to the rib. One can do a rib osteotomy for access and graft material but places the neurovascular bundle at risk unless it is explicitly protected. The parietal pleura which is the next layer is plastered over the inner surface of the rib-intercostal complex. This must be penetrated, ideally with blunt dissection, prior to entering the chest cavity. The visceral pleura, on the other hand, overlies the lung parenchyma, and a pneumothorax can result with its injury.

The relevant vascular anatomy includes on the right, the vena cava; on the left, the aorta (variable course); and traversing the field, the segmentals. If approaching on the left-hand side levels T8–L1, it is imperative to assess on preoperative imaging and angiogram for a dominant vascular cord supply in the form of the artery of Adamkewicz, as ligation of this segmental vessel unknowingly may disturb region flow to the cord. Left-sided lateral approaches will require ligation of the segmentals at the level of planned treatment and possibly adjacent levels for safety as they come off the left-side positioned aorta and transmit segmental branches posteriorly which will be encountered in cases of vertebrectomy and plate positioning.

The diaphragm is a complex but important three-dimensional dome-shaped structure to understand, particularly if planning TL approaches as it will be in the surgical access path when approaching levels from T10 to L1. Uncontrolled injuries to the diaphragm can lead to atelectasis, reduced vital capacity, and hypoxemia. It has multiple attachments and separates the thoracic from the abdominal cavity between T12 and L1 with a convex superior thoracic floor and concave inferior abdominal roof. The crura extend along the anterolateral vertebral body on each side with the left crus extending to L2 while the right extends to L3. It is innervated central to peripheral (important for incision and dissection planning) with the phrenic nerve supplies entering medially toward the periphery, formed by the C3-4-5 cervical nerves, more prevalent in its central portion (Joaquim et al. 2012). The peripheral portions of the diaphragm have sensorial afferents from the intercostal nerves (T5–11) and the subcostal nerve (T12) (Joaquim et al. 2012).

Regarding the relationship of the diaphragm to the peritoneum, the posterior portion of the diaphragm is separated from the peritoneum by a fat layer and by the superior aspect of the kidneys and adjacent structures. Posteriorly, the diaphragm forms two ligamentous bands, on either side: the medial and lateral arcuate ligament. The former arises from the tip of the 12th rib and expands around the quadratus lumborum, while the latter spans across the psoas muscles. These ligamentous bands meet on the transverse processes of L1. Also to be aware of are diaphragmatic openings which transmit structures. These are the aortic hiatus (containing the aorta, azygos vein, and thoracic duct between the left and the right crura), the esophageal hiatus (containing the esophagus and anterior and posterior vagal trunks), and the caval hiatus (inferior vena cava and branches of the right phrenic nerve) (Joaquim et al. 2012). Other small openings are also present, especially near the crus (containing the splanchnic nerves and the hemiazygos veins).

Regional wall muscles include the latissimus dorsi, intercostal, transversus abdominis, and external and internal oblique muscles as well as the quadratus lumborum. The superficial nerves such as the subcoastal (T12), Iliohypogastric (L1), and ilioinguinal (L1) nerve can run in the field of dissection and the abdominal wall planes after and be injured if any sharp dissection or diathermy is undertaken between the muscular layers. The position and morphology of the psoas muscle should also be considered for high lumbar procedures given that trans-psoas approaches to L1 and L2 still have the potential to injure the upper lumbar plexus. They generally consist of two main portions in their origins: the anterior and lower edges of the lumbar transverse processes and the lateral vertebral bodies and annuli of the lumbar vertebrae. Slight flexion at the hip in positioning can help to relax each psoas and reduce the tendency for anterior traction on the lumbar plexus.

As the approach goes further caudally to the L1 and L2 levels, the retroperitoneal structures come into play. The lumbar plexus, unless there are vertebral anomalies, does not tend to be at risk unless approach levels at T12 and lower as it is generally formed from ventral roots of L1–L4 (with variable subcostal T12 contribution) and sits in the posterior third of the psoas. Renal vessels and the position of the ureters and bowel must be considered when approaching L2 and caudally, particularly if the approach strays anteriorly. Ventral exiting branches can still be injured by retractors placed too posteriorly, even above the level of the psoas origin, and for this reason, retractor placement in the ventral anterior three quarters of the body is recommended (Arnold et al. 2012).

Operative Considerations

Preoperative Workup

The patient should be assessed from the point of view of fitness for surgery and anesthesia in the perioperative period. Where possible, all acute illness should be dealt with and the patient physiology and nutrition optimized, in a multidisciplinary fashion, before they undergo surgery. Relevant biochemistry, hematological parameters, as well as blood typing for possible transfusion should be assessed and prepared for surgery. Poor nutritional status (preoperative albumin and ferritin), current or recent smoking, and lung parenchymal radiotherapy may be more subtle to patients at risks of pulmonary complications than the obvious patients with morbid obesity and obstructive airway disease.

Pulmonary function tests are particularly relevant in the elective or semi-urgent setting where poor reserve or functional asymmetry of the pulmonological system may warrant delaying the surgery or modifying the side and type of approach.

AP/lateral X-ray erect films are ideal to assess for vertebral body size and alignment (see Fig. 3). EOS standing films, if available, give detailed study of the spine type and alignment which is important when treating lesions that have likely significantly altered the sagittal profile of the patient. CT or MRI assessment of structures at the planned operative level should be undertaken especially looking for calcification, which may cause

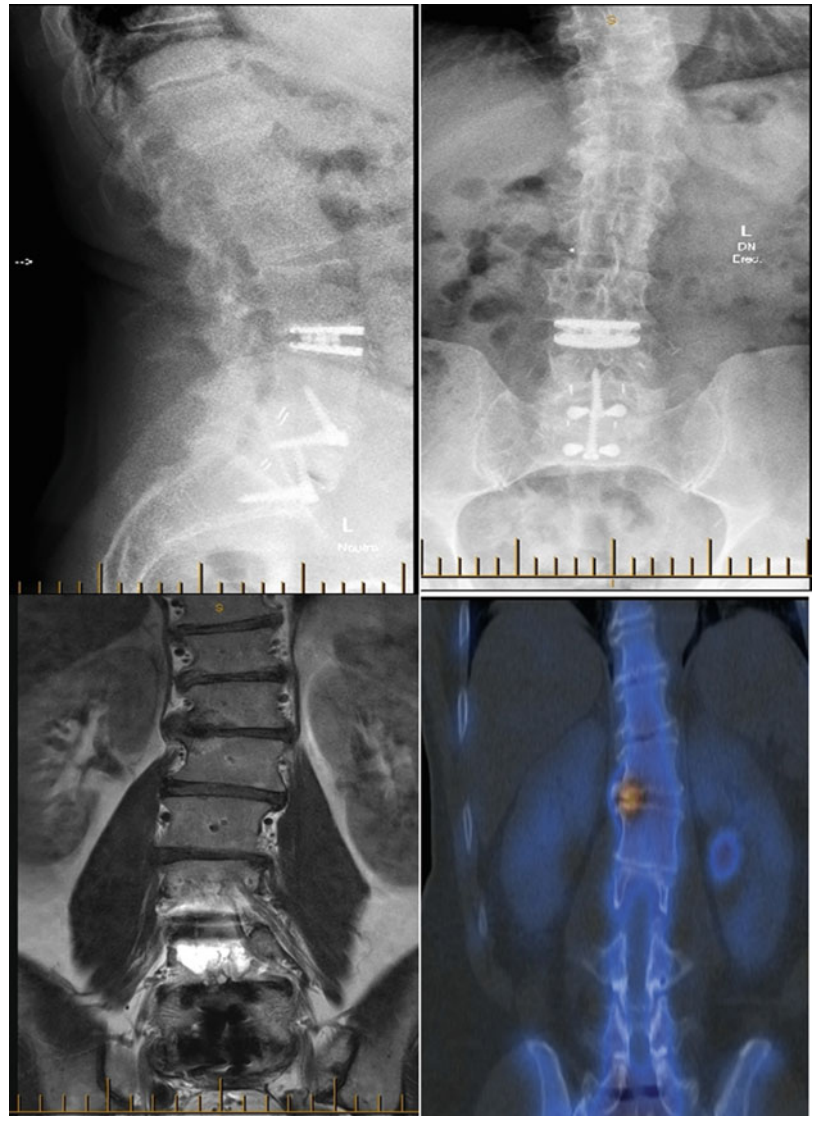

Fig. 3 Erect lateral and anteroposterior films and coronal MRI demonstrating collapsed T12/L1 disc. Note "hot spot" on SPECT scan due to collapse and focal scoliosis

operative difficulty (see Fig. 3). In the case of trauma, it will also assist with non-contiguous injury and evaluate for any posterior element injury or hematoma that may change management. The MRI also allows adequate assessment of the neural elements and position of the conus medullaris.

Neurological studies such as nerve conduction studies and/or electromyography may characterize and reveal any preoperative myelopathy or radiculopathy prior to treatment that may have implications for prognosis and patient expectations.

In the case of suspected neoplastic or infectious lesions, the local and systemic staging followed by biopsy and/or microbiological testing should be instituted to characterize the pathology (Liljenqvist et al. 2008). Diagnosis of thoracic DDD has not been well characterized. Axial ache and stiffness that changes with rest, recumbency, and different positions is suggestive. Extrapolating from lumbar studies, discogram is the gold standard, while combinations of findings on CT/MRI and pain blocks or activity on nuclear medicine scans can support a diagnosis.

Depending on the level(s) to be approached, the position of the aorta, the sympathetic plexus, and renal vessels and their relation to the psoas muscle and the spinal curvature should be studied. Scoliosis may place the aorta in the path of the lateral surgical corridor and may warrant consideration for right- rather than left-sided approach. If there is significant anomalous anatomy, then obtaining an arteriogram and/or venogram may be prudent.

Intraoperative

The procedure is undertaken under general intravenous anesthesia so as not to attenuate motor pathway signals of the neuromonitoring. As to the choice of endotracheal tube, a double lumen tube for selective lung ventilation is utilized above T8 level, whereas below T8 it is not usually necessary for MIS.

Open Lateral Approach to the TLJ

The patient is positioned lateral and commonly left side up with the most common approach to access T10–L2 being the left-sided thoracolumbar junction approach and is described adapted from the retropleural thoracotomy of McCormick (1995). Alternatives include the mini-thoracotomy and transdiaphragmatic, extrapleural (Balasubramaniam et al. 2016; Foreman et al. 2016; Graham et al. 1997; Otani et al. 1988), or left-sided thoracotomy. Pertinently, high thoracic lesions tend to be approached from the right to limit exposure to cardiovascular structures, while more caudal thoracic lesions are best approached from the left to avoid the inferior vena cava and liver.

An oblique incision is centered over the pathological vertebra/disc space as confirmed by image intensifier. The length of the incision will depend upon the number and location of levels to be treated. The incision is made over the rib belonging to the vertebrae 2 levels above the targeted discovertebral space given the caudal sloping of the ribs, e.g., 10th rib for T12. The thoracic muscles over the rib and abdominal muscles distal to the costal cartilage are divided with electrocautery. There is subperiosteal exposure of the rib, and depending whether bone grafting or interbody fusion is planned, it can either be preserved or osteotomized, protecting the caudal neurovascular bundle, for later use. The parietal pleura is opened at the posterior aspect of the wound revealing parenchyma/visceral pleura of the lung and the diaphragmatic attachment to the chest wall anteriorly.

Next, the retroperitoneal space is accessed via splitting the layers of the abdominal wall at the anterior part of the incision, and the peritoneum is peeled off from the inferior surface of the diaphragm down to the crus adjacent to the spine. It is important to leave a small (1–2 cm) cuff for later repair, and marking stay sutures periodically can be useful to aid later approximation. Smooth handheld deep retractors may be used here, but a dedicated table-mounted retraction system allows ease of access and ergonomics in a limited field.

Further steps of the approach depend on the discovertebral level(s) to be accessed as is discussed below (Vialle et al. 2015). If above T12 then the approach converts to a left-sided thoracotomy. If T12/L1 has to be exposed, the diaphragm has to be cut. If L1/2 has to be exposed, the principles of the retroperitoneal lumbar approach should be followed.

For levels T12 and above, a left-sided lung deflation is completed (see Fig. 4) and the deflated lobe retracted anterior to expose the ventral thoracic spine (Shen and Haller 2010). The parietal pleura is incised over the planned operative level (s) at the disc space and then to adjacent levels, being aware that the segmental vessels are in the midline and needing to be isolated and ligated. A subperiosteal exposure from posterior and lateral to anterior is then completed with blunt instruments protecting the great vessels anteriorly. Posterior dissection exposes the rib heads which often have to be osteotomized for adequate disc access.

For access to the TLJ, the diaphragm has to be incised to be able to access either side. As discussed in the anatomy section, the diaphragmatic innervation is from the phrenic nerve near the esophagus. Thus, it is important to incise the diaphragmatic attachments as close as possible to the chest wall as any muscle left in situ after

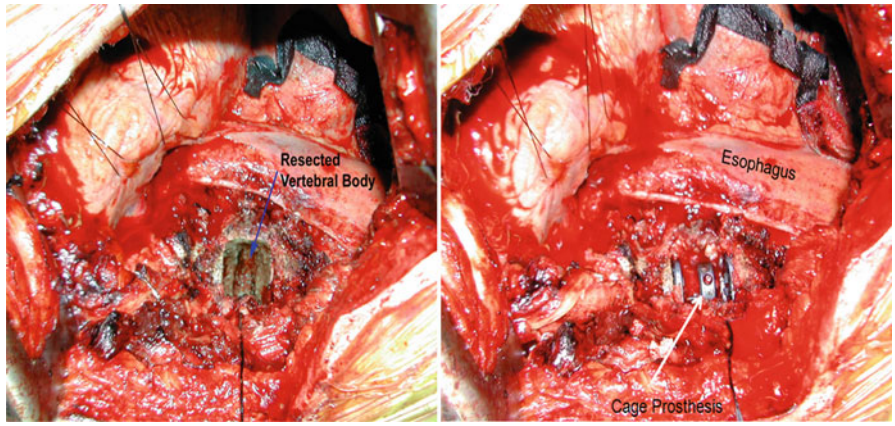

Fig. 4 Visualization via a lateral thoracotomy of low thoracic corpectomy and cage prosthesis insertion for fracture. (Copyright 2008, used with permission from CTSNet (www.ctsnet.org). All rights reserved)

incision in the periphery will undergo denervation. In the case of isolated TLJ approach (T12–L1), the diaphragm can be retracted anteriorly with the lung being retracted with a moist sponge and not requiring selective deflation. The parietal pleura is then incised longitudinally along the lateral aspect of the spine at least one level proximal to the most proximal vertebra to be treated. As in the thoracotomy approach, the segmental vessels are isolated and ligated, and the sympathetic chain is bluntly retracted and the great vessels protected.

For high lumbar levels (L1–2), the peritoneum is retracted along with the sympathetic chain anteriorly after being shifted away from the lateral abdominal wall and the psoas muscle reflected posteriorly after careful dissection on the anterior border of the muscle over the disc space and isolation and ligation of segmental vessels. Care for nearby renal vessels and the nearby great vessels lying anterior to the anterior longitudinal ligament is paramount.

Any approach with pleural breach, as distinct from an extrapleural approach, will require a chest drain insertion. One or two chest tubes are typically inserted in the midaxillary line although some surgeons prefer an anterior drain to extract air from the chest cavity and a posteriorly placed drain for drainage of blood and fluid.

The diaphragm is reattached using interrupted sutures, making sure that the parietal pleura is approximated and preferably closed over the instrumentation. The chest wall muscles that have been divided are then re-approximated.

MIS Approach

The minimally invasive approach to the thoracolumbar spine has been described, publicized, and refined since the first report by Pimenta in 2000 (Pimenta 2015). The patient is positioned in the right lateral decubitus position on a radiolucent table with the hip and knees flexed. Bony prominences and pressure points are padded, arms placed onto table attachments assessing for brachial plexus and ulnar pressure, and the torso secured either with a beanbag or table-mounted bolsters and sports tape (Elastoplast™) is also used. The choice of how to secure the torso and keep the posterior spinal elements exposed to prevent rolling during the procedure will depend on whether supplemental pedicle screws are planned from the same patient position or repositioning or a staged posterior fixation is to take place (see Figs. 5 and 6). They are taped in such a way as to afford good biplanar visualization of the affected levels. The skin can be secured with taping if access to lower lumbar levels is planned and a side bolster or break in the thoracolumbar region can be placed to open up the ipsilateral ribs and operative disc space at the TLJ. Neural monitoring including transcranial motor evoked potentials and somatosensory evoked potentials along with pertinent nerve roots is, we believe, imperative when performing direct lateral approaches.

The acquisition of proper image intensifier (II) images is important for ease of workflow. The II

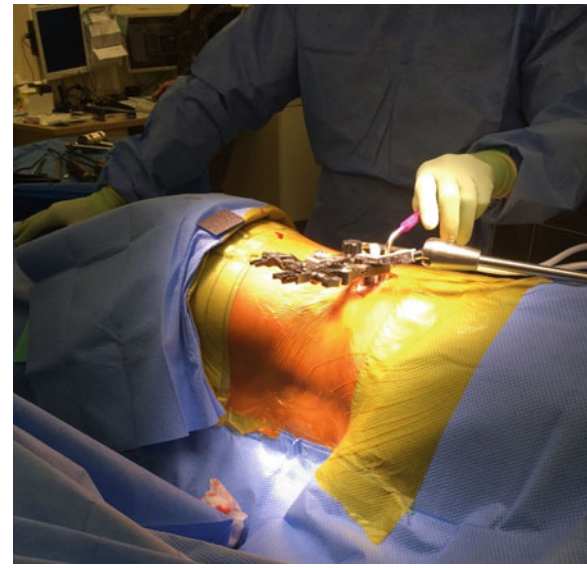

Fig. 5 Setup and retractors in place for direct, left side up lateral approach to the TLJ

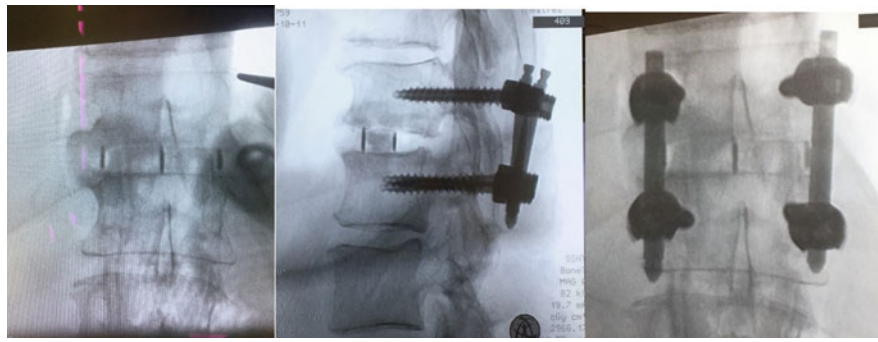

Fig. 6 Interbody insertion at T12/L1 level for same patient as in Fig. 5, followed by posterior instrumentation, all carried out without changing the position of the patient or need for redraping

generally will go over the patient who is in the lateral position and first obtain a true AP of their pedicles, and the table is adjusted until this is achieved. This allows us to correct the rotation of the spine and makes confirmation of endplate alignment in the lateral position easier. Once this correct AP position is confirmed and marked on the II machine, a position 90° orthogonal to this is utilized for the disc space access. Note, it is very important to have a well-trained radiographer for these procedures, and often it is easier to describe the AP view as being a side to side C-arm image and the lateral as being a top to bottom image so as to avoid confusion when conversing with members of the team. Given the relatively limited visual field of standard C-arms, if one cannot see the affected level and the sacrum in a single view, then it is advised to have a metallic marker placed in the affected pedicle under CT guidance prior to surgery.

The patient is then prepped and sterile draped over the shoulder and pelvis. It is important to have a large enough surgical window and imperative to have in mind an extensile approach in the event of significant bleeding occurring through a small incision. Incision planning is undertaken using fluoroscopy for level check and the 12th rib as landmark. One can use the ribs to trace up rib 2 levels above planned thoracic level(s) to choose for resection as a guide. Placement of a Kirschner wire in the spinous process immediately inferior to the pathological thoracic disc/

level has been proposed as a strategy to avoid wrong site surgery (Malham and Parker 2015).

A 4–6-cm-long oblique incision (parallel to and following the trajectory of the rib at the index level) is made at the midaxillary line, 90° lateral to the disc space (Uribe et al. 2010). Sharp dissection is carried to deep fascia, and a small rent is typically made in the deep fascia with the Bovie cautery. Blunt dissection is then carried through the intercostal muscles above the rib. The parietal pleura is then pierced in the same way as one would pass a chest drain in the setting of thoracic trauma. Typically, the right index finger can then be swept down the undersurface of the rib to palpate the transverse process. The blunt dilator can then be passed on the palmar aspect of the finger to the level of the transverse process and walked out onto either the disc or the affected vertebral body (see Figs. 7 and 8). This ensures that no visceral pleura or lung parenchyma is caught by the dilator. The position of the neurovascular bundle under the rib is considered at all times. The dilator is initially directed posteriorly away from the lung parenchyma before being brought anteriorly to the rib head over the target disc space and confirmed by lateral fluoroscopy (see Figs. 8 and 9). It is important to note the reversal of usual retractor blade positions in the thoracic spine, with the posterior blade actually being anterior with the lung retractor blade. Multiple retractors exist for the purpose of this surgery. When crossing to T12 or L1 or lower, to obtain retroperitoneal access, we prefer a tubular retractor such as a NuVasive Maximum Access™ as this allows a smaller hole to be made in the pleura and this retractor is passed through the proximal diaphragmatic attachment at the chest wall and with the dilator passing below apex of the diaphragm (Fig. 10).

Following treatment of the targeted region, provided that there be no visceral injury observed and it is a low thoracic level performed through a direct lateral approach, a drain is seldom required as the small air leak that may result is usually subclinical. Thus far, in our experience, this T12/L1 approach has never necessitated diaphragmatic repair or the passage of a chest drain. Obviously, when removing the retractor, a positive-pressure ventilation, a "bubble test," should be performed prior to definitive closure and a chest X-ray gained prior to waking the patient to ensure no significant pneumo- or hemothorax has occurred.

If the approach is to be made targeting higher lumbar levels, the transversalis fascia is one of the main components that maintain structural integrity of the retroperitoneal space. A 4 cm transverse incision is made along the lateral flank at the midline level of the index vertebral body. The incision should be made parallel to the direction

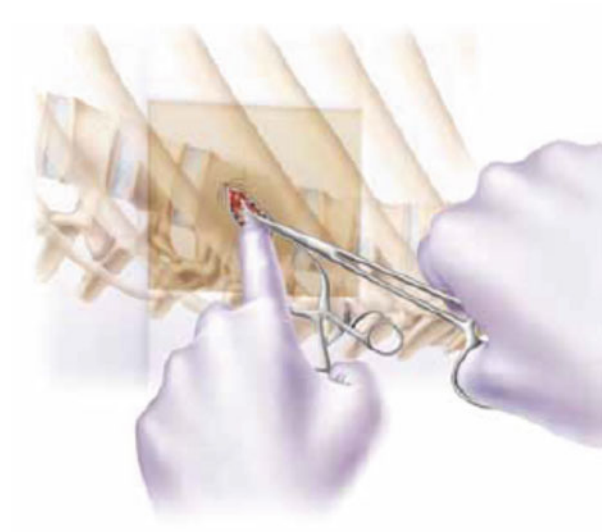

Fig. 7 Blunt dissection carried out above the rib. (Copyright 2009, used with permission from NuVasive. All rights reserved)

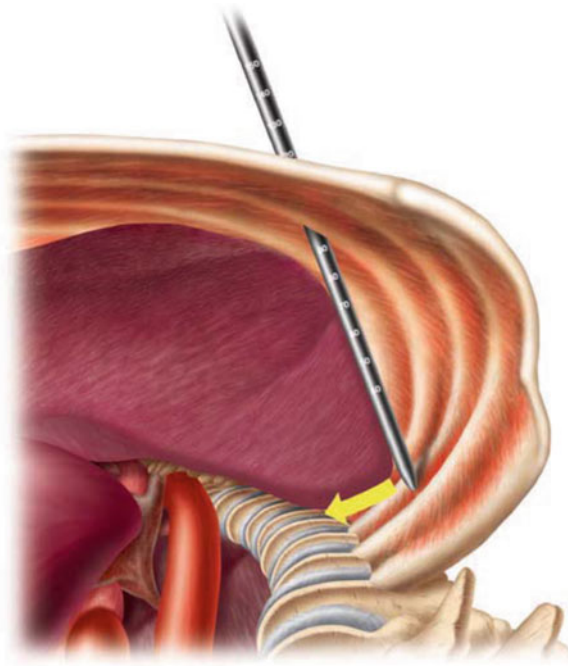

Fig. 8 The blunt dilator is initially brought posteriorly and walked down the rib until reaching the rib head overlying the operative level. (Copyright 2009, used with permission from NuVasive. All rights reserved)

Fig. 9 Retractor placement and confirmation of correct operative level on lateral fluoroscopy. (Copyright 2009, used with permission from NuVasive. All rights reserved)

of the fibers of the external oblique to minimize the possibility of injury to the motor nerves supplying them. This prevents abdominal wall pseudo-hernia formation from loss of tone to these abdominal wall muscles. Blunt dissection with anterior sweeping movements of the retroperitoneal contents is then performed to enable palpation of the psoas muscle and the transverse process of the index vertebra.

Once the operative levels are reached and illuminated retractors are in place, a removal of the rib head via osteotomy over the operative site is typically necessary for adequate access to the disc space (Fig. 11). The operative strategy can then be carried out, whether discectomy, interbody fusion, or corpectomy (Fig. 12). In the case of an interbody fusion, the macroscopic discectomy is carried out first from anterior to posterior disc

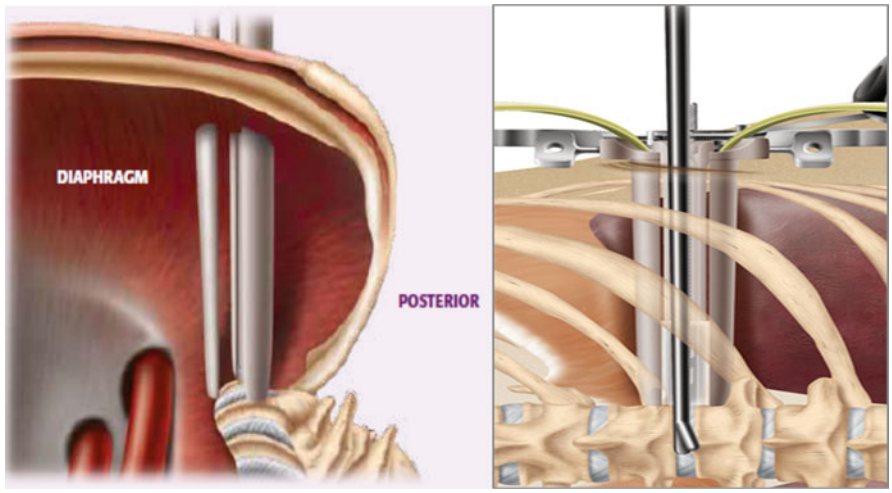

Fig. 10 Crossing of instrumentation through the diaphragm from thoracic to upper lumbar levels through small diaphragmatic incision. With the retractors in place, long instruments, such as pituitary rongeurs, can be safely passed. (Copyright 2009, used with permission from NuVasive. All rights reserved)

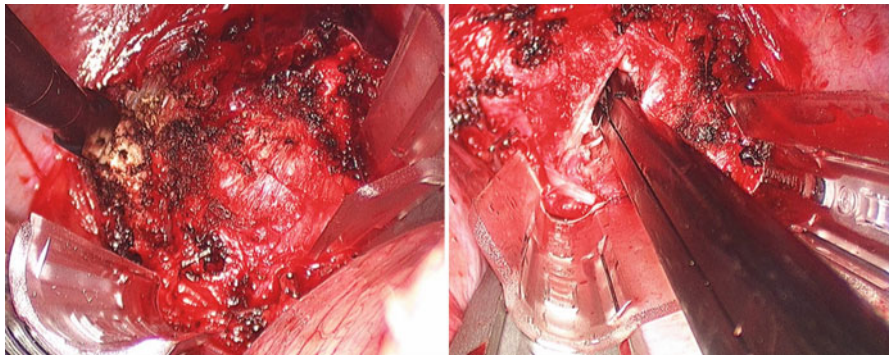

Fig. 11 Rib head osteotomy to enable adequate access to the lateral thoracic intervertebral space. (Copyright 2009, used with permission from NuVasive. All rights reserved)

space before careful resection of the posterior longitudinal ligament.

Postoperative

A chest radiograph in recovery is recommended if no chest drain has been inserted to assess for any interim pneumothorax development (Fig. 13).

Following a decision for insertion and securing of a chest drain, a chest radiograph should be obtained the first day postoperatively. If the pulmonary sacs remain expanded with no evidence of pneumothorax and the drain continues to "bubble," await approximately 24 h and remove at that time. If there is no re-expansion, then either the drain should be checked (if there is no bubbling or swinging) or a respiratory physician opinion should be obtained (Henry et al. 2003).

The ward care postoperatively will depend on the procedure performed. The common path, however, is for early graduated mobilization and aggressive chest exercises to prevent atelectasis and pneumonia. Analgesia for open thoracotomy approaches will typically be considerably more aggressive than for MIS procedures and may

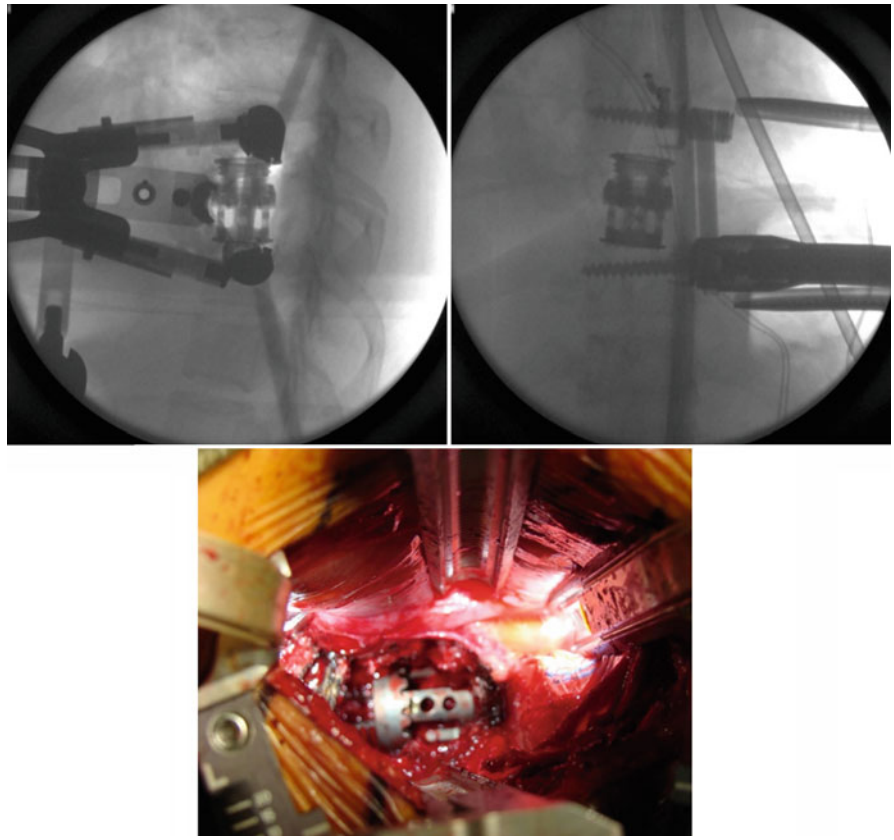

Fig. 12 Example of corpectomy and pedicle screw stabilization carried out through a lateral MIS approach. View of operative site between retractor blades. (Copyright 2009, used with permission from NuVasive. All rights reserved)

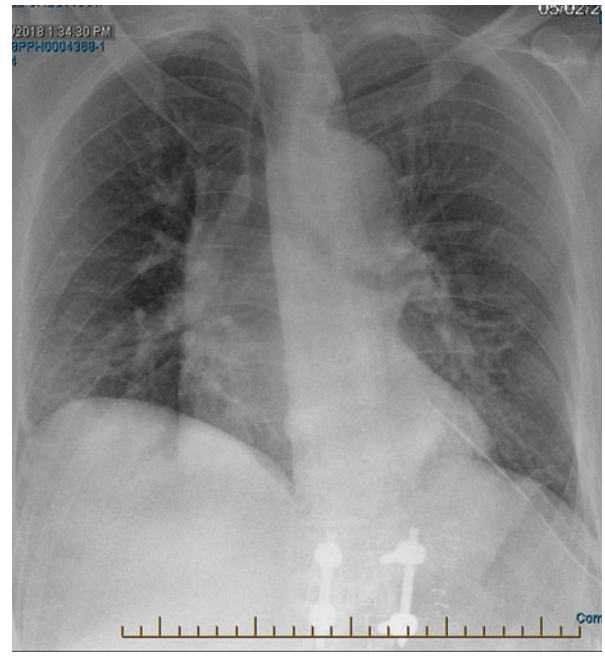

Fig. 13 Immediate postoperative chest radiograph in recovery after TLJ approach to exclude clinically significant pneumothorax with a chest drain in situ

involve a patient-controlled analgesia setup in an attempt to minimize pain-mediated pulmonary dysfunction. Hemoglobin and electrolytes are assessed routinely and corrected as required. Erect radiographs to verify position and alignment of hardware is arranged as an inpatient when the patient is able to stand.

Once safe and comfortable, the patient is discharged, and follow-up is arranged as an outpatient as postoperative week 2 for a wound review. The patient is encouraged to keep active, but avoidance of heavy lifting and explosive or rotational activities during the first 6–12 weeks is advised. The patient is then followed clinically and radiographically from a fusion perspective if interbody fusion or corpectomy or clinically if a microdiscectomy was performed.

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Surgical Approaches to the Cervical Spine: Principles and Practicalities

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Abstract

In order for surgeons to be able to achieve the best possible outcomes for their patients, it is important that they tailor their treatments to each individual patient and their condition. To achieve this, spinal surgeons in particular must be familiar with a variety of different implants and the various approaches that can be used to access the pathology. Patient positioning and preoperative planning are important, as well as identifying soft tissue corridors, which avoid damage to the numerous neurovascular structures found in close proximity to the axial skeleton.

Focusing on the cervical spine, this chapter provides discussion regarding indications, patient positioning, preparation, practicalities, as well as illustrations of the commonest approaches and surgical procedures. Approaches include the anterior (retropharyngeal, transoral), anterolateral (Smith-Robinson), lateral (Verbiest), and posterior, and for each approach, there is also a discussion of the structures at risk and a review of the literature regarding complications.

Keywords

Cervical spine · Surgical approach · Transoral · Odontoid · Retropharyngeal · Verbiest · Anterolateral · Smith-Robinson · Posterior approach

Introduction

Surgery in the cervical spine can be incredibly rewarding. The pathology at times may be severe, with a high chance of permanent disability if left untreated. Despite this, the outcomes are often

remarkably good. The complications associated with cervical spine surgery are potentially devastating; however, thankfully they are infrequent, and some are avoidable if one takes care to identify anatomy and plan the surgery diligently. This chapter will present approaches commonly, and in some instances less commonly, used to treat pathologies of the cervical spine. This is by no means an exhaustive list; there are several eponymous approaches which are infrequently used and will not be discussed at length as they are excellently described by their creators in the wider literature. This chapter will also explore the practicalities of performing these approaches, including the positioning of the patients, the structures at risk, the procedures themselves including their indications and the complications which may occur.

Anterior Surgery

Up until the 1950s, cervical spine surgery was almost exclusively performed via a posterior approach, including decompression and stabilization. The "workhorse" of cervical spine surgeons was the posterior cervical laminectomy. However, the ability to retrieve the prolapsed intervertebral disc was limited by the unretractable characteristics of the spinal cord through this approach. In 1954, Lahey (Lahey and Warren 1954) described an anterior cervical approach which he used to approach esophageal diverticula. In addition, neurosurgeons such as Dereymaeker from Louvain, Belgium, were discussing the potential of using this approach in spinal surgery. Two years later, Smith and Robinson (Robinson and Smith 1955) were the first to formally describe an anterolateral cervical approach for the purpose of spine surgery. In 1958, Smith and Robinson (1958) went on to publish the results of their first 14 cases of Anterior Cervical Discectomy and Fusion (ACDF) surgery. Popularity for this anterolateral approach grew, as it provided a new safe corridor for surgeons to access the intervertebral disc without having to venture around the spinal cord. New retractor systems were quickly developed to facilitate this approach, and surgeons such as Cloward (1958) began to refine the technique for achieving an interbody fusion. As more surgeons began to favor the anterior cervical approach further developments were seen in the implant materials and designs, including static and dynamic plates, cement and bone block spacers, interbody and corpectomy cages, and arthroplasty devices. Further anterior and lateral approaches to the cervical spine were later developed in order to give better access to the proximal and distal most vertebrae, the neuroforaminal roots and vertebral arteries. These include the transoral approach to the odontoid, the anterior retropharyngeal approach (McAfee et al. 1987) to the C1-3, the lateral (Verbiest) approach (Verbiest 1968), and the transsternal approach to the cervicothoracic junction.

Posterior Surgery

In the late 1970s, led by spinal surgeons in Japan, there was also a drive to further develop the posterior cervical operations. This was still the favored approach for the treatment of certain spinal conditions, such as myelopathy caused by ossification of the Posterior Longitudinal Ligament (OPLL,) which has a higher prevalence in patients of Japanese and Asian heritage. Posterior laminectomy was known to be associated with postoperative segmental instability, kyphosis, perineural adhesions, and late neurological deterioration. Hirabayashi (Hirabayashi et al. 1983) and Kurokawa (Kurokawa et al. 1982) developed the techniques of "open door" and "double door" laminoplasty in an attempt to avoid these problems. Since their inception, there have been several variations on these techniques including the introduction of different "spacer" implants designed to hold open the elevated lamina. Another great advancement was the introduction of the surgical microscope into spine surgery (Yasargil 1977). The superior magnification and light they provided enabled surgical wounds to shrink, thus reducing the damage to surrounding tissues, and led to the introduction of endoscopic surgery. Posterior stabilization of the cervical spine was difficult to achieve as it relied almost entirely upon wiring techniques which were not good at resisting extension, rotation, or lateral

bending forces. The introduction of translaminar, lateral mass and pedicle screws insertion techniques by surgeons such as Roy-Camille (Roy-Camille et al. 1989) and Magerl (Magerl and Seemann 1987) has greatly improved the ability of surgeons to stabilize the cervical spine from a posterior approach.

As surgical approaches to the anterior, lateral, and posterior aspects of the cervical spine have evolved, so too has our understanding of the various pathologies, facilitated through basic science research and the advancements in imaging including computerized tomography (CT) and magnetic resonance imaging (MRI). With the help of these imaging modalities, clinical evaluation, electromyography (EMG), and diagnostic injections, surgeons are now able to be more confident about their diagnoses, and in turn, more likely to select a suitable surgical strategy to achieve the goal of treatment – a good outcome for their patients.

Planning

As with any surgical treatment, it is of paramount importance that the surgeon takes care to plan the procedure fully before entering the operating theater.

Surgical Strategy

Planning starts with identifying the surgical strategy which will be used to address the pathology and achieve the surgical goal. Unfortunately, it is still commonplace to find ill-considered operations being performed on patients, which can fail to help with symptom relief and potentially cause them harm. Surgeons must make every effort to identify the underlying cause of a symptom and formulate a surgical strategy to deal with this cause, as opposed to treating just the symptom. For example, it should come as no surprise that stabilizing a degenerative C5/6 disc in a patient will do little to relieve the neck pain that they have referred up from their arthritic shoulder.

In general, the pathologies requiring treatment in the cervical spine tend to be related to tumor, trauma, infection, degenerative, or inflammatory musculoskeletal and disc disease. The sequelae of these pathologies are often either instability or compression of neural structures, which then gives a target for surgical treatment. Consequently, surgical strategies usually involve decompression, stabilization, or both.

Surgical Approach

Next, the surgeon needs to decide which surgical approach will best enable them to carry out the surgical strategy, whilst also minimizing the risk of complications by avoiding structures at risk. Most pathologies can be addressed with either an anterolateral or posterior approach, although some require both. The lateral, transoral, retropharyngeal, or transsternal approaches are more specialist approaches with narrow indications which will be highlighted within the relevant subsection of this chapter.

Intuitively, pathologies which affect the anterior structures – that is structures lying ventral to the spinal cord and roots – are often best approached from the anterior aspect. This approach enables removal of any compressive material (disc, bone, pus, tumor, or hematoma) with little manipulation of the neural structures, followed by stabilization, fusion or motion preservation, depending on the implants used. Kyphotic deformity is also an indication for an anterior approach as it enables restoration of the normal cervical lordosis by lengthening of the anterior column. Most degenerative pathologies affecting the cervical spine benefit from an anterior approach for these reasons. Trauma, tumor, or infection which compromises the integrity of the anterior column is an absolute indication for an anterior approach to enable reconstruction of the anterior column, preventing a later kyphotic deformity.

Posterior cervical pathologies are often best treated with a posterior approach. These pathologies include cord or neural compression caused by trauma, tumor infection, or degenerative disease

such as osteophytes or an in-folding of the ligamentum flavum. Dissecting through the posterior muscles and stripping them from their boney attachments is more likely to give the patients postoperative pain compared with the anterior intermuscular approach; however, it does enable a more complete decompression of the cord for the entire length of the spine. It is an extensile approach and is, therefore, ideal for treating pathology which is found at the occipito-cervical and cervico-thoracic junctions, or extensive pathology occurring at several different levels in the cervical spine. If stabilization needs to bridge to the occiput or the thoracic spine, then the posterior approach is indicated. The posterior approach is also used if intradural pathology is encountered, or if there is OPLL which is often adherent to the ventral surface of the cord.

Whichever approach is selected by the surgeon to best treat the pathology, it must be one which they are familiar with and can perform competently. There are many pathologies, such as cervical spondylotic myelopathy, where research is ongoing in trying to identify the approach which delivers the best outcomes. It is, therefore, advisable for surgeons to carefully consider all options when planning their surgical approaches.

Surgical Setup

Finally, once the tactics and approach have been confirmed, consideration should then be given to the surgical setup, including patient positioning, operating room layout, instruments and implants, list management, and additional support which may be required. Patient positioning will be covered in more detail later in the chapter. One common setup strategy is to have the cervical spine patient positioned on the operating table with their feet by the anesthetist, and their head at the other end nearer to the surgeon. This is to provide the least obstruction for the surgeon to be able to operate with the microscope and reduces the risk of contamination of the surgical field. It is important to use an operating table which is radiolucent over the areas where intraoperative X-rays may need to be taken. The need for instruments for insertion (and removal) of implants should be anticipated in advance and present before commencement of the anesthetic, along with any support staff such as neurophysiologists for intraoperative cord monitoring. With the advent of navigation and robotic-assisted surgery, spinal operating rooms can easily become cluttered with this additional equipment, implant trays, instrument trollies, microscopes, and image intensifier equipment. It is often worth planning the theater layout with adequate space assigned for all the items with the largest footprints to ensure the operation can go ahead safely. Although we are reluctant to admit it, surgeons do fatigue during the day, and so it is preferable to schedule bigger cases for the morning to reduce the risk of avoidable complications.

Ensuring the key members of the operating room team are fully informed of the preoperative plan is the simplest way of preventing mistakes and negative outcomes when unforeseen events occur in theater.

Anterior Transoral Approach to C1-C2

Indication

The transoral approach (Crockard 1985; Fang and Ong 1962; Menezes and VanGilder 1988) to the cervical spine is ideal for pathology in the anterior midline at the craniocervical junction, such as tumors. Previously, cord compression and instability caused by rheumatoid arthritis were the leading indication; however, this disease is now better treated by medication and hence the overall incidence of transoral surgery to the spine has greatly reduced (Choi and Crockard 2013).

Positioning, Preparation, and Practicalities

Nasopharyngeal bacterial swabs are taken 3 days pre-op along with antiseptic mouth washes (Watkins III 2015b). Intravenous antibiotics are

given at induction and for 7 days post-op. The patient is positioned supine with their head on a Mayfield headrest. A reinforced nasotracheal tube is inserted endoscopically and skull traction (3 kg) applied via a HALO ring. Some surgeons feel a tracheostomy is advisable in order to ensure a patent airway post-op. Antiemetics are given and a nasogastric (NG) tube is passed to reduce the risk of any regurgitation of stomach contents affecting the wound. The NG tube is retained for 5 days post-op to enable feeding as the patient will remain nil by mouth for at least 5 days post-op. A rubber loop is passed down from the un-intubated nostril and hooked round the uvula and pulled cephalad to bring it out of the field of surgery. If this is insufficient, the soft palate can be incised with a curvilinear incision around the uvula in a cephalad direction and the two flaps held clear with stay sutures. A Boyles-Davis mouth gag is then inserted to retract the tongue, being released and reapplied every 30 min to avoid tongue necrosis. The nasopharynx and laryngopharynx are packed to catch any secretions. The oropharynx is prepped with Betadine and the posterior pharyngeal tissues are copiously infiltrated with a lidocaine and 1:200,000 adrenaline solution for hemostasis (Fig. 1).

Approach

The anterior tubercle on the atlas is palpated and confirmed on X-ray. A 3 cm longitudinal midline incision is made – 1 cm cephalad and 2 cm caudal to this tubercle. Incision is made through the posterior pharyngeal mucosa, the constrictor muscles, the prevertebral fascia, and the anterior longitudinal ligament (ALL). Remaining soft tissues are then bluntly dissected off the body of C2 (below the odontoid) and the anterior tubercle of C1. At this stage the blunt dissection can be extended further laterally and longitudinally to expose the lateral masses of C1 and C2. However, one should remember that the vertebral arteries lie a minimum of 2 cm from the anterior tubercle of C1 in the foramen transversarium on either side. There is often venous bleeding just lateral to the base of the odontoid, and sharp dissection may be needed to detach the longus coli muscles from the anterior aspect of C1 and C2.

Procedure

With the C1 and C2 now exposed, the definitive treatment can begin, usually with burring away of the anterior arch of C2 to reveal the odontoid which can also be excised if indicated. The dura should be completely decompressed and if necessary, a durotomy can be performed. Access can be extended proximally to reach the clivus, although this may require further soft palate incision or formal maxillotomy. Depending on stability and the extent of bony excision, a HALO jacket or posterior stabilization may now be required.

Closure

The longus coli muscles, constrictor pharyngeal muscles, and mucosa are all closed as individual layers if possible with absorbable sutures. Any soft plate extensions are closed in one layer with an absorbable suture.

Structures at Risk

The vertebral arteries lie a minimum of 2 cm from the anterior tubercle of C1 in the foramen tranversarium on either side. They are found at the lateral edges of the joints between the C1 and C2 lateral masses, and so care must be taken to use blunt retractors laterally if exposing these joints and stay sutures should not go too deep within the lateral pharangeal wall. Care should be taken to avoid damaging the tongue or the pharyngeal mucosa with the retractors. The spinal cord and dura are located beneath the cruciate ligaments at the back of the odontoid.

Complications

In 2016, Shriver et al. published a meta-analysis of the complications related to 1238 transoral

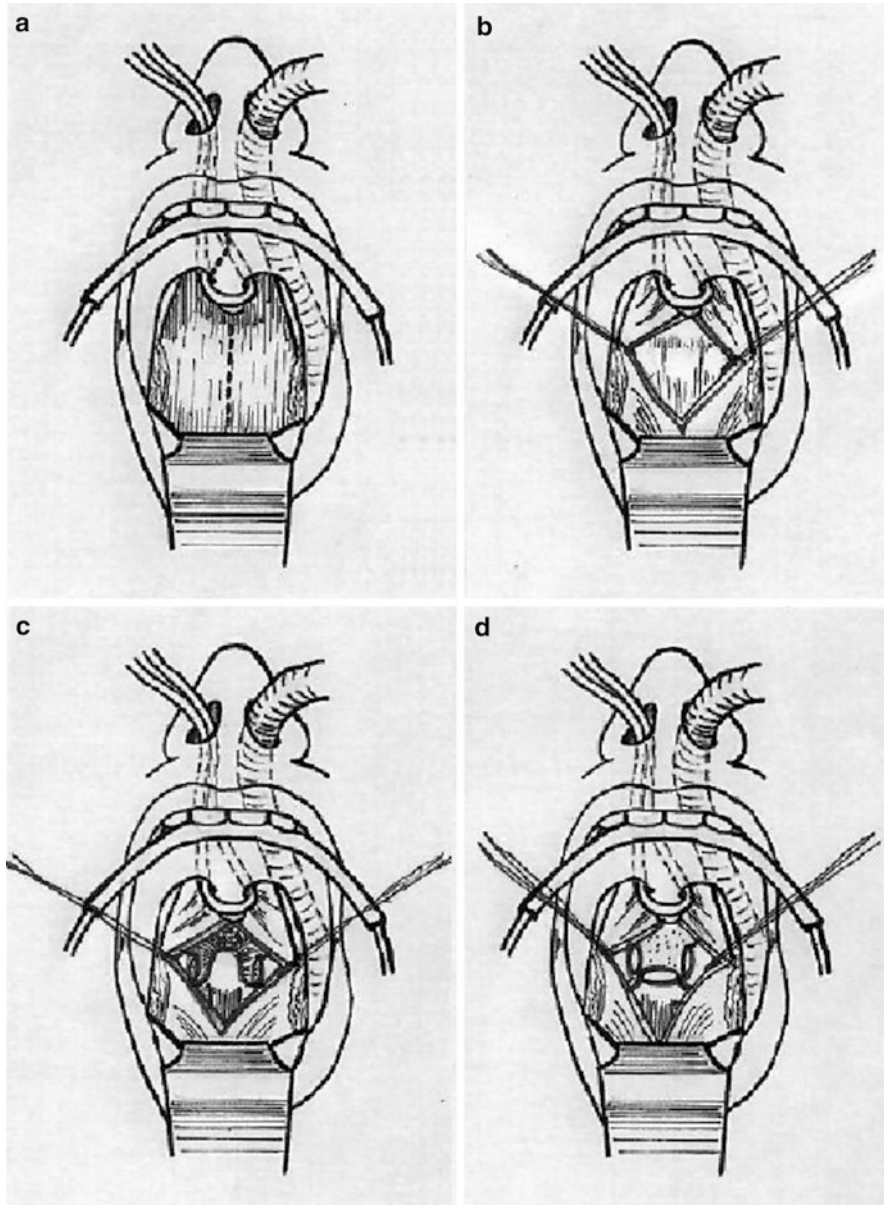

Fig. 1 Anterior transoral approach to C1-C2. (**a**) Transoral incision, including soft palate peri-uvula extension (dotted line), showing vascular loop elevating uvula and McIvor mouth gag exposing the posterior pharyngeal mucosa. (**b**) Pharyngeal mucosa, constrictor muscles, and prevertebral fascia, incised and retracted with stay sutures, exposing the ALL and longus coli muscles over the anterior tubercle of C1 and body of C2. (**c**) Anterior tubercle and arch of C1 removed with high-speed burr to reveal the odontoid process. (**d**) Ondontoidectomy can then be performed carefully with Kerrison rongeurs to decompress the cord

odontoidectomy patients (Shriver et al. 2016). The commonest reported complications were medical complications (13.9%), which were mostly respiratory with some cardiac. The mortality rate at 30 days was 2.9%. Other complications included arterial injury (1.9%), CSF leak (0.8%), meningitis (1%), pharyngeal wound dehiscence (1.7%), dysphagia (3.8%),

velopharyngeal insufficiency (VFI) (3.3%), and tracheostomy (10.8%).

Anterior Retropharyngeal Approach (C1-C3)

Indication

The anterior retropharyngeal approach (De Andrade and Macnab 1969; McAfee et al. 1987) is indicated in tumor, trauma, infection, and instability cases affecting the upper cervical spine, especially where there may be a need to insert bone graft and implants. It also enables the surgeon to extend distally past C3, which is not possible from the transoral approach without splitting the mandible.

Positioning, Preparation, and Practicalities

The patient is positioned supine with their head on a Mayfield headrest, and rotated slightly contralaterally. A reinforced nasotracheal tube is inserted endoscopically to allow better elevation of mandible. Depending upon the pathology skull traction (3 kg) can be applied using Gardener-Wells tongs. Due to the slightly awkward approach angle (cephalad under the mandible) early introduction of the microscope is advised as it serves as an excellent light source. The handheld Cloward retractor facilitates the blunt dissection and approach. The skin around the incision can be pre-infiltrated with a lidocaine and 1:200,000 adrenaline solution to reduce the bleeding from the superficial tissues during the procedure.

Approach

A 2–4 cm skin incision is made below the angle of the mandible from midline to the mid-axis of the sternocleidomastoid muscle, curving up toward the mastoid process (Watkins III 2015a). The platysma and superficial fascia are divided in line with the incision. The subplatysmal plane is developed a little proximally and distally. Care is taken to identify and protect the greater auricular nerve and anterior cervical nerve branches of the ansa cervicalis. These course around from the posterior border of sternocleidomastoid, crossing the proximal end of the muscle on their route up to give sensory distribution to the auricular and mandibular skin. The investing fascia is incised along the deep medial edge of the sternocleidomastoid muscle. The pulsation of the carotid sheath is palpated, and blunt dissection preferably with the index fingers is used to develop a plane medial to the carotid sheath and lateral to the trachea, esophagus, and strap muscles.

The neurovascular structures crossing from lateral to medial, across the carotid triangle (Fig. 2), are found in this layer. Before ligating any of these vessels it is important, at this stage, to identify the hypoglossal nerve. After descending between the internal carotid artery and jugular vein, it turns horizontally and becomes superficial over the proximal external carotid artery, traversing medial-lateral over the proximal carotid triangle, before passing deep to the digastric tendon to supply the muscles of the tongue. A nerve stimulator should be used to confirm correct localization of the hypoglossal nerve. It should then be mobilized from the surrounding tissue to enable gentle cephalad retraction along with the posterior belly of the digastric muscle. If necessary, the digastric (and stylohyoid) muscles can be divided at their tendinous junction and tagged for later repair. Access into the retropharyngeal space is prevented by the lateral-medial traversing branches of the external carotid artery, including the superior thyroid, lingual, and facial arteries. These vessels, along with their accompanying veins, are divided. The submandibular duct can be tied off and the gland removed to facilitate proximal exposure.

The carotid sheath is retracted along with the ligated stumps of the superior thyroid, lingual, and facial vessels laterally. The digastric muscle and hypoglossal nerve are retracted proximally, and the musculovisceral column is retracted medially. Blunt finger dissection is used to locate the ALL and longus coli muscles on anterior cervical spine.

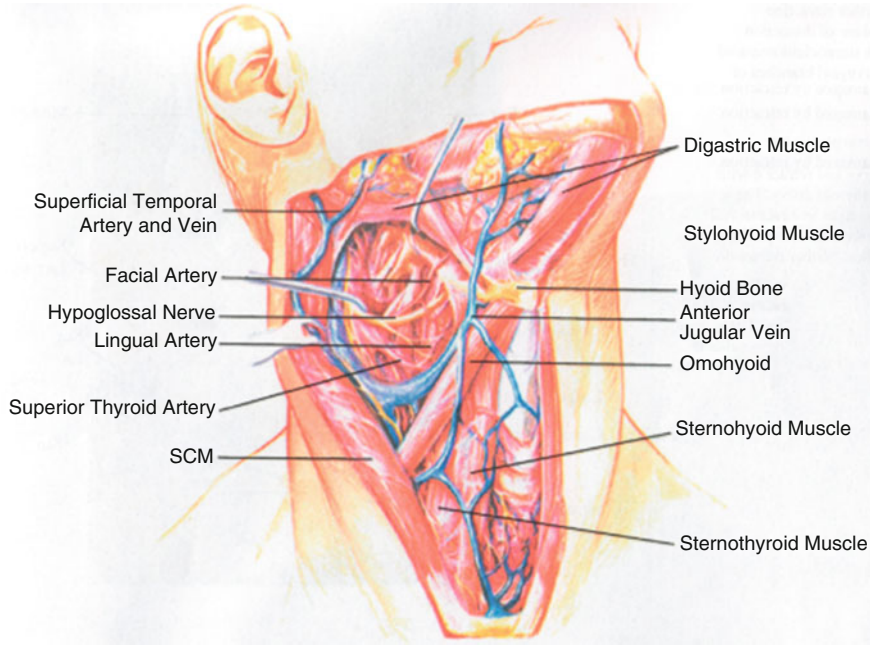

Fig. 2 Anterior retropharyngeal approach with the exposure of the carotid triangle. (From Watkins III 2015a)

The anterior tubercle on the atlas serves as a useful landmark and can be confirmed on X-ray. The prevertebral fascia and longus coli fibers are elevated, and the blunt handheld Cloward retractors are substituted for some sharp, clawed retractor blades under longus coli.

Procedure

Once the desired bony anatomy is identified, a high-speed burr is used to remove the anterior arch of C1 and the odontoid process. The tip of the odontoid process is removed before sectioning of the base to prevent superior retraction of this structure in cases of basilar invagination. The body of the odontoid is drilled, leaving a thin shell of bone posteriorly, which is carefully removed with Kerrison rongeurs. The lateral pillars should be retained as they are the primary load-bearing structures of the atlantoaxial articulation. Following decompression, supplementary stabilization is usually required. This can be accomplished with anterior or posterior instrumentation, or a halo device.

Closure

Deep closure is not required. The digastric muscle tendon is repaired, if it was divided. The platysma muscle is closed over a drain, and then fat and skin are closed in separate layers. Suture/clip removal equipment accompanies the patient during the first 12 h in case an urgent evacuation of hematoma is needed to prevent airway compromise.

Structures at Risk

Take care to identify and protect the greater auricular nerve and anterior cervical nerve branches of the ansa cervicalis crossing over the proximal sternocleidomastoid muscle. Injury to these can cause loss of sensation to the auricular and mandibular skin. When operating in the submandibular triangle, it is important to avoid damaging the marginal mandibular branch of the facial nerve. Ensure the hypoglossal nerve has been correctly identified before ligating any other vessels. Avoid excessive retraction on the stylohyoid muscle as this can injure the facial nerve as it exits the skull

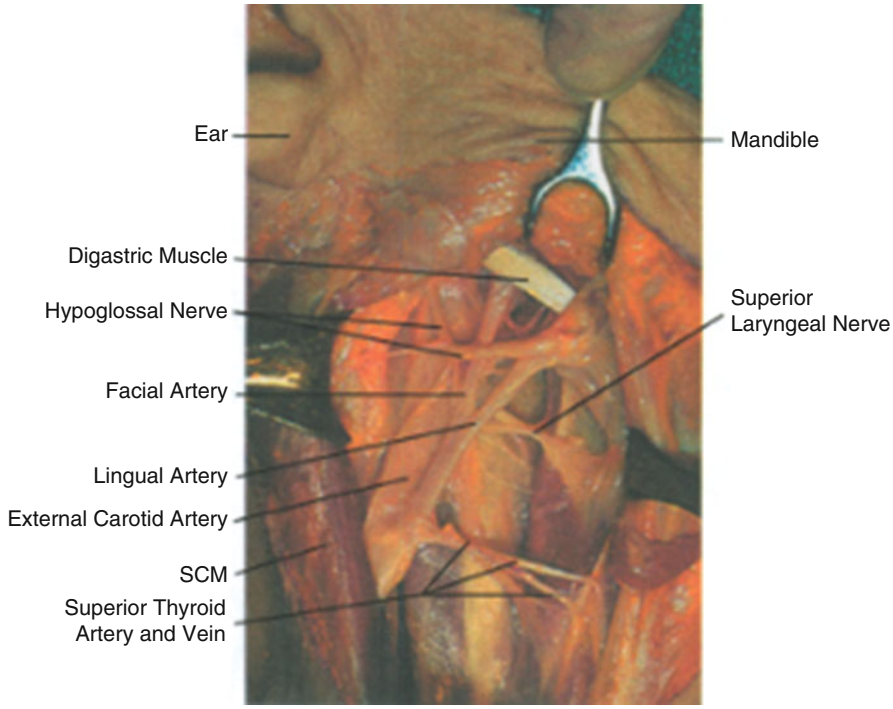

Fig. 3 Note the position of the superior laryngeal nerve, which must be protected. (From Watkins III 2015a)

through the stylomastoid foramen. It is important to identify the superior laryngeal nerves (both internal and external branches) (Fig. 3) as injury to these can lead to increased voice fatiguability, loss of high-pitched notes in singing, or even aspiration pneumonia as a result of reduced laryngeal cough reflex. They are located in the carotid triangle adjacent to the superior thyroid artery and are commonly injured by retractors. The superior laryngeal nerve should be mobilized in order to prevent retraction injury to its internal and external branches.

Complications

The commonest complaint with the retropharyngeal approach is dysphagia. Other complications include facial nerve palsy (9.4%), hypoglossal nerve plasy (4.7%), nonunion/graft displacement (6.3%), infection (1.6%), hypopharynx injuries (3.1%), and a mortality rate of 3.1%.

Lateral Approach (Verbiest)

Indication

The lateral approach to the vertebral artery was described in detail by Henry (1970) and later modified by Verbiest (Verbiest 1968) to enable additional access to the lateral aspects of the cervical vertebral bodies, the neuroforamina, and the portions of the anterior rami of the brachial plexus. Bony spurs compressing the vertebral artery or the cervical nerve roots, and neural tumors can be addressed with this extensile approach (Watkins 2015).

Positioning, Preparation, and Practicalities

The patient is positioned supine with their head on a Mayfield headrest, without any rotation. This is to avoid occlusion of the vertebral artery in cases

of spondylotic compression. The skin around the incision can be pre-infiltrated with a lidocaine and 1:200,000 adrenaline solution to reduce the bleeding from the superficial tissues during the procedure.

Approach

An oblique incision is made along the medial border of the sterncleidomastoid muscle. Skin and subcutaneous tissues are retracted, and the platysma muscle is divided longitudinally in line with its fibers. The investing layer of the cervical fascia is incised to reveal the medial border of sternocleidomastoid muscle. The plane between the muscle and the medial strap muscles is developed with finger dissection. Care is taken to identify and protect the greater auricular nerve and anterior cervical nerve branches of the ansa cervicalis. These course around from the posterior border of sternocleidomastoid, crossing the proximal end of the muscle on their route up to give sensory distribution to the auricular and mandibular skin. The sternocleidomastoid muscle is then retracted laterally and the carotid sheath is identified by its pulsation against a fingertip. The plane between the carotid sheath and sternocleidomastoid (laterally) and the musculovisceral column (medially) is further developed with blunt dissection with a finger and mounted pledgets, down to the anterior tubercle of the transverse process. The sternocleidomastoid can be released from its proximal attachment on the mastoid process if it is required. However, care must be taken to identify and protect the accessory nerve which enters the muscle 4–6 cm from the mastoid tip. After identifying the anterior tubercle of the transverse process, where longus coli, longus capitis, and anterior scalene muscles attach, it is possible to palpate medially to feel the vertebral body and disc. The longitudinal sulcus between the tubercle (laterally) and the body (medially) is the costotransverse lamellae, which forms the roof of the foramen transversarium covering the vertebral artery. Incise the prevertebral fascia longitudinally to expose the longus coli and longus capitis muscles. The longus coli muscle has three parts – two oblique parts lying over one longitudinal part. The longus capitis muscle lies longitudinally over the upper oblique longus coli. The upper vertical longus coli arises from the anterior tubercle of the atlas and then inserts on the body of C4, while the lower stretches from C5 to T3. The oblique parts insert (with the longus capitis) on the anterior tubercles on the transverse processes. The sympathetic chain lies directly anterior to the transverse processes, between the prevertebral fascia and the carotid sheath, sometimes being adherent to the latter. The sympathetic chain, including its superior (at C1) and middle (at C6) cervical ganglions, should be moved as one with the longus coli muscles from lateral to medial to access the underlying structures. In order to achieve this retraction, the muscular attachments of the oblique longus coli and the longus capitis are sharply dissected off the anterior tubercles. The dissector should be working in the acute angle the muscle fibers make with the bone (the stripping angle), which is an inferolateral direction when working on the proximal levels, and a superolateral direction when working on the inferior levels (Fig. 4).

Procedure

The bone of the anterior tubercle is removed with a rongeur, and the proximal and distal margins of the costotransverse lamellae are identified. With a small Kerrison rongeur, the bone of the costotransverse lamellae is carefully removed, and the foramen transversarium is de-roofed. In doing so it is inevitable that venous plexus surrounding the artery will bleed, and this should be controlled with light pressure. The nerve root should now be accessible underneath the mobile vertebral artery. Again, further bleeding may be encountered from the main vertebral veins which may require additional hemostatic products.

Closure

Deep closure is not required. The platysma muscle is closed over a deep drain, and then fat and skin

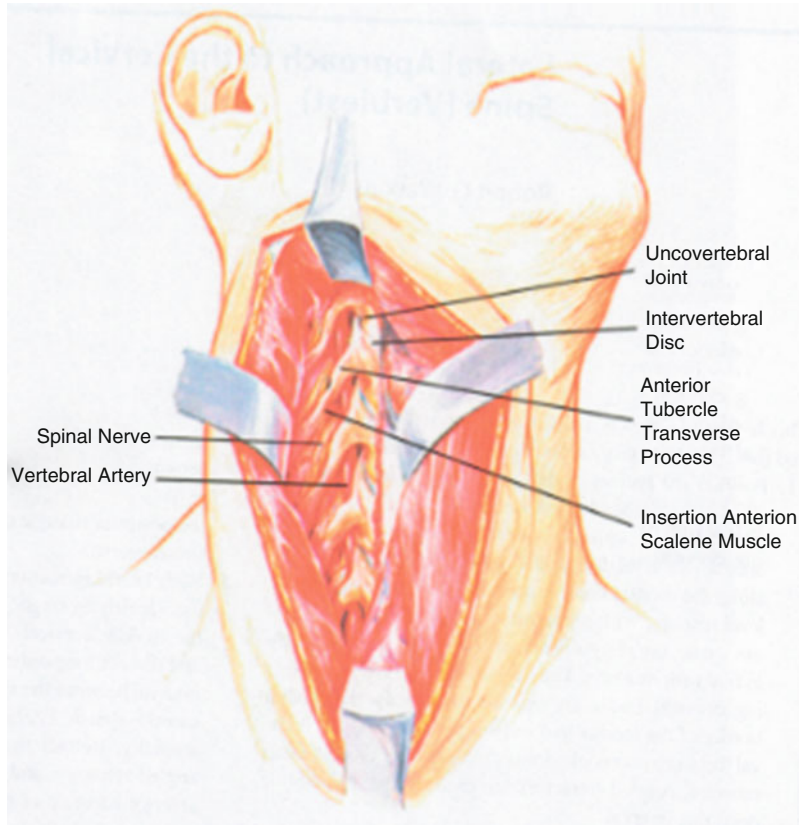

Fig. 4 Lateral approach revealing the vertebral artery running through the foramen transversarium. (From Watkins 2015)

are closed in separate layers. Suture/clip removal equipment accompanies the patient during the first 12 h in case an urgent evacuation of hematoma is needed to prevent airway compromise.

Structures at Risk

Take care to identify and protect the greater auricular nerve and anterior cervical nerve branches of the ansa cervicalis crossing over the proximal sternocleidomastoid muscle. Injury to these can cause loss of sensation to the auricular and mandibular skin. If proximal detachment of the sternocleidomastoid is required, care must be taken to identify and protect the accessory nerve which enters the muscle 4–6 cm from the mastoid tip. The sympathetic chain should be moved as one with the longus coli muscles from lateral to medial to avoid injury and a subsequent Horner's syndrome (partial ptosis, meiosis, and anhidrosis). The vertebral artery is at risk during the longus coli strip and the excision of bony costotransverse lamellae. If the vertebral artery is injured, bleeding may be controlled by a ligature above and below the lesion.

Complications

Due to a lack of published data on lateral-approach cervical surgery, it is not possible to present the complications rates from these procedures.

Anterolateral Approach (Smith-Robinson)

Indication

The anterolateral approach was borne out of the desire of spinal surgeons to treat diseases of cervical discs and the vertebral bodies, without

having to negotiate a path around the immoveable cord and nerve roots. It is indicated primarily for treatment of pathologies which lie ventral to the cord such as neural compression caused by disc, osteophyte, tumor, abscess, or bone. It is also useful in correcting instability and deformities caused by degeneration, trauma, infection, or tumor. Cervical disc arthroplasty is only possible through an anterolateral approach. This approach should enable access from C2-T2, although this range may be reduced to C3-C7 in certain patients where the mandible or the clavicle restricts further access.

Positioning, Preparation, and Practicalities

The patient is positioned supine with their head on a Mayfield headrest, without any rotation (Fig. 5). A small rolled towel, or alternatively a 500 ml bag of iv fluid, is placed between the scapulae approximately at the level of T2 spinous process. This allows for slight extension of the neck and permits the shoulders to drop back toward the table, providing more room for the surgeons' instruments. The head and neck are secured in position with soft tape or, if traction is known to be needed, Gardener-Wells skull traction. If the arms and shoulders need to be pulled caudally to enable a lateral X-ray to be taken, then they can be held in this position with soft tape to facilitate intraoperative X-rays. An inserted nasogastric tube can facilitate identification of the esophagus in difficult revision approaches; however, this is not necessary in primary cervical surgery. Although palpable anatomic landmarks such as the hyoid (C3), thyroid cartilage (C4/5), carotid tubercle (C6), or the cricoid cartilage (C6) can provide fairly reliable indication of incision location (Fig. 6), it is preferable to use a radio-opaque marking stick and an X-ray machine to map out the incision. The skin around the incision can be pre-infiltrated with a lidocaine and 1:200,000 adrenaline solution to reduce the bleeding from the superficial tissues during the procedure.

Historically, the side of the approach has generated much research interest regarding the effect of side of approach on the risk of recurrent laryngeal nerve (RLN) injury. In the original description of the procedure (1955) (Robinson and Smith 1955), the authors suggest an apparent increased traction applied on the RLN when approaching from the right side and hence they recommend a left-sided approach. Another of the earliest users of this technique (Cloward 1958) used the right-sided approach. There has yet to be any conclusive published evidence that a right-sided approach significantly increases the RLN injury rate, although a cadaveric study (Rajabian et al. 2020) does seem to show that below C5 the RLN requires more retraction to keep it from the field of surgery. For ergonomic reasons, many surgeons favor use of the same side as their hand dominance and this is likely to lead to other indirect benefits such as reduced length of surgery and retractor time. It is helpful for the theater team and the anesthetist to know of the side of the approach in advance, as the endotracheal tube may be positioned to the contralateral side and theater layout can be tailored to the advantage of the surgeon.

Approach

A transverse skin-crease incision is made from the midline to the medial border of the sternocleidomastoid at the desired level. The subcutaneous tissues are dissected and then retracted with a Mollinson retractor, exposing the platysma. The platysma is incised in line with the wound, and the subplatysmal plane is only developed proximally and distally if more than one cervical level is to be approached. The investing layer of the cervical fascia, which envelopes the sternocleidomastoid muscle, is incised along the medial muscle border. The medial musculovisceral tissues (thyroid, esophagus, trachea, strap muscles) are retracted medially with the handheld Cloward retractor, while the surgeon's index finger is used to dissect through the pretracheal fascia and palpate for the pulsation of the carotid sheath underneath the sternocleidomastoid. The superior and inferior thyroid vessels may be encountered at C3/4 and C6/7 levels, respectively, and they can either be

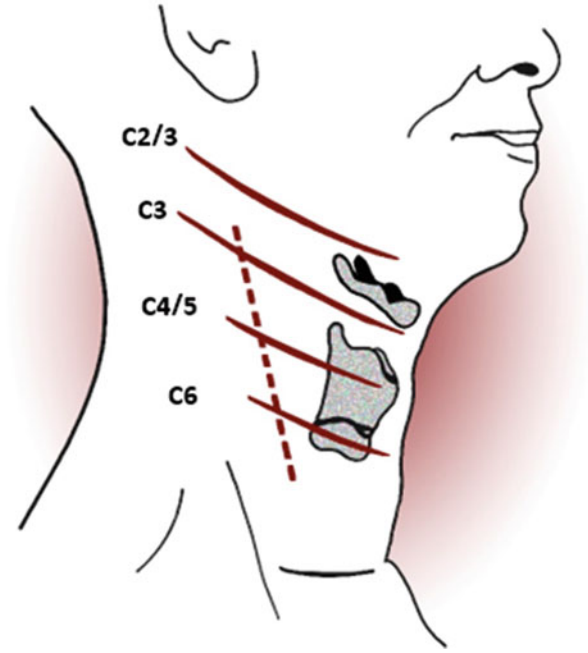

Fig. 5 Incisions related to bony anatomical landmarks including lower border of the mandible (anterior retropharyngeal approach C2/3), hyoid bone (C3), upper aspect of thyroid cartilage (C4/5), cricoid cartilage (C6)

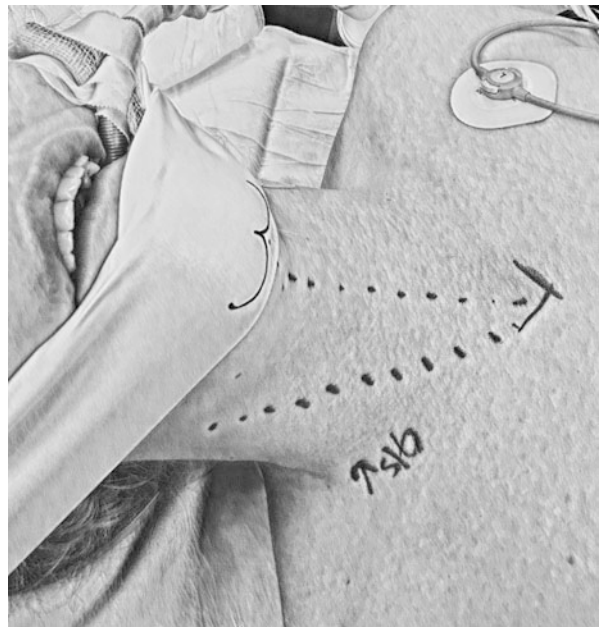

Fig. 6 Anterolateral approach positioning

retracted or ligated if necessary. Omohyoid is often encountered at the level of C6/7, and can also either be retracted or divided laterally. The former option is the author's preferred choice. A plane between the pulsatile carotid sheath and sternocleidomastoid laterally, and the musculovisceral tissues medially is further developed down to the front to the prevertebral fascia (Fig. 7). Through the smooth, white prevertebral fascia it should be easy to palpate the anterior spinal column, made up of alternating ridges and sulci of the intervertebral discs and vertebral

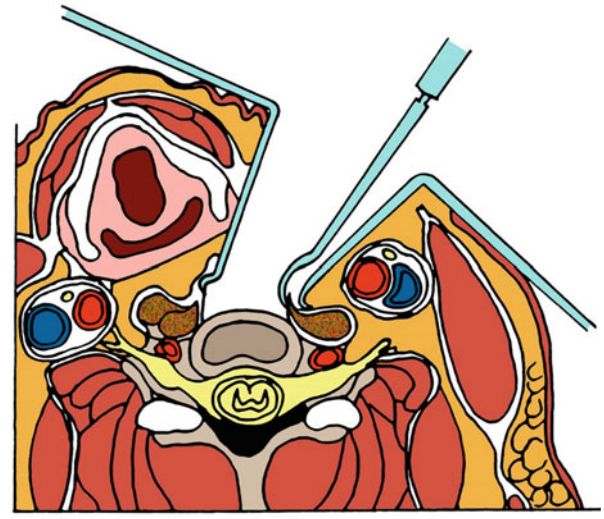

Fig. 7 Cross section of the anterolateral approach at C5/6 showing medial retraction of the thyroid, strap muscles, trachea, and esophagus, and lateral retraction of the sternocleidomastoid and carotid sheath. The longus coli muscle is elevated along its medial border

bodies, respectively. Sweeping the index finger medially and laterally should confirm the location of the midline, between the prominent longus coli and capitis muscles running longitudinally. Using toothed forceps, the prevertebral fascia is lifted at this midline point, and incised proximally and distally to reveal the ALL. A small clip is applied to the ALL and X-ray is used to confirm that the correct level has been approached. The medial borders of longus coli are elevated with insulated diathermy, and toothed retractor blades are inserted under each side (Fig. 8).

Procedure

This approach can be used to gain access to the spine for fracture fixation, such as interfragmentary lag screw fixation of the odontoid process. In this scenario dual image-intensifiers are used to simultaneously obtain anteroposterior and lateral fluoroscopy images of the odontoid. Through a C5/6 anterolateral approach, blunt finger dissection is used to dilate the prevertebral space proximally as far as the C2/3 disc ridge. A curved, radiolucent retractor is inserted into this space, and with the fulcrum of the retractor on the distal C2 body, the anterior musculovisceral tissues of the neck are levered off the anterior spine. This enables two guidewires to be driven up from the anterior inferior rim of the C2 vertebral body, across and perpendicular to the oblique fracture and as far as the subcortical bone of the proximal dens.

The anterolateral approach is invariably followed by one or more discectomies. After the correct level is confirmed on X-ray and retractor blades are secured under the medial boarders of longus coli, diathermy is used to expose the distal half of the cranial vertebra and the proximal half of the caudal vertebra, either side of the disc being removed. The midline can be identified using the midpoint between the two uncovertebral (Luschka's) joints. A scalpel blade is used to make a horizontal rectangular annulotomy, removing the ALL and anterior annulus fibrosus of the disc in one piece. A series of fine curettes are then used to scrape the cartilage from the bony endplates, taking care not to violate the end plates as this is likely to lead to spacer implant subsidence. Once some of the disc and cartilage have been removed, it is possible to increase the space inside the disc by inserting a pin distractor. This may not be necessary if the patient has skull traction already fitted. Two pins are placed in the midline, 3 mm from the edge of cranial and cauda vertebra, taking care to insert them parallel to the endplates. This will enable improved visualization of the deeper structures which are to be carefully removed under microscope guidance with 1–2 mm Kerrison rongeurs and a high-speed burr. Complete discectomy is achieved when the

posterior annulus, posterior longitudinal ligament, sequestrated disc fragments, or compressive osteophytes are removed and both neuroforamen are probed to confirm lack of any compression on the nerve roots. In the event of a corpectomy, it is useful to perform complete discectomy at two adjacent levels, as detailed here. Corpectomy can then be performed, without the risk of violating the cranial or caudal endplates which are needed to support the subsequent corpectomy cage endplates. For ACDF surgery a spacer containing a bone substitute or autologous graft is inserted into the empty disc space and a plate over the cage is optional.

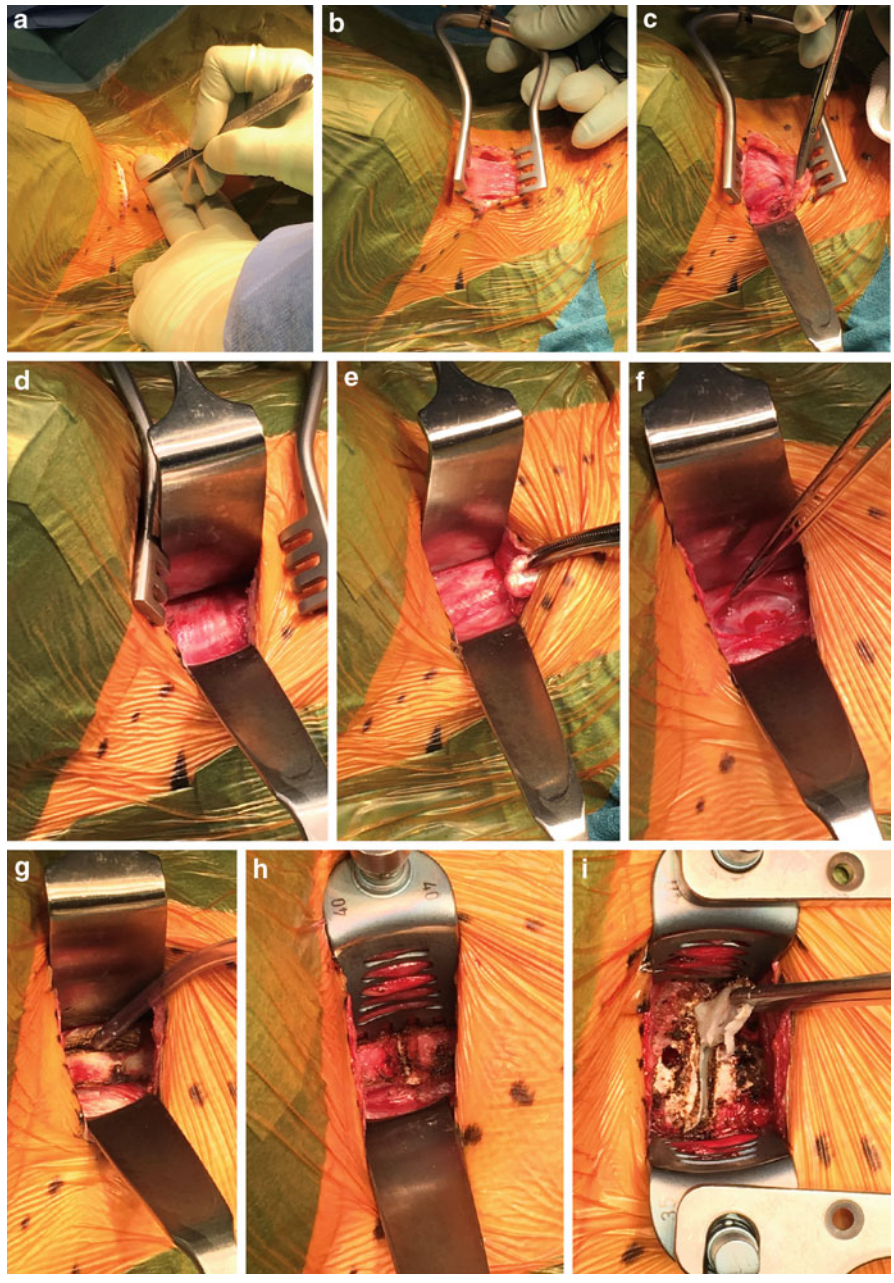

Fig. 8 (continued)

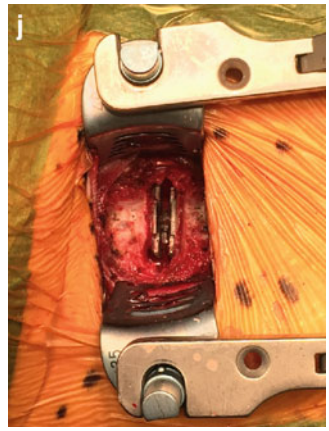

Fig. 8 Anterolateral approach. (**a**) Incision. (**b**) Platysma layer. (**c**) Platysma undermined, revealing the sternocleidomastoid (laterally) and strap muscles (medially). (**d**) Medial retraction of musculovisceral column and lateral retraction of sternocleidomastoid, revealing the carotid sheath (laterally) and pretracheal fascia (medially). (**e**) Medial retraction of the musculovisceral column, and lateral retraction of the carotid sheath, revealing the prevertebral fascia. (**f**) Elevation of the prevertebral fascia and longitudinal incision. (**g**) After the correct level is confirmed on X-ray, the medial edges of longus coli are elevated either side of the disc ridge (covered in ALL, between the longitudinal muscle bellies). (**h**) Toothed retractor blade is carefully tucked in under the longus coli. (**i**) Disc margins are cauterized, annulotomy performed, and disc removed with rongeurs and curettes. (**j**) After complete discectomy and clearance of the posterior longitudinal ligament and osteophytes, an implant is inserted (in this case a cervical disc replacement)

Closure

The platysma muscle is closed over a deep drain, and then fat and skin are closed in separate layers. Suture/clip removal equipment accompanies the patient during the first 12 h in case an urgent evacuation of hematoma is needed to prevent airway compromise.

Structures at Risk

The RLN is at risk during the approach and the time the retractor blades are in situ. It lies in the tracheoesophageal groove and so is not usually encountered during a standard anterolateral approach; it is retracted medially along with the musculovisceral structures and, hence, lies under tension throughout the procedure. The esophagus and pharynx are also at risk, and perforations of either tissue can lead to devastating complications including abscess, tracheoesophageal fistula or mediastinitis. Any abscesses need to be drained and washed out, tears should be repaired, and the patient must remain nil by mouth and receive nasogastric feeds. The sympathetic chain, which lies between the carotid sheath and the longus coli muscle, is at risk from injury if the toothed retractor blades inadvertently slip out from under the longus coli muscles, resulting in Horner's syndrome. The vertebral arteries are at risk as they lie immediately lateral to the uncovertebral joints, which may be opened by either skull traction or segmental pin distractors.

Complications

ACDF is the most commonly performed surgery using the anterolateral approach, with an average of 137,000 ACDF surgeries performed per year in the United States (Epstein 2019). A recent comprehensive review of complications associated with ACDF surgery (Smith and Robinson 1958) has found an overall morbidity rate of 13.2–19.3%. The complications rates are detailed in Table 1. Psueudarthrosis rates rose with the numbers of ACDF levels: 0.4–3% (1 level), 24% (2 level), 42% (3 level), to 56% (4 level).

Table 1 Breakdown of complication rates in ACDF surgery from literature review (1989–2019) (Epstein 2019)

Complication	Rate (%)
Dysphagia	1.7–9.5
Postoperative hematoma	0.4–5.6
Exacerbation of myelopathy	0.2–3.3
Symptomatic RLN palsy	0.9–3.1
Cerebrospinal fluid (CSF) leak	0.5–1.7
Wound infection	0.1–1.6
Worsening of radiculopathy	1.3
Horner's syndrome	0.06–1.1
Respiratory insufficiency	1.1
Esophageal perforation	0.3–0.9
Instrumentation failure	0.1–0.9

Posterior Approach (C3-C7)

Indication

In many respects the posterior approach is more straightforward, and many spine surgeons find it familiar given the large number of posterior lumbar decompressions which are performed each year. This approach is ideally suited to treating any compression of the cord or neural structures caused by posterior structures, such as ligamentum flavum, bone spurs, fracture fragments or hematomas, epidural abscesses, or tumors. Intradural surgery always requires posterior approach and laminectomy. In multilevel stenosis, the posterior approach is often preferred as it enables several levels to be addressed without the morbidity of having prolonged compression on the anterior neurovascular and visceral structures. Posterior approach surgery is also preferred in treating OPLL, large calcified disc prolapse with myelopathy, and as a revision option where anterior approach has already been performed.

Positioning, Preparation, and Practicalities

A neurosurgical head fixation device is fitted to the patient. They are then turned over into a prone position, and the device is fixed to the table (some surgeons prefer to position patients upright). The arms remain by their side on arm supports, and the bed is tilted in slight reverse Trendelenburg position to increase venous drainage and reduce blood loss. The neck is flexed to open the facet joints and to aid the exposure (Fig. 9). Excessive soft tissues around the scapular region can be pulled caudally and taped to the contralateral buttock. The spinous processes of C2 and C7 are usually palpable landmarks. However, it is always advisable to plan the incisions using lateral view X-rays. The skin around the incision should be pre-infiltrated with a lidocaine and 1:200,000 adrenaline solution to reduce the bleeding from the superficial tissues during the procedure.

Approach

A longitudinal midline incision is made in the skin, and sharp dissection down to the ligamentum nuchae. Overzealous stripping of the subcutaneous layer too widely off the ligament should be avoided, as this creates a large dead-space and increases the risk of hematoma and seroma formation. The bifid spinous processes should be palpable through the ligament. The dissection is continued through the ligamentum nuchae in the midline in order to reduce the amount of bleeding. Once the spinous process tip is visible, a small clip is attached to it, and confirmatory lateral fluoroscopic X-rays are obtained. The periosteal dissection is then continued down each spinous process, lamina, and out onto the start of the lateral masses. If posterior instrumentation is to be inserted, the dissection should continue out to the lateral border of the lateral masses. The approach is extensile distally as far as the coccyx, and proximally as far as the occiput (Fig. 10).

Procedure

All or part of the laminae can be removed to enable access to the spinal canal. Care should be taken when inserting the first rongeur or probe through the ligamentum flavum, as at that stage the canal diameter is at its tightest and the cord

Fig. 9 Posterior approach positioning, slight Trendelenburg position with neck flexed

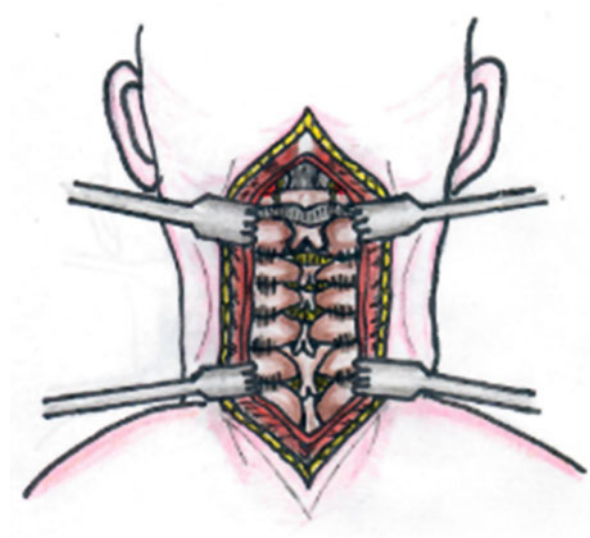

Fig. 10 Posterior cervical approach from external occipital protuberance (inion) to C7 spinous process, out as far as the lateral borders of the lateral masses in preparation for lateral mass screw fixation and fusion

may be vulnerable to injury. The high-speed burr should be used to thin the base of the lamina and only a 1 mm Kerrison rongeur should be used until the canal is mostly decompressed.

If a muscle sparing, lamina-splitting approach was planned, a high-speed burr is used between the bifid spinous process and down through the middle of the lamina. The lateral edges of the

laminae are then thinned with the burr until they can be bent out or detach from the base where they meet the lateral masses. This keeps the external muscular attachments while allowing access to the base of the lamina and then the spinal canal. Decompression can be achieved at two levels through this single split spinous process. Various laminoplasty techniques are also possible, either with or without implants.

If stabilization is required due to the extent of the decompression, the lateral masses are cleared of all remaining facet capsule tissue and the boundaries are clearly defined. The screws are then inserted using the surgeon's choice of technique.

Closure

The ligamentum nuchae is repaired over a drain. Copious infiltration with local anesthetic into the deep and superficial tissues around the wound helps to reduce the need for opiates in the immediate post-op phase of recovery.

Structures at Risk

The vertebral artery is largely shielded from the surgeon by the lateral masses, although it is at risk at the proximal end of the approach at C2, or during instrumentation of the lateral masses. It is advisable to have a 14 mm lateral mass screw loaded and ready to immediately insert, in the event of a vertebral artery injury with the lateral mass drill.

Complications

Post-laminectomy kyphosis is a risk associated with posterior approach surgery due to muscle denervation or excessive decompression. The risk increases with age, increasing numbers of levels being decompressed and if C2 is approached, and it can be as high as 47% in these groups (Nishizawa et al. 2012). Other complications associated with the posterior cervical approach include epidural hematoma (1.3%), wound infection (1.2%), C5 nerve palsy (4.6%), and spinal cord injury (0.18–2.6%) (Cheung and Luk 2016; Nishizawa et al. 2012). Complications relating to lateral mass screws include misplacement (0–7%), vertebral artery injury (1.3–4%), and neural injury (1.3%) (Cheung and Luk 2016; Nishizawa et al. 2012).

Posterior Approach (Occiput-C2)

Indication

The posterior approach to the C1/C2 may be indicated for insertion of C1/2 fixation screws, for reduction and stabilization of a fracture or dislocation, for decompression for degenerative disease, or excision of a tumor. There may be a need to extend the fixation up to the occiput.

Positioning, Preparation, and Practicalities

A neurosurgical head fixation device is fitted to the patient. They are then carefully tuned over into a prone position, and the device is fixed to the table. If the indication is for fracture fixation, a lateral X-ray is obtained to see if adjustments are needed to reduce any displacement which may have occurred during the proning of the patient. The arms remain by their side on arm supports, and the bed is tilted in slight reverse Trendelenburg position to increase venous drainage and reduce blood loss. The neck is flexed under fluoroscopic guidance to allow correct placement of the C1/2 fixation screws. The external occipital protuberance, the first palpable spinous process (C2), and the most prominent spinous process (C7) are usually palpable landmarks. However, it is always advisable to plan the incisions using lateral view X-rays. The skin around the incision should be pre-infiltrated with a lidocaine and 1:200,000 adrenaline solution to reduce the bleeding from the superficial tissues during the procedure.

Approach

A midline incision is made from the external occipital protuberance down to the mid-cervical spine. Overzealous stripping of the subcutaneous layer too widely off the ligament should be avoided, as this creates a large dead-space and increases the risk of hematoma and seroma formation. The bifid spinous processes should be palpable through the ligament, especially those of C2 and C7. The dissection is continued through the ligamentum nuchae in the midline, in order to reduce the amount of bleeding. Once the spinous process tip is visible, a small clip is attached to it, and confirmatory lateral fluoroscopic X-rays are obtained. The periosteal dissection is then continued down the C2 spinous process, lamina, and out onto the lateral masses, and up onto the occiput. The C1 posterior arch is deep between the C2 spinous process and the occiput. The tissues over the posterior arch are carefully dissected outward up to about 1.5 cm from the midline, using either a knife or bipolar diathermy. The vertebral artery runs over the cranial part of the arch and enters the spinal canal behind the lateral mass of atlas (Jeanneret 2015). Only the superior part of the midportion of the posterior C1 arch is prepared. A small sharp elevator is used to identify and subperiosteally clear the cranial surface of the C2 lamina. On sliding along the edge of the lamina, the elevator will meet the isthmus of C2, at which point the soft tissues cranial to the elevator contain the C2 root with its venous plexus. This can be elevated to expose the C1/2 articulation. It can also be ligated leading to occipital numbness but reducing the chance of a painful neuroma caused by constant impingement by a C1 lateral mass screw on a retained C2 nerve root.

Procedure

At this stage either transarticular screws can be passed supplemented with a wired fusion of the spinous process tips. Alternatively, smooth-shank screws can be passed into the lateral masses of C1 and pedicle screws into C2, once again using the fine elevator to feel the trajectory of the C2 pedicles and the C1 lateral masses. The two pairs of polyaxial screws are then connected to the rods to complete the stabilization. If C1 is not to be instrumented, its posterior arch need not be exposed, and rather more exposure of the occiput is required to accommodate the occipital plate. Once fixed to the occiput, the plate can be connected to the cervical screws with two rods bent to 90° to fix the head in a position which will permit a forward gaze.

Closure

The ligamentum nuchae is repaired over a drain. Copious infiltration with local anesthetic into the deep and superficial tissues around the wound helps to reduce the need for opiates in the immediate post-op phase of recovery.

Structures at Risk

The main structure at risk is the vertebral artery. It is most vulnerable to injury during lateral dissection along the posterior arch of the atlas, and one should not attempt to dissect tissues more lateral than the greater occipital nerve (Singh et al. 2011).

Complications

Complications related specifically to upper cervical approaches include adjacent segment disease (7%), pseudoarthrosis (6%) and problems with the occipital plate screws, loosening (4.2–7%), and CSF leak (0–4.2%). As with lower cervical surgery, post-laminectomy kyphosis is a risk associated with posterior approach surgery due to muscle denervation or excessive decompression. The risk increases with age, increasing numbers of levels being decompressed and if C2 is approached, and it can be as high as 47% in these groups (Nishizawa et al. 2012). Other complications associated with the posterior cervical approach include epidural hematoma (1.3%),

wound infection (1.2%), C5 nerve palsy (4.6%), and spinal cord injury (0.18–2.6%) (Cheung and Luk 2016; Memtsoudis et al. 2011; Nishizawa et al. 2012). Complications relating to lateral mass screws include misplacement (0–7%), vertebral artery injury (1.3–4%), and neural injury (1.3%) (Nishizawa et al. 2012).

Conclusions

Preparation for cervical spine surgery commences in the outpatient clinic when a condition is diagnosed based upon symptoms, signs, and investigation findings. Surgeons will then make plans on how best to treat the condition and weigh up the advantages and disadvantages of each treatment option. Eventually, they will arrive upon the approach, which is least invasive for the patient, most likely to achieve the surgical goal, and is within their capabilities – in that order of importance. It is clear from reading this chapter that there are often several options for treating the same conditions, which is fortunate as not all patients suit the same approach for a single condition. For example, a music teacher who leads a choir may reasonably have their radiculopathy treated with a posterior cervical foraminotomy to avoid the rare complication risk of an RLN palsy, whereas their pathology could equally have been treated with an ACDF, and may have resulted in less neck pain afterwards.

Once the surgical plan has been made, it is also important to have contingency plans in place to help the surgeon navigate through unexpected challenges that may be encountered in the operating room.

Knowing the anatomy before performing surgery around the cervical spine is of critical importance given the devastating consequences of the complications which can occur. Hopefully, with a better understanding of the various approaches available and their anatomical detail, the surgeon will be better equipped to select the best options for their patients and deliver their management proficiently.

Cross-References

- ▶ Anterior Spinal Plates: Cervical
- ▶ Cervical Spine Anatomy
- ▶ Cervical Total Disc Replacement: Heterotopic Ossification and Complications
- ▶ Cervical Total Disc Replacement: Technique – Pitfalls and Pearls
- ▶ Interbody Cages: Cervical

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Intradiscal Therapeutics for Degenerative Disc Disease

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Abstract

Chronic low back pain is one of the leading causes of adult disability globally. Currently there are no therapeutic options that target the commonest pathophysiology of back pain which is intervertebral disc degeneration. Intradiscal therapeutics aim to treat some aspects of the pathological disease processes, by regenerating or assisting biophysical characteristics of the intervertebral disc. Intradiscal therapies include biological therapy, cell-free implantation, and anti-inflammatory agents and research conducted into these areas will in time elucidate an effective intradiscal therapeutic for disc degeneration. This chapter reviews the horizon of this exciting area of development.

Keywords

Intradiscal therapeutics · OP-1 · GDF-5 · GDF-6 · HGF · PRP · Link-N · Statins · HSC · Hypertonic dextrose · Chymopapain · Gellified ethanol · Oxygen-ozone · Methylene blue · Hyaluronate hydrogel · Fibrin sealant · Il-6R MAB · Glucocorticoids · Celecoxib

Introduction

Chronic low back pain is one of the most common musculoskeletal diseases worldwide, with 70–85% of adults experiencing back pain at some time in life (Andersson 1999). The accepted leading cause for chronic low back pain is intervertebral disc (IVD) degeneration, with sciatic pain associated with posterior IVD herniation (Luoma et al. 2000). Current treatments such as discectomy or analgesia only target the clinical symptoms of the disease rather than treating the pathological process itself. Intradiscal therapeutics aim to treat aspects of the pathological disease process, by regenerating or assisting (by way of aiding or augmenting) biological processes and thereby physical characteristics of the IVD.

Biological Therapy

Biological therapies function by regenerating an aspect of the IVD. Within early disc degeneration biological therapies involve enhancing anabolic extracellular matrix (ECM) molecules, or to lower the levels of catabolic ECM molecules. Biological therapies focus growth factors to promote anabolic molecule synthesis, either by direct or indirect stimulation (Moriguchi et al. 2016). A presentation of promising and unfavorable results allow insight into which model would be the most appropriate to pursue for bedside therapy.

Bone Morphogenic Protein 7

Bone morphogenic protein 7 (BMP-7), also known as osteogenic protein-1 (OP-1), is part of the bone morphogenic protein (BMP) family which regulates many aspects of embryonic skeletal development, including osteoblast and chondrocyte differentiation, cartilage and bone formation, mesoderm patterning, and craniofacial and limb development (Wan and Cao 2005). OP-1 is used clinically as an adjunct to treatment of fractures and atrophic long bone nonunion. OP-1 has been used within posterolateral lumbar fusion as a substitution for autologous bone. However a large prospective, randomized, multicenter

clinical trial of 295 patients suggested in the 4 year follow-up that autograft appeared to have superiority in bridging bone formation (Hustedt and Blizzard 2014). Hence, it was reasonable to investigate a clinically available molecule as a possible intervertebral disc regenerator rather than a spinal fusion enhancer.

The rationale of OP-1 is to increase anabolic ECM proteins. Within the context of IVD regeneration, OP-1 has been experimented in animal trials involving rats, rabbits, and canines, with the disc degeneration models including needle puncture, nucleus pulposus aspiration, compressive loading, chondroitinase induction, and spontaneous degeneration. Delivery of OP-1 into the IVDs has either been direct OP-1 protein injection or cell-based and viral-based OP-1 gene transfer. OP-1 has been demonstrated to increase disc height and MRI T2 intensities compared to the control, indicating its strong ability to regenerate degenerated discs. OP-1 was found to enhance disc mechanical function, maintain spine stability, and alleviate pain-related behaviors. However, the rabbit and mice models used mostly keep the notochordal cells into adulthood, whereas in humans they disappear before the age of 10 and hence the animal IVDs may contain more regenerative capabilities than the human IVD. Moreover, within humans the natural degeneration is a slow process, whereas within the models the applied degeneration is acute and may not mimic the natural human degenerative process (Li et al. 2017). On the other hand, notochordal cells disappear when degeneration is induced prior to OP-1 or other therapeutic injections. Care should be taken when OP-1 delivery is used to treat human disc degeneration due to the differences between human and animal discs.

Research into human IVD regeneration has undergone in vitro experiments. Within a cadaveric model, human nucleus pulposus (NP) cells grown in a medium containing OP-1upregulated proteoglycan synthesis and accumulation, and prevented a decrease in cell numbers (Imai et al. 2007; Wei et al. 2008). In moderately degenerated lumbar discs, capacitively coupled electric stimulation increased BMP-7-induced upregulation of aggrecan and collagen type II (Wang et al. 2017). However, degenerative human NP cells cultured with OP-1 alone, or released from a slowly degrading biomaterial, had no positive effect on the cell growth (van Dijk et al. 2017).

OP-1 has been effective in halting disc degeneration and regenerating degenerative discs within animal models. However, there has been varying results demonstrated within human NP cell regeneration. A phase 2 study was conducted in late 2000's to evaluate the safety and efficacy of OP-1 as a disc regenerator. The results of this trial are not available in the public domain. Further research is mandatory to assess the efficacy and safety of use of OP-1 into human subjects prior to consideration as an intradiscal therapeutic option for disc degeneration.

Growth and Differentiation Factor 5

Growth and differentiation factor 5 (GDF-5) is part of the BMP family and is also known as BMP-14 and cartilage-derived morphogenic protein 1 (CDMP-1). The function of GDF-5 is primarily chondrogenesis during embryonic development. It is present within the joint regions of skeletal precursors to subdivide the precursor into the individual skeletal elements, and is required in all joints for normal development (Settle et al. 2003). Mutation of the GDF-5 gene results in anomalies of development such as Du Pan syndrome, Hunter–Thomson dysplasia, and lumbar disc degeneration.

GDF-5 has been demonstrated to have some reasonable effects on intervertebral disc regeneration. Within live animal models, GDF-5 has regenerated mouse and rabbit intervertebral discs. GDF-5 has also been demonstrated within human cell experiments to increase cell numbers and matrix proteins, establishing it as a protein that can possibly cause IVD regeneration. Delivery methods of GDF-5 into live animals resulting in positive results include protein injection, viral-based gene transfer, and slow releasing biomaterials.

However, there are some disadvantages presented by GDF-5. Repeated injections of GDF-5 results in inflammation of the IVD, which impedes the biological effect of the growth factor (Walsh et al. 2004). GDF-5 has been shown to function in a dose-dependent manner, with a short

half-life of 20 min, which means repeated injections would be required in human subjects (Cui et al. 2008). The subsequent inflammation may negate any positive effects of GDF-5. A recent clinical trial NCT00813813 has been conducted assessing injections of GDF-5 into the IVD, with results yet to be published. Our center was involved in the escalating dose arm of the phase 2 multicentric outside the US study. While the average reduction in visual analogue scores for pain was good, the variability in individual patient's response and lack of sponsor support led to cessation of the development of the molecule. Finally, Clarke et al. have demonstrated within an in vitro study that GDF-5 lacked the ability to convert stem cells effectively to disc cells when compared to GDF-6 (Clarke et al. 2014).

Growth and Differentiation Factor 6

Growth and differentiation factor 6 (GDF-6) is part of the BMP family and is also known as BMP-13 and CDMP-2. During embryonic development, GDF-6 is expressed strongly in the notochordal cells of the NP, and key extracellular matrix molecules aggrecan and collagen type II coincide with GDF-6 expression (Wei et al. 2016). GDF-6 mutations are related to several disease states including Klippel–Feil syndrome, and age-related macular degeneration.

GDF-6 has had positive results in regeneration of the IVD. GDF-6 was found within mouse mesenchymal stem cell lines to induce anabolic extracellular matrix (ECM) molecules, without causing ossification, validating its possibility as a regenerative therapy. Conversely with GDF-5, the adenoviral vector transmission did not effectively increase anabolic ECM molecules to a significant level (Zhang et al. 2006, 2007). However, direct culturing of NP cells with GDF-6 elicited positive results (Gulati et al. 2015). An ovine annular puncture model with GDF-6 treatment applied simultaneously with the annular injury showed complete restoration of the IVD height after 4 months (Le Maitre et al. 2015). A rabbit annular puncture model with GDF-6 treatment applied 4 weeks after injury demonstrated faster recovery with GDF-6, and some recovery of the IVD height (Miyazaki et al. 2018).

GDF-6 has been demonstrated to be a potential future intradiscal biological therapy for IVD degeneration. There are encouraging results from in vitro and in vivo trials providing some evidence that GDF-6 can regenerate the IVD after injury. However, disadvantages to GDF-6 treatment include its cost, time to manufacture, and lack of human data. Future research would include clinical trials to assess the safety and efficacy of the molecule.

Hepatocyte Growth Factor

Hepatocyte growth factor (HGF) was first identified as a potent mitogen of primary cultured hepatocytes. HGF is essential in mammalian development, as disruption of the HGF gene resulted in impaired organogenesis of the liver and placenta and is incompatible with life. HGF is also involved in formation and trophic support of vital organs such as the kidneys, lungs, heart, and brain. The receptor for HGF was identified as c-met proto-oncogene product (c-Met) and the HGF-c-Met signalling pathway leads to multiple biological responses in a variety of cells including mitogenic, morphogenic, and antiapoptotic activities (Funakoshi and Nakamura 2003; Nakamura et al. 2011)

The therapeutic approaches for HGFwithin animal models have been very effective for the treatment of chronic fibrosis in various disease models, such as liver cirrhosis, chronic kidney disease, dilated cardiomyopathy, and lung fibrosis (Nakamura et al. 2011). There have been few human clinical studies with HGF, however a recent randomized, double-blind, placebo-controlled clinical trial of hepatocyte growth factor plasmid for critical limb ischemia demonstrated the safety and efficacy of HGF treatment using naked plasmid (Shigematsu et al. 2010). There are currently several clinical trials occurring in the context of cardiac therapy for conditions such as acute coronary syndrome, myocardial infarction, and critical limb ischaemic.

For the treatment of intervertebral disc degeneration limited research has been conducted. A rat

tail disc degeneration model was applied, and a slow release biomaterial was used as the vehicle to deliver HGF. The experiment resulted in an increase in T2-weighted signal intensity on MRI, improved histological score, and stronger immunohistochemical responses demonstrating some prevention of IVD degeneration (Zou et al. 2013). In a rabbit cellular in vitro model HGF promoted NP cell proliferation, inhibited apoptosis and inflammatory cytokine expression, however did not affect matrix protein production (Ishibashi et al. 2016). The results suggest that HGF alters matrix catabolism and hence may be used as an adjunct to prevent degeneration. However as there is no improved anabolic effect, HGF alone may not induce IVD regeneration. Further studies within animal models to elucidate the exact expression of HGF and its receptor c-Met within the IVD is required to research the anabolic response elicited. HGF may be a potential adjunct within future intradiscal IVD therapy.

Platelet-Rich Plasma

Platelet-rich-plasma (PRP) is obtained by concentrating platelets and blood products with the use of a centrifuge. PRP can contain up to eight times the products found in blood and includes not only platelets but a variety of growth factors such as epithelial growth factor (EGF), platelet-derived growth factor (PDGF), transforming growth factors (TGF), and vascular endothelial growth factor (VEGF). Many of these growth factors are stored in granular storage compartments within the platelets, which must be activated to release their contents. The concentration of growth factors parallels the increased concentration of platelets. PRP can increase collagen content, accelerate endothelial regeneration, and promote angiogenesis. Whilst the scientific basis remains to be elucidated, due to ease of availability, and no intellectual property disputes, PRP has been used for various applications such as assisting repairs of the common extensor tendon of the elbow, rotator cuff tendons, and knee articular cartilage (Monfett et al. 2016).

PRP contains growth factors which are claimed to be beneficial in regeneration of IVD degeneration. Within in vitro models of both human and animal cells, PRP increased proteoglycan and NP cell proliferation, as well as upregulated ECM synthesis. PRP also downregulates proinflammatory cytokines and reduces their detrimental effect upon the NP cells (Yang et al. 2016). Within rabbit in vivo models, PRP increases the water content present on T2 MRI within the IVD suggesting a restoration of matrix function, and in some studies increased the disc height of the PRP-injected IVDs. Within rat models, there was an increase of water content present within T2 MRI. The animal models suggested PRP to be appropriate for treatment of IVD degeneration (Monfett et al. 2016; Obata et al. 2012). It remains unclear whether a specific factor helps the PRP achieve its intradiscal effect, or it is the cells and associated media.

There have been clinical trials assessing the safety and efficacy of PRP. Autologous blood cells are used, and are activated by calcium chloride, which is advantageous as there is little side effects using this technique. However, a disadvantage with this technique is that there is variability in the concentration of growth factors within the PRP. Another disadvantage is the vehicle of delivery, as injections themselves can induce inflammatory responses. However, there have been encouraging results presented from a double-blinded randomized control trial with 47 patients, with reduced pain and increased function even up to 2 years later (Tuakli-Wosornu et al. 2016). A feasibility trial observed the effects of stromal vascular fraction and PRP, essentially PRP enhanced with adipose-derived stem cells (ADSC), and within 15 patients after 6 months there was decrease in pain, increase in flexion, and no adverse effects (Comella et al. 2017). The trials suggest PRP may have potential to lower back pain.

PRP has encouraging findings particularly within the clinical setting. Future research would involve phase 2 and 3 trials discovering which group of patients would receive the most benefit from the treatment, finding the optimum concentration for PRP, and combining with other biological and stem cell therapy to find the most effective treatment.

Link-N

Link-N, also known as DHLSDNYTLDHDRAIH is the N-terminal peptide of the link protein. The role of Link-N is to stabilize the proteoglycan aggregates, by binding both to aggrecan and hyaluronate. Link-N is generated by the cleavage of human link protein by stromelysins 1 and 2, gelatinase A and B, and collagenase between His(16) and Ile(17) (Mwale et al. 2003). As Link-N is a synthetic peptide, it has the possibility of being financially beneficial as it is cheap to produce.

Link-N has been researched mainly within the context of IVD repair. Link-N functions by binding to the BMP receptor II, which establishes a classical feed-forward circuit converging on SMAD 1/5 activation. The feed-forward loop is the BMP-RII inducing BMP-4/7 synthesis which activates BMP-RI to produce SMAD 1/5, whilst the BMP-RII also itself induces SMAD 1/5 production (Wang et al. 2013). Link-N is proteolytically cleaved by AF cells into a bioactive short form of the peptide (sLink-N), into a residue spanning amino acid residues 1–8.

Link-N has been demonstrated to increase anabolic ECM proteins. Within both animal and human in vitro models, Link-N has been shown to induce the production of collagen type II, aggrecan, and glycosaminoglycan content. Within an in vivo rabbit annular puncture model, Link-N increased the disc height, increased anabolic proteins, and decreased catabolic cytokine levels (Mwale et al. 2011; Wang et al. 2013). Within a human in vitro model, sLink-N increased the levels of collagen type II and aggrecan. However, Link-N has a limited capacity to overcome catabolic and proinflammatory cytokine expression presented within severely degenerated NP cells (AlGarni et al. 2016; Bach et al. 2017).

Link-N has the capability to upregulate anabolic ECM proteins within human IVD cells, however this may be limited within the late stages of degeneration. It may be able to prevent or regenerate early stages of IVD degeneration. As part of the mechanism of Link-N is activating the BMP-4 and BMP-7 pathways, caution should be taken as these are potentially osteogenic growth factors. The safety and efficacy of Link-N is yet to be established, however the promising results and financial benefit lead Link-N to be an attractive molecule for further research for an intradiscal therapeutic for disc degeneration.

Statins

Statins function by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase and are the most efficient agent to reduce blood cholesterol with good tolerance. Statins alter the conformation of the enzyme, making the effect very specific. Statins also have anti-atherosclerosis effects, reducing incidents of coronary events (Stancu and Sima 2001).

Simvastatin activates BMP-2 gene expression, a growth factor which stimulates osteoblast proliferation but inhibits osteoblast differentiation, making it an ideal candidate for stimulation of bone formation (Mundy et al. 1999). However within the human IVD cells, BMP-2 facilitated the chondrogenic gene expression of human IVD cells with no evidence of bone nodule formation, and simvastatin was demonstrated within rat IVD cells to upregulate BMP-2 expression and stimulate the production of anabolic ECM molecules (Zhang and Lin 2008). Simvastatin loaded into a hydrogel carrier, injected into rat tails which had undergone annular needle puncture, increased anabolic ECM molecules, collagen type II, and the density on MRI improved (Zhang et al. 2009). Simvastatin was demonstrated within a rat model to function more effectively if injected within a hydrogel carrier, than a saline model, with improvements within MRI and histology and higher gene expression of anabolic ECM molecules (Than et al. 2014). Simvastatin was demonstrated to suppress several catabolic ECM molecules, suggesting that simvastatin may not only be effective in inducing NP cells to express regenerative ECM molecules, but may also help prevent any further degeneration (Tu et al. 2017).

Lovastatin is very similar to simvastatin, with the same mechanism of action, similar hydrophobicity, and same method of metabolization by cytochrome P450 3A. A difference is in reduction

of LDL-cholesterol. To reduce cholesterol by 25–30%, 10 mg of simvastatin are required, whereas 20 mg of lovastatin is needed for the same effect (Neuvonen et al. 2008). Simvastatin was shown to stimulate BMP-2 production, and as they have a similar mechanism of action, lovastatin was researched. Within human nucleus pulposus cells in vitro lovastatin upregulated collagen type II genes and chondrogenesis gene SOX9 (Hu et al. 2011). Within a discography-induced rat model, lovastatin was shown to increase anabolic ECM molecules, whilst suppressing collagen type I production which leads to fibrotic scar tissue (Hu et al. 2014).

The early research presented has shown statins to have positive results for intervertebral disc regeneration. However, as the statins mechanism of action for intervertebral disc regeneration rely on the BMP-2 pathway, it is appropriate to consider results of trials investigating BMP-2. BMP-2 has positive results, including inducing mitosis and increasing anabolic ECM molecules, however it has also been demonstrated to reduce proteoglycan content, initiate ossification of the annulus fibrosus, and accelerate osteophyte formation (Belykh et al. 2015). Furthermore, there has been no assessment of regeneraion on disc height and whether catabolic molecules have an effect upon statins function. Whilst early findings are promising, more research is required to assess if statins can be a feasible treatment for intradiscal therapy of disc degeneration.

Haematopoietic Stem Cells

Haematopoietic stem cells (HSC) are progenitor cells which have the capability to differentiate into cellular elements of blood and maintain blood cell production throughout an individual's whole life. HSC transplantation was one of the first proven clinical uses of stem cells, and is being researched to be used as a cure for haematological malignancies (Barriga et al. 2012). HSCs were the first cell therapy used with living humans for treatment of IVD diseases (Wu et al. 2018).

There has been very limited research between HSCs and IVD treatments. According to a prospective analysis of 10 patients found after 1 year, intradiscal HSC injections had 0% reduction in their pain (Haufe and Mork 2006). Moreover, a rabbit model of determining the fate of injected human HSC and MSC cells within coccygeal discs discovered no detection of HSC cells after 21 days, whereas the MSC cells survived and differentiated into a chondrocytic phenotype (Wei et al. 2009). These were the only two studies found assessing HSC in the context of IVD degeneration.

Currently there is little evidence to suggest HSCs have the potential to assist in the treatment of IVD diseases. However, there have been very few studies and hence there is a potential for future research to investigate the relationship between HSC and the IVD, including if within cellular contexts HSC can survive in an avascular tissue such as the IVD, and if they can be differentiated into a chondrocytic phenotype. HSCs are currently unsuitable to be an intradiscal therapy for IVD degeneration.

Hypertonic Dextrose

Prolotherapy is a minimally invasive technique where percutaneous delivery of a therapeutic results in influx of macrophages, fibroblasts, and other molecules with the final goal of new collagen formation strengthening the connective tissue, reducing pain, and disability (Linetsky and Manchikanti 2005). Hypertonic dextrose has been used as a prolotherapy agent for a range of chronic pain conditions with positive results. Prolotherapy within the intervertebral disc may result in improvement of discogenic pain due to modulation of chemoreceptors for pain (Miller et al. 2006).

There have been clinical trials assessing the use of hypertonic dextrose within IVD degeneration. Miller et al. studied advanced lumbar disc pain within 76 patients, with 43.4% of patients having a sustained treatment response with an improvement in pain reduction by 71% after 18 months (Miller et al. 2006). Many other trials have been conducted in treating chronic low back pain, however the hypertonic dextrose has been injected into the surrounding soft tissue, or other

areas of the vertebrae including the lamina, spinous process, and vertebral body, with prolotherapy providing significantly greater long-term pain reduction than corticosteroid injection in patients with sacroiliac joint pain (Hauser et al. 2016).

The principle of prolotherapy is introducing a small irritant, to create a low-level inflammatory reaction to induce fibroblasts, growth factors, and other cytokines to induce proliferation and create new connective tissue to strengthen the area (Hauser et al. 2016). Within the intervertebral disc, inflammation induces a degenerative response, and can accelerate degenerative disease (Carragee et al. 2009). Future research into hypertonicdextrose would involve its effect on the IVD, and its long-term safety. Due to the mechanism of prolotherapy theoretically inducing disc degeneration, despite the prospective trial presented having some benefits, it will be with great caution and skepticism that clinicians will assess hypertonic dextrose as a future therapeutic intradiscal treatment for degenerative IVD diseases.

Summary of Biological Therapies

The growth factors BMP-7, GDF-5, and GDF-6 have been demonstrated to be possible sources of future therapy for IVD degeneration, however there is still more research to be conducted. HGF may have a role, but as an adjunct to therapy as an anticatabolic agent. PRP is currently being used in clinical trials, however further results are needed to assess its efficacy. Link-N and statins function through other growth factors which are yet to be established for effective IVD therapy, yet they might bring about possible positive results. HSC and hypertonic dextrose have shown little improvements and probably do not have a role in future intradiscal treatments of IVD degeneration.

Chemonucleolysis

Chemonucleolysis is a percutaneous intradiscal injection to dissolve the nucleus pulposus. This aims to reduce intradiscal pressure, reducing pain within cervical and lumbar disc herniations. Moreover, destruction of the dermal nerve endings which are present in IVD degeneration within the cartilaginous end plate may also result in pain relief. Interestingly, this technique is used within animal models to induce disc degeneration (Norcross et al. 2003). An exploration of chemonucleolysis will elucidate whether it is an effective treatment for pain relief, or an inducer of degeneration.

Chymopapain

Chymopapain is a proteolytic enzyme derived from the latex of papaya (*Carica papaya*). It is a chemonucleolytic agent, which functions by causing dehydration and degradation of nuclear proteoglycans. Chymopapain was first introduced in 1964 and used in the treatment of lumbar disc herniation until the 1980s, with production discontinued in 2003. Chymopapain treatment involved using a minimally invasive injection with local anesthetic.

There were several clinical trials assessing chymopapain's treatment of symptomatic lumbar disc herniations. Two meta-analyses have been completed investigating chymopapain, which have been summarized by Varshney and Chapman (2012; Couto et al. 2007; Gibson and Waddell 2007). The meta-analyses concluded that chymopapain was superior to placebo in the treatment of symptomatic lumbar disc herniations, with fewer patients having subsequent surgery. In comparison with the gold standard of microdiscectomy, despite gross heterogeneity between 12 studies, surgery was found to be superior to chymopapain for treatment and long-term outcomes. Concerning the safety of chymopapain, the anaphylaxis rate was 0.5%, with a total mortality rate of 0.02%. Compared to microdiscectomy mortality rate of 0.1%, it was considered a safer procedure (Nordby et al. 1993).

The FDA maintains chymopapain on its discontinued product list, however not for reasons of effectiveness. Simmons and Fraser suggest several reasons for the loss of popularity and eventual discontinuation of chymopapain, including poor

techniques leading to complications, inappropriate patient selection including patients allergic to papaya, changes in attitude of early rehabilitation after surgery, and use of targeted epidural steroids (Simmons and Fraser 2005). Regarding future research for treatment of degenerated IVDs, chymopapain would not treat the disease state, only causing possible symptomatic relief through chemonucleolysis.

Gelified Ethanol

Pure ethanol is an effective agent to induce chemonucleolysis. However, it is radiopaque and is injected blindly, with a risk of an undetected leak into the epidural space. The leak can damage all components of the IVD, giving rise to severe pain. Gelified ethanol (GE) is pure ethanol enhanced with ethyl cellulose to increase the viscosity of the liquid and regulate its diffusion, thus reducing the risk of epidural leaks, and radiopaque tungsten for visualization (Theron et al. 2007, 2010). GE has advantages over similar techniques as it does not cause the allergic reactions of chymopapain, and it has a more lytic effect than oxygen-ozone.

There have been several trials assessing the safety and efficacy of GE. A preliminary study of 276 patients demonstrated safety of the technique with no pathologic event recorded after 4 years, and patients had an increase in function and reduction in pain (Theron et al. 2007). Thirty-two patients who failed treatment of oxygen-ozone chemonucleolysis therapy were treated with GE, with success within 75% of the patients (Stagni et al. 2012). A further 80 patients with lumbar and cervical disc herniations were treated with GE, and 3 months later 85% of lumbar disc herniation patients and 83% of cervical disc herniations obtained significant improvement in function and reduction of pain (Bellini et al. 2015). Twenty-nine patients with L5-S1 disc herniations with failed conservative treatments were treated with GE, and at the 6–12 month follow-up 66% of patients obtained a 50% relief of pain, with only three patients not experiencing any pain relief from the treatment (Houra et al. 2017).

GE has been demonstrated to be effective at treatment of radicular leg pain, compared with low back pain. The pathophysiological mechanism of radicular pain is most likely a combination of somatic pain from the outer annulus and adjacent ligaments, and neuropathic pain from nerve root compression and chemical inflammatory reaction. GE, by reducing the pressure caused by herniations, serves to reduce this radicular pain. GE's mechanism of action is destruction of the nucleus pulposus, rendering it unsuitable for treatment of degenerative disorders other than disc herniation.

Oxygen-Ozone

Oxygen-ozone (O_2-O_3) is a chemonucleolysis agent which is used in the treatment of lumbar disc herniation. The mechanism of action relies on the chemical properties of both oxygen and ozone. Oxygenation leads to reduced pain due to the oxidization of proinflammatory mediators and improves microcirculation within the compressed areas. Ozone is an unstable allotropic form of oxygen, and reacts with proteoglycan glycosaminoglycans (GAG) to form oxidization products smaller than the original GAGs, reducing the osmotic pressure of the NP, and causing dehydration and shrinking the disc (Murphy et al. 2016; Muto et al. 2004). Empirical studies have demonstrated the optimal concentration of ozone per millimetre of oxygen to be 27 μg (Iliakis et al. 2001).

Several clinical studies have been undertaken assessing O_2-O_3 therapy for treatment of lumbar disc herniation. Intradiscal injections of O_2-O_3 have been demonstrated to reduce pain and improve function after 1 month (Murphy et al. 2015), 6 months (Lehnert et al. 2012), 6 months with an additional paraganglionic injection (Andreula et al. 2003), and after 2 years intradiscal injections alone (Das et al. 2009). Intraformational injections have also been demonstrated to have success after 6 months with about 75% reduction in pain (Bonetti et al. 2005; Perri et al. 2015). And peri radicular with paraganglionic injections have had 80% success after 6 months and 75% at 18 months (Muto et al. 2004).

O_2-O_3 therapy has been demonstrated to be effective in treating the symptoms of disc herniation. However, there are some risks to the therapy, as the dose of ozone must not exceed the capacity of antioxidant enzymes. Excess ozone leads to accumulation of the superoxide anion (O_2-) and hydrogen peroxide (H_2O_2), which can cause cell membrane degradation (Andreula et al. 2003). The injections also present a source of infection, as demonstrated by a case study involving an infection of Achromobacter xylosoxidans following O_2-O_3 therapy (Fort et al. 2014). Similarly, to GE, O_2-O_3 is unsuitable for treatment of IVD disorders other than pain caused by herniation.

Methylene Blue

Methylene blue, also known as methylthioninium chloride, can be used as both medication and a dye. It is part of the WHO Model List of Essential Medicines, particularly as an antidote for poisonings. Methylene blue is an inhibitor of nitric oxide synthase, and guanylate synthase. It has been used in a wide variety of treatments, including improving arterial pressure in septic shock, treatment of methemoglobinemia, neutralization of heparin, and more. Methylene blue has also been used as a dye to locate lesions within parathyroid glands, intestinal lumen, lymph nodes, and as a rapid detection method for Helicobacter pylori on histology. Adverse effects of methylene blue include toxicity in high doses to the renal system, cardiovascular system, and pulmonary system. Contraindications include patients with renal insufficiency, and G6PD-deficient patients (Ginimuge and Jyothi 2010).

Methylene blue has shown to destroy dermal nerve endings. Part of the pathophysiology of pain from intervertebral disc degeneration is ingrowth of new nerve vessels. A pilot study of 72 patients was conducted under the rationale that methylene blue would destroy nerve fibres growing within the annulus, alleviating discogenic pain. The study found after 2 years from treatment, 91.6% of patients were satisfied with their outcome, and 89% of patients had obvious to complete alleviation of pain (Peng et al. 2010). A clinical trial with 33 patients assessed the use of methylene blue injections for low back pain, and had 81% success at 3 months, however after 12 months only 54% of patients had reduced pain and increase in function (van Dijk et al. 2017). A study of 24 patients discovered 87% of patients to have alleviation of back pain, and improvements in physical function after an average of 18 months (Peng et al. 2007). Another study of 20 patients found after 1 year that only 20% of patients had successful alleviation of pain (Kim et al. 2012), and a retrospective case series of 8 patients only identified 1 to have any benefits from methylene blue injections (Gupta et al. 2012).

Methylene blue has been demonstrated within the previous clinical studies to have varying results. There are differences in measurements of pain and assessments of function; however the general trend is that methylene blue is appropriate for reduction of short-term pain, and loses its potency over time. Factors contributing to this may include dissipation of the methylene blue, and regrowth of nerve endings, or a more complex pathophysiological system may be causing the pain. There have been little assessments on the effect of methylene blue on the histology of the intervertebral discs, and future research would identify the exact response of the intervertebral disc to methylene blue. Methylene blue has been shown to have varying degrees of success, however a lack of understanding about its function on disc cells makes its use simply for pain alleviation, and symptom control, but not treating the root cause of the disease state and may be an effective adjunct in finding a cure for disc degeneration.

Summary of Chemonucleolysis

Chemonucleolysis is a destructive tool which can be very effective in the reduction of pain during disc herniation. Chymopapain was found to cause anaphylaxis, due to the papaya content. The other agents have found to provide useful short-term benefits, however long-term outcomes vary. This technique does not treat the cause of the degeneration and is only useful for the treatment of pain caused by herniation of disc content.

Chemonucleolysis may be useful in destruction of the intradiscal nerve endings, however, it will only serve as either a very specific treatment or an adjunct to any future therapy developed.

Cell-Free Intradiscal Implantation

Intradiscal implantations are used either after nucleotomy procedures to mimic the mechanical properties of the IVD, or as a mechanism to repair annular fibrosus defects. They can also become a medium in which the NP cells can migrate into and proliferate within. They are able to be manufactured prior to surgery and then implanted.

Hyaluronate Hydrogel

Injectable hyaluronate hydrogels (HH) are cell-free intradiscal matrix implantations that have been proposed to limit disc degeneration following a nucleotomy procedure. HH have an anti-inflammatory effect within the intervertebral disc, and also provide a growth-permissive environment for NP cells and MSCs (Isa et al. 2015; Priyadarshani et al. 2016).

HH has been investigated within several animal models. Hyaluronic acid alone reduced degeneration on imaging following nucleotomy procedures in nonhuman primate lumbar spines (Pfeiffer et al. 2003). Within a rabbit annular puncture model of IVD degeneration, cross-linked HH and cross-linked chondroitin sulphate hydrogel retained MRI T2 intensity for 3 months, and histologically had increased proteoglycan staining (Nakashima et al. 2009). Within a sheep nucleotomy model, after 6 months HH completely regenerated sheep IVD histologically, biochemically, and radiologically (Benz et al. 2012). However, within a porcine nucleotomy model, HH did not affect the regeneration of the IVD, and caused further annular scarring and localized annular inflammation (Omlor et al. 2012). Within each of these animal models, the exact makeup of the HH is different, with the best results of Benz et al. incorporating autologous serum solution into their injectable HH solution.

HH has been demonstrated to be an effective medium for IVD cells to proliferate. A gel culture with 4% hyaluronan cross-linked with serum albumin was demonstrated to be a viable medium for the culturing of human IVD cells, and chondrogenic MSCs, stimulating the release of anabolic ECM molecules (Benz et al. 2010). Human NP cells cultured for 8 weeks within a HH showed functional matrix accumulation and synthesis, and these results were higher at lower density of NP cells (20 million cells per millilitre) (Kim et al. 2015). A study cross-linking type-II collagen HH with 1-ethyl-3(3-dimethyl aminopropyl) carbodiimide (EDC) was also demonstrated to be a viable growth medium for culturing of NP cells (Priyadarshani et al. 2016). Another hydrogel with chitosan and hyaluronic acid cross-linked with glycerol phosphate promoted ADSC proliferation and nucleus pulposus differentiation (Zhu et al. 2017).

HH is a potential future intradiscal therapy for degenerative IVD disease. Advantages of HH include its versatility and ability to create different cross-linking to find the optimal hydrogel for regeneration of the NP. It also has the capacity to be a growth medium for NP cells and MSCs, potentially improving its regeneration ability. However, as the variability of the animal models demonstrate, not only is there a capacity for HH to cause complete regeneration, there is also the possibility of HH solutions to cause more degeneration. Care must be taken in future research to develop an HH which is both efficacious and safe. HH has the potential to be an effective intradiscal therapy for IVD degeneration.

Fibrin Sealant

Fibrin sealant (FS) can be used within surgery to prevent local haemorrhaging complications. It functions by consisting of two components, factor XII and fibronectin (the sealant) and thrombin and albumin (the catalyst) (Canonico 2003). When the sealant and catalyst are mixed, they create a fibrin monomer, and a stable clot. Fibrin is required for normal wound healing, and factor XII and fibronectin is important for fibroblast proliferation

and adhesion. Within the IVD the fibrin sealant would function to seal annular fissures from proinflammatory substances and facilitate disc healing (Buser et al. 2011).

Fibrin has been shown to be an alternative three-dimensional cell carrier to cultivate porcine and rabbit NP cells in vitro (Sha'Ban et al. 2008; Stern et al. 2000). In vitro FS was demonstrated to decrease proinflammatory cytokine levels in both human and porcine cells (Buser et al. 2014). Within a porcine nucleotomy model FS preserved the disc architecture, reduced section of inflammatory cytokines, and recovered the mechanical properties lost from the nucleotomy. FS also increased proteoglycan synthesis and inhibited progressive fibrosis of the NP (Buser et al. 2011). A prospective clinical trial of 15 patients found improvements in pain relief and function at weeks 15, 26, 52, and 104 with low complication rates (Yin et al. 2014).

Guterl et al. added genipin (Fib-Gen), a plant-based chemical cross-linker with low cytotoxicity, alongside cell adhesion molecules fibronectin and collagen and successfully improved the shear properties of FS (Guterl et al. 2014). Fib-Gen was injected into in vitro bovine IVDs which had undergone nucleotomy, and shown to effectively seal any defects, and prevented IVD height loss from the induced compressive force. Fib-Gen maintained AF cells, and NP cells migrated into the gel (Likhitpanichkul et al. 2014). Fib-Gen has also been demonstrated to be an effective drug carrier, maintaining a constant slow release of infliximab, and more effectively than FS alone (Likhitpanichkul et al. 2015). Long et al. elucidated the biomechanical properties of Fib-Gen, by performing annular injuries on bovine coccygeal IVDs in vitro and repairing the defect with Fib-Gen within a scaffold. Long et al. demonstrates Fib-Gen to reduce disc height loss, had little herniation risk, but could only partially restore disc biomechanical behaviors (Long et al. 2016).

FS is a promising therapy due to its potential for multipurpose action. Whist originally intended to seal annular fissures and prevent ingrowth of nerve vessels leading to pain, the possibility of being loaded with pharmaceuticals allows for optimization of the treatment. Moreover, the creation of Fib-Gen and attempts to biomechanically replicate the NP provide an adjunct treatment to perform alongside discectomy. Cellular migration of NP and AF cells within FS and Fib-Gen also may strengthen the material within in vivo trials. However, care must be taken as there may be fibrin instability and solubility over time, particularly when exposed to cells, and currently it does not provide the same mechanical properties as the IVD (Colombini et al. 2014). FS has the potential to be an effective intradiscal therapeutic, either as an adjunct to pharmacological therapy or as an adjunct to discectomy.

Summary of Cell-Free Intradiscal Implantations

Both HH and FS are promising as they can not only repair or restore some mechanical function of the IVD, but they can also house either NP or stem cells for continued treatment. However, large drawbacks include trying to compare the studies, as each proposes a different formula for the creation of the hydrogel. Another disadvantage is that they cannot fully match the durability and mechanical properties of the IVD, leading to degradation and possible replacement after an unknown period of time. Intradiscal implantations have the potential to be used alongside biological treatments to be an effective intradiscal therapy for IVD degeneration.

Anti-Inflammatory Agents

Anti-inflammatory agents are used to reduce the catabolic ECM molecules within IVD degeneration. They also reduce proinflammatory cytokines which are a source of pain. They achieve this through preventing their synthesis, and directly inhibiting their action upon the cells.

Interleukin-6 Receptor Monoclonal Antibody

Tocilizumab is a recombinant monoclonal IgG1 antihuman interleukin-6 receptor antibody (IL-6R mAB). Also known as Atilizumab, it is an

immunosuppressive drug used within the treatments of disorders such as rheumatoid arthritis, and systemic juvenile idiopathic arthritis (Rosman et al. 2013). IL-6 is an inflammatory cytokine which functions by activating the 130 gp signal transducer, inducing angiogenesis, and amplifying activity of adhesion molecules. Tocilizumab was found to be beneficial and safe for treatment of rheumatoid arthritis in cases of nonresponse to anti-TNF-alpha therapy or when anti-TNF-alpha therapy is contraindicated (Rosman et al. 2013).

IL-6 expression is secreted by intervertebral discs, with raised expression present in herniated discs. IL-6 levels are also upregulated in degenerative IVDs, and upregulates other catabolic cytokines that attribute to intervertebral disc degeneration. IL-6 is also a cause of discogenic pain, as it induces apoptosis of neuronal cells in the dorsal root ganglion, which may contribute to allodynia and hyperalgesia (Risbud and Shapiro 2014).

There have been few experiments concerning IL-6 and IVD regeneration. A mouse degeneration model demonstrated IL-6R mAB to reduce IL-6 expression, and decreased pain-related peptide release within the dorsal root ganglions (Sainoh et al. 2015). A prospective comparative cohort study revealed tocilizumab to provide short-term, 2 weeks, relief of back pain (Sainoh et al. 2016). An in vitro trial elucidated human degenerative annular fibrosus cells induces the expression of IL-6 through the JAK/STAT pathway, and therefore may be causally linked to IVD degeneration (Suzuki et al. 2017).

IL-6 is a catabolic factor which contributes towards IVD degeneration. It is unclear if IL-6 is the principal cytokine involved in the development of IVD degeneration, or functions as an ancillary to other cytokines. Future research is required to clarify this relationship, however IL-6 treatment would only slow the degenerative process, and would not be able to induce regenerative capabilities.

Glucocorticoids

Glucocorticoids are a class of corticosteroids and are created endogenously within the adrenal cortex. The function of glucocorticoids is to reduce the synthesis and release of a variety of inflammatory mediators (Becker 2013). Vertebral degenerative changes at the lumbar spine can be classified into a three-stage system using Modic classification (Modic et al. 1988). Within Modic type 1, the cartilaginous end plates have a high amount of proinflammatory cytokines, and increased vascularity, indicating an inflammatory reaction and Modic type 1 changes are closely associated with chronic lower back pain (Beaudreuil et al. 2012). The rationale of glucocorticoids is to stop the inflammatory process, and provide symptomatic relief and prevent further degeneration.

Clinical trials have illustrated glucocorticoids to have a mixed effect in the treatment of chronic low back pain. Glucocorticoids have a mostly positive effect at reducing pain and improving function within the short term, up to 1 month (Beaudreuil et al. 2012; Benyahya et al. 2004; Buttermann 2004; Fayad et al. 2007; Nguyen et al. 2017) and no effect after 12 months (Khot et al. 2004) with only one paper revealing glucocorticoids to have no effect within early time periods (Simmons et al. 1992). Conversely, Benyahya et al. found after 6 months 43.5% of 67 patients had improvements in pain reduction and function (Benyahya et al. 2004). Long-term results were improved when combined with an alternative therapy such as O_2-O_3, with paraganglionic glucocorticoid injections providing treatment and increased function at 1 month and 6 months (Andreula et al. 2003; Murphy et al. 2015) and combined with a polypeptide, positive results after 3 and 6 months (Cao et al. 2011).

Concerns about glucocorticoids include a risk that it can cause degeneration and primary calcification as demonstrated within a rabbit model (Aoki et al. 1997). Moreover intradiscal procedures can create inflammation (Ulrich et al. 2007) and possibly contribute to IVD degeneration (Carragee et al. 2009), with the potential of glucocorticoids to have a toxic effect on intradiscal cells. Glucocorticoids has been generally very well tolerated within the clinical trials presented. Glucocorticoids may have symptomatic relief for a short time of chronic low back pain, however as its mechanism is only preventing inflammation, future research may reveal it to be a helpful adjunct with other treatments, as opposed

to a cure. As an intradiscal treatment glucocorticoid is currently only appropriate for short-term symptomatic relief, and inappropriate for curative treatment.

Celecoxib

Celecoxib is a nonsteroidal anti-inflammatory drug (NSAID), and was the first cyclooxygenase-2 (COX-2) selective inhibitor introduced into clinical practice. Inhibition of COX-2 results in anti-inflammatory and analgesic effects, with fewer gastrointestinal side effects than NSAIDs. Celecoxib is eliminated by hepatic metabolism involving primarily the CYP2C9 protein, with a half-life of 11 to 16 h (McCormack 2011; Shi and Klotz 2008). COX-2 inhibitors can be effective in reducing back pain and reducing degeneration, as they prevent the formation of proinflammatory cytokines such as prostaglandin E2 (PGE2), which shifts the environment to a catabolic state leading to regeneration. However, systemic delivery of COX-2 at levels high enough to alleviate chronic low back pain is associated with comorbidities and side effects, hence a localized delivery system would provide more effective pain relief with fewer side effects (Tellegen et al. 2018).

Celecoxib does not reduce the rate of nerve growth within the nucleus pulposus (Olmarker 2005). Canine models have demonstrated that separate hydrogels are safe and feasible when loaded with celecoxib, with one study having significant improvement in 9 out of 10 canines, and at 3 months only 3 having recurring back pain, however no changes in %DHI or MRI T2 brightness (Tellegen et al. 2018; van Dijk et al. 2015). Within a bovine NP cellular model replicating herniation, celecoxib reduced PGE2 proving within the intervertebral disc celecoxib is effective in reducing catabolic enzymes (van Dijk et al. 2015). Within a cox-2 knockout mouse experiment (Cox-2 −/−), the deficiency causes delay in the ossification of lumbar vertebral endplates, and plays a role in IVD degeneration by affecting the sonic hedgehog and BMP signaling pathways (Ding et al. 2018).

Celecoxib can reduce the levels of the catabolic molecule PGE2. However, there has been no evidence so far that celecoxib has other effects than in reducing pain, and potentially reducing the rate of degeneration. Future research would involve perfecting the hydrogel to load with celecoxib, and then observing if within humans it can reduce pain levels as demonstrated within canines. Other future research into the relationship between COX-2 and intervertebral disc development may lead to a novel solution to prevent early degenerative disease. However with the current evidence, Celecoxib may be an effective adjunct in preventing pain alongside other intradiscal therapies for disc degeneration.

Summary of Anti-Inflammatory Agents

Intradiscal anti-inflammatory agents have mixed results within the treatment of IVD degeneration. Tocilizumab has promising results, but has not been trialled in clinical practice. Glucocorticoids have been demonstrated to have a positive early response, albeit with negative long-term results, and celecoxib is unknown if it can reduce pain. More evidence is required for the effectiveness of intradiscal applications of anti-inflammatory agents, and at most they might be a useful adjunct with treatments for intradiscal therapies of IVD degeneration.

Summary

The following Table 1 is a summary of the current research of intradiscal therapies.

Conclusion

Biological therapies, intradiscal implantations, and anti-inflammatory agents have been explored as possible future intradiscal therapies for IVD degeneration. The most promising research is within the biological and intradiscal therapies, as they have the possibilities of working in conjunction to halt degeneration, induce regeneration, and

Table 1 A summary of the studies of intradiscal injections and implants. BMP-7, bone morphogenic protein 7; OP-1, osteogenic protein 1; GDF-5, growth and differentiation factor 5; GDF-6, growth and differentiation factor 6; HGF, hepatocyte growth factor; IL-6R mAB, interleukin-6 receptor monoclonal antibody; HSC, haematopoietic stem cell

	Studies of intradiscal injection/implants					
			Development stage			
Category	Drug/Material	Product name	Preclinical study (animal)	Clinical trial	Available on market	Reference
Biological	BMP-7	OP-1	X (rabbit)	X (Phase 1)	X	Imai Y et al. 2007
	GDF-5	rhGDF5		X (Phase 1 and 2a completed) $n = 40$		NCT01158924
	GDF-6		X (sheep)			Wei A et al. 2009
	HGF		X (rat)			Zou F et al. 2013
	Platelet-rich plasma		X (rabbit)	X (Phase 2) $n = 112$	Autologous	NCT02983747 Monfett M et al. 2016
	Link-N		X (rabbit)			Mwale F et al. 2011
	Simvastatin	Zocor	X (rat)		X	Than KD et al. 2014
	Lovastatin	Mevacor	X (rat)		X	Hu MH et al. 2014
	HSC			X (Pilot study) $n = 10$	Autologous	Haufe SMW and Mork AR 2006
	Hypertonic dextrose			X (Pilot study)		Miller MR et al. 2006
Chemonucleolysis	Chymopapain			X (Pilot study) $n = 17$	X	Jenner JR et al. 1986
	Gelified ethanol	Discogel	X	X (Phase 1) $n = 40$	X	NCT02343484 Stagni S et al. 2012
	Oxygen-ozone			X		Muto M et al. 2004
	Methylene blue		X	X (Phase 1) $n = 40$	X	NTR2547 (NL) Geurts JW et al. 2015
Cell-free intradiscal implantation	Hyaluronate hydrogel		X (rabbit)			Nakashima S et al. 2009
	Chondroitin sulfate hydrogel		X (rabbit)			Nakashima S et al. 2009
	Fibrin sealant	BIOSTAT BIOLOGX		X (Phase 1) terminated	X	NCT01011816 Yin W et al. 2014
Anti-inflammatory	IL-6R mAb	Tocilizumab;Actemra; RoActemra		X (Phase 1) $n = 31$	X	Sainoh T et al. 2016
	Glucocorticoid	Hydrocortancyl (Prednisolone)		X (Phase 4) $n = 137$	X	NCT00804531 Nguyen C et al. 2017
	Celecoxib	Celebrex	X (dog)		X	Tellegen AR et al. 2016 OARSI Abstract

provide support for the recovering IVD. Anti-inflammatory agents may be used as an useful adjunct for therapies, however their efficacy is not yet conclusive. There are currently no intradiscal therapies available, however with the development of so many different avenues of research the promise for treatment being soon available is great.

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Replacing the Nucleus Pulposus for Degenerative Disc Disease and Disc Herniation: Disc Preservation Following Discectomy

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Abstract

Low back pain is the leading cause of years lived with disability worldwide and thus a significant burden on the economy and healthcare systems. Degenerative changes and/or repetitive abnormal loading in the lumbar spine could lead to structural failures of the intervertebral disc and herniation of the nucleus pulposus, all of which may manifest as chronic back and/or leg pain. Although lumbar discectomy is a clinically beneficial procedure for appropriately selected disc herniation patients, revision discectomy rates range from 2% to 18% within the first decade of the primary discectomy, especially in patients younger than 65 years. Discectomy being a tissue discarding procedure may compromise the biomechanical integrity of the disc and accelerate its degeneration. Nucleus replacement (NR) implants present a promising option to address some of the challenges surrounding lumbar discectomy. An NR implant may be used as an adjunct to discectomy to preserve the biomechanical integrity of the disc and minimize recurrent herniation of the nuclear tissue. Nonetheless, a systematic review of the literature on clinical outcomes for NR implants revealed high rates for endplate remodeling and implant subsidence. A detailed multiscale understanding of the mechanisms of disc herniation and reherniation, closure of the annular defect, and the ability to tailor geometry and material properties for individual patients are needed to develop the next generation of NR implants.

Keywords

Intervertebral disc · Disc degeneration · Disc herniation · Discectomy · Nucleus replacement implants

Introduction

Low back pain (LBP) is the leading cause of years lived with disability (YLD) worldwide, contributing approximately 57.6 million years to the total YLDs in 2016 (followed by migraine contributing 45.1 million years) and a lifetime prevalence that exceeds 80% in the industrial world (Connelly et al. 2006; Vos et al. 2017). In the United States alone, the total costs associated with low back pain exceed US$ 100 billion per year, two-thirds of which are a result of lost wages and reduced productivity (Katz 2006). Although the factors leading to LBP are largely unknown, it is frequently due to the defects or failures of the intervertebral disc (IVD) resulting in the herniation of the inner disc (pulposus) material which causes irritation and/or mechanical compression of the spinal cord or the exiting nerves, often resulting in pain, neurologic deficit, or both.

Structure and Function of a Healthy IVD

The IVD is a fibrocartilaginous structure that has a mechanical role of absorbing and transmitting loads acting on the spinal column. Together with the facet joints, the IVD completes the three-joint complex at each motion segment in the spinal column. There are three primary components in an IVD: an inner jellylike material called the nucleus pulposus (NP), an outer tough fibrocartilaginous structure called the annulus fibrosus (AF), and the vertebral endplates (EP) which serve as a transitional zone joining the IVD to the vertebrae above and below (Fig. 1).

The NP is a hydrated mass of gelatinous tissue in the center of the IVD, primarily composed of large amounts of proteoglycans with sparsely arranged collagen fibrils serving as supporting

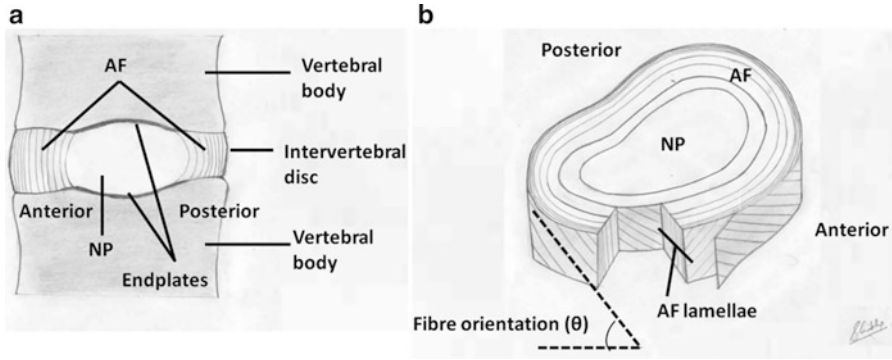

Fig. 1 Schematic representation of an adult intervertebral disc (IVD). (**a**) Midsagittal section of the IVD attached to the vertebral bodies, showing its primary components: nucleus pulposus (NP); annulus fibrosus (AF); and endplates (EP). (**b**) Three-dimensional view of the IVD illustrating the oblique and counter-oblique fiber orientation in adjacent lamellae

matrix. Bottlebrush-shaped proteoglycan molecules contain a protein core and hydrophilic glycosaminoglycan (GAG) chains (Cassinelli and Kang 2000). The high concentration of GAGs increases the osmotic pressure of the NP and allows it to swell and resist large compressive loads (Buckwalter 1995; Kroeber et al. 2002). While proteoglycans make up roughly 50% dry weight of the NP, the NP is also composed of approximately 25% collagen (Cassinelli and Kang 2000; Maroudas et al. 1975; Trout et al. 1982). Collagen type II is highly prevalent in the NP, and its concentration decreases toward the peripheral AF (Cassinelli and Kang 2000). The cells within the NP are sparse and are responsible for the maintenance of the extracellular matrix (Cappello et al. 2006).

The AF is a composite structure comprising ground substance and concentric layers (lamellae) of collagen type I fibers arranged in a regular crisscross pattern and attached circumferentially to the endplates (Hukins 2005). The AF is composed of more than two-thirds collagen, and proteoglycans make up only a small percentage of its composition (Cassinelli and Kang 2000; Maroudas et al. 1975). Within each lamella, the orientation of the fibers varies, alternating at approximately $\pm 20^\circ$ on the ventral side and continuously changing up to $\pm 45^\circ$ toward the dorsal side (Cassidy et al. 1989). The outer lamellae are stiffer and more densely packed than the inner ones (Holzapfel et al. 2005; Mengoni et al. 2015). In addition to axial compression, the AF withstands stresses in the tangential and radial directions. The NP and the inner AF contain only chondrocytes, while the outer AF contains mostly fibrochondrocytes (Melrose et al. 2008).

The top and the bottom of the IVDs are capped with EP (Fig. 1). The EP consists of a bony and a cartilaginous component which serves to balance conflicting biophysical demands. The bony endplates (BEP) provide the strength required to resist mechanical failure, whereas the cartilaginous endplates (CEP) facilitate chemical transport due to their porous nature (Lotz et al. 2013). In the lumbar spine, the cranial BEP is significantly thicker (1.03 ± 0.24 mm) and denser than the caudal BEP (0.78 ± 0.16 mm) (Wang et al. 2011). Within lumbar EPs, regional variation in stiffness exist, with the periphery stronger than the center, posterior stronger than the anterior, and the posterolateral sites in front of the pedicles being the strongest (Grant et al. 2001).

Together, the AF and the EPs serve to contain the NP, and in a healthy IVD, an osmotic pressure gradient provides the flow of nutrients to the NP. The IVD does not contain nerve tissues beyond the outer layers of the AF and the EP (Fagan et al. 2003; Ozawa et al. 2006). With no direct vascular supply, the IVD is the largest avascular component of the human body, relying entirely on diffusion for nutrition as well as the elimination of the waste products.

Degenerative Disc Disease (DDD)

Disc degeneration is one of the many progressive changes in the human body primarily attributable to natural ageing and is not a disease as much as it is a process. Magnetic resonance imaging (MRI) studies have shown that morphologically similar degenerated discs can be symptomatic or asymptomatic, which supports the hypothesis that a painful disc is a result of biochemical rather than morphological changes (Boos et al. 1995; Brinjikji et al. 2015). As early as the first two decades of life, the disc starts undergoing a progressive alteration in biochemical and morphological characteristics, which subsequently alters its biomechanical properties (Haefeli et al. 2006; Vernon-Roberts et al. 2007).

The etiology of disc degeneration is not well understood. One of the primary causes is thought to be the failure of nutrient supply to the disc cells, which may happen due to endplate calcification or other factors that affect the blood supply to the vertebral body such as atherosclerosis (Nachemson et al. 1970). A relationship has been found between loss of cell viability and fall in nutrient transport in scoliotic discs (Urban et al. 2001). Abnormal mechanical loads are also thought to initiate injury that leads to disc degeneration (Lotz et al. 1998; Stokes and Iatridis 2004). Lastly, genetic predisposition has been confirmed in twin studies as well as by reports of an association between disc degeneration and polymorphisms of matrix macromolecules (Paassilta et al. 2001).

Biochemical Changes

The composition and organization of the extracellular matrix in an IVD largely govern its mechanical properties. The balance between synthesis, breakdown, and accumulation of the matrix macromolecules determines the quality and integrity of the matrix and thus the mechanical behavior of the disc itself. The extracellular matrix in an IVD comprises two main macromolecules which have distinct composition, structure, and function. The collagen network, formed mostly of type I and type II collagen fibrils and making up approximately 70% and 20% of the dry weight of the AF and NP, respectively, provides tensile strength to the disc and anchors the tissue to the bone (Eyre and Muir 1977). Aggrecan, the major proteoglycan of the disc, has negatively charged GAG chains which attract water molecules, thereby maintaining tissue hydration and creating an osmotic pressure gradient within the NP (Johnstone and Bayliss 1995).

The most significant change to occur in an IVD with degeneration is the loss of proteoglycan molecules (Lyons et al. 1981). The bigger proteoglycan molecules break down into smaller fragments resulting in a loss of GAG chains, which leads to a gradual loss of hydration in the disc matrix and is primarily responsible for a fall in osmotic pressure within the NP. With degeneration, the collagen population in the disc can alter in type and distribution, but the absolute quantity of collagen does not change significantly. The relatively thin type II collagen in the nucleus is replaced by denser type I collagen with increased cross-linking between the collagen fibrils, making the nucleus more fibrotic, which is thought to further hinder tissue-fluid exchange (Duance et al. 1998). The barriers created by increased cross-linking reduce the rate of turnover and repair of collagen and proteoglycans, altering homeostasis within the IVD and resulting in the retention of damaged macromolecules (Adams and Roughley 2006).

In a normal disc, aggrecans, because of their high concentration and charge, prevent the movement of large uncharged molecules such as serum proteins and cytokines into and through the disc matrix (Maroudas 1975). The fall in concentration of aggrecans could result in an unchecked loss of osmotically active small aggrecan fragments from the disc, and increased penetration of large molecules such as growth factor complexes and cytokines into the disc. The increased vascular and neural ingrowth observed in degenerated discs is likely associated with proteoglycan loss because disc aggrecan has been shown to inhibit neural ingrowth (Melrose et al. 2002).

Hydration of the AF extracellular matrix, which serves to facilitate waste and nutrient exchange, is crucial to imparting viscoelasticity

properties to the disc (Gu et al. 1999; Travascio et al. 2009). Both extra- and intrafibrillar fluids are responsible for the AF hydration. The intrafibrillar fluid that closely adheres to collagen fibers provides long-term AF hydration. The earliest known compositional change in proteoglycan loss reduces both the AF extra- and intrafibrillar fluid capacity and swelling pressure while impairing its overall load-bearing capability (Johannessen and Elliott 2005; Yao et al. 2002). On the other hand, extrafibrillar fluid, which is responsible for nutrient and waste (i.e., lactic acid) transport, moves freely across the AF. Drop in the AF osmotic pressure secondary to the lack of extrafibrillar fluid reduces the efficiency of nutrient-waste exchange and leads to a decrease in pH and consequently lactic acid accumulation (Iatridis et al. 2007; McMillan et al. 1996). Both decrease in pH, which leads to acidity increase, and insufficient nutrition across the AF impair cellular metabolism and increase the risk of disc degeneration (Cassinelli et al. 2001). Therefore, any undesirable changes in the AF extra- and intrafibrillar fluids lead to dehydration, alter osmotic and viscoelastic properties, and may result in disc degeneration (Gu et al. 2014; Murakami et al. 2010).

Morphological Changes

Macroscopic analysis of midsagittal slices of human lumbar IVD of individuals ranging from newborn to senile age has revealed the temporospatial variation of age-related morphological changes in the disc (Haefeli et al. 2006). Degenerative processes in the disc start in the first two decades of life with transformation in the NP, mucous degeneration, AF disorganization, alteration of the EP, and osteophyte formation (Fig. 2). After the initial phase of significant alterations, degenerative changes remain constant over the next two decades before increasing again after the fourth decade (Haefeli et al. 2006).

The initial morphological changes are followed by the appearance of nuclear cleft and subsequent radial and concentric tears in the annulus in the fifth decade of life. Radiating annular tears rarely extend to the outer AF and are thought to be a consequence of clefts originating in the NP (Vernon-Roberts et al. 2007). Rim lesions typically occur independent of annular tears and substantially later in life (Haefeli et al. 2006; Vernon-Roberts et al. 2007). With progressive degeneration, an ingrowth of nerve fibers and blood vessels beyond the outer AF is observed which is often associated with discogenic pain (García-Cosamalón et al. 2010; Stefanakis et al. 2011). Although disc height narrowing with DDD has been reported in some studies, Twomey and Taylor (1987) contradicted this opinion by showing that the average disc height is maintained in old age, with the distance between the anterior and posterior corners of the vertebral bodies decreasing and the IVD expanding centrally to become increasingly convex (Butler et al. 1990; Twomey and Taylor 1987). Nonetheless, in some cases, severe tissue destruction (including cleft and tears formation as well as rim lesions) may occur in the first two decades of life, which presents an enormous challenge for any prophylactic tissue engineering repair attempt.

Disc herniation can be considered as one specific feature of disc degeneration that is much more closely related to mechanical loading (exceeding tissue strength) and pain than other features of degeneration such as signal intensity on MR scans and biochemical changes. Examination of autopsy or surgical specimens suggests that some degenerative changes, such as nuclear desiccation and fragmentation and preexisting tears in the AF, are necessary before a disc can herniate (Moore et al. 1996). In extruded disc tissue material, isolated fragments of AF and EP are much less common than the NP (Moore et al. 1996).

Biomechanical Changes

In healthy conditions, the high water content within the NP creates hydrostatic pressure which contributes to sustaining large loads acting on the spinal column. The compressive spinal loads are uniformly distributed to the AF through hydrostatic pressure, which creates hoop stresses within the AF. The fiber orientation of the AF is suitable

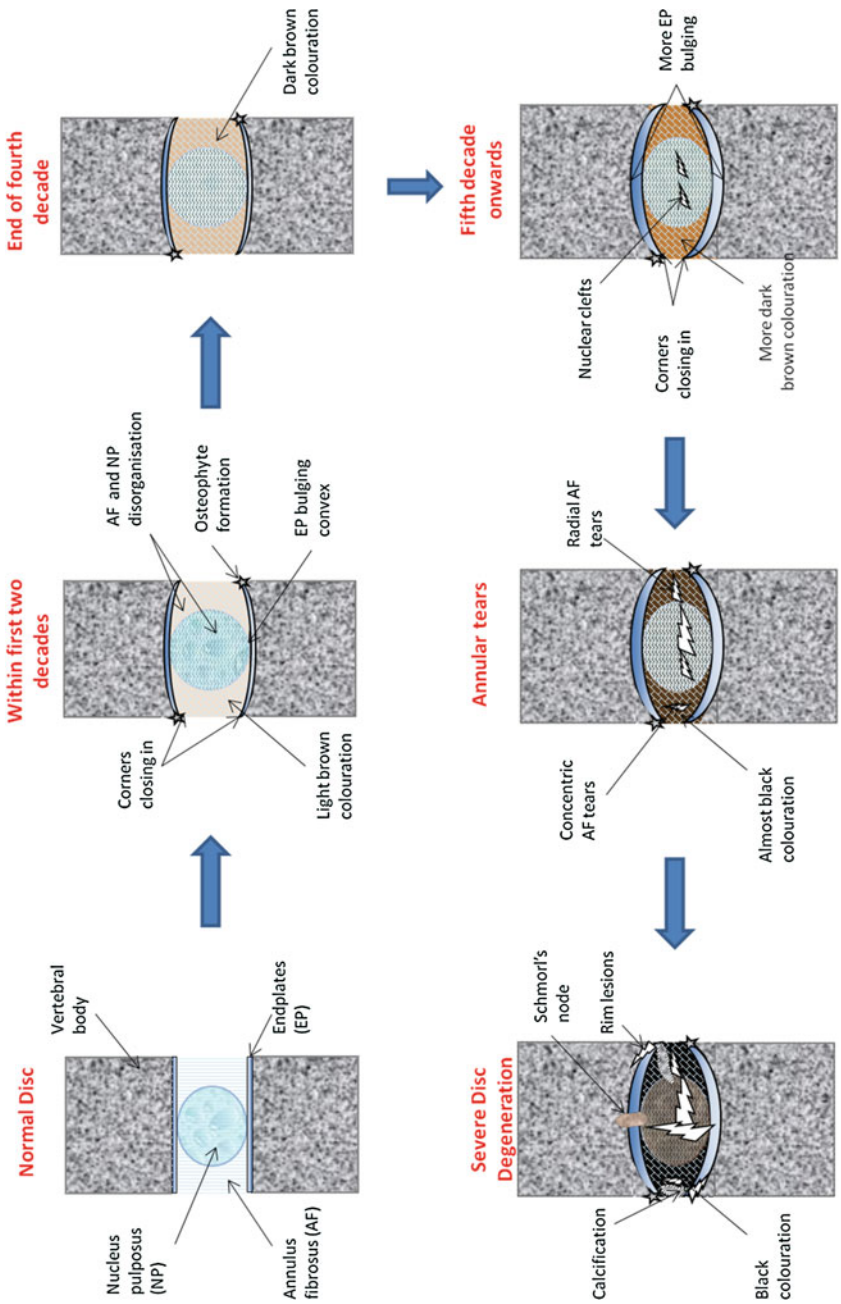

Fig. 2 Schematic representation of the course of macroscopic degeneration in the human lumbar intervertebral discs. Age or degeneration-related structural abnormalities combined with complex repetitive mechanical loading in the disc could result in disc prolapse or herniation (Fig. 3). A disc may, however, herniate without degeneration if loaded severely enough, and the degenerative changes found in the herniated disc material probably occur after herniation has taken place, as a result of tissue swelling, leaching of proteoglycans, and revascularization (Fig. 3d) (Adams and Hutton 1986; Lama et al. 2013)

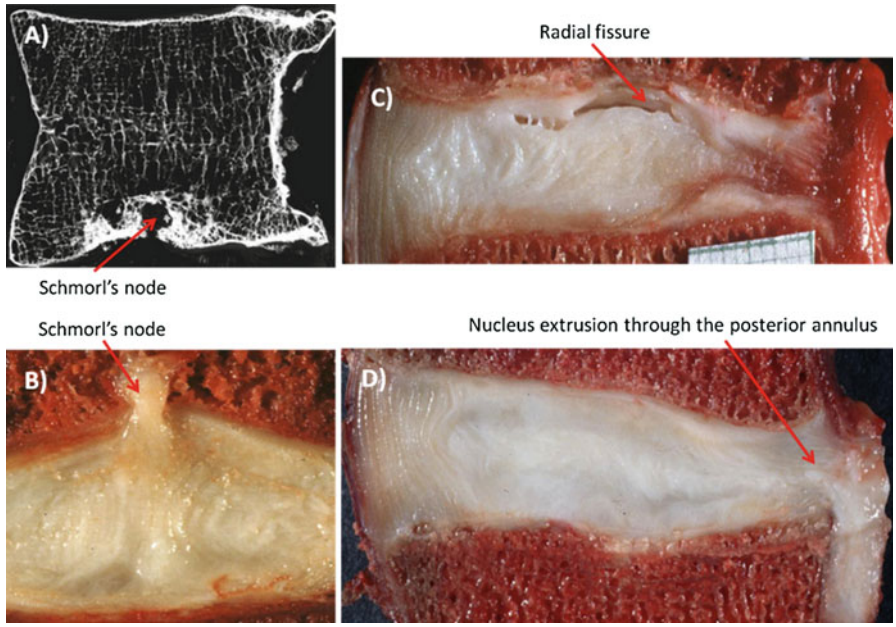

Fig. 3 Structural defects in lumbar intervertebral discs due to degeneration and/or mechanical overloading. (**a**) Microradiograph of a midsagittal slice of a cadaver vertebral body showing Schmorl's node and bone remodeling around it. (**b**) A cadaver disc which has herniated through the endplate in response to compressive loading shows decompressed nucleus and bucking of inner annulus walls. (**c**) A cadaver disc showing a complete radial fissure in the posterior annulus. (**d**) Nucleus extrusion through the posterior annulus due to abnormal bending and compressive loads in an otherwise nondegenerate disc. (Images adapted from Adams and Dolan 2016, with permission)

to resist hoop stresses generated by the hydrostatic pressure.

Degenerative changes in the biomechanical properties of the disc can occur due to changes in either material properties of the individual NP and AF tissues or due to consequent morphological changes in the substructure of the disc. The process is thought to initiate in the NP, with a decrease in its proteoglycan concentration and a gradual change in collagen type, making the nucleus more fibrotic, stiffer, and severely limited in its ability to generate hydrostatic pressure. Degenerated NP tissues have significantly lower swelling stress ($P_{sw} = 0.037 \pm 0.038$ MPa degenerate, $P_{sw} = 0.138 \pm 0.029$ MPa nondegenerate), lower effective aggregate modulus ($H_A^{eff} = 0.44 \pm 0.19$ MPa degenerate, $H_A^{eff} = 1.01 \pm 0.43$ MPa nondegenerate), and a higher permeability ($k_a = 1.4 \pm 0.58 \times 10^{-15}$ m^4/N-s degenerate, $k_a = 0.9 \pm 0.43 \times 10^{-15}$ m^4/N-s nondegenerate) (Johannessen and Elliott 2005). In the degenerate AF, the fiber orientation becomes disorganized, and the nonlinear elastic response also varies consequently (Schollum et al. 2010). The response of the degenerate AF tissue has been shown to be of a twofold increase in the toe-region modulus in tensile testing, which correlated with age, as well as fiber reorientation toward the loading direction (Guerin and Elliott 2006; O'Connell et al. 2009). Although the water content within the AF is not affected by degeneration, material property parameters such as Poisson's ratio, failure stress, and strain energy density are strongly influenced by the level of degeneration (Michalek et al. 2009).

The above changes in biochemical, morphological, and biomechanical properties of the disc combined with complex repetitive loading may result in the structural failure of the disc and present in the form of disc herniation: either protrusion or complete rupture of the AF walls followed by the expulsion of the NP material (extrusion or sequestration). The inflammatory material from the disc (particularly the NP) may

cause chemical irritation and mechanical compression of the cord and the exiting nerves and contribute to radicular back and/or leg pain (Goupille et al. 1998; Omarker and Myers 1998). Therefore, a common approach to the clinical treatment for painful disc herniation is surgical removal of the herniated material to unload the nerves (discectomy) (DeLeo and Winkelstein 2002; Loupasis et al. 1999).

Herniation and discectomy may accelerate disc degeneration. The loss of NP material results in decreased pressure within the disc, progressive loss in disc height, inward buckling of the inner annulus, and an increased bulging of the annulus under compression (Brinckmann and Grootenboer 1991; Frei et al. 2001; Meakin and Hukins 2000). In an in vitro study on human lumbar discs, Brinckmann and Grootenboer (1991) demonstrated that, on average, removal of 1 g of disc tissue resulted in a height decrease of 0.8 mm and a radial bulge increase of 0.2 mm under compressive loads. Removal of 3 g of central disc tissue lowered the intradiscal pressure to approximately 40% of its initial value (Brinckmann and Grootenboer 1991).

Although discectomy provides immediate relief from leg/back pain in most cases, the procedure is a tissue discarding one, in which the most frequent adverse events are the recurrent herniation of the residual nuclear tissue, progressive disc height loss, and reoccurring back/leg pain. An additional risk following discectomy is the loss of disc height which has been linked to the amount of nucleus material removed at the time of surgery (Tibrewal and Pearcy 1985; Yorimitsu et al. 2001). In turn, there is an alteration of the entire spinal column kinematics, and as the more nuclear material is removed from within the disc, the less capable it is of supporting the spinal loads.

Filling the nucleotomized cavity with a biologically inert replacement material has the potential to restore biomechanical characteristics of the disc and mitigate the progressive loss in disc height. Our group has conducted preliminary work to assess biomechanical efficacy of a non-hydrogel silicone-based in situ curing nucleus replacement (NR) implant, the Kunovus Disc Device (KDD, Kunovus Pty Ltd., Australia) in restoring the bending stiffness of a human lumbar motion segment following discectomy. A finite element modelling study to evaluate changes in bending stiffness of a L3–L4 motion segment revealed that compared with the baseline intact state, a complete nucleotomy significantly increases annular bulge (flexion, 0.65 mm; extension, 0.18 mm) and average Von Mises stress in the annulus (flexion, 38%; extension, 6%) (Fig. 4). Although partial filling of the nucleotomized cavity with the KDD was not able to restore the synergistic biomechanical interaction between the AF, EP, remnant NP, and the NR implant; complete filling of the cavity restored the biomechanical characteristics of the motion segment close to the normal intact state levels (Fig. 4).

Nucleus Replacement Implants

Nucleus replacement (NR) implants present a promising option for restoring and preserving the biomechanical integrity of an IVD and address some of the challenges surrounding discectomy procedures. These implants fill the treatment gap between nonsurgical care and invasive surgical procedures such as fusion and total disc replacement (TDR).

Essential Design Criteria

An NR implant must meet five essential criteria to be considered for clinical use:

1. Biocompatible and durable to survive the lifespan of the recipient.
2. Maintain the disc height, stabilize motions across all axes of movement, and restore normal distribution of loads in the motion segment.
3. High conformity in the nucleotomized cavity to avoid device migration and subsidence
4. Optimal stiffness to avoid excessive wear and/or remodeling of the EP. An overly compliant implant will overload the AF and fail to maintain the disc height.

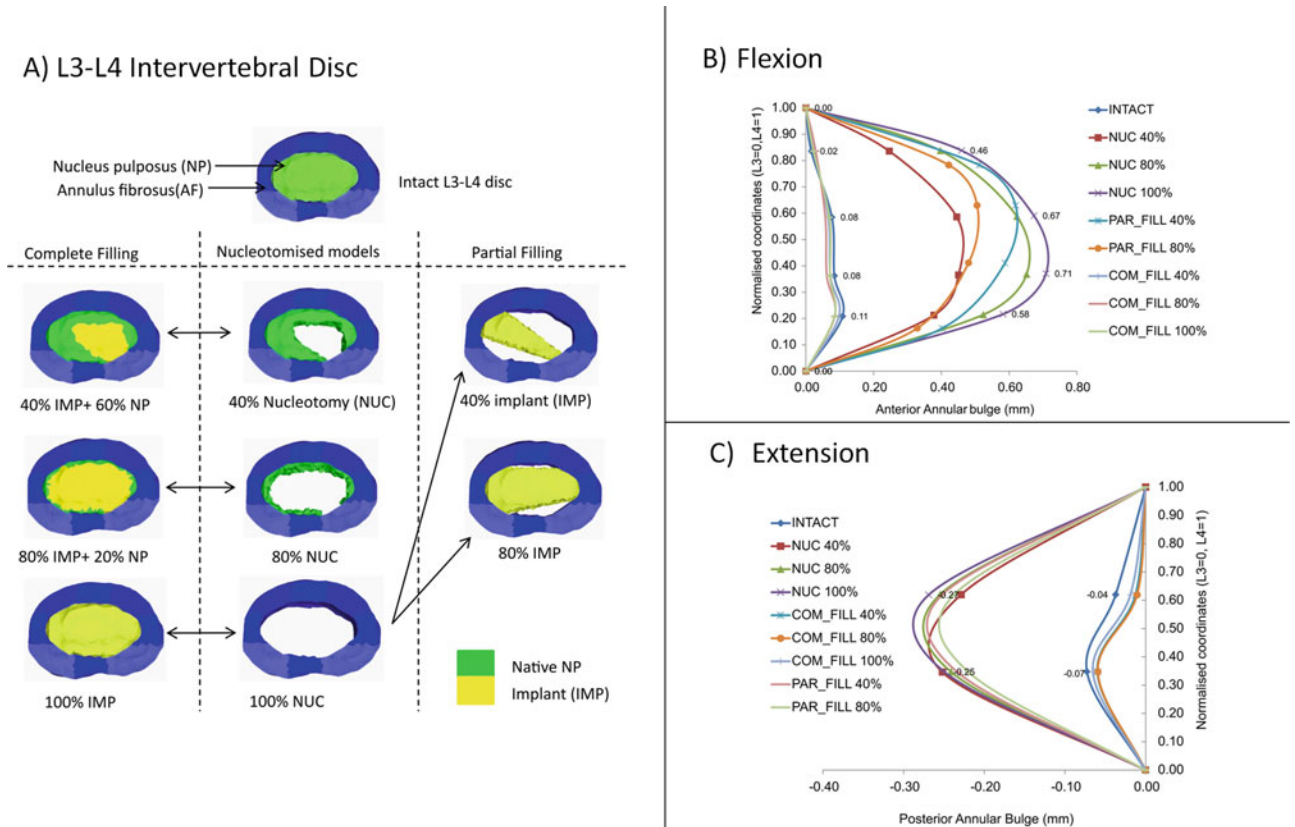

Fig. 4 (**a**) Finite element (FE) models of the L3–L4 intervertebral disc were assembled representing the disc in the intact state, different states of nucleotomy, partial and complete filling with the Kunovus Disc Device (KDD, Kunovus Pty Ltd., Australia). Multisegment FE models of the lumbar spine (L1–L5) were loaded in flexion and extension bending moments (±10 Nm) with the L5 vertebra fixed in space. (**b**) Anterior annulus bulge in the midsagittal plane of the L3–L4 disc in different states during peak flexion loading. (**c**) Posterior annulus bulge in the midsagittal plane of the L3–L4 disc in different states during peak extension loading. Only complete filling of the nucleotomized disc with the KDD implant restored the annular bulge to the intact state levels

5. Easy to implant as an adjunct to discectomy, minimize any additional damage to the AF during implantation. Easy to remove in the instance of any adverse event during or after surgery.

Classification

A number of NR implants have been developed so far, with an unaccounted number of them still under development. Some of these NR implants are at different stages of clinical use, while others have been abandoned. Based on the design principles and materials used, NR implants may be divided into various categories (Fig. 5).

Clinical Outcomes: A Systematic Review of Literature

A systematic literature search into currently available clinical data on NR implants published in various journals and book chapters between January 1988 and March 2017 was conducted using Scopus and Medline online databases. After removing duplicate articles across both the databases, and further screening through reading abstracts, a total of 12 articles were found, which presented short-term ($\leq$1 year), mid-term (1–3 years), and long-term (>3 years) clinical and radiological follow-up data on NR implants. One article reported data on three different NR implants (PDN, NuBac, PNR) (Pimenta et al. 2012). Two articles reported short-term and mid-term clinical results (Ahrens et al. 2009; Balsano et al. 2011). Due to variations in implant designs and materials used, studies were not directly comparable; and therefore, articles were grouped based on the type of implant reported (Table 1).

Preformed Mechanical

NuBac (Pioneer Surgical Technology, Michigan): NuBac is a two-piece prosthesis made from PEEK, with a ball-and-socket-type articulation between the two pieces (Fig. 6). Short-term clinical follow-up data for 49 patients were presented in two separate studies (Alpizar-Aguirre et al. 2008; Balsano et al. 2011). Balsano et al. further presented mid-term clinical data for 166 patients implanted with the NuBac device (Balsano 2014; Balsano et al. 2011). Pimenta et al. (2012) reported long-term follow-up data for 19 patients implanted with the NuBac device. Table 2 presents clinical and radiological follow-up data for the NuBac implant.

Preformed Elastomer

Prosthetic disc nucleus PDN (Raymedica, Minnesota): The PDN implant comprises a special hydrogel pellet core encased in a polyethylene jacket that helps maintain device shape when subjected to heavy spinal loads (Fig. 7). The expanding hydrogel constrained within the jacket is designed to provide the lifting force in the intervertebral disc space to maintain the disc height and remain flexible at the same time. In order to minimize the size of annular opening required for implantation, the device is implanted as two separate units, connected by means of a tethering suture (Klara and Ray 2002).

Among NR implants, clinical data for PDN is most widely reported in the literature. Three separate studies have reported short-term clinical data for a total of 84 patients implanted with PDN (Bertagnoli and Vazquez 2003; Jin et al. 2003; Shim et al. 2003). Four additional studies have reported long-term follow-up data for a total of 199 patients implanted with PDN (Klara and Ray 2002; Pimenta et al. 2012; Selviaridis et al. 2010; Zhang et al. 2009). Table 3 presents clinical and radiological follow-up data for the PDN implant.

In Situ Curing

In situ curing injectable materials have been the recent focus of research in NR implants due to their ability to conform to the shape of the nucleotomized cavity and cure within the disc. These NR implants can be delivered using a minimally invasive surgery and, in principle, are designed to overcome endplate remodeling and

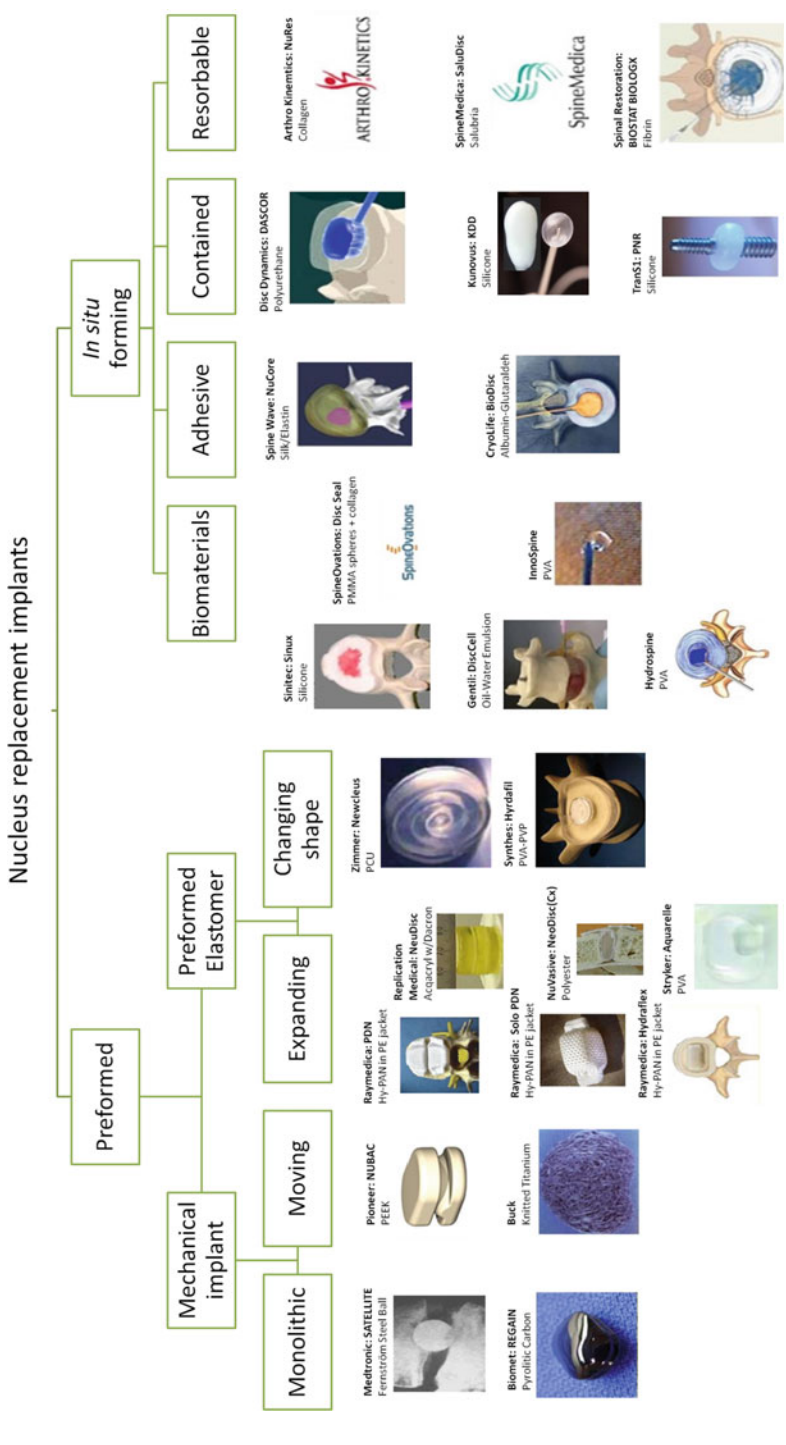

Fig. 5 A broad classification scheme for nucleus replacement implants

Table 1 Medline and Scopus online database search between January 1988 and March 2017 revealed that clinical and radiological follow-up data are available for five nucleus replacement implants

Type of implant	Implant name	Studies with clinical data	Manufacturer	Material
Preformed mechanical	NuBac	2 (short-term), 2(mid-term), 1(long-term)	Pioneer Surgical Technology, Michigan	PEEK
Preformed elastomer	PDN	3(short-term), 4(long-term)	Raymedica, Minnesota	Hydrogel pellet in PE jacket
In situ curing	DASCOR	1(short-term), 1(mid-term)	Disc Dynamics, Minnesota	Polyurethane
	NuCore	1(mid-term)	Spine Wave, Connecticut	Silk and elastin
	PNR	1(long-term)	TranS1, Colorado	Silicone

Fig. 6 NuBac implant comprises two articulating pieces made using PEEK. (Image adapted from Ordway et al. 2013, with permission)

implant migration issues associated with the preformed NR implants. A number of in situ curing NR implants have been developed using a variety of materials (Fig. 5); however, clinical and radiological follow-up data is only available for the following: DASCOR (Disc Dynamics, Minnesota), NuCore (Spine Wave, Connecticut), and Percutaneous Nucleus Replacement (PNR) (TranS1, Colorado) (Fig. 8).

Ahrens et al. (2009) reported short-term (n = 70, 1 year) and mid-term (n = 41, 2 years) clinical data for 85 patients implanted with the DASCOR device (Ahrens et al. 2009). Berlemann and Schwarzenbach (2009) reported mid-term clinical data for 14 patients implanted with the NuCore device. Pimenta et al. (2012) reported long-term clinical data for 26 patients implanted with the PNR device. Table 4 presents clinical and radiological follow-up data for the above three in situ curing implants.

Lessons Learnt

In all of the above studies, the average age of patients receiving an NR implant was 35–45 years, and therefore the implant was expected to function for five to six decades. The premise behind using an NR implant is to restore mobility and salvage structures in a functionally suboptimal disc which would otherwise be sacrificed in more invasive spine surgeries. Although short-term and mid-term clinical results have been promising (pain scores, functional outcomes, disc height preservation, intra-op, and post-op complication rates), reoperation rates in the long-term remain a matter of serious concern, particularly for the mechanical and preformed NR implants. In 199 patients implanted with PDN and followed for a minimum of 4 years, endplate remodeling rate was 32%, subsidence rate was 26%, and reoperation rate was 27%. For in situ curing implants, although conformity with the shape of the nucleotomized cavity has theoretical advantages in distributing loads to the adjoining structures, there is a dearth of long-term clinical follow-up data to show any translational benefits of this design principle.

A stiff implant in the nucleus space could lead to remodeling of the endplates and result in implant subsidence, whereas a compliant implant (or a nucleotomized cavity) may offload the endplates and overload the annulus, consequently increasing the likelihood of annulus degeneration, implant extrusion, or both. Perhaps, the *one-size-fits-all* philosophy for the material properties of NR implants may not be able to address all the design objectives in individual patients, and future

Table 2 Table summarizing short-term (≤1 year), mid-term (1–3 years), and long-term (>3 years) clinical and radiological follow-up data (average values) for patients implanted with NuBac device (Pioneer Surgical Technology, Michigan)

NuBac	VAS score	ODI score	Disc height	References
Short-term (49 patients)	7.3 (pre-op) → 2.9 (3mths) → 1.8 (1yr)	58 (pre-op) → 23.2 (3mths) → 18 (1yr)	9.4 mm (pre-op) → 13 mm (6wks) → 12.5 mm (3mths)	Alpizar-Aguirre et al. (2008) and Balsano et al. (2011)
Mid-term (166 patients)	7.7 (pre-op) → 2.5 (2 yrs)	55.4 (pre-op) → 15.7 (2 yrs)	N/r	Balsano et al. (2011) and Balsano (2014)
Long-term (19 patients)	N/r	N/r	N/r	Pimenta et al. (2012)

NuBac	Endplate changes	Migration rate	Subsidence rate	Reoperation rate	References
Short-term (49 patients)	0%	0%	0%	0%	Alpizar-Aguirre et al. (2008) and Balsano et al. (2011)
Mid-term (166 patients)	N/r	0%	0%	0%	Balsano et al. (2011) and Balsano (2014)
Long-term (19 patients)	31.6%	21.1%	21.1%	52.6%	Pimenta et al. (2012)

N/r not reported, *VAS* visual analog scale, *ODI* oswestry disability index

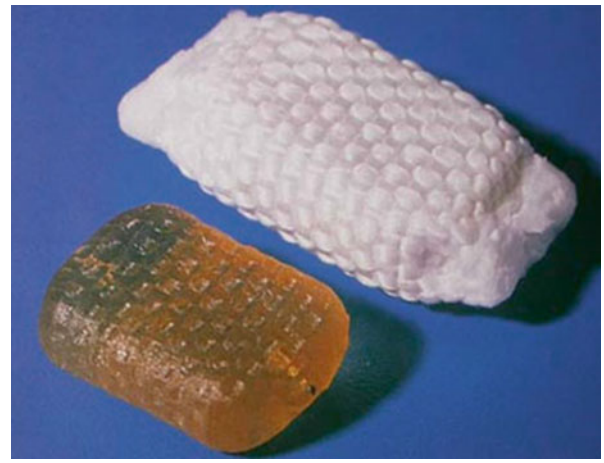

Fig. 7 Prosthetic disc nucleus (PDN) comprises a hydrogel pellet core encased in a polyethylene jacket. (Image adapted from Schnake and Kandziora 2016, with permission)

NR implants will need to provide clinicians with tools to customize material properties and geometry to suit their patient's needs.

While the implant geometry and material properties are important parameters in meeting the design objectives for an NR implant, the clinical success will also rely on the quality of vertebral subchondral bone, extent of endplate calcification, and structural integrity of the AF; and therefore a careful selection of patients is important.

Disc Preservation Following Lumbar Discectomy

Lumbar Discectomy: Clinical Outcomes

Lumbar discectomy in disc herniation patients results in significantly better clinical outcomes when compared with nonsurgically treated patients (Atlas et al. 2005; Weinstein et al.

Table 3 Table summarizing short-term (≤1 year) and long-term (>3 years) clinical and radiological follow-up data (average values) for patients implanted with prosthetic disc nucleus PDN (Raymedica, Minnesota)

PDN	VAS score	ODI score	Prolo score	Disc height	References
Short-term (84 patients)	8.5 (pre-op) ➔ 3.1 (1 yr)	53.9 (pre-op) ➔ 18 (6 mths) ➔ 16.5 (1 yr)	5 (pre-op) ➔ 7.6 (6mths) ➔ 7.3 (1 yr)	9.4 mm (pre-op) ➔ 10.8 mm (6 mths) ➔ 10.8 mm (1yr)	Bertagnoli and Vazquez (2003), Jin et al. (2003), and Shim et al. (2003)
Long-term (199 patients)	6.6 (pre-op) ➔ 1.6 (8yrs)	52 (pre-op) ➔ 10.3 (4 yrs) ➔ 6.2 (8 yrs)	4.5 (pre-op) ➔ 8.9(3 yrs)	8.5 mm (pre-op) ➔ 8.7 mm (4 yrs)	Pimenta et al. (2012), Klara and Ray (2002), Selviaridis et al. (2010), and Zhang et al. (2009)

PDN	Endplate changes	Migration rate	Subsidence rate	Reoperation rate	References
Short-term (84 patients)	Scleroses, 33.3% Modic changes, 28.6%	0%	12%	7.1%	Bertagnoli and Vazquez (2003), Jin et al. (2003), and Shim et al. (2003)
Long-term (199 patients)	32.2%	13.6%	26.1%	27.1%	Pimenta et al. (2012), Klara and Ray (2002), Selviaridis et al. (2010), and Zhang et al. (2009)

VAS visual analog scale, *ODI* oswestry disability index

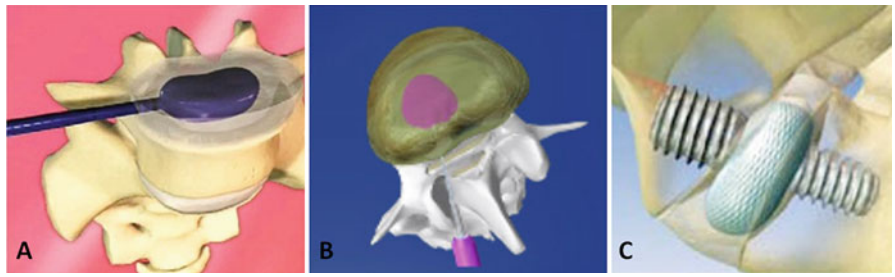

Fig. 8 (**a**) DASCOR comprises two-part curable polyurethane and an expandable balloon. (**b**) NuCore implant is an injectable 100% synthetic recombinant protein hydrogel. (**c**) PNR consists of a titanium screw system anchoring itself onto the superior and inferior vertebrae, with a central membrane that is filled with curable material and acts as the nucleus. (Image adapted from Serhan et al. 2011, with permission)

2008). Although lumbar discectomy is a clinically beneficial procedure for appropriately selected patients, revision discectomy rates range from 2% to 18% within the first decade of the primary discectomy (Virk et al. 2017; Watters and McGirt 2009). The survivorship rate for first lumbar discectomy is particularly lower for patients younger than 65 years when compared with older patients (Virk et al. 2017).

It remains unknown whether limited discectomy (LD) or aggressive discectomy (AD) provides better clinical outcomes for the treatment of lumbar disc herniation patients with radiculopathy. In a systematic review of 44 studies, the reported incidence of short-term (<2 years) recurrent leg or back pain was similar after LD (mean, 14.5%; range, 7–16%) and AD (mean, 14.1%; range, 6–43%) (McGirt et al. 2009a). In the long-term (>2 years), the reported incidence of recurrent back or leg pain was 2.5-fold less after LD (mean, 11.6%; range, 7–16%) compared with the AD (mean, 27.8%; range, 19–37%). However, the reported incidence of recurrent disc herniation after LD (mean, 7%;

Table 4 Table summarizing mid-term (1–3 years) and long-term (>3 years) clinical and radiological follow-up data (average values) for patients implanted with in situ curing nucleus replacement implants (DASCOR, NuCore, and PNR)

	VAS score	ODI score	Disc height	References
DASCOR – mid-term (70 patients)	7.6 (pre-op) ➔ 3.3 (1yr) ➔ 3.3 (2yrs)	57.5 (pre-op) ➔ 25.2 (1yr) ➔ 23.2 (2yrs)	N/r	Ahrens et al. (2009)
NuCore – mid-term (14 patients)	3.6 (pre-op) ➔ 1.1 (2yrs)	43 (pre-op) ➔ 10 (2yrs)	100% (pre-op) ➔ 93% (2yrs)	Berlemann and Schwarzenbach (2009)
PNR – long-term (26 patients)	N/r	N/r	N/r	Pimenta et al. (2012)

	Endplate changes	Migration rate	Subsidence rate	Reoperation rate	References
DASCOR – mid-term (70 patients)	1.4%	1.4%	2.9%	10%	Ahrens et al. (2009)
NuCore – mid-term (14 patients)	64.3%	0%	0%	0%	Berlemann and Schwarzenbach (2009)
PNR – long-term (26 patients)	N/r	N/r	N/r	57.7%	Pimenta et al. (2012)

VAS visual analog scale, *ODI* oswestry disability index

range, 2–18%) was significantly greater than that reported after AD (mean, 3.5%; range, 0–9.5%) (McGirt et al. 2009a).

LD may result in shorter operative time, a quick return to work, and a decreased incidence of long-term recurrent back pain, but at a significantly greater risk of long-term recurrent herniation compared with AD. Aggressive removal of the remanent nucleus is effective at decreasing reherniation but at the cost of significantly poor long-term clinical outcomes and low patient satisfaction (McGirt et al. 2009a).

Various risk factors have been identified for the recurrent herniation of the disc. Smoking and occupational lifting are known to increase the likelihood of recurrent herniation (Miwa et al. 2015). Discectomy patients with preserved disc height postoperatively generally have favorable results, but the risk of recurrent disc herniation is high in this population (Yorimitsu et al. 2001). In a retrospective study of 75 lumbar disc herniation patients, 8 of whom re-herniated after primary microdiscectomy, the authors found that the mean body mass index (BMI) of patients with recurrent herniation (33.6 ± 5.1) was significantly higher than those without recurrence (26.9 ± 3.9) (Meredith et al. 2010). In a prospective study of 108 lumbar disc herniation patients undergoing first-time discectomy and followed for up to 2 years, the authors observed that the mean annular defect area was significantly greater in recurrent herniation patients compared with no-recurrence patients (46 ± 20 vs. 32 ± 14 mm^2) (McGirt et al. 2009b). Mean annular defect was also significantly larger in patients with symptomatic early reherniation (within 4 months after surgery) compared to later herniation (57 vs. 39 mm^2) (McGirt et al. 2009b). Clinically silent recurrent disc herniation is common after lumbar discectomy, but treatment is recommended only when correlating radicular symptoms exist (Lebow et al. 2011).

Nucleus Replacement Implants as an Adjunct to Discectomy

Annulus repair following discectomy may be beneficial for retaining the intradiscal material. While patients with tall and healthy discs preoperatively have the most to gain with annular closure (thus reducing the amount of nucleus that needs to be removed), repair of the annulus is not able to restore the biomechanical characteristics

of the disc, and further annular tear adjacent to the repair is possible due to persistent fragmented nuclear material present in the disc cavity. A prospective, multicenter, randomized control trial of 750 patients treated for herniated lumbar discs and randomly assigned in a 2:1 ratio to discectomy with annular closure and discectomy without annular closure found no significant difference in the clinical outcomes (including the recurrent herniation rates) between the two surgical cohorts at 2-year follow-up mark (Bailey et al. 2013).

Discectomy remains one of the rare surgical procedures where the tissues lost to herniation and removed during the surgery are not replaced with any prosthesis. Nucleus replacement implants can be used as void-fillers during a standard discectomy procedure to (1) restore the structural and mechanical integrity of the disc; (2) restore load sharing and synergistic interaction between the implant, remnant NP, AF, and the EP; (3) minimize loss in disc height and accelerated degeneration of the AF; and (4) minimize recurrent disc herniation by acting as an annular-closure-plug.

Furthermore, there has been a growing interest in the development of alternative minimally invasive technologies for the treatment of degenerative disc disease in otherwise healthy patients who suffer from unremitting pain due to damaged and bulging intervertebral discs, and are not responsive to nonoperative care. These patients are candidates for spinal fusion but retain a workable disc height and undamaged facet joints. These patients would benefit from an option which would provide lower risks than spinal fusion and similar improvement in quality of life. The loss of disc function can be mitigated by replacement of the NP with a biologically inert material with a goal of maintaining the disc height and function.

Other Potential Uses of Nucleus Replacement Implants

Pedicle screw-based posterior dynamic stabilizers (PDS) are nonfusion spinal implants that aim to restore normal load sharing and kinematics in a degenerate spinal motion segment (Chamoli et al. 2014). Because these implants are posteriorly placed, the center of rotation of the motion segment is shifted posteriorly upon implantation compared with that of an intact spine; and therefore anterior load sharing cannot be satisfactorily achieved using a PDS implant alone. The cyclic nature of the pedicle screw loading and the micromotions at the bone-screw interface likely increase screw loosening and pullout rates and is one of the major reasons for the implant failure. Replacing the core of the degenerated disc with an NR implant and using PDS as an augmenting device may have the potential to overcome this problem.

An NR implant may be used in hybrid constructs for prophylactic dynamic stabilization of segments adjacent to the fused levels, which could reduce hypermobility and impede the accelerated degeneration of the adjacent segments. The NR implants are advantageous over commonly used TDR implants in hybrid constructs, as they are less invasive, salvage disc structures, and more closely mimic the kinematic signature of an intact motion segment.

Conclusions

Degenerative changes and/or repetitive abnormal loading in the lumbar spine could lead to structural failures of the intervertebral disc and herniation of the nucleus pulposus, all of which may manifest as chronic back and/or leg pain. Although lumbar discectomy is a clinically beneficial procedure for appropriately selected disc herniation patients, revision discectomy rates range from 2% to 18% within the first decade of the primary discectomy, especially in patients younger than 65 years. Nucleus replacement (NR) implants present a promising option to address some of the challenges surrounding standard lumbar discectomy. These implants could be used as void-fillers during a standard discectomy procedure to: restore and preserve the biomechanical integrity of the disc, impede progressive disc degeneration and loss in disc height, and minimize the incidence of recurrent herniation. Nonetheless, long-term follow-up results for the present NR implants reveal high

rates for endplate remodeling and implant subsidence. A detailed multiscale understanding of the mechanisms of disc herniation and reherniation, closure of the annular defect, and the ability to tailor geometry and material properties for individual patients are needed to develop the next generation of NR implants.

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Spinal Fusion Evaluation in Various Settings: A Summary of Human-Only Studies

62

Jose Umali, Ali Ghahreman, and Ashish D. Diwan

Contents

Abstract

Degenerative spinal conditions may lead to abnormal motion and biomechanical instability of diseased spinal segments, resulting in pain, deformity, and neural element compromise. Various spinal fusion techniques have been developed over the years to address spinal segment instability. Degenerative conditions of the lumbar spine can be addressed through different approaches in terms of fusion. These include posterolateral fusion, posterior lumbar interbody fusion, and transforaminal interbody fusion, which are performed with the patient lying prone. Anteriorly, degenerative lumbar

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spine conditions can be addressed with anterior lumbar interbody fusion, direct lateral (transpsoas) lumbar interbody fusion, or oblique lumbar interbody fusion (using an anterior to psoas approach). The cervical spine with degenerative changes can be treated with fusion anteriorly, using anterior cervical discectomy and fusion, or posteriorly, with posterior cervical decompression and fusion. The success or failure of the fusion procedure is determined on the absence or presence of pseudarthrosis based on clinical findings supplemented by diagnostic evidence of bridging bone. Imaging modalities most commonly used for evaluation of fusion include radiographs, magnetic resonance imaging, and computed tomography, with CT as the gold standard for assessment. Recent studies support CT as the imaging modality of choice, with some studies presenting different techniques that may aid in the evaluation of fusion status. In the hope of attaining higher outcomes for fusion along with decrease in morbidity associated with graft harvest, several bone graft substitutes and extenders have been developed. Several studies have been produced supporting their use. None have provided clear-cut evidence or recommendations that would help determine any advantage of one bone graft substitute/extender over the other.

Keywords

Fusion · Pseudarthrosis · Cervical spine · Lumbar spine · Radiographic evaluation · Bone graft · Graft substitutes

Introduction

Degenerative spinal conditions can lead to abnormal motion and biomechanical instability of affected spinal segments, which can result in pain, deformity, neural element compromise, or deterioration. The degenerative cascade is believed to have a complex multifactorial etiology. The process itself may be secondary to aging, genetic factors, metabolic disorders, low-grade infection, neurogenic inflammation, autoimmune response, toxic, or mechanical factors (Hadjipavlou et al. 2008). In order to address spinal segment instability, numerous surgical fusion techniques have been developed over the years.

Several fusion techniques have been described in literature. For the cervical spine, surgeons utilize either anterior cervical discectomy and fusion or posterior cervical decompression and fusion. The most commonly performed fusions are on the lumbar spine. Degenerative conditions of the lumbar spine may be addressed with different techniques such as posterolateral fusion, posterior lumbar interbody fusion, transforaminal interbody fusion, and anterior lumbar interbody fusion. Recently introduced is the so-called lateral interbody fusion [direct lateral interbody fusion (DLIF)/extreme lateral interbody fusion (XLIF™)], which employs a transpsoas muscle approach, and its variation, the oblique lateral interbody fusion (OLIF), a technique that uses the plane anterior to the psoas muscle for its approach. All these procedures do come at a cost, as patients who undergo these operations run the risk of developing complications related to surgery. Fusion strategies have been improved upon with the use of minimally invasive techniques, with goals of limiting blood loss, soft tissue injury, operative time, immobilization, incidence of wound infections, and hospital stay in properly selected patients (Mummaneni et al. 2013; Bach et al. 2014).

Since the inception of various fusion techniques, several studies have been produced that focus on the evaluation and analysis of their clinical and radiologic outcomes. The development of new bone graft substitutes has also prompted investigators to closely examine these products to better understand the possible benefits that they can offer to patients undergoing fusion surgery. With this in mind, the objective of this chapter is to present a comprehensive review and discussion of spinal fusions in human studies.

Clinical Presentation of Pseudarthrosis

Fusion is said to occur once the bone graft within or around a spinal motion segment is deemed absent of any pseudarthrosis or

non-union. Pseudarthrosis refers to the failure of spinal fusion diagnosed more than a year after surgery. Patients with pseudarthrosis may or may not present with any symptoms. If symptomatic, they may complain of axial or radicular pain and be diagnosed with "refractory back syndrome." These may also be associated with claudication or myelopathy as well. Clinical findings are not reliable in the diagnosis of pseudarthrosis. Confirmation is achieved preferably through surgical exploration, but this can be assessed noninvasively through a number of imaging modalities. These imaging modalities include X-rays, computed tomography (CT), magnetic resonance imaging (MRI), bone scan, ultrasound, and radiostereometric analysis.

Imaging Techniques

Routine orthogonal radiographs are requested upon follow-up to determine the progression of arthrodesis, which can be observed as increasing opacification and bridging trabecular bone at the bone graft margins. Static orthogonal radiographs may be inadequate for some surgeons due to its inability to identify motion at the spinal fusion segment. Although controversial, lateral flexion-extension radiographs have been used to rule out motion at the spinal fusion segment, hardware failure, and issues with sagittal alignment (Raizman et al. 2009; Gruskay et al. 2014b). Further assessment can be done by making use of different methods such as measuring the Cobb angle and also by making use of Simmons method and Hutter methods (Hutter 1983; Simmons 1985). Although widely used by both spine surgeons and radiologists, these have problems in terms of concordance with findings on CT images (Figs. 1 and 2).

Computed tomography can be very helpful in instances where there is no evidence of progression of fusion on radiographs. Fusion is present once note of bony trabeculation is found across the fusion level with absence of radiolucency at the graft-vertebral body interface. The downside with using CT scans is its decreased sensitivity to fusion due to metallic artifacts secondary to instrumentation implanted within the spine. The incidence of metallic artifacts has lessened with

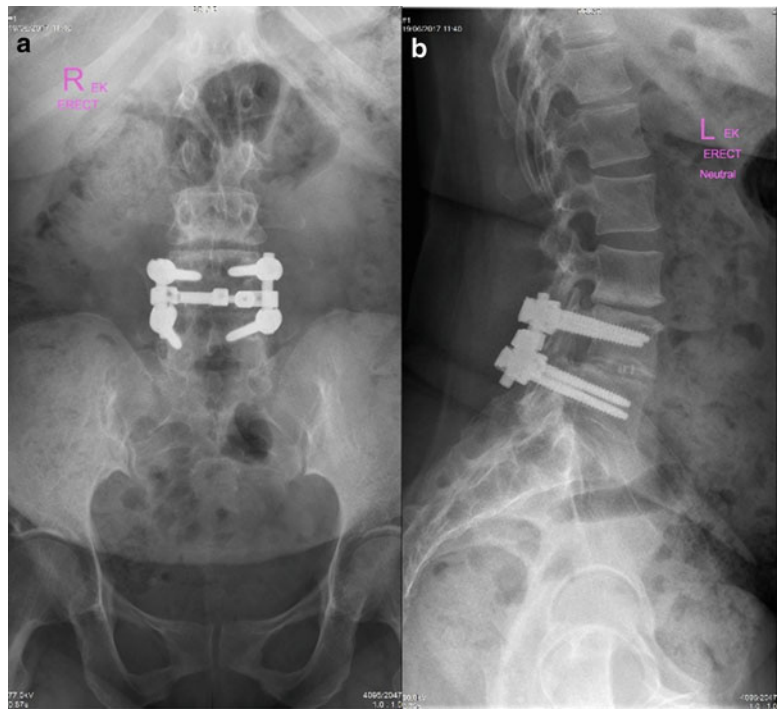

Fig. 1 Standard AP (**a**) and lateral (**b**) X-ray views of the lumbar spine. Posterior decompression and TLIF were performed at L4–5. Note presence of bridging bone at said level

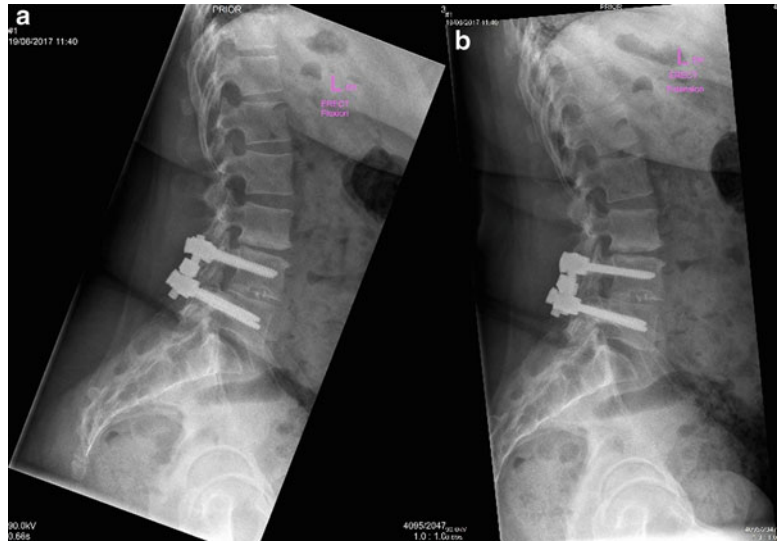

Fig. 2 Flexion (**a**) and extension (**b**) views performed to rule out motion at fused segment

the advent of titanium implants. Despite this disadvantage, computed tomography has been deemed as the gold standard imaging modality for assessing the presence of fusion (Raizman et al. 2009; Gruskay et al. 2014b) (Fig. 3).

Other imaging modalities available for assessing spinal fusion include magnetic resonance imaging, bone scintigraphy, ultrasound, and radiostereometric analysis. MRI is not routinely used for spinal fusion evaluation due to its susceptibility to artifact formation from metallic implants, and its clinical utility, while promising, is not yet established (Kitchen et al. 2018). It is more useful in identifying stenosis and presence of adjacent segment degeneration. Bone scintigraphy is able to ascertain the level of metabolic activity of the spine. Increased uptake is noted in areas of heightened biologic activity and blood supply which may suggest non-union. This is of limited use due to its low sensitivity (50%) and specificity (58%) when compared to surgical exploration. Ultrasound was found to be able to ascertain the presence of fusion if there was note of hyperechoic and shadowing interface across vertebral segments. On the other hand, the presence of scattered and nonbridging echogenic foci indicates possible pseudarthrosis. This imaging modality was found to be more suitable for patients who have undergone posterior instrumentation which may produce artifacts in CT or MRI scans. Radiostereometric analysis allows for three-dimensional imaging of spinal motion in vivo. The use of this imaging modality has been limited to research purposes, despite its high accuracy, and requires bony insertion of tantalum beads (Raizman et al. 2009; Gruskay et al. 2014b).

Multitudes of studies have been performed to evaluate fusion in different regions of the spine. Evaluation of success for a particular technique relies on a combination of clinical and radiologic outcomes. The difficulty lies on properly assessing the quality of evidence and strength of recommendations presented by these studies (Guyatt et al. 2009) (Table 1).

Fusion of the Cervical Spine

Anterior Cervical Discectomy and Fusion (ACDF)

Cervical disk degeneration may present as axial neck pain associated with radiculopathy or myelopathy. Anterior cervical discectomy and fusion is the accepted standard treatment for symptomatic cervical disk degeneration. After removal of the pathologic disc, fusion is carried out via standalone cages inserted into the intervertebral disk space or supplemented by an anterior plate. The cage allows for bridging union of vertebral bodies

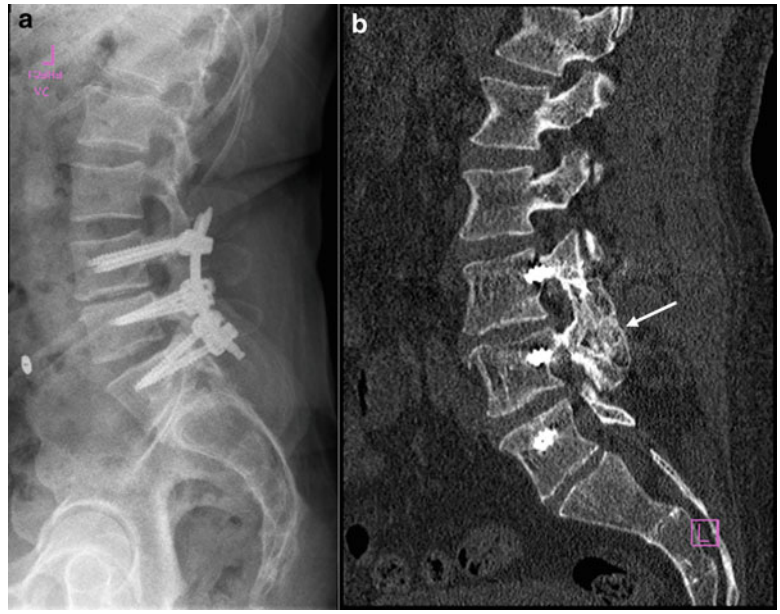

Fig. 3 Lateral radiograph (**a**) of instrumented posterolateral fusion performed from L3 to L5. Sagittal cut of CT scan (**b**) shows abundant fusion mass (arrow) over posterolateral gutter adjoining the levels from L3 to L4. Bridging bone was absent in between L4 and L5

Table 1 Imaging modalities for evaluation of fusion

Imaging modality	Advantages	Disadvantages	Utility
Radiographs	Picks up opacification and bridging bone along graft margins Low cost Easy to perform Dynamic radiographs can be used to assess for translational or angular motion of fusion segment	Occasionally miss presence of bridging bone or bony trabeculations Low radiation exposure	++
Computed tomography	Greater ability to determine presence or absence of bridging bone or bony trabeculations between fusion segments Identification of hardware failure/loosening	Higher radiation exposure compared to radiographs Dynamic CT not common practice Artifact formation from metallic implants may prevent visualization of bone bridges	++++
Magnetic resonance imaging	More useful in identifying stenosis and adjacent segment degeneration	Prone to artifact formation from metallic implants Static imaging modality	+
Bone scintigraphy	Increased uptake due to heightened biologic activity may be secondary to non-union	Low sensitivity (50%) and specificity (58%)	−
Ultrasound	Alternative imaging modality that identifies pseudarthrosis which may present as areas of nonbridging echogenic foci between vertebral segments No radiation	Limited to patients with posterior instrumentation	+
Radiostereometric analysis	Capable of three-dimensional imaging of spinal motion in vivo High accuracy	Limited presently to research purposes Requires tantalum bead insertion around prosthesis	++

to take place once fusion has set in. The addition of a plate is believed to allow for higher fusion rates, decreased pseudarthrosis, decreased graft dislodgement, resistance to segmental kyphosis, and less need for external immobilization.

Several imaging modalities can be used for the assessment of fusion at the cervical level. Besides assessing the quality of fusion present, specific measurements are utilized depending on the specific type of imaging modality used. These measurements are most often taken from dynamic radiographs through the use of lateral flexion and extension views.

The assessment of fusion status through dynamic radiographs is dependent on currently accepted criteria. For example, the US FDA previously defined successful fusion as less than 3 mm of translational motion and less than 5° of angular motion in the lumbar spine. These criteria are also applied in the assessment of successful fusion in the cervical spine (USSDHHS et al. 2000). Traditionally, motion was assessed by measuring the Cobb angle. This has been difficult to evaluate as there is very minimal motion detected with this method. An alternative to the Cobb angle method is the interspinous method (Cannada et al. 2003). In general, there is also low interobserver agreement as well with regard to the assessment of cervical spine fusion on dynamic films (Taylor et al. 2007) (Fig. 4).

A retrospective chart review of 383 patients treated ACDF with a total of 1155 postoperative visits was performed from 2002 to 2007 to determine the utility of radiographs in postoperative monitoring of fusion status. These patients were classified according to normal versus abnormal history and physical examination presentations and also by normal and abnormal radiographs. Patients with normal history and physical examination findings were rarely found to be managed/not left alone [5/879 (0.57%)]. There were 276 visits with abnormal history and physical examination findings. Abnormal radiographic findings were found in 34 out of the 276 visits (12.3%). Revision surgery was advised in 44% of these visits with abnormal radiographic findings (15/34). This study concluded that postoperative radiographs had limited utility in patients with normal history and physical examination findings independent of normal or abnormal radiographic results (Grimm et al. 2013).

A prospective clinical study attempted to evaluate the reliability of detecting pseudarthrosis after anterior cervical fusion using radiography, CT, and MRI as compared to surgical exploration. The investigators found that assessment of fusion status via CT is most closely related with findings upon surgical exploration when compared to the other imaging modalities. This was assessed by evaluating the agreement between findings on surgical exploration and the different imaging modalities and through paired interobserver reliability. Mean Kappa statistics for agreement between intraoperative and radiographic findings were 0.67 (plain radiographs), 0.81 (CT), and 0.48 (MRI), while mean Kappa statistics for paired interobserver reliability were 0.46 (plain

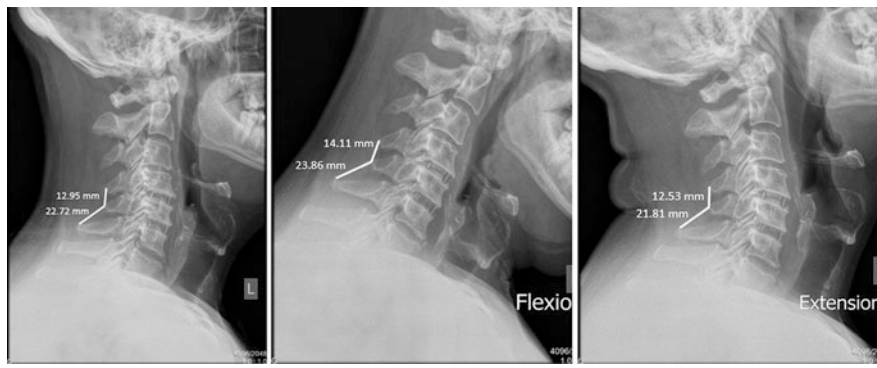

Fig. 4 Lateral X-ray views of the cervical spine showing method of measuring interspinous process distance

radiographs), 0.82 (CT), and 0.32 (MRI) (Buchowski et al. 2008).

On the other hand, Park et al. (2015) found that CT scans may overestimate the rate of fusion after ACDF. They performed a radiographic analysis of patients who had undergone ACDF. This study attempted to compare the fusion rates with CT scans and dynamic radiographs at 3, 6, and 12 months postoperatively. Their results show that the fusion rates post ACDF assessed via radiographs and CT scans were 26% versus 79%, 41% versus 79%, and 65% versus 91% at 3, 6, and 12 months, respectively. This study concluded that overestimation of fusion rates was present upon assessment with CT scans. This is due to the static nature of the fusion levels being assessed. Radiographs, when compared to CT scans, are assessed taking into account dynamic and static factors for fusion.

Ouchida et al. (2015) performed a study comparing the ability of functional computed tomography in determining fusion status versus functional radiography in patients post ACDF. This study was able to determine that functional CT scanning was superior in detecting non-union when compared to functional radiography. Radiographs showed fusion rates of 83.9% and 91.1% at 6 months and 12 months postoperatively, respectively. On the other hand, CT scans revealed considerably lower fusion rates at 6 months (55.3%) and 12 months (78.6%). Patients found to have incomplete union were shown to develop more neck pain postoperatively.

Ghiselli et al. (2011) attempted to determine the gold standard for assessing pseudarthrosis of the cervical spine. This study investigated the ability of CT imaging versus quantitative motion analysis with dynamic radiography to examine for presence of fusion. Findings from imaging were then compared to those found in the patients intraoperatively. The amount of angular motion on radiographs thought to correlate with pseudarthrosis was at more than 4°. The study found this parameter provided for high specificity with a positive predictive value of 100% but was coupled with a low sensitivity as shown by a negative predictive value of 52%. Fusion on CT was defined as presence of bridging bone. CT scans were shown to have a positive predictive value of 100% and a negative predictive value of 73%. This was comparable to the negative predictive value with the use of quantitative motion analysis on dynamic radiographs once the accepted angular motion was changed to a value of greater than one degree (73%). The researchers were then able to determine that by making use of both CT scans and the modified angular motion (1°) on radiographs produces a positive predictive value of 100% and negative predictive value of 85%, thus improving the specificity in detecting for presence of pseudarthrosis in the cervical spine.

Posterior Cervical Decompression and Fusion (PCDF)

Posterior cervical decompression and fusion can be performed through varying techniques. Decompression in itself can be done via different methods. These include laminectomies and laminoplasties, often done in patients with cervical spondylotic myelopathy, which allow for extensive decompression of the cervical canal with potential for postoperative instability of the motion segments. Foraminotomies limit the extent of destabilization and are strictly indicated in patients with stenosis at the foraminal level only. Fusion can be achieved via multiple techniques supplemented with instrumentation through the use of screw fixation. The instrumentation can either be performed with application of lateral mass screws or pedicle screws (Fig. 5).

Lee et al. (2017) analyzed the fusion and graft resorption rates in 56 patients who underwent posterior cervical fusion with pedicle screw instrumentation 1 year postoperatively under CT imaging and dynamic radiography. The patients who participated in this study were classified into three groups according to the type of graft used for posterolateral fusion (autograft, allograft, or mixture of both). Mean resorption rates were as follows: 56.2% (autograft), 75.9% (mixture), and 91.5% (allograft). Despite the resorption rates mentioned, the overall fusion rate was 98.2%.

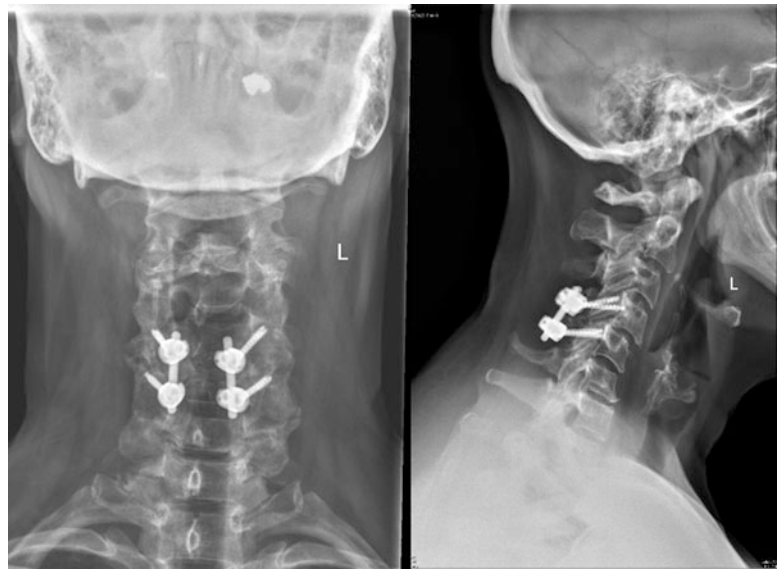

Fig. 5 Posterior cervical decompression and fusion at C4–5 with lateral mass screws

A retrospective case series by Dorward et al. reported on the fusion rates and complications associated with the use of recombinant human bone morphogenetic protein-2 (rhBMP-2) in patients treated with posterior cervical fusion. A majority of patients included in the study were operated on to revise previous surgeries (84.2%). Several patients were also found to have preexisting cervical pseudarthrosis (42.1%). Successful fusion was noted in 89.5% of patients. Radiographic evidence of non-union was found in the remaining 10.5%. Pseudarthrosis occurred in patients with fusions that spanned either occipitocervical or cervicothoracic junctions. Complications were noted in 14 patients (24.6%), with superficial wound infection, pain from fusion levels, and pseudarthrosis being among the most common (Dorward et al. 2016).

Fusion of the Lumbar Spine

Degenerative conditions of the lumbar spine may present as back pain with radiculopathy or other forms of neurologic deficits in patients. These warrant fusion of spinal motion segments with or without decompression of the pathologic intervertebral disk. Techniques utilized for the fusion of the lumbar spine will depend on the type of approach. Several techniques available for the posterior approach include posterolateral fusion, posterior lumbar interbody fusion, and transforaminal interbody fusion, which are then supplemented by posterior pedicle screw instrumentation. Another method for achieving arthrodesis of the spine is by performing anterior lumbar interbody fusion. This technique utilizes a retroperitoneal approach to access the lumbar spine. Recently developed variations of this technique include the direct lateral interbody fusion and oblique lateral interbody fusion. The former gains access to the intervertebral disk via transpsoas technique, while the latter approaches the disk space through a corridor just anterior to the psoas muscle.

Posterior Lumbar Decompression and Fusion

Fogel et al. (2008) determined the accuracy of fusion assessment of posterior lumbar interbody fusions with the use of plain radiographs and computed tomography in comparison to findings on surgical exploration. Successful fusion was found in 168 out of 172 (97%) motion segments fused upon surgical exploration. Interbody fusion had a success rate of 87% (X-ray) and 77% (CT),

while posterolateral fusion was 75% (X-ray) and 68% (CT). They were able to determine that plain radiographs and CT imaging were both accurate in the assessment of fusion status when compared to findings on surgical exploration of the lumbar interbody and posterolateral fusion levels. The investigators also found that CT is unlikely to provide any additional significant information if there is strong evidence of fusion or pseudarthrosis on plain radiographs (Fig. 6).

Carreon et al. (2007b) performed a blinded cross-sectional study on plain radiographs and fine-cut CT scans to evaluate intra- and interobserver reliability and agreement for assessing single-level instrumented posterolateral fusions. Plain radiographs with anteroposterior and lateral flexion-extension views and fine-cut CT scans with sagittal and coronal reconstructions were performed 1 year postoperatively. Fine-cut CT scans were found to have greater interobserver and intraobserver agreement as compared to plain radiographs. Agreement on fusion status between plain radiographs and CT scans ranged from 46% to 59% only. Another study by Carreon et al. (2007a) showed that radiographic findings of facet fusion and posterolateral fusion on fine-cut CT scans yielded 96% fusion rate on surgical exploration. The kappa statistic for interobserver reliability for evaluating facet fusions was moderate (0.42) and for posterolateral fusions was found to be substantial (0.62). The probability of solid fusion on surgical exploration was higher when bilateral posterolateral gutter fusion was present (89%) compared to bilateral facet fusion on CT scan (74%). The study found several poor predictors for non-union upon surgical exploration, which include absence of fusion of unilateral or bilateral facets or through one posterolateral gutter.

The utility of magnetic resonance imaging (MRI) for the evaluation of fusion status post PLIF has been explored in the past. A prospective study investigated the use of MRI in the assessment of PLIF using carbon fiber reinforced polymer cages. The most reliable radiographic finding is the presence of bridging bone within the carbon cage on the coronal planes based on MRI. Kroner et al. concluded that MRI is a reliable imaging

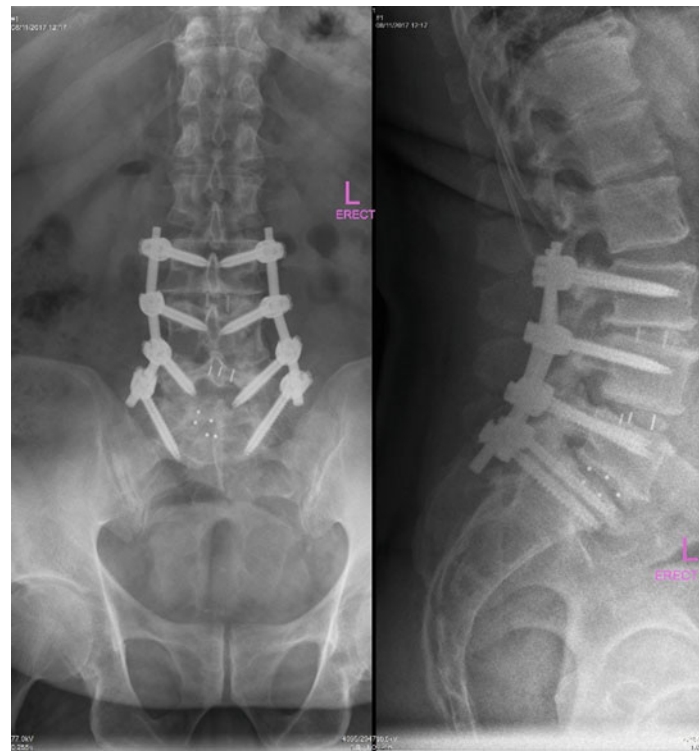

Fig. 6 Multilevel TLIF spanning L3 to S1

method for detecting pseudarthrosis after a period of 2 years post fusion (Kröner et al. 2006).

Nakashima et al. (2011) compared the ability of dynamic radiographs and CT scans with the lumbar spine in flexion and in extension to identify the quality of arthrodesis or fusion in patients who had undergone PLIF. There were 81 patients with a total of 97 fused levels included in the study and were followed for more than 12 months after PLIF. Dynamic radiographs revealed fusion in 90.7% of all operative levels at 10.7 months postoperatively. Patients were then further evaluated, revealing 87.6% fusion on flexion CT and 69.1% fusion on extension CT. Pseudarthrosis detection on extension CT was found to be significantly higher compared to dynamic radiography and flexion CT.

Anterior Lumbar Interbody Fusion (ALIF)

Carreon et al. (2008) once again evaluated the reliability and accuracy of CT imaging versus surgical exploration in determining fusion status, this time around on patients who had undergone anterior lumbar interbody fusion with metallic cages implanted. The study aimed to establish the interobserver reliability with regard to the presence or absence of bridging bone, as well as the anterior and posterior sentinel signs on CT and actual findings of fusion or pseudarthrosis upon surgical exploration of the lumbar spine. On average, 67% of the cases were correctly classified as fused (93% sensitivity, 46% specificity). Interobserver reliability was found to be fair (kappa 0.25). The investigators were able to conclude that their CT scans had a high false-positive rate of determining fusion (Fig. 7).

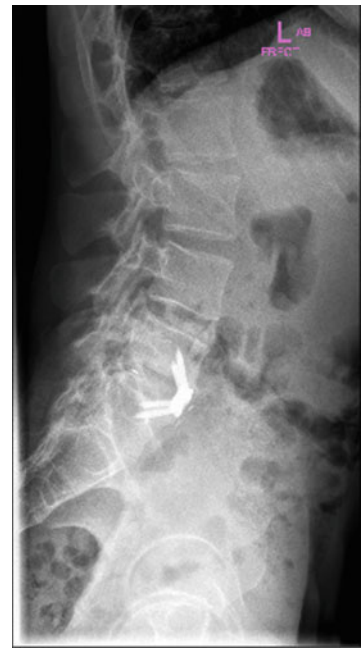

Fig. 7 ALIF performed at L5-S1. Bridging bone well appreciated at fused segment

Lateral Lumbar Interbody Fusion [Direct Lateral LIF (Transpsoas) and Oblique LIF (Anterior to Psoas)]

Clinical and radiologic evaluation of fusion rates with the use of lumbar interbody fusion via direct lateral/transpsoas approach (XLIF) along with varying types of graft material (autograft, calcium triphosphate, and Attrax) was performed by Berjano et al. (2015). Patients who had undergone the procedure from 2009 to 2013 were assessed through clinical evaluation and CT scans with a minimum of 1-year follow-up. CT scans were evaluated with complete fusion defined as presence of bridging bone within the interbody space. Pseudarthrosis was defined as complete absence of graft material within the cage or where there was presence of radiolucency. Complete fusion was found in 68 out of 78 operated interbody levels (87.1%). Stable but incomplete fusion was noted in eight levels (10%), while pseudarthrosis was identified in only two operated levels (2.6%). Comparison of fusion rate by graft material used revealed successful arthrodesis with autograft in 75% in patients, Attrax in 83%, and calcium trisphosphate having the highest fusion rate of 89% (Figs. 8 and 9).

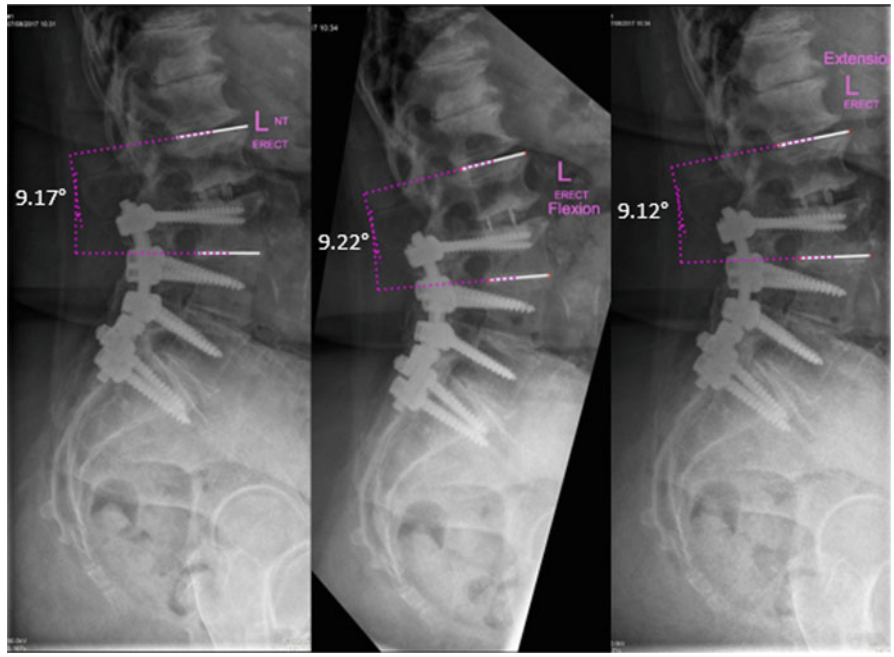

Fig. 8 Lateral views of the lumbar spine post XLIF for adjacent segment degeneration at L2–3. Cobb method was utilized to assess for motion at fusion segment

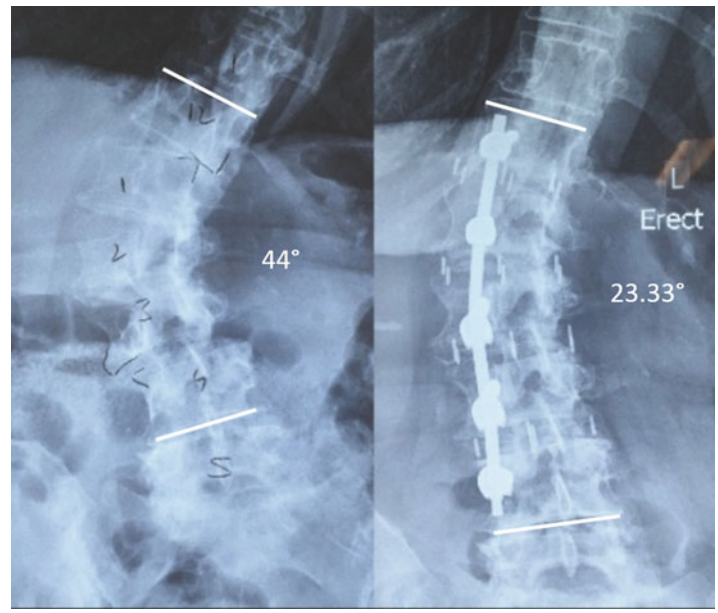

Fig. 9 Degenerative lumbar scoliosis treated with XLIF from T12 to L4. Preoperative curve was at 44°. Correction of 23.33° was achieved after XLIF

Factors to Consider for Further Imaging Evaluation in Pseudarthrosis

Plain radiographs are routinely requested for initial postoperative evaluation of postoperative spinal fusion. These have been found to be inadequate in detecting pseudarthrosis. A retrospective review by Klineberg et al. (2016) evaluated the reliability of anterior fusion grading systems and the ability of health-related quality of life (HRQOL) outcomes to predict pseudarthrosis. Its results showed that the grading system used to evaluate for the presence of fusion missed many pseudarthroses that were confirmed surgically and with fine-cut CT. Low Scoliosis Research Society (SRS) and Oswestry Disability Index (ODI) scores compared to preoperative baseline were found in patients with apparent pseudarthrosis. Patients with poor HRQOL scores indicate the need for further advanced investigations in order to address the possibility of pseudarthrosis (Klineberg et al. 2016).

In light of clinical findings and despite the presence of additional imaging investigations to validate any suspicions of non-union after fusion, there is still great difficulty in reliable confirmation of pseudarthrosis. Besides the prerequisite identification of de novo bridging bone and absence of translational and angular motion spanning the fusion segment, one must also take into account the resorption of the bone grafts, substitutes, and extenders as well. Once pseudarthrosis is confirmed, revision surgery may then be performed in appropriate cases. Autografts or allografts are used again, with possible augmentation through bone graft substitutes or extenders, if these were not used during the index surgery, to increase the possible chances of successful rate of fusion.

Evaluation of Bone Graft Materials for Fusion

With all the techniques available for fusion of the spine, the question of which bone graft material should be used is still up for debate. Autogenous iliac crest bone graft provided similar effectiveness in terms of fusion rate, pain scores, and functional outcomes when compared to local autogenous bone graft and allograft. The use of iliac crest bone graft in spinal fusion is still considered the gold standard due to its osteogenic, osteoconductive, and osteoinductive properties, despite the possible complications associated with harvesting. These included postoperative donor site pain, hematoma, infection, pelvic fracture, and nerve palsy. One study found that use of autogenous iliac crest bone graft in spinal fusions was associated with increase postoperative blood transfusion, extended operative time, and increased length of stay in hospital (Gruskay et al. 2014a; Tuchman et al. 2016). Bone graft substitutes and extenders have thus been developed, which not only address the possible problems that arise with bone graft harvesting but also increase the potential for solid arthrodesis of the spine (Kaiser et al. 2014). Despite the increased number of bone graft substitutes at hand, evidence to support their superiority over autogenous bone graft and allografts is low and hard to come by. Herein lies the difficulty in selecting the most appropriate bone graft material or substitute to aid in achieving successful arthrodesis of the spine (Buser et al. 2016).

Bone allografts can be differentiated into fresh-frozen and freeze-dried products. Both are said to be incorporated slower and to a lesser degree compared to autografts. In terms of fusion rates, autografts are still superior versus allografts alone or in combination with autografts. Fresh-frozen allografts are also found to be stronger, more immunogenic, and more completely incorporated as opposed to freeze-dried allografts. This has also been found to work well when used in anterior lumbar fusion for reconstruction procedures with resulting good fusion rates (Ehrler and Vaccaro 2000). Strong recommendations have also been made with regard to the use of allografts in ACDF, ALIF, and posterolateral lumbar fusion. At present, there is still need for more investigations on its use in TLIF (Gibson et al. 2002; Thalgott et al. 2009; Miller and Block 2011; Buser et al. 2016).

Demineralized bone matrix (DBM) functions as both an extender and augmenter of bone graft material. Its advantages include safety in terms of having no risk of disease transmission and its respectable storage and shelf life. This bone graft

material is not without its disadvantages. Studies have shown varying efficacy and poor predictability, with variable degrees of osteoconductive potential with unknown effect on bone formation due to the different carrier types. The manufacturing process is also unregulated, thus leading to fluctuating amounts of bone morphogenetic proteins found in the different DBM products available in the market (Rihn et al. 2010; Aghdasi et al. 2013; Tavakol et al. 2013). Thalgott et al. (2001) investigated the efficacy of coralline hydroxyapatite with or without DBM as an extender of autogenous bone graft in patients who had undergone instrumented posterolateral fusion. There was an overall fusion rate of 92.5% for this study, but a lower fusion rate was found in patients that had DBM added into the autogenous bone graft (89.3%).

Bone morphogenetic proteins (BMPs) are known for their powerful osteoinductive potential evidenced by their ability to produce ectopic bone, promote spinal fusion, and induce fracture healing. rhBMP-2 and BMP-7 have been found to be safe for use in certain conditions for spine surgery, particularly in ALIF and in revision PLIF (Burkus et al. 2002; Vaccaro et al. 2005). The said products have been involved in off-label use as well, such as in ACDF, TLIF, and PLF. However, judicious use and awareness of their side effects and different dosage effects in different anatomic locations are critical. Concern has risen with regard to the safety and effectiveness of the off label of BMPs. In a systemic and review and meta-analysis by Fu et al. on the effectiveness and harms of rhBMP-2 on spinal fusion, it was found that rhBMP-2 had no clinical advantage over iliac crest bone graft but were not associated with the morbidity of harvesting and difficulties with autograft volume. Several complications have also been found to occur in respect to the type and region of the spine where the fusion was performed. Retrograde ejaculation and other urogenital problems were found to be associated with the use of rhBMP-2 in ALIF although it has been proposed to be approach related, where other authors have found a 0.7% rate with retroperitoneal approaches (Scott-Young 2014). There was an increased risk of wound complications and dysphagia when this particular BMP was used for ACDF which were likely dose related. Although event rates were found to be low, this isolated study also found an increased risk of developing cancer in association with the use of rhBMP-2. These are contrary to the findings of Simmonds et al., who found increased fusion rates with the use of rhBMP-2 and inconclusive evidence with regard to the increased incidence of cancer (Fu et al. 2013; Simmonds et al. 2013). Currently, there does not appear to be any cause-effect relationship between rhBMP2 and cancer.

Ceramics act as bone graft extenders designed with optimized porosity and pore size to allow for bony ingrowth. The advantages attributed with this type of bone graft material are its availability, cost effectiveness, and no risk of disease transmission. The varying resorption rate across the different types (calcium sulfate, beta-tricalcium phosphate, and hydroxyapatite) of ceramics presents as a limiting factor, particularly calcium sulfate, in spine surgery (Rihn et al. 2010). The material is best used to augment the fusion mass and is not recommended as a stand-alone substitute for actual bone graft material. A prospective study found that hydroxyapatite-bioactive glass ceramic used as a stand-alone bone graft substitute had a high incidence of resorption with poor consolidation noted in 95% (21/22) of patients who had undergone instrumented posterolateral fusion (Acharya et al. 2008). Other studies that claim good results with the use of calcium phosphate ceramics were found to have the ceramic mixed with local autograft harvested from the site of decompression (Fujibayashi et al. 2001; Dai and Jiang 2008). Tricalcium phosphate has been found to provide excellent results in ACDF and posterolateral lumbar fusion. The use of beta-tricalcium phosphate (94%) for ACDF yielded fusion rates comparable to those of hydroxyapatite (90%) after 2 years of follow-up. Early fusion rates at 6 months (46%) and 1 year (69%) post ACDF were higher with beta-tricalcium phosphate versus hydroxyapatite (24% at 6 months and 49% at 1 year). Beta-tricalcium phosphate was found viable in patients treated with instrumented posterolateral fusion. Radiographs taken at 24 and 36 months post fusion showed good fusion status with no signs of motion on flexion or extension (Dai and Jiang 2008; Sugawara et al. 2011) (Table 2).

Table 2 Known spinal fusion evaluation methods for various regions and approaches

Fusion region	Approach		Method(s) of fusion assessment	Comments
Cervical	Anterior (ACDF)		X-rays Flexion-extension views Cobb angle Simmons Uses reference points >2° extension is pseudarthrosis Hutter Overlap of images Cannada et al. 2003 Measure interspinous process distance doi: 10.1097/00007632-200301010-00012 Findings on CT have higher correlation with findings on surgical exploration when compared to x-ray and MRI (Buchowski et al. 2008) doi: 10.1097/BRS.0b013e318171927c Combination of CT and dynamic radiographs improved specificity in determining pseudarthrosis (Ghiselli et al. 2011) Modified angular motion (>1°) on radiographs doi: 10.1097/BRS.0b013e3181d7a81a Functional (flexion and extension) CT was found superior over functional (dynamic) radiography in determining non-union (Ouchida et al. 2015) doi: 10.1007/s00586-014-3722-z	Postoperative x-rays of limited value for determining fusion in patients with normal history and physical findings (Grimm et al. 2013) doi: 10.1016/j.spinee.2013.01.018 CT images may tend to lead to overestimation of the presence of fusion due to their static nature (Park et al. 2015) doi: 10.1097/BSD.0b013e31829a37ac
	Posterior (PCDF)		X-rays Flexion-extension views Cobb angle Simmons Hutter CT	High resorption rates noted for allografts and auto/allograft mixture compared to autograft alone (Lee et al. 2017) Despite resorption rates, average fusion rate across different types of grafts was 98.2% Doi: 10.1016/j.wneu.2016.12.027 Non-union in 10.5% of patients after posterior cervical fusion with rhBMP2 use (Dorward et al. 2016) Most common in occipitocervical or cervicothoracic junctions doi: 10.1097/BSD.0b013e318286fa7e
Lumbar	Interbody fusion	Anterior (ALIF, XLIF)	X-rays Flexion-extension views Cobb angle Simmons	Overestimation of fusion status on CT when compared to findings on surgical exploration (Carreon et al. 2008)

(continued)

Table 2 (continued)

Fusion region	Approach		Method(s) of fusion assessment	Comments
			Hutter CT	doi: 10.1016/j.spinee.2007.12.004 XLIF fusion success rate (Berjano et al. 2015) Complete fusion 87.1% Pseudarthrosis in 2.6% of patients Difference in fusion rate between Attrax (83%) and calcium triphosphate (89%) was not statistically significant doi: 10.1007/s00586-015-3929-7
		Posterior (PLIF, TLIF)	MRI was a viable tool for detecting pseudarthrosis in patients 2 years post PLIF (Kroner et al. 2006) doi: 10.1097/01.brs.0000218583.43398.e3 Extension CT had higher ability to detect pseudarthrosis compared to flexion CT and dynamic radiographs (Nakashima et al. 2011) doi: 10.1007/s00586-011-1739-0	Fusion success rate was higher using on x-ray (87%) versus CT (77%) (Fogel et al. 2008) doi: 10.1016/j.spinee.2007.03.013
	Posterolateral fusion		Interobserver and intraobserver agreement greater with CT compared to radiographs (Carreon et al. 2007b) doi: 10.1016/j.spinee.2006.04.005	Solid fusion on surgical exploration noted when there is presence of bilateral posterolateral fusion compared to facet fusion (Carreon et al. 2007b) doi: 10.1097/01.brs.0000259808.47104.dd Fusion success rate was higher using x-ray (87%) than CT (77%) (Fogel et al. 2008) doi: 10.1016/j.spinee.2007.03.013

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Effects of Reimbursement and Regulation on the Delivery of Spinal Device Innovation and Technology: An Industry Perspective

63

Emma Young

Contents

Abstract

Since the 1990s regulation has been relatively unchanged in the world's second largest medical technology sector, the European Union. However, recent medical device-related incidents involving breast implants and hip replacements have prompted urgent regulatory and compliance reforms. Against the background of increasing global healthcare costs and an aging population, medical devices including spinal devices are about to undergo one of the industry's most transformational regulatory changes. What does this mean for current and potential innovators of new medical device technologies and their beneficiaries? What will future reimbursement and regulatory frameworks look like, and what will be their impact on medical device technology investment? Navigating the complex requirements of innovative medical device development such as increasing regulatory burden and a multitude of differing payer uncertainties can often be the hurdle to sustained device innovation for many companies.

Keywords

Reimbursement · Regulatory · Innovation · Healthcare expenditure · Medical Device Directive · Medical device regulation · Therapeutic Goods Administration · CE mark · Spinal devices · Medical device

NB: this work is not related to the views or opinions of Prism Surgical

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Introduction

Healthcare systems are organized, financed, and regulated in different ways around the world, but most would agree that universal access to innovative technology and quality healthcare at an affordable cost to both the individual and society is an elementary need. Almost all OECD (Textbox 1) countries have universal health coverage for a core set of services (OECD 2015). Statistics on healthcare expenditure and financing are often used to evaluate how a country's healthcare system responds to the challenge of universal access to quality healthcare.

Textbox 1 What is an OECD Country?

The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental economic organization with 36 member countries, founded in 1961 to stimulate economic progress, stability, and world trade (OECD 2018). It is a forum of countries describing themselves as committed to democracy and the market economy, providing a platform to compare policy experiences, seeking answers to common problems, identify good practices, and coordinate domestic and international policies of its members. Most OECD members are high-income economies and are regarded as developed countries.

Source: Based on information from OECD (2018).

Healthcare expenditure is defined as expenditure on health goods and services, including investment in equipment and facilities. As defined by the Australian Institute of Health and Welfare (2017), this definition closely follows the definition that the OECD System of Health Accounts framework provides. It excludes expenditure that is incurred outside the health sector, personal activities, and where health is not the primary expected benefit.

At the macrolevel, health expenditure in Australia is considered within the context of changes in the economy and population growth. The focus is on total health expenditure. Total health expenditure in 2015–2016 in Australia was reported at $170.4 billion–$6.0 billion higher in real terms than 2014–2015 and $63.2 billion higher than in 2005–2006 (AIHW 2017). Health's share of Australian gross domestic product (GDP) has continued to rise, from 8.68% in 2005–2006 to 10.3% (Table 1) in 2015–2016 (AIHW 2017). The share of the economy (or GDP) represented by health continues to steadily grow as reflected in Table 1. Non-government sources (individuals, private health insurance funds, and other non-government sources) contributed an estimated 32.7% toward total health spending in 2015–2016 (AIHW 2017).

The European Union (EU) healthcare spend, as a percentage of GDP, aligns itself closely with the Australian experience. The European Union (EU) reports total health expenditure in 2014, in terms of GDP, ranging as high as 10.9–11.4% in countries such as Germany, the Netherlands, France, the UK, and Switzerland (Table 2) (Eurostat 2017).

In the USA, the National Center for Health Statistics (2017) recorded the total US national health expenditure in 2015 to be US$3.2 trillion, 17.8% of the national GDP. In 2017, it was reported that health expenditure rose to 18.3% of national GDP.

Health systems across the globe are required to rapidly develop and respond to a multitude of factors such as new medical technologies, new health services, and greater access to them, changing health policies and organizational structures and more complex financing mechanisms. Access to healthcare and greater patient choice are increasingly scrutinized against the background of financial sustainability. New medical technologies are improving diagnoses and treatments, but they are also increasing health spending. Medical technology is often viewed as a primary contributor to increased healthcare expenditure. The prospect that spending pressures will escalate raises questions around the benefits and costs of technology advances and the processes for evaluating them. Life expectancy continues to increase steadily in OECD countries, rising on average by

Table 1 Total Australian health expenditure and GDP, current prices, and annual health to GDP ratios of 2005–2006 to 2015–2016

Year	Total health expenditure ($million)	GDP ($million)	Ratio of health expenditure to GDP (%)
2005–2006	86,685	998,458	8.68
2006–2007	94,938	1,087,440	8.73
2007–2008	103,563	1,178,809	8.79
2008–2009	114,401	1,259,280	9.08
2009–2010	121,710	1,297,508	9.38
2010–2011	131,612	1,410,442	9.33
2011–2012	141,957	1,491,741	9.52
2012–2013	146,953	1,527,529	9.62
2013–2014	154,671	1,589,940	9.73
2014–2015	161,617	1,617,016	9.99
2015–2016	170,386	1,654,928	10.3

Data source: AIHW (2017)

3–4 months each year. In 2013, OECD (2015) life expectancy at birth reached 80.5 years, an increase of over 10 years since 1970. This rise in average life expectancy continues to increase the need for treatment of illness and chronic diseases. Interestingly and despite the highest OECD health spend, the US Center for Disease Control and Prevention (2017) recently reported that the 2016 US life expectancy at birth was 78.6 years for the population as a whole – 0.1 year less than it was in 2015. This recent statistic from the largest healthcare economy in the world has sharpened the focus on the relationship between healthcare spend and its effect on overall health improvement.

The Australian Productivity Commission's work on the Economic Implications of an Ageing Australia (Productivity Commission 2005) found that most of the growth in health expenditure over the last 20 years was due to factors such as a greater demand for health services, in combination with the adoption of new technologies. Modelling estimates prepared as part of this report confirm that technology has played an important role in driving total real healthcare expenditure growth. It is reasonable to expect that technologies such as medical devices will continue to play a key role in influencing healthcare expenditure.

As knowledge increases there is a constant uptake of improved, innovative, and inventive medical technology, such as medical devices. However, the rapid advances in device technology continue to drive medical costs upward. It has become increasingly difficult to balance the dual responsibilities of controlling healthcare expenditure while simultaneously enhancing the welfare of its beneficiaries, particularly when it comes to coverage decisions for costly new medical devices. Patient demographics are shifting toward a greater emphasis on notions of well-being and increased activity levels, including an expected standard of health and technology delivery that will enable an aging population to lead more active lives for longer. To be concise, patients expect a better quality of life for longer. Rapid developments in new technologies and their increasing complexity will place demands on regulatory requirements to adapt, as patients increase their awareness of newly developed technologies through sources such as the media and the Internet. At any one time, there are thousands of new technologies undergoing development, most of which will fail to progress to end commercial availability. As a result it is often difficult to identify effective technological advances, let alone the implications for health expenditure.

The influence of a new medical technology on health expenditure will depend on factors such as but not limited to:

- Whether the medical advance will increase or decrease the cost of a particular procedure or treatment
- How the number of procedures undertaken will change as a result of the new medical device

Table 2 2014 EU healthcare expenditure total, per inhabitant and as a percentage of GDP

EU Member	Total health expenditure (EUR million)	EUR per inhabitant	Ratio of health expenditure to GDP (%)
Belgium	41,711	3722	10.4
Bulgaria	3640	504	8.5
Czech Republic	11,841	1125	7.6
Denmark	27,517	4876	10.4
Germany	321,720	3973	11.0
Estonia	1223	931	6.1
Ireland	19,148	4147	9.9
Greece	14,712	1351	8.3
Spain	94,534	2034	9.1
France	236,948	3582	11.1
Croatia	2886	681	6.7
Italy	145,938	2401	9.0
Cyprus	1184	1389	6.8
Latvia	1297	650	5.5
Lithuania	2265	772	6.2
Luxembourg	3091	5556	6.3
Hungary	7473	757	7.2
Malta	–	–	–
Netherlands	72,475	4297	10.9
Austria	33,795	3957	10.3
Poland	25,987	684	6.3
Portugal	15,583	1498	9.0
Romania	7727	388	5.1
Slovenia	3189	1546	8.5
Slovakia	5256	970	7.0
Finland	19,523	3575	9.5
Sweden	48,154	4966	11.1
United Kingdom	222,609	3448	9.9
Iceland	1138	3476	8.8
Liechtenstein	294	7906	–
Norway	35,132	6389	9.4
Switzerland	60,276	7361	11.4

Data Source: Eurostat (2017)

- Whether the advance will change the place of treatment, for example, an inpatient to an outpatient basis

Moreover, it is inappropriate to consider only the potential expenditure effects of technology advances in isolation of their expected efficacy and clinical benefits. Spinal pathology and related back pain are among the most prevalent contributors to health expenditure in the world. Within the Australian adult population, the results of a "cost-of-illness" study (Walker et al. 2003) of low back pain (LBP) estimated the direct cost of LBP in 2001 to be AU$1.02 billion, with indirect costs at AU$8.15 billion producing a total cost of AU$9.17 billion. LBP in Australian adults represents an exponential health problem with significant economic burden.

Care for individuals with a spinal pathology, related symptoms, and operative care have long been associated with rising healthcare costs and productivity losses, costing the world's largest

Table 3 EU medical device classification

Class 1	Low risk Non-sterile. Self-certified. Registered within each member state they are sold within
Class 1 (measuring/ sterile)	Low-medium risk Provided sterile and/or have a measuring function.
Class IIa	Medium risk Special controls. NB assessment. Used to diagnose and monitor. Limited invasiveness
Class IIb	Medium risk Full QMS and targeted review of design or technical files by NB. Surgically invasive/implantable
Class III	High risk Similar to IIB + full design review by NB Implants support or sustain human life. Present a potential, high risk of illness/injury

healthcare market, the USA, US$86 billion in 2005 (Bisschop and Tulder 2016). Bisschop and Tulder (2016) state that spinal pathology and related back and neck symptoms are among the most common health problems and are ranked number one with respect to years lived with disability. The global burden is so great that it has compelling and urgent ramifications for health policy, planning, and research in all jurisdictions.

Growth of the global spinal device market is estimated to reach US$17.27 billion by 2021 as reported in a 2017 market research study (Markets and Markets 2017). A number of contributing factors include the rising incidence and prevalence of spinal disorders, development of technologically advanced medical devices, and the global rise in an aging population. The challenge for the payers and regulators in any jurisdiction is to craft a standard for policy, reimbursement, and regulatory provision that both protect patient safety and efficacy while preserving some incentive to spur authentic device research and innovation. Reimbursement policies and supporting frameworks for innovative medical devices differ significantly from the regulatory requirements. With this in mind, what are the effects of reimbursement and regulation frameworks on the delivery of spinal device innovation?

The Regulatory Effect

Medical devices cannot be placed on the European market without conforming to the strict safety requirements of European legislation. In the European Union or EU, three directives cover the medical device sector. Collectively known as the Medical Device Directive (MDD), this legal framework regulates the safety and marketing of medical devices in Europe and is largely mirrored throughout the Australian medical device approval process under the authority of the Australian Therapeutic Goods Administration (TGA). Of the three directives, it is the Medical Device Directive (93/42/EEC) that regulates implantable spinal devices such as screws, rods, cages, plates, and total disc replacements.

Medical device regulations around the world begin by assessing the risk of a device and, more specifically, the risk of the intended use of the device. The regulatory requirements or "burden" are proportional to the estimated risk. The lowest risk or "class" of device (Table 3), such as a reusable surgical instrument, is self-certified. These low-risk devices are required to meet general controls and be registered in their respective jurisdiction. The highest class of device, such as hip replacements and heart valves, must undergo stringent premarket assessment by a qualified body before market placement. Within the European Union, all medical devices are placed into one of the four graduated categories, using the classification rules listed in the Directive 93/42/EEC Annex IX.

Under the Therapeutic Goods Act 1989, medical devices must be included in the Australian Register of Therapeutic Goods (ARTG) prior to supply in Australia, unless exempt. The TGA's current regulatory framework is based on the model recommended by the Global Harmonization Task Force (GHTF) (Textbox 2). A conformity assessment is the key mechanism for assuring a medical device is safe and performs as intended. Conformity assessment certification is issued by a conformity assessment body, and the degree of assessment rigor is determined by the risk classification of the device.

Textbox 2 What is the GHTF?

Founded in 1992, the Global Harmonization Task Force or GHTF was created in an effort to respond to the growing need for international harmonization in the regulation of medical devices (*IMDRF* 2018b). *The GHTF was a voluntary group of representatives from regulatory authorities and members of the medical device industry. The representatives from its five founding members (the EU, the USA, Canada, Japan, and Australia) were divided into three geographical areas, Europe, Asia-Pacific, and North America, each of which highly regulates medical devices using their own unique regulatory framework.* GHTF principles are similar to and largely based on the member countries framework in that device classification is risk based and assessed by third-party bodies. There are a number of jurisdictions such as Japan who currently operate their regulatory frameworks on the GHTF principles.

The GHTF organization had been a mainstay among the regulatory harmonization movements, and the initiative was arguably the most successful effort to harmonize medical device standards around the globe. The GHTF was discontinued with its mission taken over by the International Medical Device Regulators Forum (IMDRF) in late 2011, a successor organization comprised of officials from regulatory agencies around the world (*IMDRF* 2018b).

The TGA issues conformity assessment certification under the Australian regulatory framework, while European-notified bodies issue conformity assessment certification under the European regulatory framework. There is great similarity between the Australian and European processes with both frameworks based on the GHTF principles.

Signed in 1998 and effective since 1999, the mutual recognition agreement (MRA) between Australia and the European Community (EC), known as the EU-AU MRA, officially recognizes the competence of conformity assessment bodies located in the EU to assess compliance of certain types of medical devices with Australia's regulatory requirements. Conversely, the MRA recognizes the competence of Australia's Therapeutic Goods Administration (TGA) to assess medical devices for compliance with EU requirements. According to the TGA (2013), this practice recognizes that conformity assessment is an intensive and potentially expensive process and that unnecessary duplication would increase the costs of many medical devices for consumers and create disincentives to supply products in Australia's small medical devices market.

However, changes to the provisions of the EU-AU MRA came into force on the 1 January 2013 to exclude particular medical devices from the scope of the agreement. Medical devices excluded from the MRA include high-risk devices such as active implantable devices (AIMDs) and class III (high risk) medical devices. Exclusion of these medical devices will continue until confidence-building activities have been undertaken by Australia and the European Union. Certain additional medical devices incorporating materials of biological origin are also principally excluded, with no confidence-building phase planned.

Medical devices covered under the terms of the amended MRA that have undergone a conformity assessment procedure by an EU-recognized notified body and are in compliance with Australian medical device regulations are included by the TGA on the Australian Register of Therapeutic Goods (ARTG). In practice, 97% of applications for inclusions in the ARTG are certified medical devices by EU notified bodies (TGA 2013).

Textbox 3 What is a CE Mark?

CE marking is the medical device manufacturer's claim that a product meets the essential requirements of all relevant European Medical Device Directives. The Directives outline the safety and performance

(continued)

requirements for medical devices in the European Union (EU). The CE mark is a legal requirement to place a device on the market in the EU.

Although a device may be granted an EU approval (CE mark) (Textbox 3), for companies whose devices do not qualify under the amended MRA between Australia and the EC, they must apply for a conformity assessment procedure to be conducted by the TGA. Although the TGA's regulations and approval processes are similar to those applicable in the EU, the full TGA registration process can take anywhere from 2 to 18 months to complete, depending on the risk classification of the device, prior conformity assessment sources, and whether the TGA determines that an audit is required.

A key feature of the European medical device legislation is that it defines what is commonly known as the Essential Requirements or the "ERs." Medical devices can only be placed in the European market if they satisfy the Essential Requirements criteria, specified in Annex I of the Medical Device Directive 93/42/EEC. All medical devices must comply with these requirements. Manufacturers are required to verify each device type or model against each of the requirements, determine whether the requirement is applicable, and demonstrate documented evidence of compliance. In this respect, it is reasonable to assert that Annex I is the foundation of the Medical Device Directive (MDD).

The MDD outlines the core elements that companies need to have in place. It sets out and defines the conformity assessment processes required to assess whether a device is in conformity with the directives, and it lays down precise obligations on the part of the device's legal manufacturer (IOM 2010). Competent authorities (CA), notified bodies (NB), and authorized representatives (AR) are all involved in the CE marking process. Competent authorities exist in each member state and designate, control, and monitor the notified bodies, govern clinical trials, and monitor post market vigilance activities. Notified bodies ensure and certify the safety and compliance of devices and their manufacturers in accordance with the relevant criteria.

The legislation itself is underpinned by "standards." European standards or harmonized standards adopted by a recognized European Standards Organization such as CEN or CENLEC allow manufacturers, other economic operators, or conformity assessment bodies to use these designated harmonized standards to demonstrate that products, services, or processes comply with relevant EU legislation. Other commonly utilized standards are written by the International Organization for Standardization (ISO), while others are in the form of "EU guidelines" called MEDDEVs and GHTF guidance documents.

The European and Australian regulatory frameworks are similar to the US system in that they are all constructed on a risk-based classification system (Table 3). These risk-based frameworks are more similar than different. However, despite the similarities there remains enough difference between them that complying with one does not guarantee compliance with the other. It has been long reported that devices cleared by the FDA have been declined by EU notified bodies and vice versa.

Within Australia, the USA, and the European Union, the highest risk devices have development paths that are heavily regulated and expensive to both commercialize and maintain on the market. In the USA, class III or novel devices require a Premarket Approval (PMA) (see ► Chap. 18, "FDA Premarket Review of Orthopedic Spinal Devices"). Sorenson and Drummond (2014) report over the past 10 years approximately 2% of medical devices have undergone the PMA process, and unlike PMA, direct evidence of safety and effectiveness is usually not required for a 510 (k) application with only 10–15% of those applications containing any clinical data. Medium-risk or class II devices in the USA are usually required to undergo the 510(k) review process, which determines principally whether the new device is "substantially equivalent" to previously marketed or "predicate" devices. Class III (high risk) devices or novel technologies deemed to not possess substantial equivalence undergo the more

stringent PMA process. These technologies must demonstrate safety and efficacy through clinical studies.

Similarly in Europe the evidence requirement increases with the risk of the device. The majority of spinal devices is approved through demonstrating safety and performance in relation to the intended purpose. In most cases the evidence submitted for premarket approval of spinal devices is from non-clinical origins, extensive literature reviews to similar products or small clinical trials. This pathway presents opportunity to market approval with the least regulatory burden.

The large disparity in regulatory burden between class II and class III medical devices allows the development of smaller companies and more rapid innovation cycles for the low-medium-class devices. While small companies have completed US PMAs, the majority of high-risk devices are developed by the larger device organizations (IOM 2010).

The two factors that have the biggest impact on regulated device development are review cycle time and the level of evidence required for approval. The influence and impact of a short device review cycle can be illustrated when comparing US PMA products to European class III devices. The Institute of Medicine (2010) explains for the very reason that the US review cycle time for these products is twice as long as the current European cycle; not only are inventive products introduced later to the US markets, but the US markets often forego revised models of product as the innovation and approval cycles outside the USA are generally much swifter to market.

However, sweeping reforms of the rules that govern the regulation of the medical device sector in Europe represents one of the most disruptive changes to affect the industry in recent times. When the European medical device regulation commonly referred to as the MDR replaces the current set of Medical Device Directives (MDD), companies will have 3 years to comply with a broad scope of new rules for almost every kind of product in the medical device spectrum. Under the new regulations, medical device companies will have to provide substantially more clinical evidence to gain market access or even maintain existing products on the market. Companies will need to conduct audits to determine the new rules' impact on maintaining and upgrading device portfolios. Companies can expect a significantly more costly path to compliance in the European Union. The costs associated with compliance may force a number of companies to take strong steps, such as discontinuing existing device lines or considering acquisition proposals (De Busscher et al. 2016).

The result of this transformation anticipates a stronger, more accountable device industry that may look considerably different from todays (De Busscher et al. 2016). The EU MDD has been in effect since the 1990s. Incremental changes to the text have occurred along the way due to new and emerging technologies which have both challenged the framework and identified gaps. However, it was a series of well-known device events (Textbox 4) that emphasized to both policymakers and the industry an urgent need for regulatory reform to ensure patient safety concerns were adequately attended. On the 26 September 2012, the EU announced a package of reforms to provide a more stringent regulatory framework for medical devices to ensure a higher level of protection of human health and safety (TGA 2013).

Textbox 4 Why Regulatory Reform Was Required

2011 The US FDA warned of serious complications associated with the use of urogynecologic surgical repair mesh after nearly 2874 medical device reports (MDRs) in a 3-year period including injury, death, and malfunction[1]. One thousand five hundred three were associated with pelvic organ prolapse (POP) and 1371 for stress urinary incontinence (SUI).[1]

2012 Poly Implant Prothèse (PIP), a French company, was revealed to have knowingly sold breast implants made with industrial grade silicone rather than medical grade. The reported probability of PIP rupture at 10 years is 25–30% versus 2–15%

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reported in standard silicone implants[2]. It is reported that approximately 300,000 women were affected.[2]

2010 DePuy (Johnson & Johnson) voluntarily recalled the ASR (metal on metal) hip replacement system after an Australian National Joint Replacement Register (NJRR) reported a failure rate of 13% at 5 years for the device – unacceptably higher than the average. Ninety-three thousand people worldwide were implanted with an ASR device[3]. The ASR hip replacement was removed from the Australian market in 2009 after intervention by the Australian TGA.[3]

[1]Source: SCENIHR (2013)

[2]Source: CDRH (2011)

[3]Source: TGA (2011)

The introduction of the new EU MDR which entered into force on 25 May 2017 marks the start of a transition period for manufacturers selling medical devices into Europe and other jurisdictions that recognize and approve a CE-marked device under the EU regulations. The MDR, which replaces the Medical Device Directive (93/42/EEC), has a transition period of 3 years. The extensive and long-awaited regulation will come into force in May 2020 and more closely reflects the current FDA scrutiny of product safety by placing stricter requirements on subjects such as clinical evaluation, post market clinical follow-up, and increased traceability of devices through the supply chain. The implications of the new EU MDR on the global medical devices sector are enormous. The European medical technology market is significant and important for the industry, estimated to contribute 31% of the global total (Eucomed 2013).

Traditionally, small and medium companies who did not have the revenue to conduct expensive PMAs in the US viewed the European market as an opportunity to innovate and collect valuable clinical performance data. As more detail has emerged about the composition of the EU MDR, it has become apparent that the full impact of the changes will extend beyond the regulatory framework. Among a plethora of new requirements, a CE mark will require pre- and post market clinical studies, data transparency, tightening of vigilance reporting, and the introduction of a unique device identification (UDI) system similar to that recently introduced into the USA. Additionally, a number of medical devices will be reclassified such as spinal total disc replacement which will increase in its defined risk classification from class IIb (medium risk) to class III (high risk).

According to a recent report by Makower et al. (2010), current FDA and EU regulatory frameworks are creating almost impossible barriers to authentic device innovation. Due to their usually limited financial resources, the future regulatory environment will be particularly challenging for start-up companies who have historically played a key role in driving innovation. Compliance with regulatory legislation is generally viewed as a driver of complexity and cost for medical device businesses, whose regulatory people are tasked with ensuring that the companies who employ them are compliant while curtailing the risks and costs associated with it. However, it is becoming increasingly apparent that tackling frameworks such as the future EU MDR goes beyond the remit of even the most resourced regulatory teams (De Busscher et al. 2016).

Providing data on both new and existing medical devices may require revision and the need to conduct new clinical studies. De Busscher et al. (2016) estimate that some devices will need to have their safety and efficacy validated clinically or be at risk of being removed from the global market. The proven technology concept commonly referred to as "grandfathering" of legacy devices is one of the key changes of the new MDR determined by the commission to now require supporting clinical evidence in compliance with the current standards and regulations.

De Busscher et al. (2016) propose that the additional clinical evidence requirements likely to be stipulated by the EU MDR will mean that products in development may take longer to obtain commercialization, which is likely to impact further on revenues and the raising and allocation of capital. Additionally, the notified bodies that regulate and certify manufacturers of medical devices and

technology will undergo significant changes. Under the EU MDR, the notified bodies' requirements and responsibilities will intensify. Many in the industry fear this will lead to further delays in product certification and audit assessments.

These are transformational shifts for medical device companies. Accessing the EU market or gaining CE mark by complying with current and future regulations, restructuring operations, and planning future business pathways will become an increasingly burdensome activity. For at least a decade, Europe has remained a favorable market entrance for many innovative medical devices joining the market. After obtaining a CE mark (EU approval), a manufacturer could further validate their device clinically and thereby build a complete dossier of evidence that would be both required and beneficial to secure future FDA approval. Leading up to and beyond the EU MDR becoming an industry reality in 2020, this familiar path will need to be reviewed with Europe possibly becoming a less attractive first market destination (De Busscher et al. 2016). It is difficult to estimate how the cost of compliance with this future regulatory framework will financially burden a medical device company. In 2013 Eucomed, an industry body, conducted an industry-wide survey on the financial impact of the updated EU MDR (Table 4).

A reflection of increasing burden and its impact is the reported declining numbers of regulatory submissions for new medical devices in the USA over the past several years. The annual Emergo (2017) study examined approximately 15,000 510(k) applications cleared by the FDA between 2012 and 2016, finding not only that numbers of US applicants have steadily declined but also that the overall number of 510(k) applications cleared by the agency hits a 4-year low in 2016. In an era of greater scientific knowledge and more technology advancements than any other time in history, industry experts question what forces are driving genuine medical technology innovation and invention in a negative direction.

Table 4 Forecast MDR compliance costs (Eucomed 2013)

€17.5b (US$18.9 billion) cost to industry if a centralized premarket authorization system is implemented
€7.5b (US$8.1 billion) cost to industry of compliance with a UDI (unique device identification) system, improvements in labelling, and clinical performance data
€17.5 m (US$18.9 million) cost to small-medium-sized enterprises (SMEs) to bring a new class III product to market under a clinical premarket approval system

Device manufacturers continue to argue that the device industry is fundamentally different from other industries such as the pharmaceutical industry taking into consideration that the engineering and quality frameworks required to support development, market approval, and continuous device innovation are increasingly onerous (Reed et al. 2008). In general, devices tend to have faster commercial cycle times and tend to be characterized by incremental improvements to existing technologies. This difference is increasingly identified by major bodies such as the FDA, evidenced by The FDA Modernization Act defining the "least burdensome approach" (CDRH 2002). The least burdensome concept is defined as a successful means of addressing a premarket issue that involves the smallest investment of time, effort, and resources (e.g., money) on the part of the submitter and FDA, to help ensure scientific integrity while affording a high degree of public health protection and expediting the availability of new device technologies (CDRH 2002).

However, an issue continues to arise when that incremental evolution of technology occurs and the suitability between that technology and existing regulatory pathways does not exist. The prospect of piloting through the increasing requirements of product development and regulatory approvals to then confront a multitude of differing payer uncertainties is often a hurdle to sustained device innovation for many companies.

The Reimbursement Effect

Achieving approval by a regulatory body in any jurisdiction does not imply that a product will be reimbursed by payers or private insurers. Whereas

regulatory approval focuses on safety and efficacy, the payers tend to strongly consider the cost savings and cost-effectiveness in determining whether to cover a new technology. Suitable costings for reimbursement must be obtained while ensuring reimbursement rates are appropriate and balanced accordingly with the cost and benefits of new technologies and expected yet increasing standards of care.

For example, in Australia a new technology pending the classification may gain regulatory approval with the Therapeutic Goods Administration (TGA) without delay. However, in order to commercialize the innovation in the Australian private health system, the device must gain payer reimbursement through approval by the Minister for Health via the government-administered Prostheses List (PL). The Prostheses List Advisory Committee or PLAC's primary role is to make recommendations and provide advice to the Minister for Health. The PLAC advises on the listing of medical devices and their reimbursement benefits. Using evidence provided by the manufacturer, the PLAC makes recommendations on the most clinically efficacious and cost-effective devices. This ensures that privately insured Australians have access to a range of medical devices that are both clinically and cost-effective. Similar to many jurisdictions around the world, approval by the Australian regulatory body (TGA) does not guarantee reimbursement by the government's Prostheses List arrangements. Reimbursement and/or payer coverage can be the factor which decides whether a new medical device will succeed or fail, and the common goal of reimbursement or payer policies around the world is maintaining that balance between cost- and clinical effectiveness of a new technology.

Payment issues are of increasing concern to the healthcare industry. Most who are connected with healthcare acknowledge the rising costs of healthcare and the need to find ways of managing costs more effectively. In fact, some continue to point to technology as a major cause of these increasing costs. The emphasis on cost and the role of technology in costs have placed a large part of the onus on the device industry. It is a prominent inclusion of the company consciousness that innovation is not just creating a better device but includes creating a more cost-effective or financially sustainable alternative to the current offerings (IOM 2001). Of course, it is not that simplistic, and it is challenging for a medical device company to fulfil the criteria for novelty and superiority with cost-effectiveness while also fulfilling the required regulatory principles of clinical safety and efficacy.

Cost is guaranteed to be in the innovation and invention equation, but where do the benefits to patient outcomes place in that equation? In the current global device environment, providers are increasingly pressured to use cost-saving technology as opposed to cost-effective technology. Manufacturers are forced to consolidate, to fashion technologies into commodities, and often to compete on the basis of price alone (IOM 2001). The Institute of Medicine (2001) assert too often pricing contracts and rationing, which are often employed in a number of cost frameworks, fail to balance with the patient benefit and effectiveness side of the equation. There is a multitude of different parties that have an effect on payments for technologies such as multiple insurers and/or government structures who all vary in their approval frameworks for that payment.

Definitive reimbursement is an essential part of the overall concept, design, development, and marketing of the medical device life cycle. For many decades, new innovations have been developed and launched into a market in which prospective payment systems and unanticipated changes have forced key stakeholders to operate in an increasingly efficient and lean manner. The key message is that new innovations must fit within a diminishing yet dynamic operating margin imposed by cost-constrained third parties.

Within the Australian framework, manufacturers of innovative device technology must have an associated procedural code included on the Australian Medicare Benefits Schedule (MBS) for commercial release within the private health system. This is the list of procedures, tests, and consultations for which the Australian Medicare System will subsidize. The MBS is fundamental to the Australian health system and is a prerequisite for private payer device reimbursement.

Devices cannot be included on the Australian Prostheses List (PL) if a related MBS item number does not exist. This requirement can be challenging for the suppliers of authentic innovative or inventive technologies if solid clinical efficacy has not been established. In any market an understanding of these key relationships is essential. Innovative technology that offers substantial clinical and economic improvements may struggle to obtain reimbursement if payer frameworks are not well understood.

Early stage reimbursement strategies are vital for the acceptance and success of an innovative or inventive device. It is absolutely critical for a device company, large or small, to obtain coverage and attract investors. In venture capital there are two important aspects for consideration: feasibility and market acceptance (IOM 2001). The Institute of Medicine (2001) maintains the regulatory and healthcare payment environment which introduces additional levels of risk and uncertainty. In those cases where uncertainty of reimbursement for a particular device under development exists, securing funding for that innovative or inventive technology becomes problematic. While US firms have the dominant position in critical markets, the global industry argues that a large number of innovative devices and clinical breakthroughs are often the product of the smaller businesses. According to the Institute of Medicine (2001), 72% of medical device companies employ fewer than 50 people. Eucomed (2013) reported small-medium-sized companies accounted for 95% of the 25,000 companies in the European medical device industry, while in the USA Stirling and Shehata (2016) report that 80% of the 6500 companies in the medical device sector are small (less than 50 employees).

Smaller companies are nimble and responsive, with a tremendous tolerance for uncertainty and are therefore well suited to be the source of innovation for medical devices. It is the smaller companies that drive a substantial portion of true industry innovation, yet the Institute of Medicine (2001) states that historically out of approximately 6 ideas, only one device will make it to commercial success. An organic advantage by any company is attained by leveraging their knowledge or IP. The Institute of Medicine (2001) asserts that in a global business environment, the small incubators of technology are particularly challenged with respect to increasing financial pressures.

Many small companies lack the infrastructure required to meet worldwide regulatory and marketing activities. The larger companies have an ability to assist with the delivery of innovative technology created by the smaller entities through exchanges such as acquisition, joint ventures, strategic partnerships, contract research, licensing, and royalty agreements (IOM 2001). Large medical device companies have the ability to bring scale to the challenge of globalization and successful product development. The key factors that determine product investment, demand, and eventual commercial success are whether the device is reimbursable or not and the quantum of that reimbursement.

The success of a medical device requires both strategic and coordinated planning. It must be followed by a timely execution of stakeholder-specific promotion, information, and development plans. The most innovative and/or inventive medical devices may never establish commercial success if there is a failure to constrain costs or convince stakeholders of that new technology's increase in value. This was illustrated by the familiar case of the Charité Artificial Disc Replacement (Textbox 5).

The Charité Artificial Disc was originally developed at the Charité University Hospital in Berlin, Germany, in the mid-1980s by leading spine specialist Professor Karin Büttner-Janz and Professor Kurt Schellnack. In 2003 DePuy Spine acquired the Link Spine Group, Inc. for $US325 million gaining exclusive worldwide rights to its principal product, the SB Charité Artificial Disc (Arida et al. 2006). The Charité was FDA approved in October 2004 as an alternative to spinal fusion surgery. While pre-launch, physician and patient dynamics were strongly in DePuy's favor, it did not suppress the negative response from hospitals and payers alike. With strong payer resistance and little hospital and provider enthusiasm, Charité sales waned. In 2006, DePuy announced plans to release 5- and 10-year data

in the future for the Charité (Johnson and Johnson 2006) in the hope of reviving the prospects of what was a revolutionary advance in the spinal device sector.

Textbox 5 Innovation and Reimbursement: A Case Study

The Charité Artificial Spinal Disc was once viewed as revolutionary surgical technology. In October 2004 Charité was the first total disc replacement (TDR/ADR) on the market to receive US regulatory approval and be commercialised for the anterior replacement of diseased lumbar discs.

At the time of a 2006 report by Arida et al. (2006) "The Charité: Lessons in the Launch of a New Medical Device," Charité's commercial success was in doubt. Charité had failed to convince the third-party payers that its use should be covered and reimbursed. On the 14 August 2007, the Centers for Medicare and Medicaid Services (CMS) determined that lumbar artificial disc replacement was not reasonable and necessary for the Medicare population over 60 years of age. CMS further determined that for those Medicare beneficiaries less than 60 years of age, there was no national coverage determination, leaving coverage decisions to be made on a local basis (CMS 2007). Payers cited a lack of evidence that the Charité was as effective as promoted. Follow-up clinical evaluations of the device and the complexity of the surgical procedure cast further doubts about its safety and effectiveness (Sparks et al. 2011).

According to Sparks et al. (2011), the Charité device did not become a physician preference item, and its adoption was actively opposed by purchasing departments and other administrative decision-makers. Summarizing the reports of Arida et al. (2006) and Sparks et al. (2011), DePuy failed to support Charité's launch and subsequent commercialization in the following critical areas:

1. *A disconnect occurred between Text the devices positioning as an alternative to a modern spinal fusion method where the clinical trial supporting this claim was a non-inferiority claim comparing Charité to the BAK cage, a somewhat controversial procedure that had been largely discontinued due to poor outcomes.*
2. *The Charité was priced around US$11,500, approximately 2.5 times that of the BAK cage and BMP (US$4500 each), without securing new procedural codes at or before launch. At that time the Charité was being sold in Australia and Europe for US$4500–$5000. DePuy did not possess a proactive strategy or economic data to prove this but relied on patients, physicians, and advocacy associations to push for reimbursement.*
3. *DePuy largely ignored the role of worker compensation insurance carriers in influencing other payers by not studying the long-term effects of Charité on return to work and productivity gains. A clinical paper was also released in 2004 as a result of the 2003 landmark study "Total Disc Replacement for Chronic Low Back Pain…," which concluded that there was no definitive clinical evidence that disc replacement surgery was efficacious or resulted in fewer adjacent segment problems. The net effect created scepticism in the surgical community over the true clinical value of arthroplasty.*

Sparks et al. (2011) summarize that DePuy did not fully appreciate that the conventional clinical endpoints used to secure regulatory approvals are not necessarily the outcomes that the payer uses making coverage decisions nor the outcomes hospitals use for purchasing purposes. DePuy did not build the body of evidence necessary to establish comparative safety and effectiveness of Charité with payers and

(continued)

physician groups alike (Sparks et al. 2011). Without coverage and clinician support, hospitals were not able to justify the purchase of the Charité device for both cost and coverage reasons, and this very inventive and innovative device failed commercially.

Conclusions

Society places a premium on the delivery of innovative technologies to ensure optimal healthcare. Patients are educated, informed, and interested in their health treatment choices and the outcomes associated with that choice. However, to deliver high-quality innovative technologies, it takes an increasingly substantial investment of time and cost to meet stringent regulatory and payer requirements.

End reimbursement and regulatory obligations are the factors which decide whether a new medical device will succeed or fail. There is no doubt, despite greater knowledge, innovative devices are under increasing regulatory scrutiny, escalating development costs and declining reimbursement. Authentic innovation and invention in the spinal devices sector have slowed down substantially. The spinal device industry is saturated with creative differences or "me too" products that fall within the least burdensome "predicate," "equivalent," or "grandfathering" application processes.

The upcoming European texts defining what constitutes the regulatory requirements of a new or existing medical device will have a profound impact on the innovation pipeline. The challenge for a medical device company to fulfil the criteria for novelty, superiority, and cost-effectiveness while also fulfilling the increased regulatory principles of safety and efficacy will become increasingly difficult. The ultimate impact of regulation on innovation will be viewed empirically. The balance between innovation-inducing factors and the compliance costs generated may differ on a case-by-case basis. Additionally the amount of time required to satisfy regulatory requirements will be essential to enable future innovations.

The investment required to obtain approval will no doubt change, with a profound emphasis on implantable medical devices and small entrepreneurial businesses. The work required to obtain a CE mark under the new EU MDR will place a heavier emphasis on solid clinical dossiers, premarket, and post market, both for new products and iterations of existing products. The assessment process inevitably will take longer than it does today.

This constitutes a concern for device companies who invest huge resources to release a device to market and clinicians who strive to deliver superior technology to their patients. Even after successful clinical data is obtained, the ultimate financial result of investment may be questionable, since payments for products and services through reimbursement mechanisms are not guaranteed.

Accompanying the ratification of the EU MDR is an expectation that a number of intended positive outcomes will transpire. With prodigious access to information, the clinician and the patient are well informed of negative medical device reports such as the incidences presented in Textbox 4. The increased regulatory requirements of the MDR may restore patient and clinician confidence in the medical device industry, ensuring trust in both the quality and the safety of the product. Compliance with these new regulations is predicted to be onerous, costly, and distracting; however all involved with the delivery of healthcare should be reminded of the ultimate goal – better patient safety and quality of product. Investment in transparent clinical processes, better traceability, and the ability to better contain adverse events involving medical devices can only be a positive step toward industry endurance.

The challenge for all stakeholders in the global device market is to craft a standard for policy, reimbursement, and regulatory provision that protect both patient safety and efficacy while carefully preserving incentive to induce the delivery of innovative and inventive technologies.

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Anterior Lumbar Spinal Reconstruction

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Abstract

The anterior lumbar approach for spinal pathology is a powerful method to achieve reconstruction. It enables wide discectomy, restores disc and neuroforaminal height, optimizes sagittal alignment, and affords large cross-sectional area of endplates for spinal implants while avoiding neural retraction and posterior muscular damage. It is arguably underutilized given the need for a considerable volume of training and need for comfort with abdominal anatomy and vascular handling that is required in its safe application. The preparation of a patient and surgical setup as well as common techniques for anterior lumbar surgery are described in this chapter. Knowledge of assessment techniques and handling of vascular structures in their normal, anomalous, and pathological states is critical for safe and efficient performance of the procedure. Equally, recognition of vascular problems and measures to deal with them enables spinal surgeons to safely expand their indications for this technique which is aided through a multidisciplinary approach and collaboration with a vascular surgery service.

Keywords

Anterior lumbar interbody fusion · Total disc replacement · Hybrid · Retroperitoneal · Transperitoneal · Vascular anatomy · Atherosclerosis · Vascular injury · Vascular repair · Ureteric injury · Combined vascular and spinal reconstruction

Introduction

The anterior approach offers a number of advantages over the other interbody access techniques currently being utilized. The exposure from L1 to S1 vertebral bodies is possible from the direct anterior transperitoneal approach, the midline rectus splitting approach, the para-rectal splitting retroperitoneal approach, and the oblique and lateral approaches. This provides the surgeon access to the disc and vertebral bodies for multiple indications. The decision about which approach is applicable is dependent on many variables that will be discussed in the review. As such, the anterior approaches that are available provide considerable versatility to treat a variety of pathologies with proven therapeutic success.

Spine surgeons around the world are utilizing the anterior approach to treat pathologies in the anterior column. The incidence of anterior procedures has increased substantially since the publication of multiple Food and Drug Administration class I randomized clinical trials on the results of total disc replacement (TDR) and anterior lumbar interbody fusion (ALIF) that recognized that patient-related outcome measures were improved dramatically and show no signs of decay (Gao et al. 2011). This advance in fusion techniques and the maturation of the therapeutic utility of total disc replacement has led to the increased need for the anterior exposure of the lumbar spine. Most spine surgeons perform their own approaches to the cervical spine but few perform their own approach to

the lumbar spine, instead utilizing "access surgeons." There are two main reasons: The first is the fear of the complications, particularly vascular injury, and the second is the variable and low quality of training provided in the orthopedic and neurosurgical training programs with respect to anterior access, techniques, and utility.

Anterior access requires the surgeon to be familiar with intra-abdominal, retroperitoneal, and vascular anatomy and its variances. Thorough preoperative review of the vascular anatomy is essential, as is the ability to provide a safe mobilization or dissection of the vasculature and ability to repair vascular injury should it arise.

One author has been performing their own access to the spine since 1996 with over 5000 approaches, the majority via the midline rectus splitting retroperitoneal approach (Holt et al. 2003). The indications and pathologies that he has treated have expanded over time such that in complex cases, he utilizes the knowledge and skills of a senior vascular surgeon who has had over 35 years' experience in vascular surgery. The involvement of a vascular surgeon in spinal surgery for the inexperienced surgeon contributes to the efficient and immediate repair of vascular injuries. Hamdan et al. (2008) stated that while exposure to the lumbar spine can be readily accomplished via a retroperitoneal approach, minor vascular injuries during exposure, mostly venous, are not uncommon. Most are easily repaired but occur more frequently when L4-5 is part of the exposure and less commonly when L5-S1 alone is exposed. Major injuries occur in less than 2% of patients.

As the surgeon's volume performance threshold increases (Regan et al. 2006), there is a natural expansion of indications to treat complex deformity, tumor, infection, revision anterior procedures at index, and adjacent levels ranging from patients with pristine vessels through to patients with combined multilevel degenerative disc disease and complex vascular pathologies (calcific atherosclerosis and aortoiliac disease). The vascular surgeon can provide expertise with endovascular techniques such as angioplasty and stenting and open techniques such as repair, endarterectomy, and bypass.

Indications

Anterior reconstructions provide biomechanical support by stabilizing the anterior column. This stabilization can now be performed by static and/or dynamic technologies (Scott-Young et al. 2018a). The common indication for anterior reconstructions is for degenerative conditions that have been recalcitrant to conservative therapeutic modalities (Fritzell et al. 2001). These include discogenic pain secondary to degenerative disc disease (DDD) and internal disc disruption (IDD) (Sehgal 2000). Other degenerative conditions include degenerative spondylolisthesis, isthmic and dysplastic spondylolisthesis, DDD with large herniated discs with verified radiculopathy, post discectomy recurrence and instability, iatrogenic instabilities following posterior decompressive procedures, degenerative de novo scoliosis, and anterior reconstruction for pseudoarthrosis following failed posterolateral, transforaminal, and lateral fusions.

Rare and "red flag" conditions that are commonly treated include vertebrectomy for tumor, trauma, and infection. The treatment of flat back syndromes, deformity, and congenital abnormalities to restore sagittal and coronal balance are often best treated with anterior reconstructions whether it be at single or multiple levels (Kim et al. 2017). The spino-pelvic revolution (Labelle et al. 2005) has enlightened the spine community on its relevance and importance. The sagittal plane can be considered as an open chain of interconnected segments from head to pelvis. The shape and orientation of each segment are closely related and influence the adjacent segment biomechanics (Roussouly et al. 2011). Hence, the enormous influence that consideration of sagittal balance is having on spinal surgery (Labelle et al. 2005).

Benefits

There are many benefits in having anterior surgery skills as part of a surgeon's armamentarium. The approach allows access and treatment of disc pathologies, vertebral pathologies, and multiple levels. It is a powerful tool because it enables a

complete or near-complete excision of the disc and therefore access to the anterior cauda equina. This thorough discectomy allows for removal of herniated discs, extruded disc material, and sometimes sequestered fragments and minimizes any residual pain generators at the posterior disc-annular complex. Complete vertebral body removal for trauma, deformity, tumor, and infection is also possible. This can then be followed by reconstruction where the cage, allograft, or autograft is placed under compression. The endplate provides a large and strong cross-sectional area for supporting the reconstruction that is not afforded by the other approaches.

The anterior approach historically has been performed throughout the twentieth century and was originally used to treat Pott's disease (Ito et al. 1934). Originally, it involved a large transperitoneal approach to access the spine and would require longer recovery times. Modern anterior approaches recognize the importance of minimizing collateral damage (Fraser 1982) and as such more minimally invasive (Ito et al. 1934) or minimally destructive approaches (Ruey-Mo et al. 2008) have been developed. These incisions are limited to between 5 and 8 centimeters, generally subumbilical and utilize the retroperitoneal space to gain access to the anterior spine (Watkins and Watkins 2015). This allows a direct view into the disc space, thus facilitating proper and complete discectomy and annular release. The anterior approach is the optimal approach to allow correct positioning of the device in the midline. The goal is to maximize the size of the device in the medial lateral and anterior posterior plane. This generally minimizes eccentricity and subsidence while maximizing bone integration interface to the implant or the graft. It also allows direct visualization of the posterior annulus and posterior longitudinal ligament and one can release these tissues and thus decrease the incidence of "fish mouthing." While correct release, balancing, and positioning are important for ALIF interbody devices, it is especially important for disc arthroplasty where point loading and abnormal force transmission can result from incorrect sizing and placement.

It provides the surgeon and patient opportunities for a dynamic or static stabilization reconstruction for most symptomatic disc pathologies. DDD has been shown to cause significant morbidity and after identification of the symptomatic disc(s) they can be reconstructed with anterior lumbar interbody fusion (ALIF) or total disc replacement (TDR) (see Fig. 1). The approach can be performed via a muscle splitting incision (rectus interval) and avoids the muscular collateral damage that is associated with the other approaches. There is no devascularization or denervation of the erector spinae muscles that results from posterior approaches or damage to the psoas muscle that results from the direct lateral approach. This allows for significant reductions in patients' back and leg pain which, in turn, improves patients' function and quality of life. There are generally a shorter hospital stay, less morbidity, and faster recovery. Pradhan et al. (2002) compared ALIF and posterior fusion and found there were less blood loss and reduced transfusion rate, operative time, and hospital stay for patients with anterior fusion procedures.

The access to the anterior structures facilitates complete disc clearance and, with that, the ability to correct deformity and decompress the neuroforamen through disc height restoration. Other benefits include direct or indirect decompression of the neural elements centrally, laterally, and in the neuroforaminal region. In addition, powerful restoration of sagittal balance can be achieved anteriorly.

From a mechanical perspective, addressing the anterior column is a sound strategy in that it transmits a relatively high proportion of force and body weight and has reduced risk of subsidence from the large surface contact afforded in graft placement (see Fig. 2). When used as a stand-alone strategy, there are the additional benefits to the patient of avoidance of posterior soft tissue envelope violation or of neural retraction.

It cannot be emphasized enough that the majority of pathologies occur from diseases in the anterior column. Therefore, it is imperative that every certified spinal surgeon be able to use this access to effectively treat the patient's pathologies. By preserving the posterior and lateral paravertebral muscle and avoidance of facet joint dissection or violation as well as by restoration of disc height

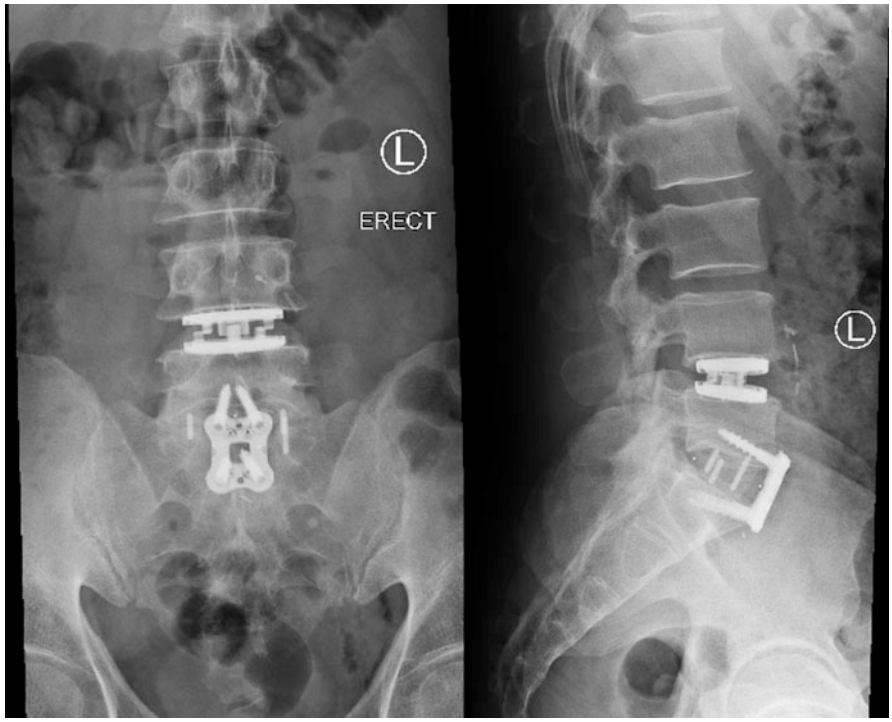

Fig. 1 The anterior approach allows efficient performance of either ALIF, TDR, or a combination of both (hybrid) procedure. Above is an example of a lumbar hybrid procedure with a constrained TDR at L4-5 and an ALIF construct at L5-S1

and lordosis, the incidence of later adjacent segment disease is also reduced. Posterior and lateral procedures do not regularly or predictably restore the disc height and lordosis. Thus, the patient is fused in a kyphotic position and their dynamic stabilizers (erector spinae) that pull them into extension are damaged.

The modern anterior approach has matured and is justified as an alternative for decompressing neural elements, alleviating instability, relieving intractable mechanical back and leg pain, and restoring functionality to the patient or addressing "failed back syndrome."

Contraindications

Contraindications can be classified as absolute and relative. Every patient should undergo a thorough medical and surgical assessment to assess any surgical and/or medical risks in the operative and perioperative period. The history and examination, focusing on cardiac and pulmonary risks, and determination of the patient's functional capacity are essential. The administration of an anesthetic and a surgical procedure is associated with a complex stress response that may present problems in the postoperative period. Assessment of the patient's overall health status is required. This incorporates referrals to specialists to investigate and treat any relevant conditions prior to surgery.

The history should include past and current medical and surgical history, current medications, allergies to drugs, and use of recreational drugs and tobacco use. Height and weight, particularly girth, is important to assess and treat prior to anterior surgery. Patients with a body mass index (BMI) greater than 25 are considered overweight, those greater than 30 are considered obese, and a BMI greater than 35 is considered morbidly obese. Patients who are obese can provide access difficulty and have higher risks and complication rates. These include hernias, wound infection and dehiscence,

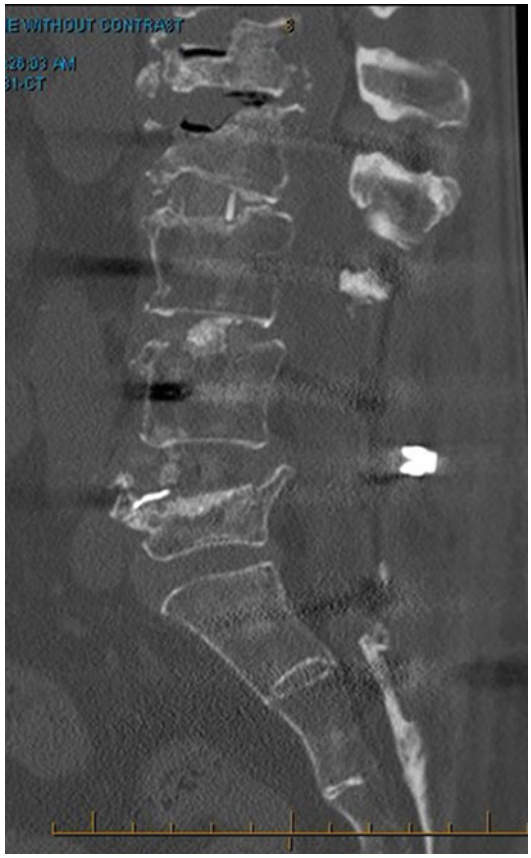

Fig. 2 Example of limitations of laterally placed interbody cages not only from limited endplate visualization and disc space balancing but through limited surface area. Failure of the construct is demonstrated here through multiple endplate/vertebral body failures in a susceptible patient

longer operative times, longer hospital stays, higher incidence of deep venous thrombosis (DVT), and possibly less successful outcomes secondary to these issues. Puvanesarajah et al. (2017) reviewed the obese and morbidly obese patients undergoing spine fusion and found that they are at significant risk of major medical complications, wound infections, and 30-day readmissions. Both groups had a longer length of stay and hospital costs. The obese have to be counselled about these risks and be active participants in weight reduction programmes.

Pregnancy, infection, severe osteoporosis, metabolic bone disease, chronic steroid use, multiple prior abdominal surgeries, implant or metal allergies, and severe psychological disorders, to name a few, are probable absolute contraindications to anterior reconstructions. Relative contraindications include any issue that may impede access or mobilization of the vessels. Therefore, conditions such as obesity, intra-abdominal scarring, retroperitoneal scarring, calcific atherosclerosis, abdominal aortic aneurysm, and prior vascular surgery need to be reviewed with respect to risk-benefit analysis. Complex vascular pathologies can be managed but require a multidisciplinary medical and surgical assessment prior to performing these complex surgeries.

Biomechanical Rationale

The basic mechanics of interbody cage fixation have been well investigated (Panjabi 1988). The strength and stability of a construct are important concepts to understand when reconstructing the anterior spine. The strength relates to the absence of structural failure of either the implant or endplate bone. The stability relates to the lack of motion between adjacent vertebrae, which is important to facilitate bone ingrowth and eventual fusion (Jost et al. 1998).

Gerber et al. (2006) found in a comparative cadaver biomechanical study that an anterior screw-plate and pedicle screws-rod constructs both substantially reduced range of motion and increased stiffness compared to stand-alone interbody cages. There was no significant difference in the amount by which the supplementary fixation devices limited flexion, extension, axial rotation, or anteroposterior shear; pedicle screws-rods better restricted lateral bending. This stability can be enhanced by insertion of ALIF cages with larger anterior/posterior dimensions and broader widths. This has the added benefit of less eccentricity and subsidence. The bone density probably plays an important role in reducing subsidence, as does the location of the cage on the endplate. Steffen et al. (1998) recommended more peripheral ring apophyseal contact was best from a biomechanical and biological perspective.

Cunningham et al. (2002) found that in the treatment of spinal deformities, structural interbody support probably is the best method to minimize longitudinal rod and screw-bone interface strain.

Moreover, anterior load-bearing structural grafts and interbody devices have been shown to increase construct stiffness, decrease the incidence of posterior implant failure, permit the use of smaller diameter longitudinal rods, and enhance the rate of successful spinal arthrodesis. The study reinforces the principles of load sharing between the anterior and posterior spinal columns and affirms the biomechanical dominance of anterior column support in circumferential spinal arthrodesis.

Watkins et al. (2014) compared anterior, transforaminal, and lateral interbody fusion techniques to determine which is most effective for restoring lordosis, increasing disc height, and reducing spondylolisthesis. They found improvement of the lordosis was significant for both the anterior and lateral groups, but not the transforaminal group. Intergroup analysis showed the anterior group had significantly improved lordosis compared to both the other groups. The anterior and lateral groups had significantly increased disk height compared to the transforaminal group. Hsieh et al. (2007) similarly found that ALIF is superior to TLIF in its capacity to restore foraminal height, local disc angle, and lumbar lordosis.

Preoperative Assessment and Preparation

Preoperative assessment and preparation of a patient for anterior spinal reconstruction should reliably and accurately identify those patients in whom operative intervention is indicated and any features in their presentation that need to be addressed or considered to make surgical intervention safe and feasible. We shall focus mainly upon the indication of treating DDD as it is by far the most common disorder.

Diagnosis

A diagnosis of symptomatic degenerative disc disease with or without radiculopathy (the most common indication for operative intervention) is usually made with history and clinical examination. A classical history of axial pain that worsens through the day and with prolonged sitting, bending, standing, or lifting that is relieved with recumbence is suggestive of IDD (Lee et al. 2016). There may be associated leg symptoms that suggest radiculopathy from a nerve root involvement due to disc herniation or multifactorial loss of neuroforaminal height (Lee et al. 2016). The clinical picture is then supported by investigations that may include typical imaging findings (degenerative bony changes on radiographs and disc degeneration with or without Modic (Modic et al. 1988) changes observed on MRI), MR spectroscopy, nerve conduction studies/electromyography, and provocative discography.

Preoperative Evaluation

Findings on the history and clinical examination that should be sought in anticipation of any contraindications to surgery or difficulty in the perioperative period include the patient's height and weight (obesity), any smoking or systemic illness that could affect healing or bone quality (e.g., osteoporosis, poorly controlled diabetes, steroid use), any coagulopathy/anticoagulants or prothrombotic tendencies, and any previous intra-abdominal surgery or conditions. Osteoporosis can be difficult to reliably quantify but a focused history and examination with investigations such as DEXA scan or fine-slice CT assessing the architecture and Hounsfield units can be suggestive of a patient that may require delay in spinal reconstruction until bone quality is sufficiently improved with medical treatment.

Screening clinically for any peripheral vascular disease (i.e., pulses), poor nutrition with sarcopenia, or any systemic illnesses (e.g., features of rheumatoid arthritis, vasculitis, or connective tissue diseases such as Ehlers-Danlos and Marfan's syndrome) is imperative. A physician to screen and optimize high-risk patients and provide a perioperative management plan is particularly useful in this regard.

Surgical Planning

In our practice, plain erect radiographs of the entire spine have been largely superseded by the use of low-dose radiation EOS™ scanning. This enables determination of all relevant sagittal, coronal, and

rotational parameters that need to be considered when planning a reconstructive strategy. A quick assessment of the pelvic parameters (pelvic incidence, pelvic tilt, sacral slope), the type of lordosis (I-IV) (Roussouly et al. 2005), and the positioning of C7 plumb line can be done to assist in planning a reconstruction strategy. EOS™ also allows for rapid calculation of the current L5-S1 disc segmental lordosis by subtracting the L1-S1 lordosis from the L1-L5 lordosis.

Restoration of the sagittal balance is the best way to obtain a good result no matter the technique (dynamic, static) or the pathological situation. The only morphological parameter that is constant throughout life is the pelvic incidence (PI). How much the present position of the spino-pelvic complex is in its anatomical position and how much is in its pathologic or functional adaption is difficult to assess (Barrey et al. 2011). When treating patients with a low-grade PI (type I or II) no unnecessary lordosis is required for reconstruction. In patients with higher PI (type 3 or 4) more lordotic augmentation should be considered. Essentially, every spinal reconstruction requires preoperative classification (Roussouly et al. 2005). Patients with hyperlordotic lumbosacral junctions and a high PI can cause difficulty in accessing the disc space given the trajectory and position in relation to the pubic symphysis (see Fig. 3). Flexion and extension films may be useful in revealing the extent of dynamic sagittal instability in the case of spondylolisthesis.

Computed tomography (CT) scans are obtained in the case of any abnormal bony morphology or defects and can help assess the bone quality (relevant to the feasibility of a stand-alone strategy and/or need for augmentation) and status of the facet joints when considering arthroplasty versus arthrodesis for a particular motion segment. For segments that appear close to ankylosed, gas in the disc space indicates movement that can aid in decision-making regarding which levels to include in the reconstruction. CT angiogram has become the standard of care for any multilevel or complex reconstruction to better define the vascular anatomy preoperatively so that any variations or difficulty can be anticipated. This will be further discussed in special vascular cases.

MRI reveals the status of the intervertebral space (quantifies amount of collapse and Modic changes) and surrounding neural structures but

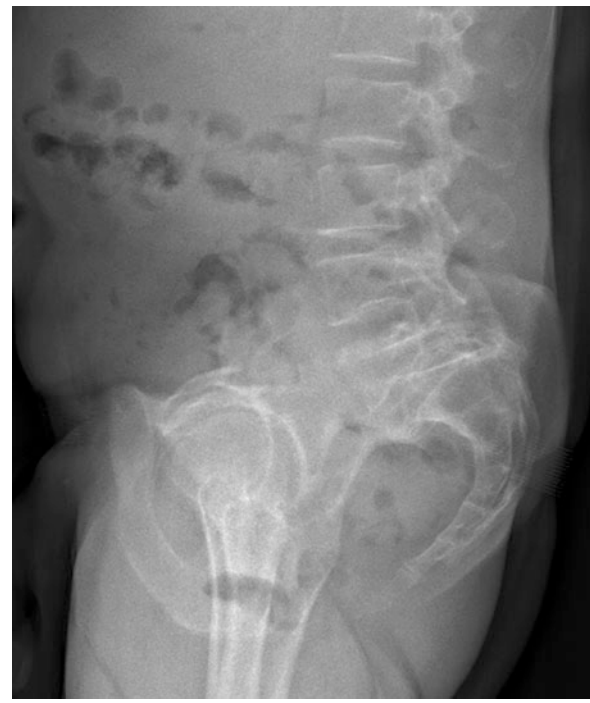

Fig. 3 Example of potential difficulty in anterior access to a L5-S1 disc in a case of dysplastic spondylolisthesis due to obliquity and relation of the disc space to the superior pubic symphysis

also the quality of the posterior elements and paraspinal muscles. This is relevant in deciding the need for retrieval of disc fragments in the canal from anteriorly or for a posterior decompression in addition to an anterior reconstruction in the case of tight multifactorial stenosis. MRI in the axial plane also reveals the presence of a fat plane behind vascular structures or, alternatively, any adhesions to an inflammatory disc.

Provocative discography gives information regarding the contribution of discs to the patient's symptomatology and should generally be performed by an independent third party assessor to exclude or include a questionable motion segment level in a reconstructive strategy (i.e., that particular level is responsible for minor or no symptoms).

Patient Optimization

Infection or bony failure in these cases with complex prostheses would be a disaster and prevention through host optimization is mandatory. Patients need to maximize fitness with maintenance of excellent nutrition including sparse amounts of sugar and simple carbohydrates but adequate protein and vitamin intake (especially vitamin C and complex B). Having optimized "protoplasm" will also favor efficient bony and soft tissue healing. In many cases dietary weight loss is mandatory not only for facilitating exposure but minimizing soft tissue and wound complications. Equally, a frail patient with sarcopenia may benefit from an appropriate strengthening and gentle aerobic program to combat osteopenia as well as higher caloric and protein intake.

Procedure

Pre-incision Setup: Equipment and Personnel

- A large well-illuminated theater and operative headlights are recommended given difficulties in adequate deep abdominal visualization that are associated with standard lights.
- We recommend the use of a Jackson Pro Table Mizuho OSI™ with capability for anterior and posterior approaches (see Fig. 4). Side brackets are placed to enable mount of the abdominal retractor system of choice. The bed is placed in a Trendelenburg position so that gravity allows the intra-abdominal contents to migrate cephalad and pillows are placed under the patient's knees to relax psoas and minimize popliteal compression syndrome.
- A large abdominal retractor is mandatory. We use a modified Thompson retraction system with multiple radiolucent blade variations whose design facilitates attachment and securing at different depths and angles. Alternatives are Omni-Tract™ and Bookwalter systems. A pin insertion (e.g., AUS) or related system for keeping the vessels positioned away from the working corridor is required (see Fig. 5a, b).

Sutures and Needle Holders for Vascular Repair

- 5/0 prolene sutures are on hand to close any cuts or tears as they occur. Smaller than this, the needles are impractical for the control and maneuver in this area of tissue.
- Make sure your vascular needle holders are strong and the teeth and ratchet not worn. In the setting of a large hemorrhage to discover faulty equipment is unsatisfactory.

Vascular Clips and Vascular/Urological Disposables

- Hemoclips also can be used after appropriate clearance of areolar tissue but the surgeon should be aware that they can be displaced by any traction required to mobilize large vessels (see Fig. 6a, b). These are best used prophylactically after isolating and skeletonizing the vessel. They can also be used as an immediate response to small vessel injury with suture as a later step. There are also some well-suited angled clamps which will control the vein edge until a suture is placed and we have these available on all the spinal trays (see Fig. 6).

Fig. 4 Examples of Jackson-type table head down in picture above (**a**) and trays of retractors and instrumentation required in pictures below (**b**–**c**)

- Vascular stents, balloons, and equipment for vascular repair or reconstruction should be available and may be deployed prophylactically, depending on the complexity of the case.
- Ureteric stenting equipment for performance by a urologist is in place for revision cases.

Personnel

- A well-trained and organized theater team is conducive to optimal results. This includes cooperative theater staff, instrument nurses, operating theater technicians, spinal and vascular trained anesthetists, prosthetic device representatives, and office and hospital surgical planners who ensure that a full range of required equipment is available and that the team is well prepared for any unexpected events.
- A Cell Saver™ autologous reinfusion provider is present for all cases.
- An assistant or surgeon skilled at patient positioning, control, and respect for vascular structures and assistance with preparation of interbody grafts facilitates theater safety and efficiency.
- Recovery nurses adept at neurological and vascular observations eases detection of

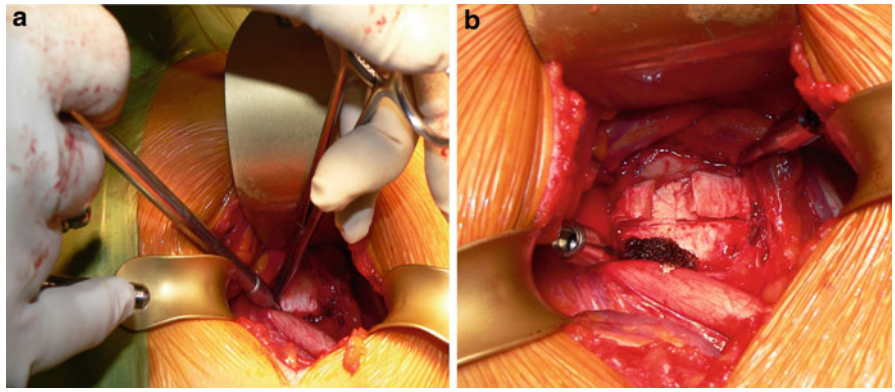

Fig. 5 Exposure of a disc space achieved with use of removable vertebral body pins, in this case AUS pins inserted by mallet and a threaded T-handle, to achieve continued retraction adjacent to a disc space. Insertion under visualization and protection from a peanut retractor (**a**) and sustained retraction for disc access (**b**)

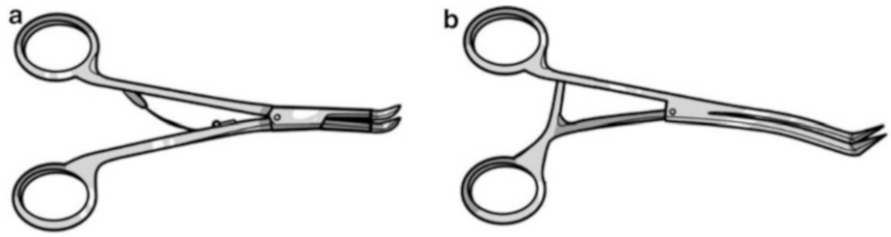

Fig. 6 (**a**) Example of hemoclip applier and (**b**) angled clamp for hemorrhage control

any unexpected immediate postoperative events.

- High dependency or intensive care ward care is recommended for complex procedures or procedures in high-risk patients.
- An inventory and equipment tray layout that not only allows anterior reconstruction but also allows for posterior procedures and vascular repair is mandatory.

Preoperative Setup: Preparation of the Patient in the Perioperative Setting

Skin Care and Preparation

- Preoperative skin care by the patient is the starting point for a successful approach by using appropriate washing and antibacterial soap in the time leading up to the operative dates. Hair should be clipped but not shaved to prevent integument compromise and, in theater, once upon the operating table the patient's skin should be scrubbed and dried. We use Betadine™ antiseptic liquid with the hand sponge from the scrub bay. Then alcoholic Betadine™ solution is used covering the whole area likely required for access including the inguinal areas. The rationale is that rarely one may require access to the vessels for stenting purposes. The skin must then dry before draping and a final cover of the wound is completed with iodine-impregnated adhesive plastic drapes (Parvizi et al. 2017).

Prophylactic Antibiotics

- Usually 2 grams of Kefzol (or an equivalent first-generation cephalosporin) is given on call of the patient to theater and coordinated so that it is in effect at the time of incision. Vancomycin or teicoplanin are considered for high-risk patients.

Anticoagulation

- The strategy is both mechanical and pharmaceutical. Enoxaparin 40 mg subcutaneously is given the evening before the procedure as a

routine. Other anticoagulants are stopped as is reasonably safe in conjunction with the advice of a physician. Positioning of pillows under the knees reduces popliteal obstruction syndrome. The addition of intraoperative calf compression pumps is continued till the next day. TEDS stockings are also worn in the perioperative period until the two-week follow-up.

Elimination

- An indwelling catheter is placed to decompress the bladder, enabling more efficient access, but also enabling monitoring of fluid output and patient comfort while having limited mobility. For retroperitoneal approaches the addition of bowel preparations is not routine, but is recommended to reduce fecal loading for transperitoneal approaches.

Autologous Reinfusion

- Cell Savers™ are set up to be used for all spinal and major vascular procedures so that there is a capability to infuse the patient's own blood in the event of unexpectedly large loss.

Patient Anesthesia and Monitoring

- An array of monitoring of general anesthesia and hemodynamic status including arterial lines is typically instituted.
- For complex deformities, intraoperative neurological monitoring is employed if osteotomies or manipulations are planned posteriorly at the same anesthetic.
- Some surgeons like to utilize an additional Doppler oxygen saturation probe on the left toe to monitor any ischemia caused by arterial retraction.

Intraoperative: Approach for Anterior Reconstruction

Approaches with a Focus on Vascular Access

Once the decision to proceed to surgery is made then the access method to be employed, whether left or right retroperitoneal (LR or RR) or transperitoneal access (TP), needs to be carefully considered. This is really a choice relating to minimizing trauma, safety in mobilizing vessels, and achieving satisfactory exposure to enable completion of the intended reconstruction. Deciding on which approach to utilize in the revision or previous abdominal approach setting has further challenges and presents a unique situation to consider. Generally, an approach to L5-S1 should be a right retroperitoneal. It should be via a rectus midline split and be kept low relative to the disc trajectory. This facilitates future left-sided approaches for adjacent segment disease should it arise. Approaches to L4-5 can be performed via a LR, RR, and TP. Generally, we would recommend a LR. The tip is to not dissect up or down as to minimize vessel or tissue trauma at adjacent levels. Approaches to L3-4, L4-5, and L5-S1 are via a LR if there are no vascular issues and if there is, then a TP approach is appropriate. Any 4 or 5 level approaches are via a TP approach. In every anterior case one should plan for a revision at the index or adjacent level in the preoperative workup. Therefore the approach needs to be atraumatic, direct, and possibly revisable.

A preoperative angiogram is only required if there is vascular pathology or variants in the anatomy that may present issues. Most vascular anatomical patterns and variants are obvious on CT scans and MRI. Always look for the presence of a fat plane under the vessels that will likely need to be mobilized, particularly the venous structures on the axial T2 images (see Fig. 7).

Retroperitoneal Approach

Nonvascular Anatomy

The primary nonvascular area of concern for the team is the genitourinary tract. On the left side, the ureter courses with its blood supply and the gonadal vessels until the ureter tracks medially over the iliac vessels at approximately the level of the common iliac artery bifurcation. More superiorly, the left kidney and its surrounding perirenal fat and fascia are encountered. Care must be taken when mobilizing the ureter to avoid devascularizing it with excessive

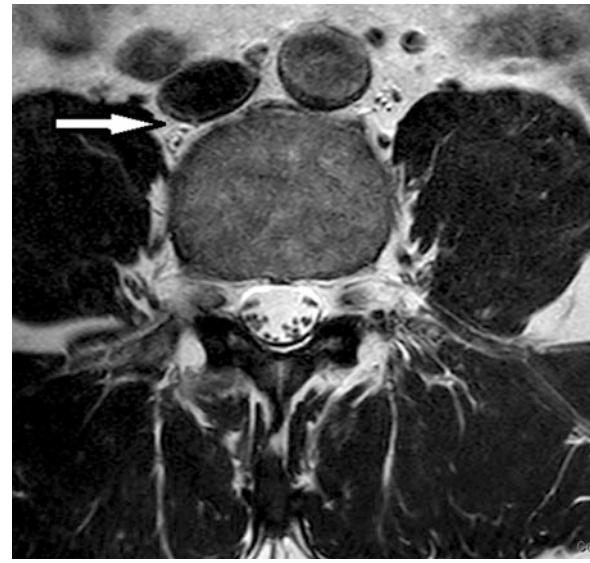

Fig. 7 Adequate fat plane visualized behind the great vessels (white arrow) prior to bifurcation as visualized at the inferior L4 vertebral body

dissection; this can be accomplished by maintaining the ureter with the peritoneum, to which it is adherent. Furthermore, knowledge of the peritoneal folds and space, basic colonic anatomy, and knowledge of the sympathetic nervous anatomy and how they relate to mobilizing the gastric sac en masse are mandatory (see Fig. 8). Details of vascular anatomy and anomalies are further discussed below.

Selection Philosophy

In general, where there is standard anatomy, non-atheromatous arteries, no major venous anomalies, and no previous retroperitoneal surgery, then the retroperitoneal approach is advantageous, with minimal gastrointestinal disturbance and satisfactory access to L5-S1, L4-L5, and L3-L4 levels.

The vast majority of routine cases require an approach to reconstruct three levels or less. The more major cases we have been involved with that required up to four and five levels of disc reconstruction with some cases needing 50 degrees of correction of lordosis are the exception rather than the norm, and we would typically favor a transperitoneal approach in this setting.

The usual approach for the most common problems at L5-S1, L4-5, and occasionally L3-4 is through an infraumbilical midline incision progressing extraperitoneal in the preperitoneum, behind the rectus, and progressing around and then back medially in front of psoas, in the retroperitoneum. This approach is typically limited more proximally by the renal vessels which appear at the L2 vertebral body. The usual approach involves the inferior mesenteric vessels being displaced forward and translated to the opposite side of the approach with the bowel sac. We start the dissection bluntly external to the peritoneum and progress laterally separating the peritoneum below the lower border of the rectus sheath. With experience division of the posterior rectus sheath is rare. The main action initially is using your left index and middle finger to gently peel away the peritoneal sac away from iliacus and then over the psoas muscles. In a single level L5-S1 approach we favor a right retroperitoneal approach as it preserves the option of a left-sided approach for any anticipated future proximal level disease surgery; conversely, in the case of pathology of two or more levels we favor a left retroperitoneal approach. Lift and shift the sac together with the ureter with your hand to the opposite side of the approach away from the iliac blood vessels and eventually the major arteries. The peritoneum is gently dissected bluntly off the vessels so they can be clearly visualized. The hypogastric plexus will move away with the peritoneum. Retraction using the table mounted retractors is then modified to display the vascular

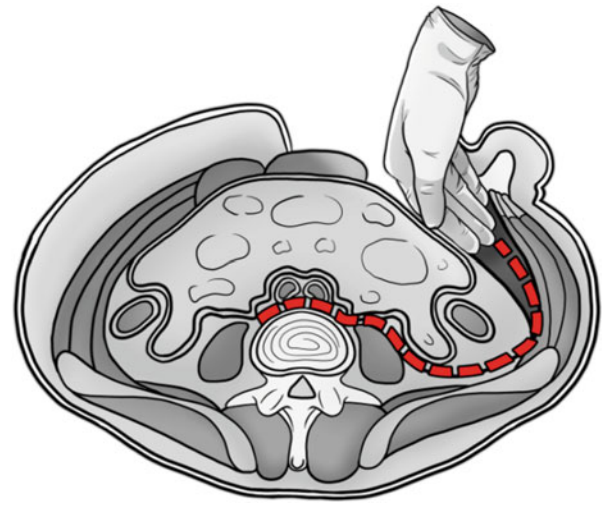

Fig. 8 Schematic of the path of the hand and dissectors around the retroperitoneum in the LR approach to the L4-5 disc. By exploiting the space and mobilizing the peritoneal sac with its contents and the ureter, safe exposure of the vessels and, ultimately, the disc can be achieved

structures and the underlying disc level that is going to be operated on.

Once the peritoneum and the hypogastric plexus have been reflected, one will encounter areolar tissue over the disc space and the anterior spinal artery and venous vessels. Tease with a peanut on a Roberts artery the areolar tissue just to the right of the sacral vessels to the lower right. Insert an AUS-style pin inferior to L5-S1 disc at its lateral margin aiming slightly toward the midline. Next insert a pin superior to the disc on its lateral margin of L5-S1 again aiming slightly toward the midline. These measures keep the right-sided vessels safely away from the surgical area. Ligate the midline sacral vessels and then get under the fat plane and gently mobilize the left common iliac vein up and to the left. Next insert the pin on the superior left of L5-S1. One can also insert another retractor pin on the lower left if needed. We favor the use of AUS™ pins to retract the vessels rather than handheld retractors. Care is needed at this level to avoid injury to the sacral venous plexus which can cause significant bleeding.

The approach to L4-5 is more complicated as the bifurcation of the aorta and the veins varies considerably and is usually closely associated. How the dissection is planned particularly depends on the venous anatomy as this is more compressible and at risk of avulsion and with careful wider dissection these can be mobilized well out of the way. In revision surgery, the fragile vein walls are liable to tears and penetration more easily as dissection is developed through the surrounding adhesive scar tissue.

In the younger patients below 55 years of age with minimal known risk factors, the vessel anatomy and positioning related to the planned operative discs and spinal levels can be deduced from the MRI studies. Often the plan of approach to L4-5 is defined as the dissection above L5-S1 progresses. It is necessary then to understand the options for exposure so that alterations to the exposure can be made – "on the hop" – as the need arises. According to Chiriano and colleagues (Parvizi et al. 2017), in a series of 405 anterior spine procedures, exposure of L4-L5 was able to be accomplished above the left CIA in 44% of cases, between the left CIA and CIV in 45% of cases, and below the left CIV in 11% of cases. An approach between the bifurcations is facilitated by a high location either at the L3 vertebral body or L3-L4 disc space, situations which occur in less than half of patients.

For the older patients it is not only the venous anatomy that is significant but there is increased risk in dealing with aging arteries affected by peripheral vascular disease. The surgeon needs to assess the possibility of problems associated with atheromatous vessels with unstable plaques, ulcers, lumps of medial calcification, displacement and tortuosity, stenosis, occlusion, or aneurysm disease; all of these may be encountered in the access to the operative level(s). The surgeons planning the operation

have to assess potential risks of arterial vessel damage, the likelihood of the type of damage, what measures to have in place to resolve problems at the time of surgery, and what to monitor postoperatively and for how long. Many vascular injuries are only detected very late because of limited understanding of the spinal surgeon, and a multidisciplinary approach to planning and assessment has a role here in reducing injury. For example, there are case reports of a major arterial occlusion such as the common iliac being overlooked for 2 weeks or an occlusion of the left common iliac vein for 2 years with the young patient presenting with severe stasis changes in the affected leg. Sachinder et al. (2011) reported on a series of 560 anterior spine exposures: five patients had arterial injuries; four were diagnosed more than 24 h after the operation with one on postoperative day 13.

The risks of manipulation of a calcified artery include fracture of plaque and dissection which can rapidly progress to vessel occlusion with limb- or life-threatening effects. With such dense calcification, safe compression and flexion of the vessel is not possible. It also should be recognized that aneurysms may be unstable and present the risk of rupture or they may be large and stiff enough to prevent access. On occasions the aortae and iliacs were occluded at the time of presentation. Patients presented with severe symptoms related to the disc degeneration and had proven radiculopathy in conjunction with their pain from vascular claudication. Before proceeding with anterior spinal surgery these patients need vascular surgical assessment.

Left-Sided Retroperitoneal Approach to L4-5 and L5-S1

A standard rectus splitting left-sided retroperitoneal approach to L4-5 and L5-S1 would be the most common and is explained here in detail. Other variants on this approach to access other levels described later use the same principles and techniques detailed below in other subsections.

It is best to palpate the abdomen once the patient is asleep on the table and be aware where the disc spaces are relative to the umbilicus and ASIS so that an appropriately placed incision is performed. The sacral promontory can often be felt by simple palpation. If there are any issues in regard to obesity or inability to palpate, then use of the image intensifier to verify the level and to optimize the trajectory of the incision and the approach to the disc is warranted. The usual incision is midline below the umbilicus. It is recommended that a larger incision be used for the obese who are sometimes brought in for surgery prior to any loss of abdominal girth that we can improve the access rather than encountering limited visualization and increased force of retraction through smaller wounds. With increasing fatty abdominal protuberance the wound may have to be extended to above the umbilicus which is typically unnecessary in patients with a BMI < 30. Given that we aim to improve the safety of the approach for patients, referral to dieticians and physiotherapists for weight loss advice is routinely performed. In some cases, where obesity is refractory over long periods to simple weight loss measures, patients are referred for weight loss surgery as a preliminary step to formal spine reconstruction.

MSY prefers to stand on the right side of the patient. The skin is incised and a diathermy is then used to dissect through the subcutaneous tissues to the rectus fascia trying to maintain full-thickness flaps to the level of the fascia (see Fig. 9a). A one centimeter incision in the rectus fascia is performed; then it is undermined with the left index finger developing the plane between the fascia and rectus muscle. The fascia is then incised with the diathermy distally and proximally extending beyond the skin incision so that you are funneling out rather than funneling in. The interval between the recti is usually identifiable with a fat plane that allows entry into the preperitoneum and by careful dissection, you can enter the preperitoneum on the left- or right-hand side depending on your approach (see Fig. 9b, c).

Next, a Langenbeck retractor is placed under the left rectus and one can see the inferior epigastric vessels travelling up to pass between the posterior border of the rectus and the superior surface arcuate ligament or posterior rectus sheath (see Fig. 9d). It is important not to disrupt these vessels, so use your right index finger to lift them gently off the preperitoneum and take the

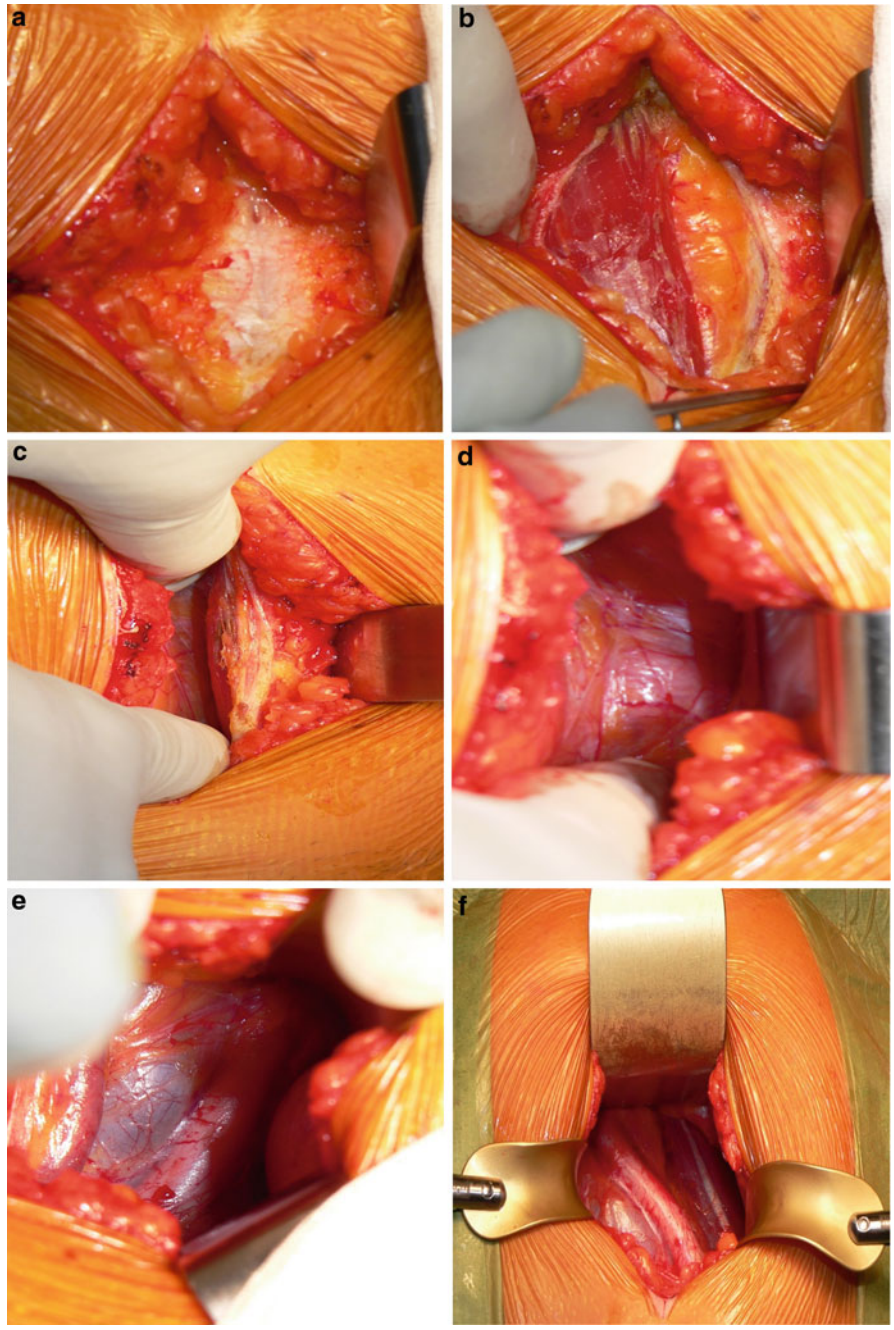

Fig. 9 (**a**) Development of full-thickness skin flaps to rectus sheath; (**b**) following incision of linea alba and posterior fascial incision, preperitoneal fat is revealed; (**c**) the window is expanded with use of fingers; (**d**) identification of superficial vascular leash (inferior epigastric vessels) for protection; (**d**) left Iliac vessels revealed after maneuver to mobilize peritoneum and peritoneal sac; (**e**) exposure of vessels overlying L4-5 following placement of malleable externally mounted retractors and mobilization of peritoneal sac/ureter

peritoneum down with your left index finger. Then, work below the inferior arcuate ligament or the posterior rectus sheath, often palpated as a "soft spot," and move toward the iliac crest. There is usually a small fat pad here that one can peel off the lateral and posterior wall essentially heading

toward the anterior superior iliac spine. Take care not to begin the dissection too deep and distal to the anterior superior iliac spine lest the iliac veins are placed at risk of an avulsion injury.

Slim, fit people can have little adipose tissue between the fascial planes, and the trick is to just persevere with use of the index and ring finger, carefully blunt dissecting the peritoneum off the wall. Once in the iliac fossa you can then peel the peritoneum off quite easily over the iliacus followed by the psoas muscle. Once the peritoneum is retracted to the medial border of the psoas, then place your right hand in the gap and then just peel the peritoneum further off the back wall on the psoas and gently roll the peritoneum off the posterior rectus sheath. This will prevent peritoneal tears. Perform this step gently and just roll your cupped or closed hand in the plane and you will feel it gently separate. The next step is to peel the peritoneum off the vessels. Usually, start down on the lumbar sacral junction. Take the peritoneum, the ureter, and the hypogastric plexus from the left side to the right. Once on the sacral promontory move your left index finger down over the promontory and spread your left middle finger right and ventrally. This maneuver helps lift the hypogastric plexus to the right and to safety. Following this, keep your left hand in the wound and then sweep with your right hand, taking the peritoneum off the vessels up at L4-5 and higher if needed. By taking the peritoneum off the vessels it allows you to assess the vascular anatomy (see Fig. 9e, f). The real benefit is that if there is a vessel injury, access above and below allows you to control the breach and repair it safely. Anterior surgery is much easier when you can visualize the vessels and manipulate them appropriately.

Leaving the peritoneum attached to the vessels is hazardous. In this setting, you cannot adequately see the anatomy and it makes a tear difficult to control; thus, working hard on making sure you can get the peritoneum reflected to give clear access is critical. When reflection of the peritoneum and its contents is performed in the manner detailed previously, the superior and inferior hypogastric plexus is reflected safely. As a consequence, the incidence of retrograde ejaculation reduces and any sympathetic side effects also reduce. There are sympathetics in the plexus and there are also sympathetics that run on the medial psoas gutters and it is important to make sure, when you do use dissection, that you avoid these areas.

Study and be aware of the vascular anatomy from the preoperative MRIs, CTs, or angiograms. Place them on radiographic lightbox in your theater and refer to them before and after reflecting the peritoneum and visualizing the vascular anatomy. This mentality and preparedness will reduce vascular injuries. The aorta, lying to the left and anterior to the vena cava, and the vena cava, lying to the right and posterior of the aorta, bifurcate at L4-5 and the venous structures normally duplicate the arterial system. This is the level where most vascular injuries occur. One can take the vessels left to right in most cases. If the bifurcation is above the L4-5 level and the common vein runs at or above the disc level, one can mobilize the vein up and to the left. At the L4-5 level, the common iliac vein usually runs under and inferior to the left common iliac artery. The trick is to obtain blunt dissect initially with Metzenbaum scissors and then with a peanut dissector and just gently tease and strip the tissue off the lateral aspect of the artery at the level of the disc to expose the disc (see Fig. 10a, b). There may be one or two iliac perforators that come off the common iliac vein that come under the artery and these just need to be clipped and ligated.

If performing an approach at L4-5 and the anatomy dictates a right to left exposure, gently tease the tissue off the artery and have a look for the iliolumbar vein. Some routinely ligate it but I do not think you must do this unless it presents a problem. So, in less than 15% of my cases I will ligate the iliolumbar vein. If you do ligate the iliolumbar vein, tie off first at the origin then reinforce it with clips. Move proximally over the disc and tease the tissues up as this helps release the vessels to mobilize them to the right and down.

If there is any vascular vessel calcification or slightly abnormal vasculature where you need to get better visualization, then you can skeletonize the common iliac artery and put a sling around it and take it over to the left. This gives complete exposure to the common iliac vein and allows mobilization down to the right. The vein has to be mobilized enough to be below the level of the

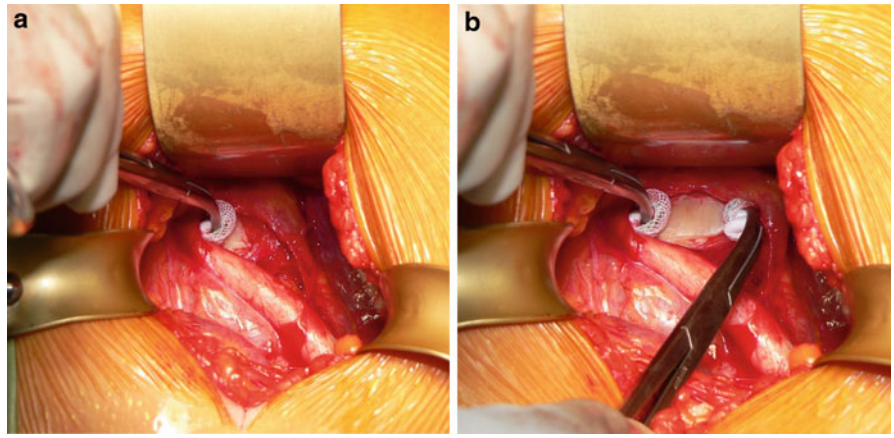

Fig. 10 (**a**) Mobilization and traction provided by periosteal plane dissection with a peanut retractor held with the left hand, (**b**) teasing of areolar tissue across the disc space by a peanut dissector held with the right hand while the left hand maintains traction

disc so that a retractor pin can be placed for retraction and access far enough to the right to allow correct positioning of the prosthesis to be obtained (see Figs. 11 and 12). Next move to the superior right side and insert the retractor pin. Then make your incision in your annulus, reflect the annulus, and insert stay sutures in the annulus to protect the adjacent areas. Normally we just use a 1 or a 2 Vicryl™ (see Fig. 12b).

Then perform a macro-discectomy (see Fig. 12b). This is best done with long pituitaries, Kerrison rongeurs, controlled movements within the intervertebral space with a long sharp Cobb, curettes, and rotational distractors as well as interbody distractors. After the bulk of the anterior disc has been removed by the pituitaries, the Cobb is used to remove the cartilaginous endplate with small, careful, controlled movements. Do not make any lateral movements or rotations as lateral movements will result in the Cobb skiving and sometimes lacerating the adjacent vascular structures and uncontrolled movements can result in penetration into the spinal canal or divots in the endplate which can compromise implantation. One needs to have the appropriate Cobb and the appropriate technique.

The cartilaginous endplate is then removed and the disc space after that is distracted so that we can pare down the posterior annular structures. From there one will usually go to the paddle distractor to increase the disc height and therefore gain access to the posterior annulus and the posterior longitudinal ligament. When one distracts, it is important to balance the lateral annuli to make sure that there is maximum exposure to the endplate and that there is parallel distraction and no evidence of any "fish mouthing."

Initially use a Charité central distractor, then insert a David distractor, and use the Cobb to get the annulus either partly off the posterior endplate superiorly and inferiorly. If it needs to be resected, then Kerrison rongeurs are utilized. After the annulus is released one can perform an internal intradiscal electrothermal therapy with bipolar diathermy, ablating the course of the sinuvertebral nerve around the posterior annulus.

From there, one should reuse the distractor paddle including a T handle paddle to ensure maximal disc height restoration and appropriate posterior release (see Fig. 13a, b). It is important to do this probably three times and to go back and check the disc space and make sure it is cleared and balanced front to back, side to side, and that you have addressed any disc herniations or releases required. If there is a disc herniation, extruded fragment, or a sequestered fragment, they can be retrieved after careful preparation of the disc space and rongeurs. Once you are back at the posterior annulus,

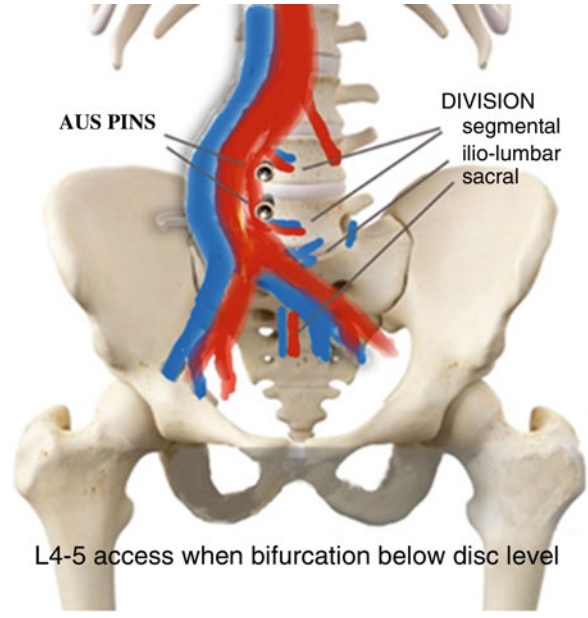

Fig. 11 With vessels held by a peanut retractor and under direct vision, AUS pins are inserted sequentially on a T handle to achieve a working corridor for disc preparation and device implantation

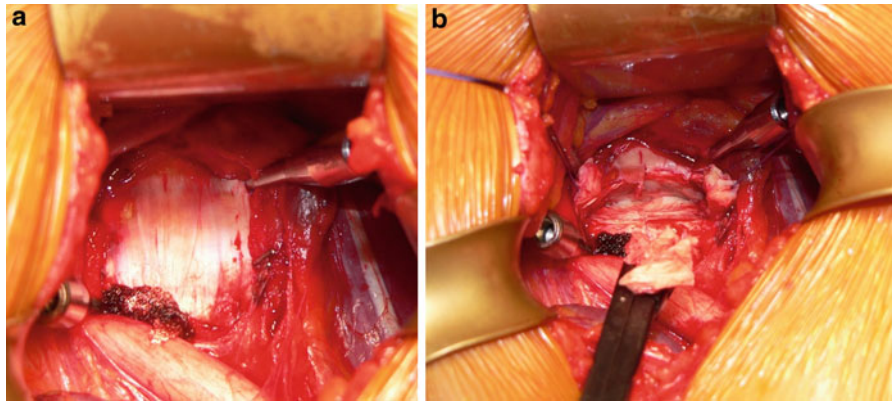

Fig. 12 (**a**) Pin retractor placement to maintain safe exposure of the disc. (**b**) Following an H-shaped annular incision, flaps are mobilized and retracted with stay sutures and a macro-discectomy can then be safely completed with careful use of a Cobb retractor and pituitary rongeurs

insert the David distractor in and rotate the panels out to the left hand side. This gives you clear access into the distracted disc space. From there you can use long Kerrison rongeurs to create a rent in the annulus. If there is a herniation, the rent will already be there. You can then follow that rent and retrieve the herniation. It is essentially just like doing and anterior cervical discectomy except that you have got much more room and you easily evacuate nuclear and annular material.

Once you have got the disc prepared, you can then make a decision about whether the device preoperatively planned for implantation is still appropriate. Whether it be a static or a motion preserving device, the important issue is to achieve maximal cross-sectional area from medial to lateral and anterior to posterior endplate as possible as this aids in supporting the chosen implant (see Fig. 14a, b). This will prevent eccentricity, reduce subsidence, and maximize the graft-bone interface opportunities. Should the endplate

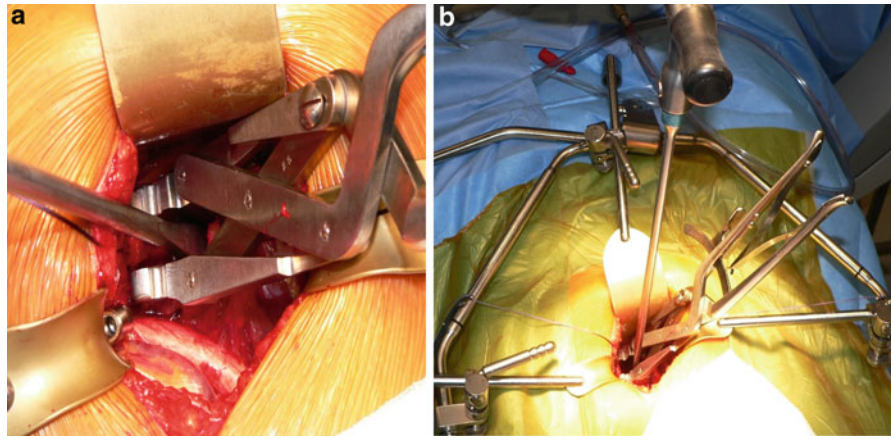

Fig. 13 (**a**) A David distractor is inserted followed by a paddle-style distractor panel to achieve disc distraction for periannular release and full access for discectomy and implantation. (**b**) Example of rotation of a distractor into the disc space splinted by the David retractor to achieve safe distraction while minimizing the risk of endplate breach

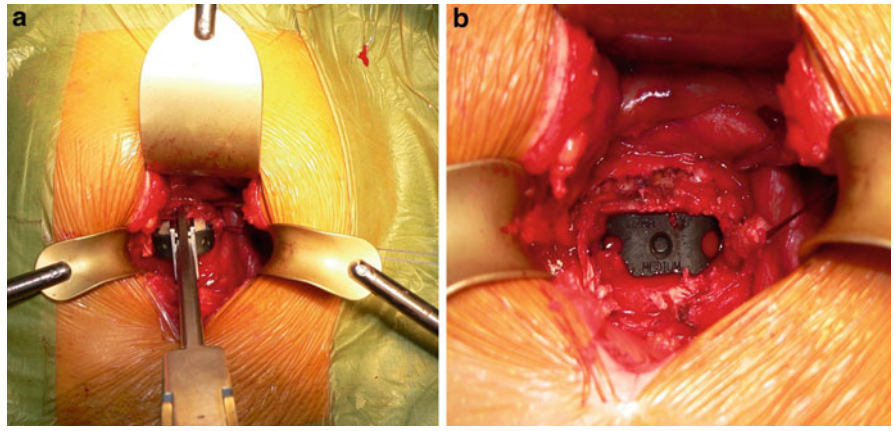

Fig. 14 (**a**) Implantation of an interbody cage loaded with graft. (**b**) Implantation and recession of interbody device prior to annular closure

or vertebral bony cancellous quality be found to be poor (often sensed via limited bony resistance with insertion of AUS pins), then vertebral augmentation should be strongly considered after implantation. This is achieved via insertion of vertebral cement into a Jamshidi needle under fluoroscopy control.

Following implantation, we harvest a fat graft and place it over the implant and then repair the annular flaps and then remove the retracting pins. Should poor quality or sparse fat be available, then use a square of Gelfoam™. The rationale for this is to close the dead space for hemorrhage and reduce the theoretical nidus for adhesions. I think that adhesion barriers should be used generally in young people, who may later require revision or treatment for adjacent segment disease. There is a preference to use Surgiflo™ with thrombin judiciously into the pin holes so that there is no hematoma, which will increase fibrosis in the postoperative period.

Next, carefully release the retractors and massage the peritoneum to the contralateral side of the approach, allowing it to fall back into its natural

position. One should generally perform this repositioning because if this is not performed, the ureter can end up in a more central position and develop a kink in its course. On the rare occasion this can result in a hydroureter above the stricture leading possibly to a hydronephrosis.

Once the peritoneum is back in position, verify the position of the implants radiographically. At this point, reconfirm hemostasis is achieved and secure the fascia with a double loop nylon, making sure the sutures pick up the fascia and not the muscle, aiming for normal tension. Close with an absorbable monofilament in the subcutaneous and subcuticular layers.

Tips on Revision Retroperitoneal Surgery

Revision surgery can be very complicated if the approach is attempted through a previous ipsilateral retroperitoneal approach. There are other options available and these include right retroperitoneal and transperitoneal (preferred). If a revision retroperitoneal approach is performed, then a ureteric stent needs to be inserted preoperatively. In revision, anterior surgery it is expected that the approach to the spine will be complicated by adhesions. Peritoneal tears are common and this may predispose to bowel injuries, ileus, and bowel obstructions in the postoperative period. At the index disc and often at adjacent discs there will be adhesions and fibrosis. This can result in distortion and tethering of vascular structures. Both of these situations greatly increase the risk of injury. As stated above our experience has found transperitoneal approach to be safer and provide a greater chance of success. On some occasions, it is not possible to access the revision level safely. This commonly occurs at the L4-L5 level where the vascular anatomy is often challenging. The vessels may be completely immobile and one must be prepared to spend time performing meticulous dissection. Sometimes the decision to abort has to be made. Consider subperiosteal dissection of the tissues which may provide surprising access on some occasions. In regards to minimizing vascular difficulties during index revision procedures, one should reconstruct over the disc replacement with fats graft or anti-adhesion barriers. This will maximize access to the level and help minimize vascular complications during revision index surgery. A team approach is required in regard to anterior revision cases and will be discussed in a later section.

Transperitoneal Approach

This approach shares the same steps to the retroperitoneal approach to the point of encountering the peritoneum and a generous incision is generally required (see Fig. 15). At this juncture, the

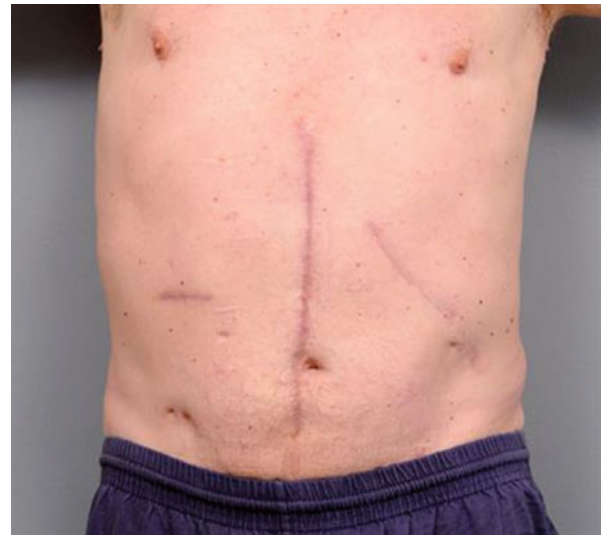

Fig. 15 Midline incision utilized for a L2-S1 transperitoneal approach in a patient with previous abdominal surgeries. Recall that safety and visualization, not the length of the scar, should be the first consideration

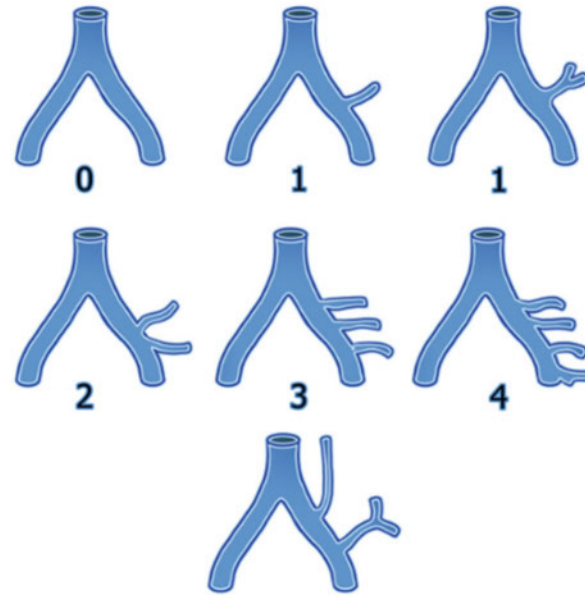

Fig. 16 Variances in the venous anatomy around the left common iliac vein. Notice increasing number of tributaries and sub-tributaries possible here as well as, in the bottom picture, the potential for the presence of an ascending iliolumbar vein

peritoneum is divided. Using the Thompson retractor, the descending colon and the sigmoid are packed into the left paracolic gutter. The transverse colon is lifted with a wide retractor and with displacement of the small bowel to the right, the duodenal-jejunal junction is defined. The major trunk vessels of the aorta and IVC are our main interest when approaching transperitoneally. Dissection nearby through the posterior peritoneum over the right aspect of the aorta allows progressive exposure of the aorto-caval space from the renal vein down aiming to remain to the right of the inferior mesenteric vein.

In the complex cases often requiring 4 level reconstruction or in revision surgery we have found it best to approach the superior aspect initially, defining the space between the aorta and vena cava dividing the segmental vessels and noting that there is often a large vein at the L3 level. In some cases, this is a retro-aortic renal vein. We progress inferiorly to the overlap of the right iliac artery over the left vein. Depending on the position of L4-L5 it may be approached by dissecting the right iliac artery free and mobilizing it and the aorta to the left and the IVC and the left vein to the right and inferiorly. Care with the superior aspect of the left iliac vein will allow control of the iliolumbar vein or neighboring branches to prevent tearing and problems with blood loss. While much attention is focused upon care for the vessel variations (see Fig. 16) and parasympathetics, attention should also be given to the nearby anterior neural structures such as the lumbosacral plexus and obturator nerve.

A lower disc may be better approached beneath the left iliac artery, displacing the vein inferiorly and to the right. In this case, it is sensible to control the vein branches along the superior border early. If the bifurcation of the main trunks is high, L4-L5 may be approached from below, similar to the L5-S1 approach with definition and ligation or clipping control of the middle sacral vessels. The aorta and the left iliac artery can also be displaced to the right, but this requires mobilization of the Iliac artery to limit the displacement forces while it is pinned. The IVC bifurcation is usually above the L5-S1 disc but may occur at the inferior edge of the disc. Adaptation of the standard approach will be required.

A vascular surgeon is required only when there are complex problems such as requirements for 3- to 4-disc level-based reconstructions and/or where there are definite arterial risks and venous anomalies or there is revision surgery.

In all of these cases a transperitoneal access is going to be safer by allowing easier treatment of complications if they occur and better controlled outcomes.

In the space between the aorta and IVC, segmental veins and arteries have to be defined, individually controlled and divided to enable freeing of enough length to allow adequate access of the disk space without tearing the major vessels. In this area, the surgeon should be aware of developmental anomalies and variations such as a 10% risk of a retro-aortic left renal vein, a horseshoe kidney, and left IVC variations (discussed below). Also one must consider abdominal aortic aneurysm and dense calcification of the arteries. These can all be recognized from the preoperative MRI or CT angiography scan and, conversely, can be a major problem if not anticipated at the time of surgery.

Tips on Approaching Operative Levels Below the Bifurcation

We choose to divide the peritoneum centrally over the sacral promontory to obtain access to L5-S1 and L4-L5 if the bifurcation is high enough. This area is usually clear of major structures and the areolar tissue can be progressively elevated until the anterior aspect of the left iliac vein is displayed. The medial edge is then clearly defined. Achieving this may take some time with slowly teasing away fibrous and vascular bands or may require diathermy and/or limited areas of sharp dissection. Once a satisfactory length of the vein edge can be visualized, attention is turned to elevating the vein and freeing it from the posterior surface. In general, it is attached to the anterior spinal ligament and surrounding fibrous tissue. Great care is required here and a combination of teasing the tissue with two pairs of forceps again with or without diathermy and sharp dissection with scissors, working to go deep into the ligament or periosteum, is used to achieve the separation. This is particularly important if this is revision surgery. The median sacral vessels can readily be isolated and controlled by dissection with the peanut dissector of any surrounding areolar tissue to allow clipping and diathermy.

Tips on Approaching Operative Levels Above the Bifurcation

Above the bifurcation the approach we usually use is between the aorta and IVC but a left lateral approach along the aorta can also be used. At the bifurcation level, the aorta can be displaced to the right with the veins. This latter area requires careful definition down the lateral edge of the vein behind the left iliac artery and requires progressive division of the iliolumbar vein, either with clips or ties, and the often multiple accompanying veins in this region, to enable de-tethering and mobilization.

As mentioned earlier, the L4-L5 level access depends on the position of the aortic bifurcation and, often, the easiest approach is between the left common iliac vein and the artery above. If the aorta is of normal size or small and of normal compliance, it is possible to dissect along the left side and retract it to the right. With this approach, care is necessary with the iliolumbar veins, which are best safely controlled early before they are avulsed from the iliac vessels. When dividing the veins attention to the local autonomic nerves is also required.

Revision and Previous Abdominal Surgery

As previously discussed, an approach to the spine in the revision setting will be complicated by adhesions close to the affected disc site affecting ability to access safe planes. The first decision again, with revision, is whether to proceed retroperitoneally or via a direct transperitoneal approach. The majority of the time for revision surgery we consider the direct transperitoneal approach to be safest with the best exposure, especially if access to more superior levels is required. When carefully performed with meticulous technique, blood loss with recent procedures has been of the order of 100 mls, even in a case where we had visualized large pressurized veins on the other side of the peritoneum (e.g., a patient with portal vein hypertension).

The retroperitoneal approach, if being made for the second time, involves tethering and scarring of the retroperitoneal space. The dissection

can be difficult and the ureter is at risk in this tissue. It is our policy to have an urologist place a removable stent as a precaution as this allows easier recognition of the ureter and greatly reduces risk of damage to it. It needs to be recognized that direct trauma is not the only way that tissue damage can occur, with ischemia from repeated dissections being associated with damage to the ureter and the femoral nerve in this region. A resultant leak or neuropathy may result.

If using retroperitoneal dissection for revision, prosthetic replacement, or fusion, our approach has been to develop the dissection plane more superiorly. With access to L4-L5, the most difficult, we commence definition and mobilization of the aorta on its left side, then progress down to the bifurcation, and continue laterally to the left common iliac artery. We have found that the common iliac vein is attached posteriorly and it becomes exposed as the artery is displaced medially. This is likely to be the riskiest part of the operation. To get adequate access the vein has to be freed along 3–4 cm of its length so that it can be displaced medially and a little inferiorly.

Before the vessels can be freed up it is important to mobilize the ureter away from them. This is assisted by having a ureteric stent placed at the commencement of the operation which we do for initial recognition in the revision to the retroperitoneum setting. As the dissection progresses it allows easier definition between the ureter and the adhesions that need to be divided.

Once the lateral edge of the vein is visualized sharp dissection is used with scissors directed posterolaterally allowing the periosteum to be divided which protects the vein. This is continued progressively until the vein is adequately freed inferiorly.

In women it is also very important to understand their gynecological history. Past surgery laterally, e.g., around the tubes and ovaries or involving the lymphatics, can increase the problem. This is pertinent as a case has been reported to us where the iliac vein was totally avulsed as distraction was applied due to dense tethering in the pelvis. Obviously, this can occur no matter which direction of approach is used. Reports of direct iliac vein trauma probably only account for a limited number of cases that have occurred.

With all the endovascular options a skilled vascular surgeon can bring to the table, we have the ability to control hemorrhage with balloons or stent grafts if a major rent in the vessel occurs. We use this with either direction of approach and have the endovascular equipment in the theater. As the potential risks include a threat to life we have considered it useful to place a left iliac vein guidewire "0.035" at case commencement using duplex ultrasound via the common femoral vein when our team has considered the risks are significant. At the end of the case the wire is removed with less risk than a standard venepuncture.

If a prosthetic disc needs to be removed, it is important that the disc type be reviewed and information be sought on disassembly techniques and recommendations from the manufacturer. With the space opened at least partially, the metal plates can be freed with the careful use of a small osteotome between disk and vertebral body and prosthetic extraction facilitated by rotation of the plates. Sometimes a partially or complete vertebrectomy is required to explant the device. Careful assessment for and removal of any collections of metallosis or polyethylene debris should occur before proceeding with standard reconstruction.

We have found the vessels are adequately protected by a Gore-Tex™ prosthetic film allowing the dissection to proceed deep to the film when it has been implanted at the initial procedure.

Ability to Transfer Between Retro- and Transperitoneal Approaches

The decision to use one type of access does not rule out use of the alternative. It is straight forward to transfer from extraperitoneal dissection if problems arise and the upper extent of the approach is not reached. The peritoneum is opened and the bowel moved to expose the interval between the IVC and the aorta. This interval can be widened to expose the upper discs for repair.

Even if surgery has been planned based on a transperitoneal approach it can be switched to retroperitoneal should problems occur. This may require adjustment of what can be achieved.

Vascular Pathology, Injuries, and How to Manage Them

Venous Pathology and Handling Techniques

The iliac veins are at most risk in the pristine abdomen no matter whether the approach to the anterior lumbar spine is made retroperitoneally or transperitoneally. The first decision is whether to proceed retroperitoneally or via a direct transperitoneal approach.

In general, the approach is simplest from the retroperitoneal aspect. There is minimal gastrointestinal manipulation, a limited incision for the patient, and the approach to L5-S1, and L4-L5 is straightforward and L3-L4 often manageable.

The veins should be identified along their edges with progressive mobilization and elevation. The risk of damage and hemorrhage is mainly from unidentified branches. It is easy to get into this problem if the retraction is continuously maintained as the branches empty and remain emptied and thus can be divided without recognition until, with reduction of tension, the depth of the wound tends to allow the severed vein to rapidly fill with blood and into the wound.

The vascular problems are twofold: either hemorrhage from cuts, tears, or avulsions or obstruction with or without thrombus. The latter can occur as the result of trauma or from repairs after the iliac has been clipped/sewn to control hemorrhage or compressed by the operative area behind the right common iliac artery.

The frequent "injury" is really a part of the dissection in the majority that can be prevented by adopting a dissection technique of stretch and relax given that these are viscoelastic structures. Branch veins can be distracted and torn from the common iliacs and vena cava and it is often the smaller veins that are mainly responsible as under distraction they are difficult to visualize when distracted but if pulled or torn can result in a sizable hole in the main vessel with the potential of copious bleeding. Allowing tissue relaxation can give these vessels a chance to fill and, once defined, be isolated and appropriately controlled. This problem is just part of the surgical approach and must be mastered to, firstly, limit injury by the technique of dissection and, secondly, to have the capacity to repair the vessel tear without significant further damage, i.e., enlarging hole or causing the result of critical stenosis or occlusion.

Usually it is the common iliac vein that is bleeding. A calm approach is required to not let this get out of hand. The bleeding needs to be controlled well enough to allow the placement of hemoclips or sutures for control without compromising the vessel lumen. If the lumen is compromised, the problem can be converted to an occlusion rather than a hemorrhage. The left common iliac can be tightly stenosed or occluded by taking large bites to control bleeding. At the time of surgery, secondary to this, all the pelvic veins will become congested as they develop an alternative pathway and feed into the right and on the ipsilateral side the iliolumbar region, this may well make further dissection more difficult and hazardous as all these small vessels will be increasingly pressurized and bleeding will be more likely to occur and more difficult to control. Postoperatively, the risk of extensive DVT is significant and adequate anticoagulation must be given. The patient should also be informed that they are likely to have a congested and swollen leg(s) and have the potential of a lifetime pressure/stasis problem.

Clusters of veins anterior to the sacrum if torn can be very difficult to control. When all else fails, osseous stapling of a mass of Surgicel™ or Gelfoam™ and Surgiflo™ or thrombin-based injectable onto the site to tamponade and coagulate the plexus can resolve a life-threatening situation (see Fig. 17).

If the solution appears very difficult, an endovascular option may be helpful. Recovery of the situation can be achieved by placing a guidewire through the common iliac vein and can allow it to be followed with a balloon to apply tamponade at the site until a formal repair can be carried out (see Fig. 18). The wire needs to be followed by imaging as it is common for the wire to travel up the iliolumbar branches.

If the bleeding is from a difficult or inaccessible site, e.g., posteriorly near the bifurcation, a covered stent may offer a means to solve the

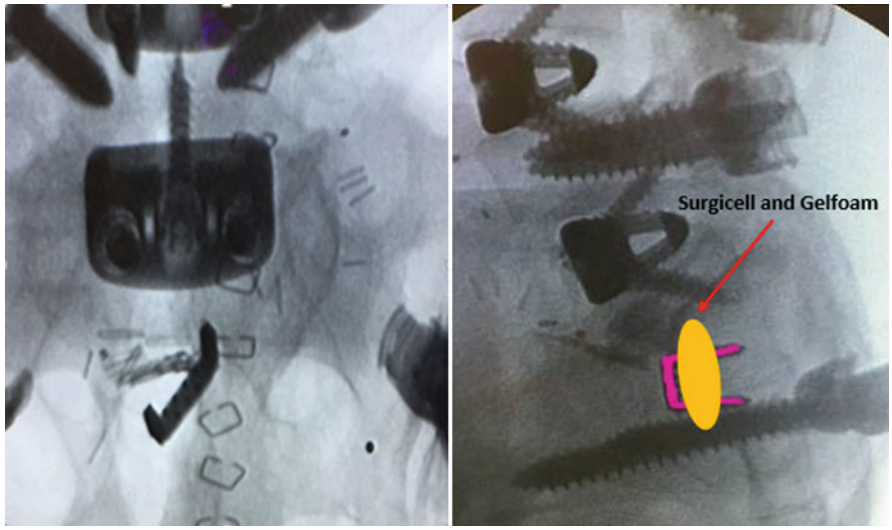

Fig. 17 Use of a Richards staple (usually found in a knee reconstruction instrument tray) for osseous purchase to secure a Gelfoam and Surgicel composite for tamponade in a case of difficult to control sacral venous bleeding

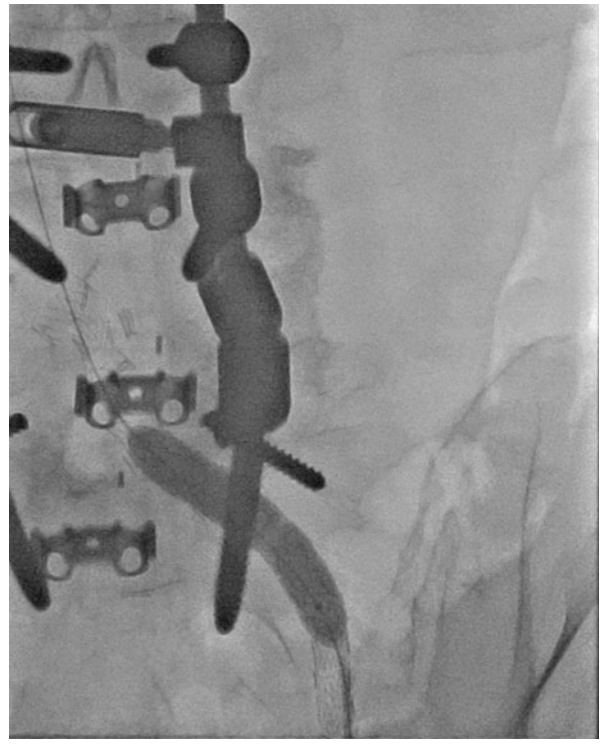

Fig. 18 Vascular balloon employed for hemorrhage control

problem. These can also be used to recanalize an occlusion.

There are no *covered* stent grafts made especially for the major veins and the iliacs often require 14–18 mm stents to fit suitably. The internal method to seal venous injuries would require a type usually used for arterial aneurysm repair. If the prosthesis does not grip inside the iliac vein, it

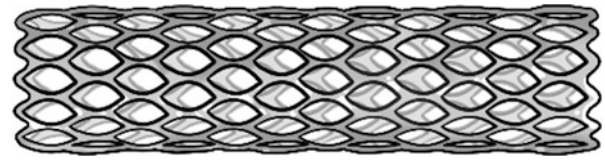

Fig. 19 Expandable stent graft

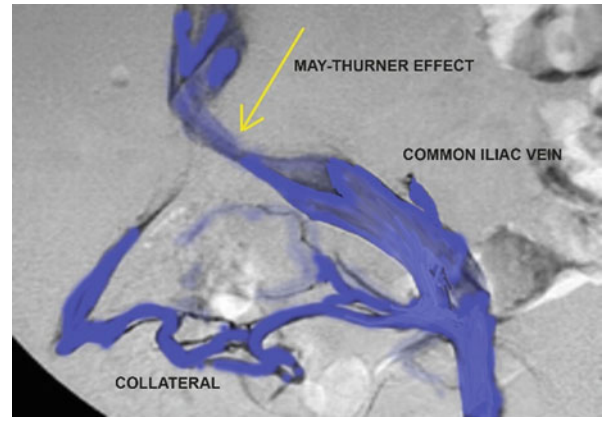

Fig. 20 May-Thurner effect of left common iliac vein compression by left common iliac artery

can end up being discovered as an embolus to the heart. These stent grafts need to be ordered as they are not usually "off the shelf." For a high-volume anterior spinal service it would be sensible to have a choice of stent grafts of different sizes to be suitable for any problems that may arise (e.g., grafts of 12, 14, 16, and 18 mm diameter and 5 cm long) on the shelf. This would generally enable suitable implants for any emergency. With experience, however, the chance of requiring this assistance with an initial approach should be very rare, but it would be useful in the more demanding setting of revision surgery.

The covered stents usually available for the larger sizes 12–14 mm are balloon expandable "Be" stent grafts or by "Atrium V12™." These covered nitinol self-expanding stent grafts maximize their size out at 10 mm but there are larger grafts usually used for iliac artery coverage in aneurysm repair that can be ordered (see Fig. 19).

Vascular surgeons have used these in situations where patients have been referred with a major vessel tear and with a repair attempted but complicated by a tight stenosis which have gone on to occlude, with ensuing serious results of massive limb swelling and stasis change. Thrombolysis with associated stenting has normalized the situation. For the case of simple stenosis (which is not all that uncommon) usually from right common iliac artery compression of the left iliac vein with swelling or a plate filling the space from behind, I prefer a bare sinus-Obliquus stent that conforms well at the IVC bifurcation.

The occlusive venous risk again is most common in the left common iliac vein. There is an anatomical variation associated with lumen compromise and flow restriction named as May-Thurner effect (see Fig. 20) which can be recognized in up to 25% of the population, particularly females.

Control and Repair of a Venous Hole

1. First, bleeding should be controlled by direct pressure on the area preferably by fingers or sponge sticks or, if necessary, placement of DeBakey vascular clamps. Help should be requested early if, upon assessment, the injury will likely require more than simple vascular repair techniques and, additionally, multiple skilled pairs of hands help the situation.
2. Then the vein should be mobilized and skeletonized above and below the site to allow the hole to be situated and visualized on the vein edge; then a series of small hemoclips can be

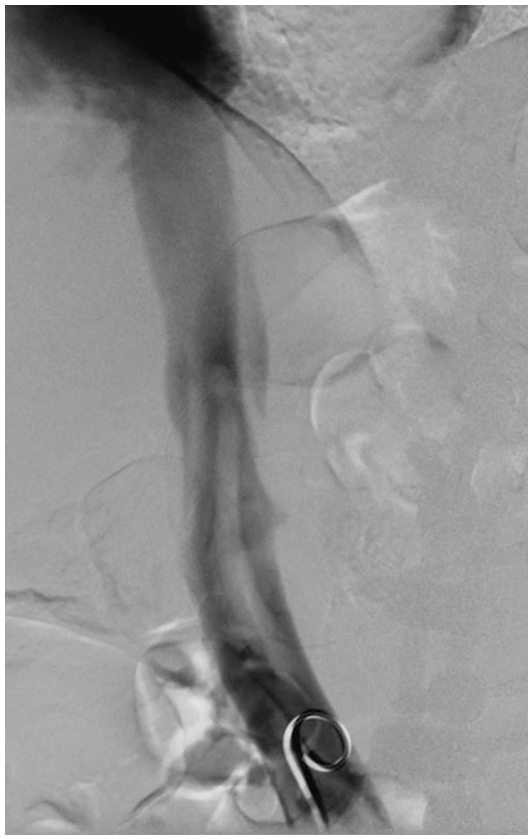

Fig. 21 IVC thrombus originating below the left renal vein after Floseal had been injected into a dural vein to control heavy bleeding during a posterior approach. Angiography at 6 months showed no residual

applied to the area to give satisfactory stable control. If necessary further stabilization can be achieved by using a 5/0 Prolene™ continuous suture to oversew the site without taking excessively large bites and tied with at least 7–8 throws.

3. Use of a sandwich repair can be a useful adjunct to close small venous pinholes without propagating further tearing. This employs a small Teflon or Dacron pledget skewered with the needle and thread twice and then slid down onto the holes for extra buttress and tamponade effect.
4. If extreme difficulty is encountered, then an endovascular wire, followed by a 10 cm angioplasty balloon, should be employed to allow control of iliac bleeding. A covered stent graft could be deployed in such instances if blood loss persists and there is a threat to the patient.
5. If the IVC is the problem, a side clamp or two small angled clamps can be applied until the site can be adequately secured.
6. The most important message is not to panic; a calm, well-considered approach is mandatory to achieve the best results.

Control of Venous Oozing

First-line management for nonspecific oozing is with judicious use of topical hemostatic agents (such as thrombin-based products) combined with an adjuvant volume filler such as Surgicel or Gelfoam. This is useful for controlling oozing from smaller veins, from vertebral body perforators, and from extradural veins. Generally, the topical hemostatic should be applied when there is no easily identifiable large bleeding source amenable to clipping, ligature, or diathermy and should then be assisted in its action by placement of the adjuvant volume filler, pressure agents (e.g., Surgicel gauze) with or without additional pressure from a packed surgical gauze. Adequate time should be given for this combination to take effect and repeating this sequence is often necessary until hemostasis is achieved. When used carefully, it will not upset the function of the cell saver. Spongostan™ can be used; however, it should not be sucked into the cell saver.

Excessive use of hemostatic agents is not without risks given its potential to be absorbed into local venous plexus, with the potential for forming and propagating clots. The vascular surgeon has been asked to treat a patient who developed a large floating clot in the IVC extending from the renal level up to the atrium (see Fig. 21). The clot developed after Floseal™ was injected into the lumen of a heavily bleeding epidural vein. He elected to manage the patient with full-dose low molecular weight heparin at a dose of 1 mg/kg twice daily, which in his experience is the most effective medication for large thrombus. It is possible that small emboli develop as the clot breaks up but no major functional problem developed and follow-up at 3 and 6 months angiography showed no residual thrombus. Furthermore, Floseal™ has been reported to have an association

with inflammatory intraperitoneal adhesions. Fibrillar™ should be used with caution in conjunction with cell saver as thrombosis and emboli have been reported.

Another uncommon technique useful in extremis, particularly in the context of sacral plexus oozing, is for direct tamponade across a wide surface area by placement of an anterior sacral Gelfoam secured to a Richards staple and then impacted into the bleeding anterior sacrum.

Arterial Pathology

Although the veins are at most risk in the pristine abdomen, the arteries are also at risk no matter whether the approach to the anterior lumbar spine is made retroperitoneal or transperitoneal and, particularly, in the elderly patient. The most significantly affected arteries are the iliac arteries and the aorta. The two most common arterial problems are either related to hemorrhage from cuts, tears, and avulsions or related to obstruction. Neither problem is common in high-volume anterior lumbar practice where protocols anticipate significant pathology.

Bleeding events that we have encountered more often relate to the retraction forces required to displace the arteries. If the local segmental vessels or the mid sacral vessels are not appropriately located and ligated/clipped and divided prophylactically, an avulsion injury is possible and will require fine suturing to control.

The tension affecting the vessels can, on occasion, result in a split at the aortic bifurcation as the iliac arteries inferior to this are distracted. This is not able to be satisfactorily repaired until the tension is released, so it is best to pack and pressurize the spot and get on and do the spinal repair and come back and resolve this problem once the spinal repair is complete.

In a similar fashion, we have seen splits and tears develop in the iliac arteries at the site of pins or local retraction. Again, careful suturing is necessary especially in these smaller vessels where technical mistakes in the repair are likely to result in stenosis or occlusion. This is not an area to be controlled with hemoclips; attempts at control with hemoclips have often required endovascular rescue for dissection and marked stenosis.

To check suspected postoperative problems a 3D CT angiogram is required and has to be assessed in multiple rotations. Careful assessment of the study is required as "normal" reports from radiology providers have been on occasion incorrect and proven to be high-grade postoperative stenosis (see Fig. 22).

The first decision in the presence of significant arterial disease is whether to proceed retroperitoneally or via a direct transperitoneal approach.

In general, the approach is simplest from the retroperitoneal aspect. As previously stated, there is minimal gastrointestinal involvement, a limited incision for the patient and the approach to L5,S1, and L4,5 is straightforward, and L3,4 can often be managed. This approach is associated with higher risk if using the ipsilateral side for revision surgery, discussed in detail in our earlier section of venous pathology. We, therefore, opt for a transperitoneal approach or, in some cases, a contralateral left retroperitoneal access (if a right-sided retroperitoneal was the previous access) in these cases. Getting to L3-L4 and above is managed by developing the space between the aorta and the IVC and, when there is extensive calcium plaques above, significant stress is built up in the process of retraction (see Fig. 23). We try and use areas relatively devoid of calcium for the main sites of displacement.

The risk of arterial thrombosis is related to arterial trauma, usually precipitated by dissection. This can occur in minimally diseased vessels but is much more likely when there is a significant degree of atherosclerosis with thick unstable areas of plaque. This is particularly so if there are areas of solid calcification (see Fig. 23). The degree of calcification will influence the risk and it is sensible to involve a vascular surgeon for the approach if the calcification is significant. We use CT 3D angiography with maximum intensity projection to provide the best assessment of the calcium effect.

Atheroma can remain undisclosed until the artery is compressed or retracted and, as such, preoperative identification provides additional

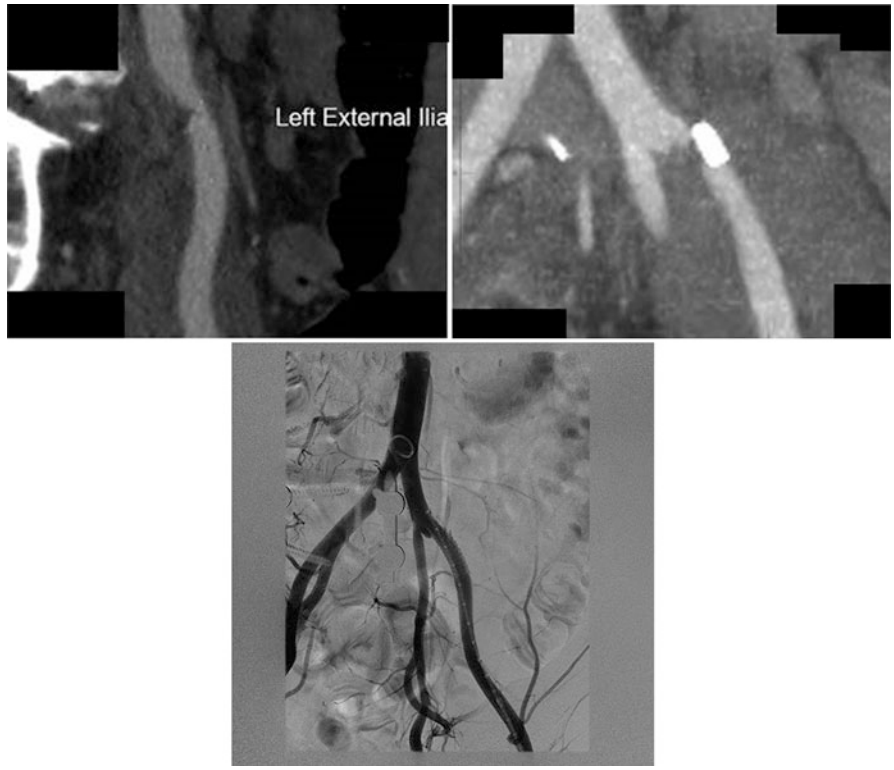

Fig. 22 Sutured tear assessed as satisfactory by radiology postoperatively but likely not assessed adequately in 3D. The problem was resolved with endovascular stent

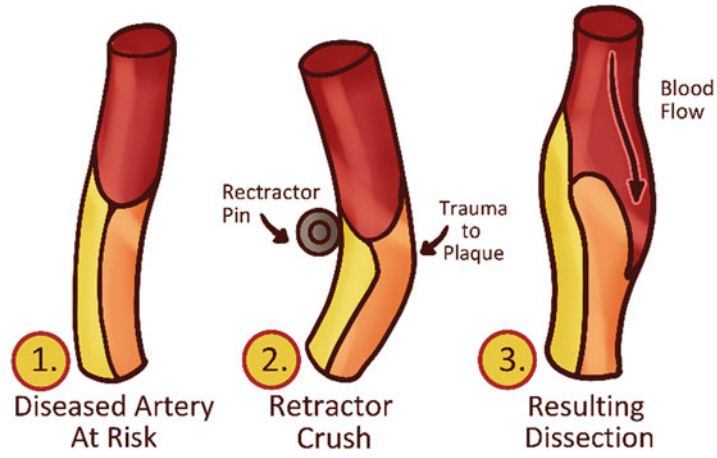

Fig. 23 Different models of injury from arterial handling

safety. While younger patients are at little risk of abdominal atheromatous disease, patients who are aged above 50 years and those who are smokers and diabetics and have other peripheral vascular disease risk factors such as hypertension or hyperlipidemia have an increasingly significant risk of involvement of the iliac artery and aorta. This includes solid plaques, ulcers, and unstable material. With extreme degrees of calcific atheroma now showing in the population, it is prudent to order a preoperative angiogram in any one aged over 50 or with multiple risk factors, particularly if multilevel

surgery is required. If an inadvertent intraoperative thrombosis is diagnosed intraoperatively, it can be treated on table with thrombectomy and stenting (see Figs. 24, 25, and 26).

In some patients, this may require the decision not to proceed with an anterior approach but rather consider alternatives such as lateral or posterior approaches, accepting their relative limitations.

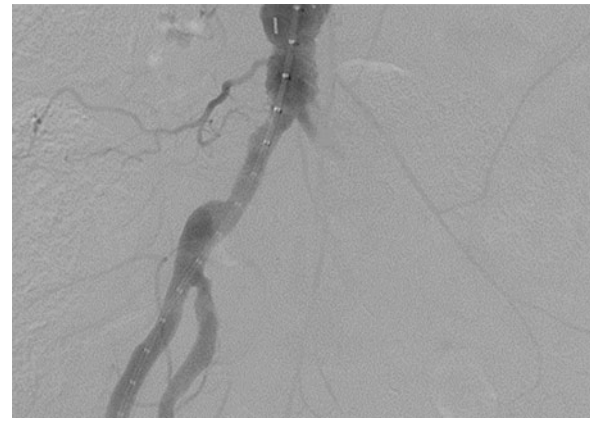

Fig. 24 Occluded iliac artery after retraction

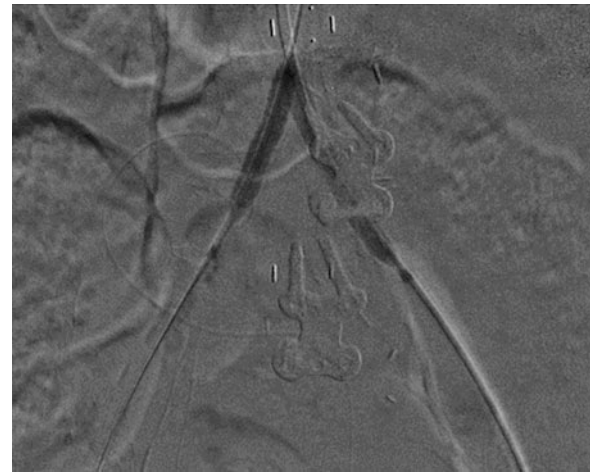

Fig. 25 Kissing stents to resolve occlusion

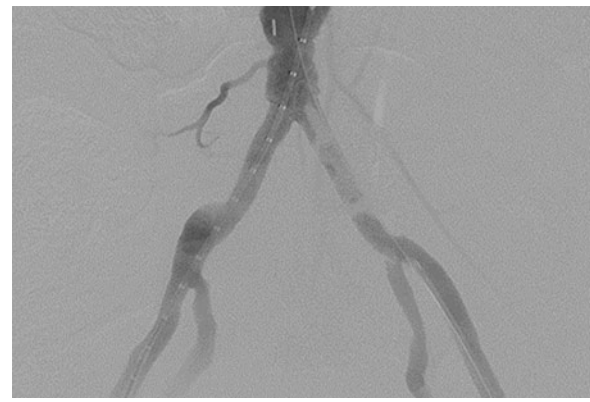

Fig. 26 Restored lumen and flow

The full extent of their limitations and disadvantages are not discussed in detail here but include the inability to fully correct alignment and lordosis, higher risk of neurological injury, higher risk of inadequate disc clearance, and risk of displacement of the prosthesis laterally, posteriorly, or anteriorly. Recognition of such difficult situations may benefit from referral to a high-volume center of excellence for anterior, transperitoneal reconstruction. As discussed below, we have used combined synchronous spinal and vascular surgery to do open vascular and anterior column reconstruction in selected patients. Not only does this provide the opportunity to treat high-risk vascular lesions but also facilitates optimal spinal reconstruction, fusion, replacement, or hybrid procedures from an anterior approach, and we have subsequently published our experience and outcomes with this technique (Scott-Young et al. 2018b).

Another way to deal with lesser disease is to presume a significant risk of dissection and prepare the patient for an endovascular procedure to accompany the main spinal operation as required. When concerned by the vascular appearance perioperatively, a guidewire can be placed via the common femoral artery and placed to the diaphragm on the side considered to be at highest risk. This is usually on the left but depends on the planned approach and the atheroma distribution in the individual patient.

Occlusion occurring by dissection happens at the site of arterial compression and distortion (see Fig. 23). It is possible to check whether there is a high-risk atheroma by carefully palpating the artery before applying the high-grade force needed to manipulate the vessels away from the target intervertebral space.

In addition to dissection and progression to local occlusion, embolization of loose cholesterol or thrombus can occur. This will usually manifest as distal limb ischemia seen as pallor and coolness but often with patchy cyanosis. The emboli can be multiple, small, and fragmented and pulses may be normal at the ankle. There is often little that can be done with this material after the event but surgical intervention, either endovascular or open, may be required to prevent further progression which may be associated with progressive patient decline, possibly culminating with death if enough tissue is compromised.

The frequency of encountering this problem in the increasing number of senior patients with spinal disease has forced us to look at prevention rather than wait until confronted by a white leg with no femoral pulse and severe pain in the postoperative period. When operating on patients with arterial lesions it is critical to have balloons, stents, and stent grafts available to address any complication as soon as it is recognized (see Figs. 24, 25, and 26). This offers much better outcomes than the reported series, where serious limb arterial ischemia from dissection and occlusion has gone undiscovered for days after the index operation. Despite meticulous surgery and preoperative assessment, total unexpected occlusion of a main vessel can occur during surgery in some patients who have minimal vascular disease.

If a previously unrecognized vascular lesion is appreciated intraoperatively, it is advisable to assess further with an on-table angiogram under image intensifier. In this case, an arterial puncture is carried out using duplex ultrasound to minimize risk. A wire and diagnostic catheter can be placed in the aorta to allow general assessment with bilateral obliques as single plane studies may give an inaccurate impression. If the disease is severe, it is sensible to leave the 4F access sheath after the catheter has been withdrawn to allow a further angiogram after the formal spinal surgery has been completed. If the wire is left in situ, it also can serve as a railroad for the deployment of angioplasty balloons and stents if required to resolve dissection and occlusion at a later time. Removal of the wire at completion is a simple matter if intervention has not been required. If a sheath has been required, the site is managed in the usual way. Local pressure for a 4F sheath is used for diagnostics. If a larger sheath has been utilized for intervention, e.g., 6F or 7F, a StarClose™ device is used. Early in our experience with the very calcified vessels we decided to use guidewire placement routinely before opening the abdomen giving a railroad to fix dissection should it occur. With experience we have found we can manage these complex vessels with

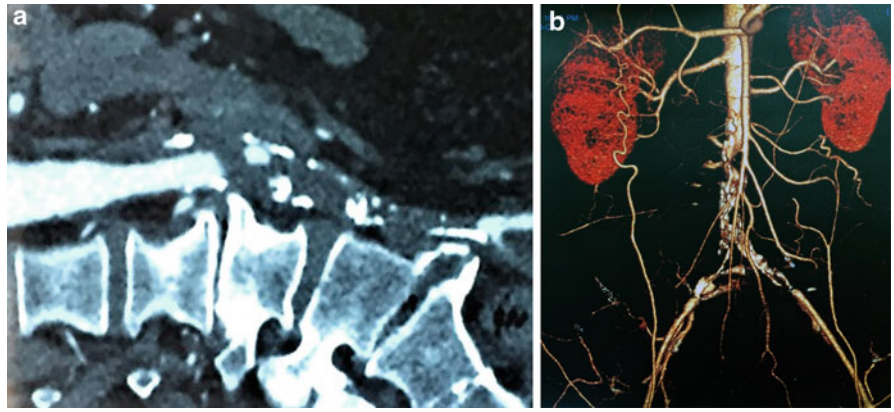

Fig. 27 CT Angiogram examples of an occluded aorta and iliac arteries in sagittal CT and 3D reconstruction modes

limited risk so the use of a pre-emptive wire has been discontinued and we treat if a problem is identified with blood flow obstruction.

Patients with substantial problems of aortic or iliac aneurysms at critical levels or functional occlusion require treatment as a priority above the spinal problem so this needs to be resolved (Fig. 27a, b). From our experience, the anterior approach is significantly superior to other methods we have undertaken, where possible, to proceed with combined synchronous surgical treatment of both problems at the same operation as detailed below (Scott-Young et al. 2018b).

The Rationale for Synchronous Treatment of Concurrent Spinal and Vascular Lesions with the Anterior Approach

When patients with combined pathology were identified, we as spinal and vascular surgeons faced problems from different aspects prior to developing a combined synchronous strategy. For example, the patient might initially present predominantly as a vascular problem with background symptoms related to spinal disease or as a primarily spinal problem with significant vascular disease. In the common case of claudication symptoms, it could be unclear whether it was mainly as a result of spinal pathology, vascular ischemia, or both processes.

Some of these patients had critical vascular problems and should we have had to make a decision for an individual operation, it would have been the vascular surgery which would have "overridden" the spine procedure in importance, in an era where endovascular treatment of AAA was increasingly common. Generally, because of the requirement for a reconstruction with either a complicated stent for the large aortic aneurysms or iliac stenosis or a full aortoiliac or aortofemoral bypass, there would have been great difficulty and significantly increased hazard in attempting an anterior spinal operation subsequently, due to the presence of the reconstruction and significant adhesions. This would leave the patient with residual symptoms from untreated spine pathology.

The other situation was that some patients, with major spinal problems indicating treatment in their own right, were found to also have moderate severity vascular pathology that warranted treatment for prevention of a critical event and the vascular treatment in a staged fashion would make future anterior spinal surgery unsafe. This subgroup of patients were challenging either because of moderate aneurysmal change (4 cm or greater) or extensive atheroma. In these situations, there is an extreme risk of dissection, occlusion, and emboli even in the primary anterior spinal approach setting.

As such, we have developed a multidisciplinary planning and review approach and

this is necessary to inform all options for treatment to the patient, including our offering of an ability to control or repair the vascular disease along with lumbar spine reconstruction under the same anesthetic (Scott-Young et al. 2018b). Considering the need for major spinal reconstruction in someone also affected by moderate to severe vascular disease, we routinely explain the risks of a combined procedure, but that it is feasible to have the benefits of anterior spinal reconstruction if we were to resolve the vascular problem. Open anterior surgery was the best method for the spinal reconstruction notwithstanding the presence of a surgical vascular lesion and, given that vascular reconstruction was possible and indicated using the same exposure, this could potentiate treatment of the vascular lesions as well as excellent access for the spinal reconstruction. This approach also meant less trauma than if the surgeries were carried out independently of each other. We considered that overall there would be less physiological stress to the patient and less overall risk (i.e., from approach-related vessel injuries and adhesions) to the patient if we managed the problems in this way and also it would allow for repair in a group who would otherwise be excluded from the best option for reconstruction of their spine. It should be emphasized, however, that this approach is only undertaken after significant planning and discussion for suitable selected patients with combined disease.

In patients who we have assessed as moderate risk we prepare them for possible intervention at the time of surgery. This may require preparation for an open endarterectomy/thrombectomy (Figs. 28 and 29) if an occlusion occurs after the vessels are forcibly displaced or an angioplasty and stent in some of the higher-risk patients. The vascular surgeon has opted to place a guidewire at the commencement of the

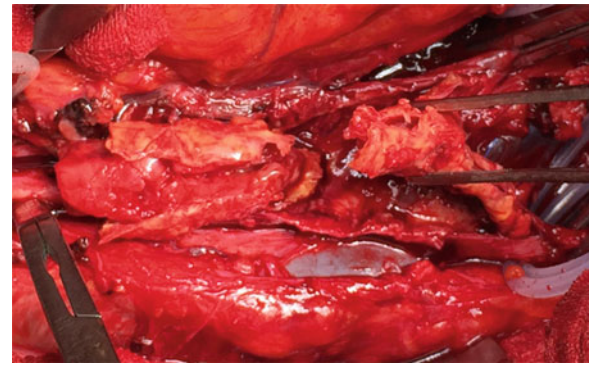

Fig. 28 Endarterectomy

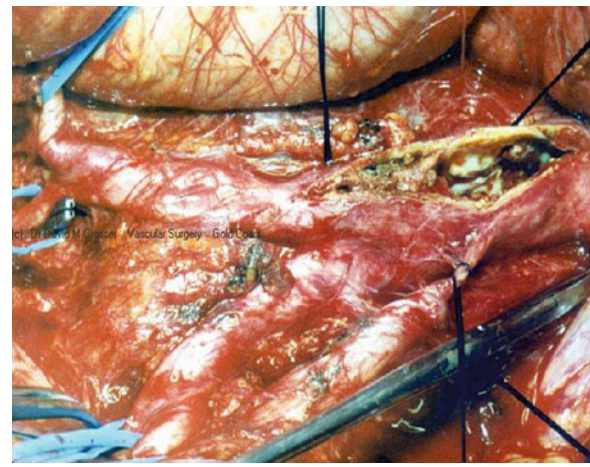

Fig. 29 Aortic iliac atheroma undergoing endarterectomy and thrombectomy

procedure so that we have immediate direct access into the artery.

As the patients required open access to the spine the decision on whether to use open repair for the aneurysms rather than endovascular depended on the fact that this was not more risky than endovascular procedures and, particularly, that in this younger group of patients, open reconstruction would be expected to give a long-lasting and durable result (in my own experience over 30 years) without the continued concern of "endoleak." "Endoleak" can occur in about 10% of endovascular AAA repairs and can present years after the intervention. Some of the vascular lesions we are presented with are extensive and circumferential or of the morphology that would make endovascular treatment difficult (see Figs. 30 and 31). The open approach would also be expected to reduce repeated exposure to CT irradiation and future risk. The same logic applies to management of the extensively diseased occluded aortas with iliac blockages also, where even with covered stent grafts, occlusive complications have been found to occur up to 10–15% with extended follow-up. The longevity with respect to the AAA reconstruction, if the patient survives 30 days postoperatively, is returned to normal.

Lesser vascular conditions require cover for the potential problems likely to occur at the time of surgery. We do this by having a vascular surgeon involved with the planning and risk stratification of selected cases and a plan for resolution if required. Be it an endovascular balloon and stenting of a stenosis or an occlusion associated with a dissection from ruptured plaque or an open endarterectomy or arterial thrombectomy, a vascular surgeon should be available for these contingencies. We are also

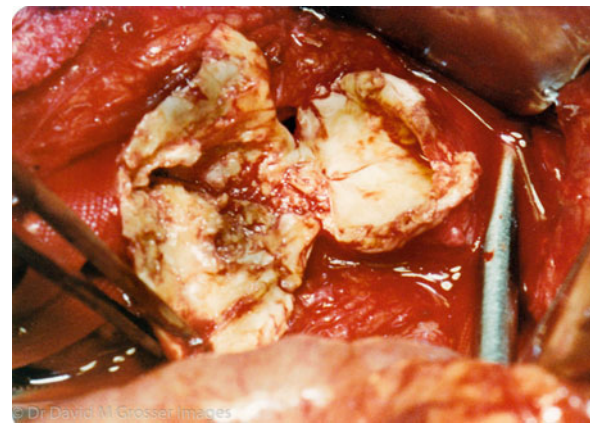

Fig. 30 Extensive circumferential atheroma

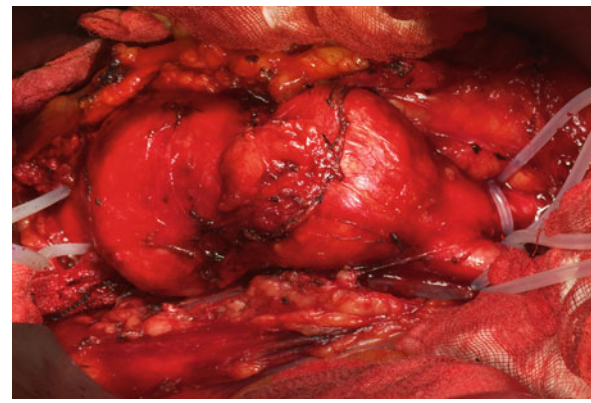

Fig. 31 Large saccular AAA prepared for reconstruction

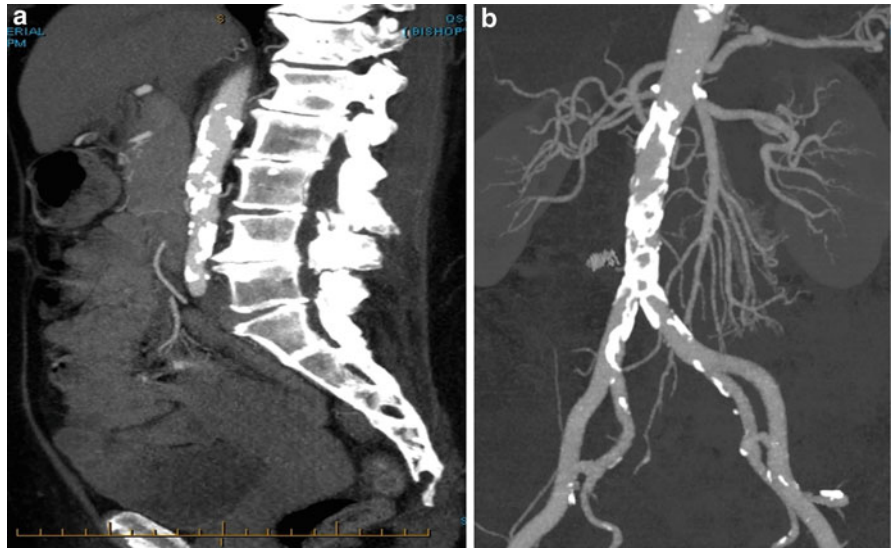

Fig. 32 The patient in this case was carefully approached for a major spine reconstruction but despite the care taken the plaque fractured and two iliacs occluded. This was corrected immediately by bilateral iliac endarterectomy and had no appreciable effect on recovery

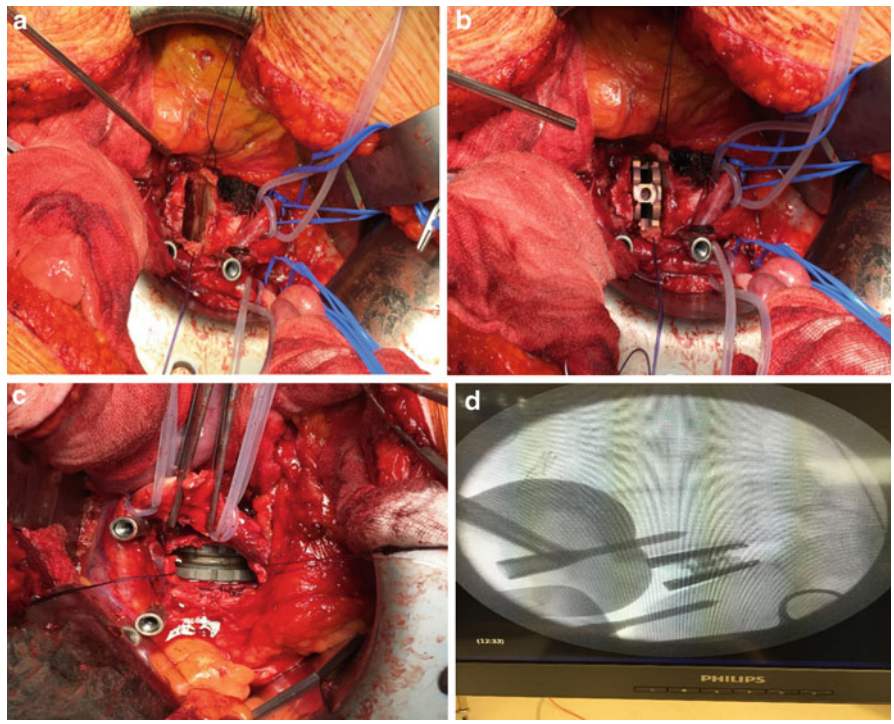

Fig. 33 Discectomy (**a**) and implantation (**b**–**d**) around open repair of aneurysm

prepared to perform an aorto-bi-Iliac or aorto-bi-femoral bypass with Dacron Gelsoft™ graft should a major problem occur (Figs. 32, 33, and 34).

As stated previously, when we are very concerned preoperatively, the vascular surgeon will place an endovascular wire or sheath via the femoral artery up to the diaphragm so that we have

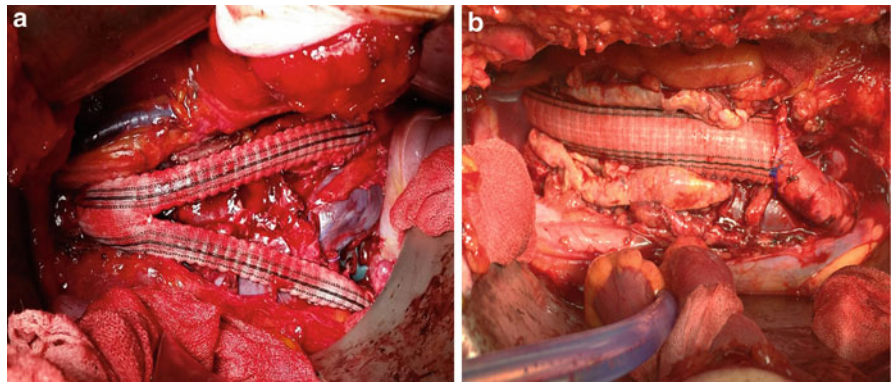

Fig. 34 Examples of aortoiliac treated openly via transperitoneal approach (**a**–**b**) combined with spinal reconstruction

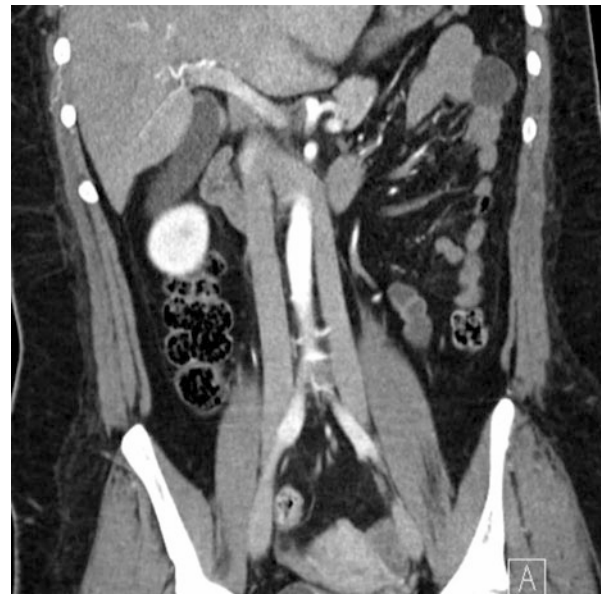

Fig. 35 Left IVC/ duplication – if it is a duplication, it can be divided if the common iliac bridges to the IVC on the right. If it is the sole or main system, it will need to be protected in the same manner as a normal IVC

a direct line for repair. It is just as important for venous control when approaching around the bifurcation at the IVC in redo surgery as there is a significant risk of tears, damage, or compression, which could result in massive bleeding or thrombosis. We have managed these with covered stent grafts when it was not possible to resolve the problem intraoperatively.

Vascular and Renal Anomalies and Variations

Duplication or left inferior vena cava with or without left iliac connection and retro-aortic vein are well described:

- If an angiogram has not been carried out, you might be surprised by a dual IVC, with the left side arising in the same area as the iliolumbar, or by a retro-aortic renal vein.
- Duplication or left IVC (see Fig. 35) can cause problems if not recognized and a standard retroperitoneal approach is used. The bifurcation is such that the best approach to L4-L5 is to the left of the aorta and superior to the left iliac artery. Before ligating this vessel make sure that the right IVC exists or you may create a problem equivalent to an acute vena caval obstruction (Fig. 36).
- A retro-aortic renal vein can cross under the aorta in the L2 or even L2/3 region (Fig. 37a, b) making sideward traction hazardous if not

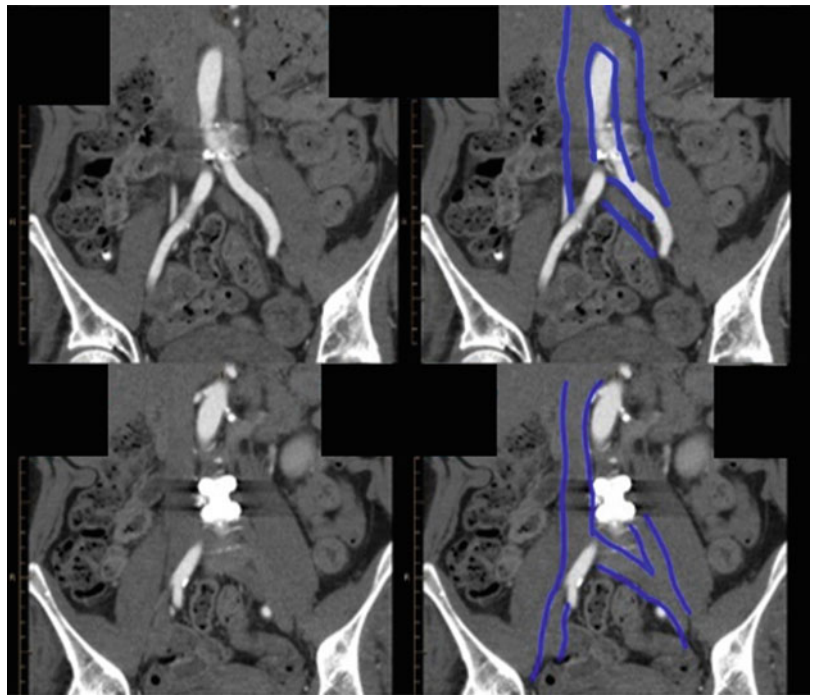

Fig. 36 Duplex IVC with a good left iliac vein; in this case the right IVC can be divided as long as adequate flow in left IVC. Not anticipated as problematic as discs requiring access are at L5-S1 and L3-L4

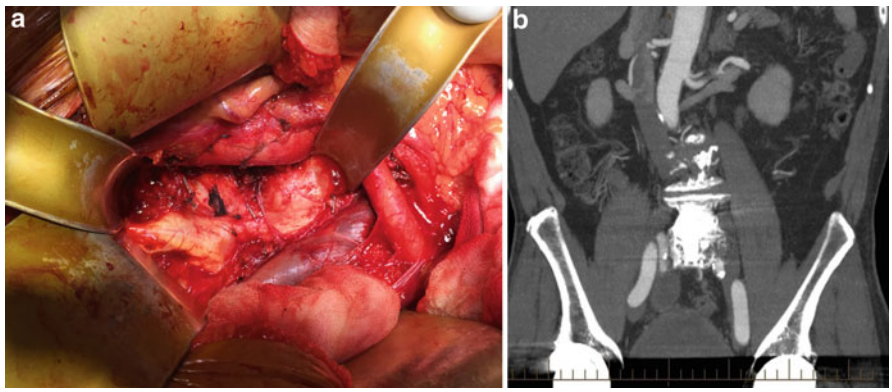

Fig. 37 Clinical (**a**) and coronal CT (**b**) images of a retro-aortic renal vein

recognized and anticipated. Consideration of whether to abandon planned treatment of a higher lumbar level needs to be given if it cannot be safely mobilized.

May-Thurner Effect: Severe Stenosis at Upper Common Iliac Vein Beneath Right Artery

Also known as iliocaval compression syndrome, the left common iliac artery compresses the left iliac vein against the L5 vertebral body. If this affected upper segment of the common iliac is traumatized requiring sutures or transverse clips, further compromise of the vein can occur. External pressure behind the vein after surgery that places plate and screws added to the anterior face of the spine can also limit the vein lumen by additional pressure. This can be resolved with stenting (Figs. 38 and 39).

Occlusion can also occur in this area secondary to emboli from the leg being trapped by the May–Thurner effect. The effect at revision

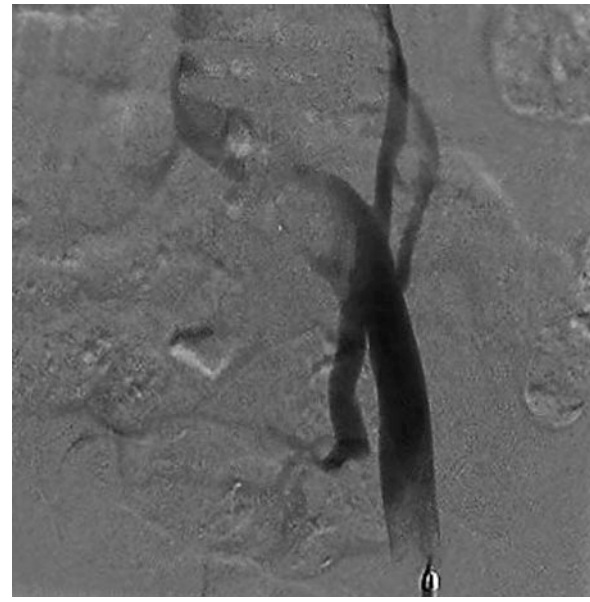

Fig. 38 Post-op external compression of iliac vein

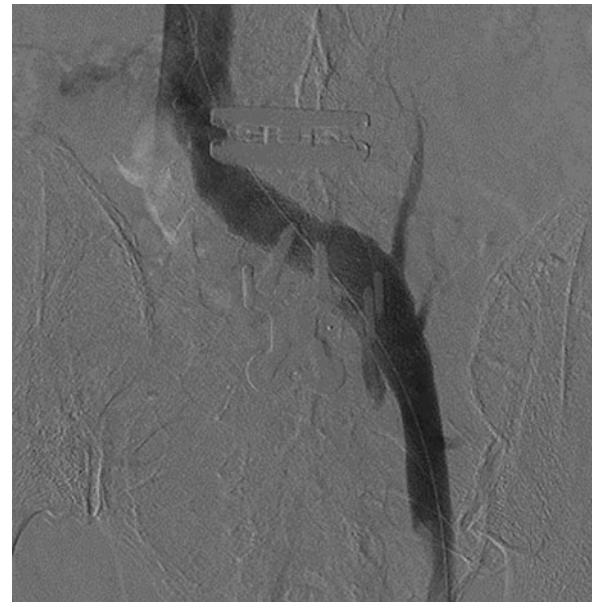

Fig. 39 Normal appearance of left iliac vein after stenting

surgery is a pelvis widely congested by large collateral veins that have developed to divert the venous flow (Figs. 40 and 41). This will make the area between the iliacs much more difficult to dissect and quite hazardous with coils of highly pressurized fragile vessels.

Untreated, the outcome can be chronic stenosis with distal congestion, a swollen leg clinically and the development of large pelvic collaterals (Figs. 41 and 42). A complete occlusion may result with the prospect of permanent stasis effects (Fig. 43).

If recognized, it would be sensible to consider recanalizing and stenting the main iliac venous system prior to any planned anterior spinal surgery as this would resolve the pressure problems and reduce the vascular compromise risk (Fig. 44a, b). The diagnosis might require a 3D CT venous angiogram to adequately assess the venous problem (Figs. 40 and 41).

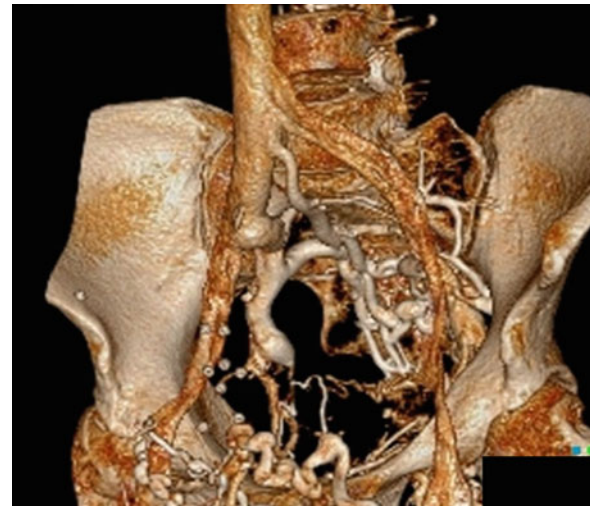

Fig. 40 3D venous angiogram demonstrates massive pelvic collateral shunts after left iliac thrombosis

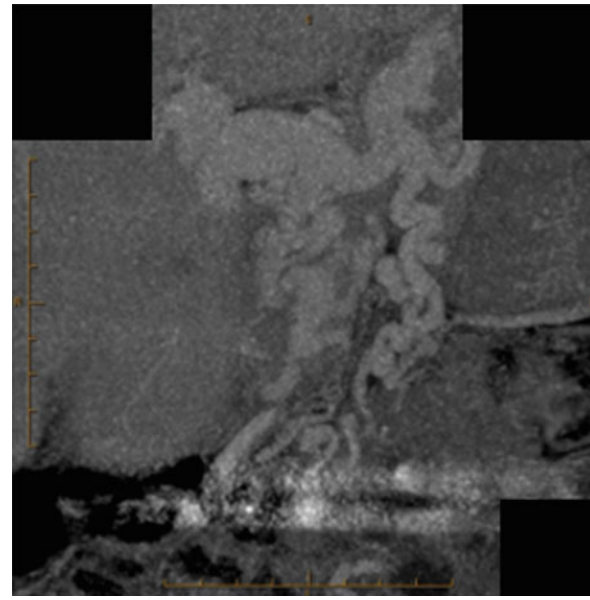

Fig. 41 Massive pelvic venous collaterals demonstrated on CT angiogram

Portal Vein Occlusion with Hypertrophy and Portal Hypertension

Other pathologies that cause significant intra-abdominal venous congestion include cirrhosis and portal vein occlusion and rare problems such as large portal vein aneurysms. These can substantially increase the hazard of the transperitoneal approach. If portal venous hypertension is recognized preoperatively it may be more appropriate to re-approach retroperitoneally in the revision setting.

Renal Anomalies: Low Lying or Horseshoe Kidneys

As well as the study of vessels on preoperative imaging, care should be taken to ensure that there are no renal anomalies that could make access dangerous or difficult. Examples of these are horseshoe kidneys that can obscure anterior access to the great vessels and low lying kidneys which often have associated anomalous vessels and pedicles that could be injured in the course of a standard retroperitoneal approach

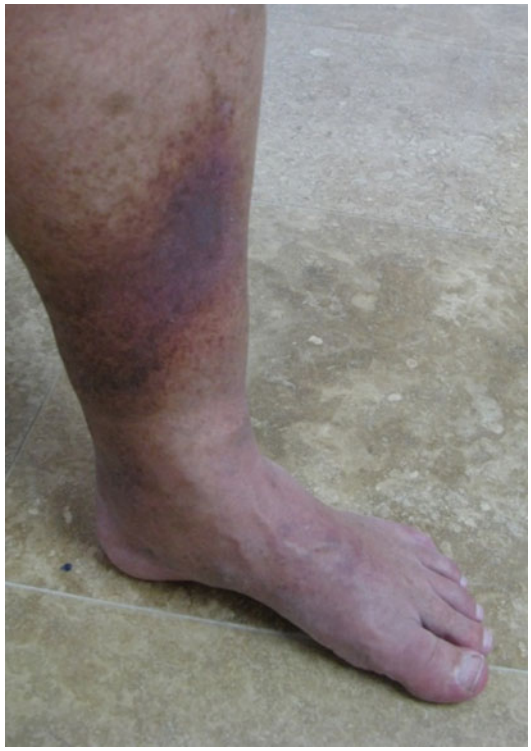

Fig. 42 Example of occluded iliac veins presenting with major leg swelling and stasis from iliac DVT 2 years after anterior spine surgery. The patient had been told nothing could be done to assist. Following treatment, the patient now has a patent vein system and normal functional leg

(see Fig. 44a, b). Preoperative consultation with a renal physician and determination of the differential function of each kidney is wise. In this case, a transperitoneal may be preferred to ensure that the renal pedicles do not undergo torsion as a result of the approach.

Postoperative Care

A team approach involving hospital medical staff and well-trained spinal nursing staff is important for prompt review of events related to anesthetic complications, hemodynamic instability, vascular events or neurological insult. Aggressive rehabilitation and specialty physiotherapy need to be involved preoperatively as well as postoperatively to guide and motivate the patients through appropriate perioperative conditioning, mobilization, and in-bed exercises to achieve optimal outcomes and restore functional motion. Judicious postoperative analgesic use is important to be run in conjunction with anesthesia, having regard from the often complex preoperative analgesia regimes these patients present with.

Ward care anticipating problems with anterior surgery is critical. Having an algorithm to manage ileus that commonly results with transperitoneal approach is helpful with regard to diet and fluid balance. For uncomplicated retroperitoneal surgery, a light diet is resumed the day following surgery. Close monitoring of the wound, patient pain control, and appropriate correction of any abnormalities in the patient's laboratory profile help to avoid complications. We aim to remove all drains and tubing (e.g., Painpump™, surgical drains) as soon as possible and complete only a short course of prophylactic intravenous antibiotics. An incentive spirometer is routinely provided as the pain from abdominal surgery can lead to splinting and atelectasis.

Regarding DVT prevention, we utilize low molecular weight heparin, mechanical calf measures and encourage high patient movement as an inpatient with outpatient aspirin and exercise prescribed until follow-up. 100 mg aspirin is prescribed as an outpatient until the first postoperative review.

We then monitor the patient routinely from a spinal point of view for follow-up then with close follow-up with a vascular surgeon for high-risk vascular patients. This includes not only radiological assessment to verify the efficacy of the correction performed but also clinical (outcome scores) and neurological (EMG) follow-up.

Conclusion

Anterior surgery for reconstruction of spine and related disorders is a vital approach to have in a surgeon's armamentarium. A variety of disorders such as degenerative, deformity, trauma, infection, and tumor can be best treated with the anterior exposure of the spine. The approach requires experience to achieve proficiency on the volume-performance curve and, in general, it is wise to have a close working relationship with a vascular surgeon.

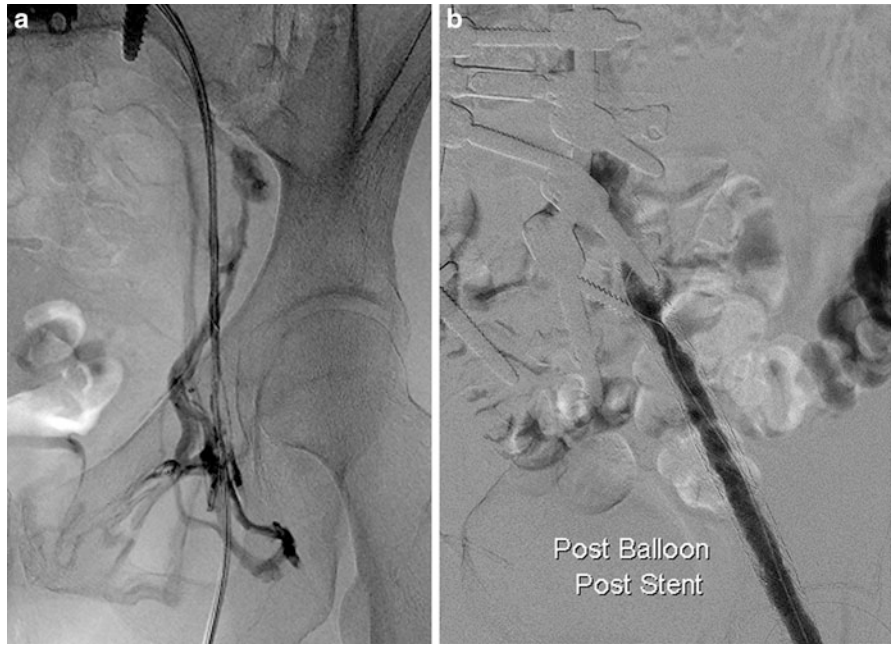

Fig. 43 (**a**) Left iliac vein occlusion. (**b**) Same case after recanalization and stent. Remains patent since, over 36 months

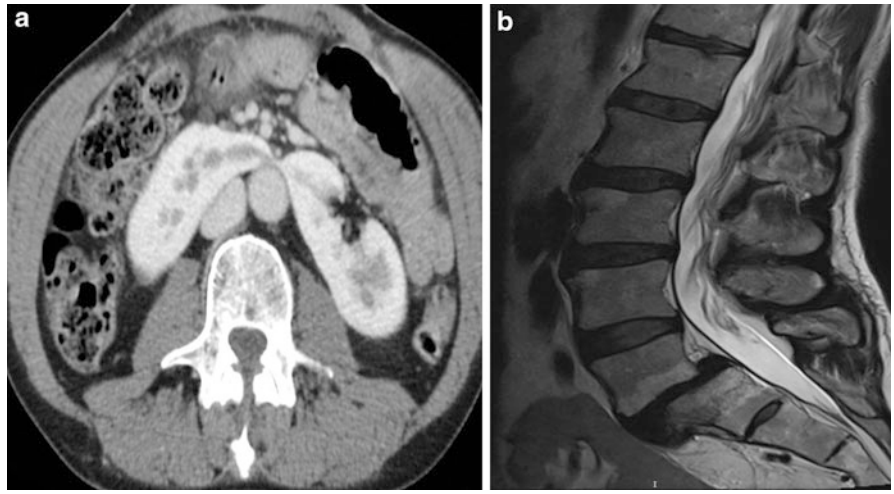

Fig. 44 Renal anomalies – (**a**) Horseshoe kidney overlying the great vessels (**b**) intrapelvic kidney lying in proximity to L5-S1 on a pre-op MRI of a patient to undergo correction of L5-S1 spondylolisthesis

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Part VII

Challenges and Lessons from Commercializing Products

Approved Products in the USA: AxiaLIF 65

Franziska Anna Schmidt, Raj Nangunoori, Taylor Wong, Sertac Kirnaz, and Roger Härtl

Contents

Abstract

Axial lumbar interbody fusion (AxiaLIF) was a device used to treat instability and disc degeneration in L4-L5 and L5-S1. Through a para-coccygeal incision and presacral approach, muscular and ligamentous dissection could be avoided. The discectomy and instrumentation was performed through via trans-sacral rod. AxiaLIF was approved in 2004 through a 510 (k) clearance from a predicate device which was an anterior thoracolumbar plate for trauma and deemed a class 2 device with a moderate risk to the patient. While early studies had encouraging results in terms of fusion rates and improvement in clinical outcome measures, most also had a conflict of interest. As the technology was rapidly adopted, the first reports of complications which were visceral injuries emerged casting doubt onto its effectiveness. Only a handful of studies focused on the long-term fusion rate, restoration of lordosis, and indirect decompression. In retrospect, it is apparent that the 510 (k) clearance and classification of the device was incorrect because the predicate was not substantially equivalent to the existing device. The experience with AxiaLIF provides a cautionary tale about new technology – that it should be safe, clinically effective, and have long-term data prior to rapid adoption.

Keywords

AxiaLIF · Para-coccygeal approach · 510 (k) clearance · Class 2 · Fusion rates · Restoration of lordosis · Indirect

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decompression · Axial lumbar interbody fusion

The Parabolic Phenomenon of a Surgical Technique

Innovation is an essential part of advancing patient care (Riskin et al. 2006; Scott 2001). All innovations at some point in time are new; the challenge is to differentiate what is safe from unsafe. The parabolic phenomenon of technological advancement was characterized by Scott et al. and starts with widespread enthusiasm and media coverage on the basis of early case studies. This provides confidence and leads to the rapid adoption of new technology as the next standard of care. As negative reports emerge, the initial enthusiasm disappears as the new device is used in gradually limited circumstances and ultimately, falls into disuse. According to this phenomenon, as complications emerge, surgeons must react quickly to warrant patient safety (Hamilton et al. 2012). In conclusion, the challenge is to introduce new devices and technologies in a way that would flatten this parabolic phenomenon and identify unsafe devices early on with no or minimal exposure to patients.

AxiaLIF as an Example for the Rise and Fall of an Approved Product in the USA

Axial lumbar interbody fusion (AxiaLIF) (Fig. 1) was FDA-approved in 2004 through a 510 (k) clearance (Rapp et al. 2011). The predicate was the K-Centrum Anterior Spinal Fixation System, which was an anterior thoracolumbar plate and screw system for trauma and degenerative spinal disease and deemed substantially equivalent.

In contrast to the predicate system, however, AxiaLIF was a novel para-coccygeal approach to the L5-S1 disc space for interbody fusion through a paracoccygeal incision. The purported advantages over traditional surgery included avoidance of neural retraction and access to the disc space for interbody fusion without muscular and ligamentous dissection. This device was FDA approved for the treatment of degenerative disc disease and spondylolisthesis at levels L4-L5 and L5-S1 (Marotta et al. 2006). Importantly, this approach was seen by early adopters as an attractive option for fusion surgery in patients who had contraindications for traditional ALIF surgery at L4-5 and L5-S1. In addition, AxiaLIF was the first true minimally invasive option (MIS) for the L4-5 and L5-S1 levels as MIS approaches gained popularity with techniques such as lateral lumbar interbody fusion (LLIF). The advent of LLIF was in parallel with MIS approaches to spinal deformity correction; however, direct lateral access to L5-S1 had not yet been described. As a result, the presacral approach from AxiaLIF was an attractive alternative (Anand et al. 2008, 2010, 2014a, b; Boachie-Adjei et al. 2013). In retrospect, it is clear that the AxiaLIF had little in common with its predicate – a thoracolumbar anterior plate system. As described in Scott's parabolic model (Hamilton et al. 2012), the first studies were favorable – but most of them were retrospectively designed and included technical publications and retrospective case series touting the safety and efficacy of the approach (Fig. 2). The case series were promising because of the surgical corridor which obviated the need for an access surgeon, lack of critical structures in the presacral space, decreased operative time, and blood loss (Marotta et al. 2006; Aryan et al. 2008). This initial enthusiasm, driven by the results of several case studies, the presumed advantages, and the possibility for an MIS approach for fusion at the caudal lumbar levels in patients whom traditional approaches were contraindicated led to adoption of the technique by many surgeons. In 2010, the first case report describing a complication was published on a patient who suffered from a rectal injury during an AxiaLIF procedure at L5-S1, which led to an ileostomy (Botolin et al. 2010). In 2011, surgeons witnessed cases of failed multisegment AxiaLIF instrumentation. Revision strategies for AxiaLIF were, therefore, developed and were performed via anterior and posterior approaches (Hofstetter et al. 2011). In the same year, a group of surgeons published their experience after a 34-month follow-up with 68 patients who underwent AxiaLIF

surgery. The overall complication rate was high at 26.5%, ranging from rectal perforation (2.9%), infection (5.9%) to pseudoarthrosis (8.8%). In contrast to the early case series, the authors had no conflict of interests (Lindley et al. 2011). In 2012 and 2013, numerous studies reported after AxiaLIF diminished disc height compared to the preoperative status as well as a loss of segmental lordosis. In these publications, pseudoarthrosis rates were high and mounting evidence from the spinal deformity literature was suggestive of the importance of lordosis, particularly at L4-5 and L5-S1 for sagittal balance, independent of fusion rates (Marchi et al. 2012; Hofstetter et al. 2013; Anand et al. 2014c). Due to improvement in some pain scale metrics (Oswestry Disability Index, Visual Analog Scale), the use of AxiaLIF continued despite a growing body of evidence demonstrating visceral complications, pseudoarthrosis, loss of lordosis, and technical reports describing revision strategies for failed AxiaLIF. For instance, some publications reported a decrease in back and leg pain with follow-up ranging from 2 to 6 years (Zeilstra et al. 2013; Tobler et al. 2013). Furthermore, a systematic literature review from 2015 demonstrated that AxiaLIF had a fusion rate of 93.15% (Schroeder et al. 2015). Interestingly, despite high fusion rates and improvement in pain scores, the authors of this systematic review concluded that AxiaLIF had a high complication rate (12.9%) and that the published literature on AxiaLIF was dominated by retrospective case series with many having conflicts of interest (Fig. 2). Follow-up of patients from the initial publications demonstrated that in long constructs for adult spinal deformity, AxiaLIF was not a good choice and an Anterior Lumbar Interbody Fusion (ALIF) was substantially better at L5-S1. The reported complication profile, morbidity of the approach, failure to achieve lordosis, and mounting evidence of need for revision surgery ultimately led to the demise of AxiaLIF (Anand et al. 2017, 2018) (Fig. 3).

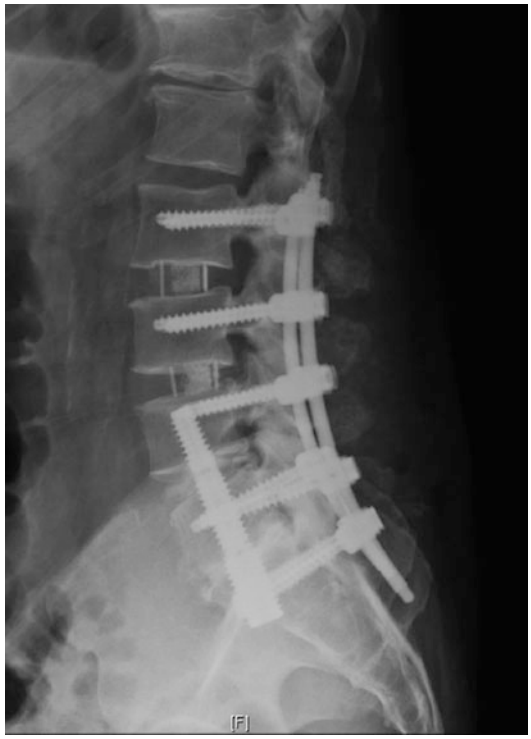

Fig. 1 X-ray showing a L2-S1 fusion with L4-S1 AxiaLIF implant

Initially, surgeons looked at improvement in pain and fusion rates, but sagittal balance and other biomechanical metrics such as pelvic

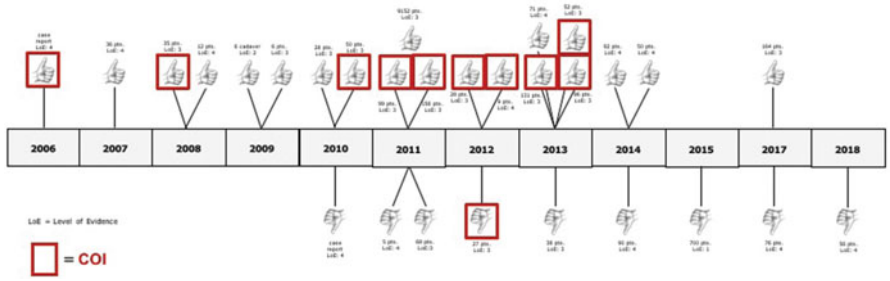

Fig. 2 Graph demonstrating the timeline of AxiaLIF publications and their overall, either positive or negative, conclusion and reported conflict of interest. The graph also illustrates the number of patients and the level of evidence

	Indirect Decompression (Volume change)	Restoration of Lordosis	Fusion rates	
2006	-	-	-	Marotta et al.
2007	-	-	-	Stippler et al.
2008	-	-	✓	Aryan et al.
	-	✓	-	Anand et al.
2009	-	-	✓	Luther et al.
	-	-	-	Erkan et al.
2010	-	✓	✓	Anand et al.
	-	-	-	Botolin et al.
	-	-	✓	Bohinski et al.
2011	-	-	-	Gundanna et al.
	-	-	✓	Tobler et al.
	-	-	-	Hofstetter et al.
	-	-	-	Lindley et al.
	-	-	✓	Gerszten et al.
2012	-	-	✓	Bradley et al.
	-	✓	✓	Marchi et al.
	-	✓	✓	Issack et al.
2013	-	✓	✓	Anand et al.
	-	-	✓	Tobler et al.
	-	-	✓	Zeilstra et al.
	-	✓	✓	Hofstetter et al.
	-	-	✓	Whang et al.
2014	-	✓	-	Anand et al.
	-	-	✓	Anand et al.
	-	✓	✓	Anand et al.
2015	-	✓	✓	Schroeder et al.
2017	-	-	✓	Zeilstra et al.
	-	✓	-	Anand et al.
2018	-	✓	✓	Anand et al.

L5/S1 Surgery Goals:
- Study without presenting data on fusion rates, restoration of lordosis, or indirect decompression.
✓ Study, which is presenting data on fusion rates, restoration of lordosis, or indirect decompression.

Fig. 3 Figure demonstrating whether AxiaLIF study presented data on fusion rates, restoration of lordosis, or indirect decompression

incidence, lumbar lordosis, sacral slope, and pelvic tilt were not primarily examined. In the early years of AxiaLIF, a series of company sponsored meetings were organized and the "Association of Presacral Spine Surgeons" was established with the idea of bringing together surgeons who were interested in this novel presacral approach. One of the authors of this present chapter (RH) remembers

a meeting in 2009 when the presented cases clearly showed adequate fusion but the absence of lordosis and lack of restored disc height at L5/S1. This led to heated discussions among the contestants. Ironically, AxiaLIF emerged as a surgical technique at the same time that the influential work by Glassman et al. established the significance of lumbar lordosis to long-term patient outcomes, which began an era of investigation into global spinal alignment parameters (Glassman et al. 2005). Since 2012, and after several years of thorough follow-up, one of the initial authors of AxiaLIF (NA) utilized national seminars to repeatedly caution against using AxiaLIF at the bottom of long constructs for cases of adult spinal deformity. The limitations with the AxiaLIF technique were published by the same author (NA) in 2014 (Anand et al. 2014c). It is now understood that these global metrics may be substantially more important to patient outcomes than high fusion rates alone.

The rise and fall of an approved product in the USA such as AxiaLIF is a great example demonstrating the necessity for constant follow-ups, reflection, timely reporting, the recognition of a significant complication profile, and the failure to address sagittal alignment parameters, which were beginning to be understood as an increasingly important surgical goal, especially at L4/5 and L5/S1 (Schroeder et al. 2015). The predicate for AxiaLIF was the K-Centrum Anterior Spinal Fixation System, a device that was not equivalent to AxiaLIF in terms of the type of implant or access corridor, but received 510 (k) clearance anyways, demonstrating a loophole in the approval process. In retrospect, AxiaLIF should have been mandated as a class 3 device with an attention to safety, subsidence, indirect decompression, restoration of lordosis, and fusion rate.

Conclusions

The lesson to be learned from this failed product is that rapid adoption is not advisable unless independent groups can verify the data obtained by studies that may have conflicts of interest. For instance, Bisschop et al. described that the market approval process for all new spinal device implants should include at least one randomized controlled trial (Bisschop and van Tulder 2016). If favorable results are reported, this randomized controlled trial should then be repeated by different investigators and compared to the standard surgical device or product. In addition, Bisschop's publication also advocated for multi-institutional follow-up for at least 5 years to track long-term outcomes. In the case of AxiaLIF, one group of surgeons followed the recommendations outlined by Bisschop et al. and found that it was not an optimal device during long-term follow up with their patients, despite promising early results (Anand et al. 2008, 2010, 2013, 2014a, b, c, 2017, 2018).

The experience with AxiaLIF provides a cautionary tale about the enthusiastic adoption of new technology. New technology should be safe, clinically- and cost-effective, improve patient outcomes, and at least match the standard of care. Long-term data characterizing safety and effectiveness, without conflicts of interest, are essential. In addition, it also demonstrates that the goals of surgery may evolve and shift over time. When this occurs, the technology should undergo a thorough evaluation to determine whether it fits in the current clinical framework. In the case of AxiaLIF, our understanding of the importance of global sagittal alignment parameters and indirect decompression had significantly advanced by the time AxiaLIF was being utilized. The failure of AxiaLIF should not hamper innovative surgical techniques – but does provide lessons into the importance of long-term data and the duty of surgeons to ensure patient safety and outcomes (Bisschop and van Tulder 2016; Herndon et al. 2007) (Figs. 2 and 3).

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Spine Products in Use Both Outside and Inside the United States

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Tejas Karnati, Kee D. Kim, and Julius O. Ebinu

Contents

Abstract

The spine product market in the United States and that of the rest of the world shares many similarities but also has significant differences. The FDA approval process of medical devices in the United States has a more stringent, often inconsistent, and prolonged pathway to final approval than when compared to the CE marking process in Europe. In fact, a large number of spinal implants have not yet been either approved or used as widely in the United States as compared to the rest of the world. There are three main spine product categories, namely lumbar artificial discs, interspinous spacers, and dynamic stabilization systems that can be identified as "new" and not as widely used in US markets. After analyzing why some of the products in these categories failed the FDA approval process, we present other unique spine products widely used in European and other international markets but not so commonly seen in US markets.

Keywords

Spine products · CE marking · FDA · Medical devices · Premarket approval · Dynesys · DIAM · Barricaid · LimiFlex · M6-L · Helifix

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Introduction

Spinal pathology is one of the most common health problems patients face in North America. Management of such pathology is associated with increasingly high healthcare costs (Raciborski et al. 2016). While the aging population is an important factor associated with these costs, another contributing factor includes the market approval process of spinal implants. According to a recent study in 2017, the global spinal product market is valued at over $14.4 billion USD and is projected to reach $18 billion USD by 2023 (https://idataresearch.com/product-category/spine/). The United States, with its vast medical resources and large population of spine surgeons, is undoubtedly the largest spinal product market, valued at $7.7 billion USD in 2017. In contrast, the European spinal market's total value is just over one-quarter the size of the US at $2.05 billion USD. Interestingly, China is the fastest growing market and, as of this writing, has surpassed the combined market value of 15 countries in Europe at $2.73 billion USD (https://idataresearch.com/product-category/spine/). The purpose of this chapter is to focus on the spine product market in the United States and highlight the differences with those of the European and international markets.

Given the enormous economic impact of spinal products in the healthcare systems of both the United States and Europe, it is imperative to understand the differing spinal products that are available for use in both continents. Additionally, an appreciation of the subtle differences in the approval processes of medical devices in the United States compared to Europe, and an analysis of why some products failed the US Food and Drug Administration (FDA) approval process, will provide further insight into the underlying differences between the two continents.

For the purposes of this chapter, we will focus on three specific spinal product categories: dynamic stabilization systems, artificial intervertebral discs, and interspinous and interlaminar stabilization/distraction devices. These categories were specifically chosen because of the relatively sparse usage of such devices in the US market when compared to the European and other international markets. Each of these product categories has specific examples of products that are either not widely used in the United States or not even approved at all by the FDA. In order to understand why certain products are not available in the US market whereas the same products have been widely used in Europe for many years, a thorough understanding of medical device regulations is important.

Therefore, we will first describe the FDA approval process of such spinal implants and compare and contrast it with respect to the European medical device regulatory process. We will then specifically discuss three case studies of spine products (the Dynesys® Dynamic Stabilization System, the Barricaid® Annular Closure Device, and the DIAM® Spinal Stabilization System) that failed to meet the rigors of the FDA approval process and shed light on the circumstances that led to their failure. Lastly, we discuss products that are not yet approved by the FDA in the United States but are widely used in the European and other international markets. Although there are a myriad of financial, regulatory, and clinical factors that contribute to the differing spine products in use among the US and European markets, we will attempt to highlight three case studies of spine products currently only approved in the European market: the M6®-L Lumbar Artificial Disc, the Helifix® Interspinous Spacer System, and the LimiFlex™ Spinal Stabilization System.

FDA Approval Process Compared to the European Process

From the standpoint of the FDA, medical devices are categorized into three regulatory classes (Sastry 2014). The medical devices that have the lowest risk of causing harm (i.e., thermometers, tongue depressors) are categorized as Class I medical devices. Devices that have some potential harm (i.e., powered wheel chairs, pregnancy test kits) are categorized as Class II medical devices and typically require premarket notification 510(k). Class III devices present significant risk and most require premarket approval (PMA) (Sastry 2014).

Most spinal products fall under Class II and Class III designation.

When a device manufacturer submits a 510(k) premarket notification, the manufacturer must demonstrate that the device is at minimum as safe and as effective ("substantially equivalent") to another already existing legally marketed device ("predicate device") (Rome et al. 2014). In their submission documents, the device companies must compare their device to the predicate device and demonstrate substantial equivalence. In order to meet the requirements of "substantial equivalence," the device must have the same intended use as the predicate device but not necessarily the same technological characteristics (as long as the device does not raise new questions of safety and effectiveness) (Rome et al. 2014).

The Premarket Approval (PMA) process is usually required for devices that pose a significant risk of illness or injury (i.e., Class III devices) or even devices that were found not substantially equivalent to Class I or Class II predicate devices through the 501(k) process (Lauer et al. 2017). Typically, the PMA process occurs in four steps: limited scientific review, in-depth review, advisory panel review, final deliberations and decisions for previously unapproved devices (Lauer et al. 2017). During the limited scientific review part of the process, the FDA will decide whether or not to file the submission at all; instance in which the FDA will refuse to file a submission are not uncommon. If information is incomplete, unclear, or would not stand up to scientific scrutiny, the FDA may refuse to even go forward with filing. During the in-depth review part of the process, the agency will evaluate the device's safety and effectiveness (French-Mowat and Burnett 2012). Safety and efficacy are typically demonstrated through clinical trials and scientifically validated research. The key difference of the European approval process with that of the US is the focus on "efficacy" (French-Mowat and Burnett 2012; Sorenson and Drummond 2014). As we will see later, the European approval process is predicated on safety but not necessarily "efficacy." The third step is the advisory panel review, which consists of a panel of experts independent of the FDA that hold a public meeting. After conclusion of the meeting, the advisory committee submits a final report to the FDA. In the fourth and final step, the FDA will issue either an "approval order," an "approvable letter," a "not approvable letter," or an order denying approval (French-Mowat and Burnett 2012; Sorenson and Drummond 2014).

Often, in order to gather safety and effectiveness data to support a PMA application or a 501(k) submission, the FDA can grant an investigational device exemption (IDE) to a medical device. An IDE allows the investigational device to be used in a clinical study (Ament et al. 2017). Therefore, some of the products that we will discuss later on in the chapter are currently being used under an investigational device exemption until further data can be obtained.

In contrast to the FDA medical device approval process, the CE Mark is a certification mark that indicates conformity with health, safety, and environmental protection standards for products sold within the European Economic Area (EEA) (Mishra 2017). The key difference between the US and European approval processes lies in a device's "efficacy." In the US approach, the FDA assesses the device's effectiveness as well as its risk of harm; however, the CE mark indicates simply that the medical device satisfies certain high safety, health and environmental protection requirements (Mishra 2017). In short, the FDA approval process ensures that a device both poses no harm to consumers but also does what it claims to do. The US approach is not without its critics, who argue that this dual goal of "safety and efficacy" adds inordinate time and unpredictability to the approval process without in fact establishing the effectiveness of the device (Heneghan and Thompson 2012).

With its unpredictable, inconsistent, prolonged, and often expensive path, the FDA's approval process is widely considered more cumbersome than the CE marking process (Heneghan and Thompson 2012). Typically, there is a 1- to 3-year delay in launching new medical devices into general clinical practice in the US compared to in Europe according to a 2012 report by the Boston Consulting group after analyzing approvals from 2000 through 2011 of devices

that were "the most innovative and potentially risky medical technologies" (those requiring PMA) (Kramer et al. 2012). Nevertheless, while the CE mark may be less arduous to obtain, some argue that it is a less powerful certification (Mishra 2017). Especially after the widely publicized breast implant scandal of the early 2000s, in which a French company sold silicone implants (which had CE mark approval but not approved by the FDA) that were later recalled after it was found they had been fraudulently manufactured with unapproved silicone gel, the FDA approval process is sometimes seen as safer for consumers (Lampert et al. 2012). Interestingly, the FDA approval means that the device is approved for use in many parts of the world, while the CE mark has restrictions, sometimes even within the EU. Importantly, even though a medical device has a CE marking, there is no guarantee that the device will be widely accepted by physicians or reimbursable by the government in each European country (https://www.ecnmag.com/article/2012/02/which-way-go-ce-mark-or-fda-approval).

Case Studies of Failed Spinal Products in the United States

Having established the important differences and similarities of the medical device approval process between the United States and Europe, we now turn our discussion to three specific spinal products that failed the FDA approval process: Dynesys® Dynamic Stabilization System (Zimmer Biomet), Barricaid® Annular Closure Device, and the DIAM® Spinal Stabilization System.

Before a discussion of Dynesys or any other pedicle screw-based dynamic stabilization systems can be had, the principle of dynamic stabilization must be described. Dynamic stabilization, also known as soft stabilization or flexible stabilization, involves insertion of flexible materials rather than the traditional rigid ones to allow some movement along the instrumented area of the spine (Tyagi et al. 2018). Essentially, dynamic stabilization devices place the posterior structures under tension and create a focal increase in lordosis. This process may shift load transmission so that certain positions are more tolerable and may limit motion so that painful positions are not experienced (Gomleksiz et al. 2012). As of this writing, no dynamic stabilization devices have received approval from the FDA for use other than as an adjunct to spinal fusion. Once of these dynamic stabilization systems, the Dynesys® Dynamic Stabilization System by Zimmer Spine, was not granted a PMA initially by the FDA for standalone dynamic stabilization and then later was only approved as an adjunct to spinal fusion.

According to the FDA, the Dynesys® Dynamic Stabilization System is intended to "provide immobilization and stabilization of spinal segments as an adjunct to fusion in the treatment of and following acute and chronic instabilities or deformities and failed previous fusion" (https://www.accessdata.fda.gov/cdrh_docs/pdf6/K060638.pdf). The device consists of a titanium alloy pedicle screw and a spacer that consists of surgical polyurethane that holds the vertebrae in a more natural anatomical position; a nylon-like cord runs through the spacers and is pulled taut to limit flexion movements (see Fig. 1) (Dynesys Dynamic Stabilization System 2015).

Initially, Dynesys was granted a 501(k) clearance in March 2004 since it was considered to be "substantially equivalent" to the Silhouette® spinal fixation system. However, the Dynesys system as a standalone device for non-fusion stabilization was later recognized by the FDA as a new type of treatment, and consequently Zimmer Biomet had to apply for a PMA. On the 4th of November 2009, the PMA application for this device was rejected (https://medtech.pharmaintelligence.informa.com/MT028146/Panel-Rejects-Zimmers-Dynesys-Spine-Stabilization-Device).

The Dynesys system was rejected by the FDA despite initially being granted a 501(k) approval. Although the Dynesys system was considered to be substantially equivalent, it should have been regarded as a new dynamic stabilization technique as opposed to a new type of posterior technique (Bisschop and Van Tulder 2016). The Dynesys system thereby received its 510(k) approval long before the first and only randomized control trial was conducted (Bisschop and Van Tulder 2016).

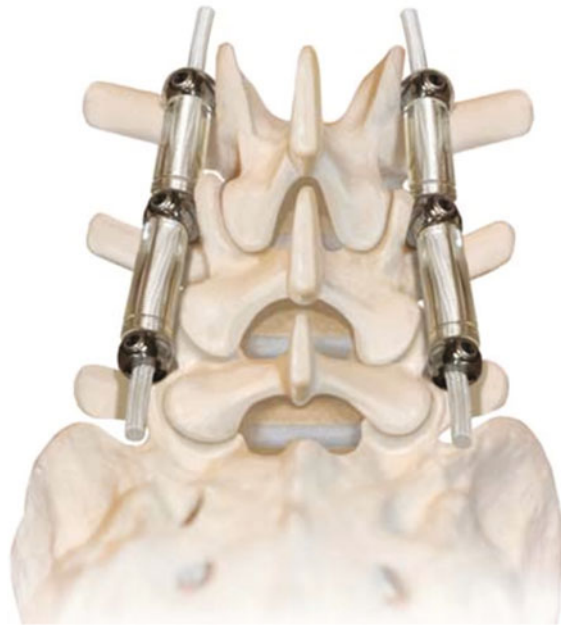

Fig. 1 Dynesys device with titanium pedicle screws, polyurethane spacers and nylon cord the limits flexion (Dynesys Dynamic Stabilization System 2015)

During this time period where there was little published research, the device was in clinical use in Europe since 1999 with over 40,000 patients receiving implants. Consequently, there was not enough evidence in the period between the 510(k) approval and the rejected PMA application to determine whether this device resulted in improved health outcomes compared to standard treatments (Bisschop and Van Tulder 2016). Indeed, short-term clinical results seemed favorable, while long-term complications arose: screw loosening, adjacent segment degeneration, late infection. In a 2010 study of 71 patients undergoing decompression using the Dynesys stabilization system, radiographic evidence of screw loosening occurred in 19.7% of patients (Ko et al. 2010). Of note, the radiographic findings of screw loosening failed to show any associated adverse effect on clinical improvement. The FDA reviewers also pointed to potential bias in the company's study, noting that a majority of patients were treated by researchers with a financial interest in the company. Admittedly, this bias could have been due to chance which would further question the relevance of such a bias claim (Ko et al. 2010).

Another example of a spinal product that failed the FDA's PMA process is the DIAM® Spinal Stabilization System by Medtronic. The device is an "H" shaped silicone and woven polyester device which is sandwiched between two adjacent spinous processes of the lumbar spine (see Fig. 2) (Phillips et al. 2006; DIAM™ 2019).

Once seated in the interspinous space, the device is secured by polyester cables and titanium crimps. This design helps stabilize movement in both flexion and in extension (Phillips et al. 2006). Medtronic described to the FDA that the device was intended to alleviate pain "through the reduction of stresses on the overloaded posterior disc and facet joints," while it "re-tensions the supraspinous ligament and other ligamentous structures" (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM486374.pdf). It was first implanted in France in 1997 and has been used for more than 10 years outside the United States (Hrabálek et al. 2009). However, on February 19, 2016, the FDA's orthopedic and rehabilitation devices advisory panel unanimously recommended rejection of Medtronic's DIAM® spinal stabilization implant (https://www.fiercebiotech.com/medical-devices/fda-advisory-panel-votes-against-recommending-approval-medtronic-spine-implant).

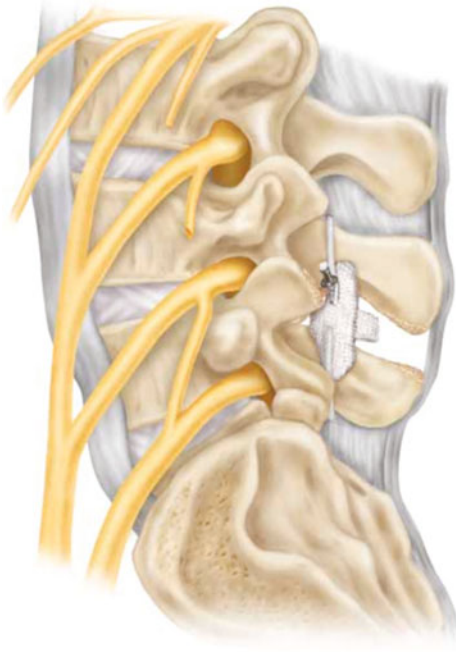

Fig. 2 DIAM® Spinal Stabilization System (DIAM™ 2019)

According to the analysis of the pivotal clinical trial, the FDA expressed significant concerns with the study design. The study population was too heterogenous; there were multiple, potential diagnostic subgroups included in clinical trial. Some of the investigational and nonoperative control subjects were subsequently treated with surgery at adjacent levels, or surgery involving more than one spinal level (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM486692.pdf). Furthermore, the screening algorithm was also questioned. It was unclear how a symptomatic level was identified in subjects with multilevel degenerative spinal pathology, whether if subjects had subacute versus chronic degenerative spinal pathology, or if subjects were experiencing primary versus recurrent low back pain. Moreover, some patients randomized to the DIAM® group were allowed to undergo the same nonoperative treatments as the control group. Investigational and nonoperative control patients were also free to pursue non-prescription therapies such as massage and acupuncture. In addition, 60.8% of all of the nonoperative control patients crossed over to receive treatment with the DIAM® investigational device after at least 6 months of treatment lending itself to potential bias on the estimate of the treatment effect (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM486692.pdf).

Perhaps the most controversial of the list of concerns that the FDA had were the observed radiographic spinous process erosions and fractures. In the pivotal study, a total of 44.0% (37/84) of subjects were observed to have had an erosion at either the superior or inferior spinous process (or both locations) at 36 months (Crawford et al. 2013). Superior spinous process fractures were observed by the core laboratory in 7.7% (14/181) of the DIAM® subjects at the 12 months timepoint (Crawford et al. 2013). Medtronic representatives pointed to the fact that published literature has documented that plain radiographs may lack sensitivity for the detection and diagnosis of spinous process fractures in subjects with interspinous process spacer devices (https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/OrthopaedicandRehabilitationDevicesPanel/UCM486692.pdf). Despite numerous appeals by Medtronic, the DIAM® Spinal Stabilization System is currently only approved for use as an investigational device until further data can be obtained.

Finally, our discussion of case studies of FDA medical device approval failures will end on the Barricaid® annular closure device. The Barricaid® annular closure device is a permanent implant that is used after a limited lumbar discectomy is performed. The device consists of a polymeric mesh that sits in the posterior intervertebral disc space and is connected to a metallic anchor that is attached to the vertebral body and essentially blocks an opening in the anulus, thereby preventing re-herniation of the nucleus pulposus (see Fig. 3) (Parker et al. 2016; Hahn et al. 2014). The device is particularly effective in patients in whom a limited discectomy is performed with resulting large annular defects and a higher chance of re-herniation. More specifically,

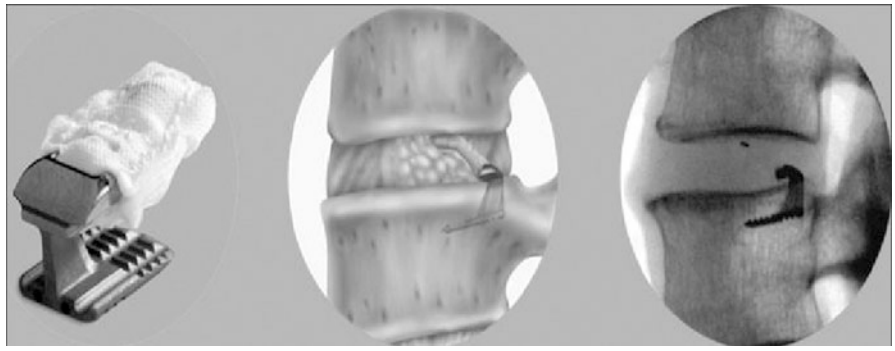

Fig. 3 A metal anchor is inserted parallel to the surface of the endplate and the polymeric mesh forms a barrier that prevents re-herniation of the intervertebral disc (Hahn et al. 2014)

it was indicated in patients with radiculopathy (with or without back pain), a posterior or posterolateral herniation, characterized by radiographic confirmation of neural compression using MRI, and a large annular defect (e.g., between 4 and 6 mm tall and between 6 and 12 mm wide) determined intraoperatively post discectomy, at one level between L4 and S1 (Hahn et al. 2014).

Barricaid's company, Intrinsic Therapeutics, initially submitted an Investigational Device Exemption (IDE) to start a clinical trial in the United States but the IDE was never approved due to safety concerns, so the company performed clinical trials outside of the United States (OUS), including a randomized clinical trial (RCT), to support initiation of a US clinical study (Ledic et al. 2015). FDA and Intrinsic therapeutics never reached consensus on OUS study design, associated protocols, or documents, but the RCT clinical data and nonclinical studies were submitted in a PMA (Ledic et al. 2015). The clinical trial included 554 randomized patients (Klassen et al. 2017). Its purpose was to determine whether a microdiscectomy with a bone-anchored annular closure device resulted in lower re-herniation and reoperation rates and increased overall patient clinical success, when compared to traditional lumbar discectomy without defect closure. The group treated with Barricaid had significantly lower rates of re-herniation (12% vs. 25%, $P < 0.001$), reoperations to address recurrent herniation (5% vs. 13%, $P = 0.001$), and index-level reoperations (9% vs. 16%, $P = 0.01$). However, one main criticism was the high rate of end-plate lesions in the Barricaid group. Eighty-eight percent of the patients receiving Barricaid had endplate changes versus 40% of control patients. The control patient's changes were smaller on average and appeared to stabilize sooner than the Barricaid patient's changes. The Barricaid endplate changes were larger and had a distinctive radiographic feature – according to the FDA's radiologist. Furthermore, some of these endplate changes were lytic in nature and were radiographically distinct from Schmorl's nodes and endplate changes. Furthermore, there were also device integrity issues in the clinical study. The study collected data on 63 implant and instrument retrievals during the study and commercial use and found that the average retrieval was 2.4 ± 1.8 years (Range = 0.1–5.8 years) after implantation (Ledic et al. 2015). The implant was removed primarily due to mesh detachment, migration, new or worsening pain, and/or instability (Ledic et al. 2015). For all these concerns, the FDA panel voted on December 2017 against approval.

Spine Products Approved Outside the United States

After having discussed those products that have failed the FDA approval process, we now turn our attention to those products that are widely used in the European market but not yet approved or widely used in the United States. There are three categories of spinal implants that are currently used widely in the European and other international markets but for a myriad of reasons are not so commonly seen in the US markets: lumbar artificial

Table 1 Lumbar artificial discs

Device name	FDA approval	Manufacturer
ProDisc®-L	Yes – single level	DePuy Synthes
INMOTION®	Yes – single level	DePuy Synthes
Activ-L™	Yes – single level	Aesculap®
Cadisc™-L	No	Rainier® Technology
FlexiCore®	No	Stryker®
Freedom® Lumbar Disc	No	AxioMed®
M6®-L	No	Spinal Kinetics™
XL TDR®	No	NuVasive
Maverick®	No	Medtronic®
Kineflex-L™	No	SpinalMotion®

Table 2 Interspinous/interlaminar devices

Device name	FDA approval	Manufacturer
Coflex® Interlaminar Stabilization Device	Yes	Paradigm Spine
Superion® Indirect Decompression System	Yes	VertiFlex, Inc.
DIAM™ Spinal Stabilization System	No (only IDE)	Medtronic Sofamor Danek
Aperius™-PercLID™ System	No	Medtronic
FLEXUS™	No	Globus Medical
Wallis® System	No (only IDE)	Zimmer Spine
In-Space	No	Synthes®

discs, interspinous devices, and dynamic stabilization systems. Although a substantial number of devices in all three categories exist and are currently manufactured, only a couple of these devices are approved for use in the United States. Although not an exhaustive list, Tables 1 and 2 list lumbar artificial discs and interspinous devices that are currently available and are used in different markets throughout the world. For the purposes of this chapter, we will discuss the M6® artificial disc systems by Spinal Kinetics, the Helifix® Interspinous Spacer System by Alphatec® Spine, and the LimiFlex Spinal Stabilization System by Empirical Spine, all of which have been in use in the European markets for many years but not yet approved for use in the United States.

Spinal Kinetics (Sunnyvale, CA) is the manufacturer of the M6 artificial disc systems and has, as of this writing, exceeded 50,000 total implantations of their M6-C Cervical and M6-L Lumbar artificial discs in international markets (https://www.odtmag.com/contents/view_breaking-news/2017-07-25/spinal-kinetics-surpasses-50000-implants-of-its-m6-artificial-disc). M6-C was launched in 2006 and is now approved for use by the FDA in the US markets, while M6-L was launched in 2010 and is currently not FDA approved but used extensively in international markets and has the CE mark (Formica et al. 2017). The M6-L artificial disc has an artificial nucleus pulposus (made from polycarbonate urethane) and an artificial ring of fibrous material (made from polyethylene) and is designed to provide physiologic motion in 6 degrees of freedom (2 degrees in each axial, coronal, sagittal planes). As of this writing, this system is the only artificial disc with 6 degrees of freedom. The inner disc is sandwiched by two titanium outer plates with keels for anchoring the disc into the vertebral body (http://www.spinalkinetics.com/patients/m6-l-artificial-lumbar-disc/). According the manufacturer, the M6-L disc is intended for use for treatment of symptomatic degenerative disc disease (DDD) at one or two adjacent levels between

L3 through S1 and may even have up to maximum 3 mm of spondylolisthesis at the intended level (http://www.spinalkinetics.com/patients/m6-l-artificial-lumbar-disc/). The M6-L disc is currently approved for use in the European Union countries, Australia, New Zealand, Russia, South Africa, Brazil, and United Arab Emirates.

There are a number of artificial lumbar discs that are approved for use in the United States and a wider array of discs that are not yet approved. Although it is by no means an exhaustive list, Table 1 contains a list of the currently used lumbar artificial discs in the United States and international markets (Food and Drug Administration 2012a, b, c).

In addition to lumbar artificial discs, interspinous and interspinous stabilization/distraction devices are also not as widely used in the US market as they are used in international markets. Before we discuss the various interspinous spacer devices used outside the United States, it is worth discussing the rationale behind interspinous distraction. There is no widely accepted term in spine literature, but lumbar interspinous process decompression (IPD) is also known as interspinous distraction, posterior spinal distraction, or interlaminar stabilization. These procedures have been proposed as minimally invasive alternative procedures to laminectomy and fusion (Landi 2014). By distracting the adjacent spinous processes and/or lamina and thereby restricting extension in patients with lumbar spinal stenosis and neurogenic claudication, these interspinous distractor devices can alleviate symptoms that arise from neural compression (Lee et al. 2015). These devices enlarge the neural foramen, decompress the causa equina, and act as spacers between the spinous processes to limit extension of the spinal interspace. Because of the minimally invasive nature of placement of these devices, proponents argue that such techniques lead to shorter hospital stay, preservation of local bone and tissue, reduced risk of cerebrospinal fluid leakage, and is reversible in such a way that it does not limit future treatment options. Some potential complications of these spacer devices are fracturing of spinous processes, incorrect positioning, and mechanical failure of the devices (Lee et al. 2015).

Of the devices that have been commercialized for placement between the spinous process or lamina of a motion segment in the US and international markets, only two such devices are approved for use in the United States: Coflex® Interlaminar Stabilization Device and the Superion® Indirect Decompression System. There is one interspinous spacer device not approved in the United States but widely used in the European markets that we will describe: the Helifix® Interspinous Spacer System. A list of some other interspinous devices can be found in Table 2 (Food and Drug Administration 2012a, b, c).

The Helifix® Interspinous Spacer System is essentially a PEEK (polyetheretherketone) implant that is self-distracting (Pintauro et al. 2017). It has a helical design that essentially can be "screwed in" between the spinous processes of adjacent vertebra. It has a percutaneous delivery mechanism through a posterolateral approach (https://atecspine.com/product-portfolio/thoracolumbar/helifix-interspinous-spacer-system/). After a 2–3 cm incision is made lateral to midline and, under fluoroscopy, a guidewire is inserted to find the interspinous space. Once another instrument, called the ligament splitter, dilates through the interspinous ligament, a dilator trial is positioned between the superior and inferior spinous processes (Gazzeri et al. 2014). Once proper fit is established, the Helifix device is inserted with a rotating movement of the self-distracting helical tip in the interspinous area. This device stretches the ligamentum flavum and the posterior fibers of the annulus fibrosus, thus enlarging the spinal canal (Gazzeri et al. 2014).

Lastly, the LimiFlex™ spinal stabilization system by Empirical Spine received its CE mark in 2009 and has been used to treat more than 2000 patients thus far, primarily in Europe (https://limiflex.com/healthcare-professionals/). The FDA has approved the device for investigational use and a clinical trial has been approved in patients with lumbar spinal stenosis with up to Grade I degenerative spondylolisthesis. The pivotal trial is a multicenter, prospective, concurrently controlled, non-blinded study in which patients will be

randomized to receive either decompression and LimiFlex device implantation or decompression and posterolateral fusion. The LimiFlex device consist of two dynamic titanium rods each with a roller screw and a pre-attached ultrahigh molecular weight (UHMW) polyethylene textile band that straps around adjacent spinous processes. The two titanium rods sit on either side of adjacent spinous processes in a vertical position and the textile band is wrapped around the two spinous processes (LimiFlex Surgical Technique Manual: https://limiflex.com/wp-content/uploads/LB-10108.001.A-LimiFlex-STM_english-for-mail.pdf). By turning the screwing mechanisms on the roller screw part of the titanium rods, increased tension is created on the textile band that increases the angle of lordosis along two adjacent lumbar spinal levels. The pivotal study started in July 2017 in the United States and is expected to conclude in December 2023 (https://clinicaltrials.gov/ct2/show/NCT03115983).

Conclusion

The spine product market is replete with a wide variety of solutions for all of the different spinal pathologies, chief among them being back and neck symptoms. Although many spine products are concurrently used both in the United States and the wider international markets, there are quite a few spinal implants that have not yet been either approved or used as widely in the United States. There are three main spine product categories, namely lumbar artificial discs, interspinous spacers, and dynamic stabilization systems, which have a substantial selection of products that have been in use in the European market for many years. However, as a result of the FDA medical device approval process and its insistence on both safety and efficacy in evaluating spinal products, many of these devices are either still under investigation or outright rejected. In fact, an evaluation of some of the case studies of the FDA approval process of certain spine products has taught us valuable lessons. Ideally, new spinal devices should improve patient outcomes with increased safety at reasonable societal costs. As we have seen from studying the reasons behind the failure of some of the spine products, the main goal prior to dissemination of spinal implants or devices is to have a rigorous evidence-based evaluation. Only then can a successful product emerge from the FDA approval process that will ultimately both be safe for consumers and decrease healthcare costs in the long term.

At the same time, innovation must also be at the forefront of our minds, and spine surgeons in the United States must rapidly evolve and evaluate certain technologies that are widely used in the rest of the world. As we have seen from the extensive list of interspinous spacers, posterior dynamic stabilization systems, and artificial discs that are in use in the international markets, we must critically evaluate and employ the most effective devices available by conducting high-quality evidence-based studies so that our patients can have more surgical options when it comes to the vast array of spinal pathologies that they experience.

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Trauma Products: Spinal Cord Injury Implants

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Contents

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Abstract

The incidence of acute traumatic spinal cord injury (SCI) in the USA is approximately 27–81 cases per million people per year with cervical SCI being the most common site of injury. Despite early surgical decompression, secondary injury and the cascade of effects in the ensuing days and months remain one of the biggest barriers in achieving recovery in these patients. A host of pharmacologic, cellular, immunomodulatory, and rehabilitative interventions have been employed over the past several decades in an attempt to improve functional outcome in this population. Though no single intervention is likely to provide a cure, important information has been gained about the heterogeneity of this population and the myriad physiological processes underlying the acute and chronic phases of injury. Herein, we provide a broad overview of the underlying pathophysiology, discuss various cellular, structural, and pharmacologic therapies tested, and address the challenges and insights gained from completed SCI trials.

Keywords

Spinal cord injury · Spinal implants · Functional regeneration · Neuroprotection · Neuromodulation · Trauma products · Brain machine interface

SCI Background: Demographics, Economic Burden, and Grading Systems

Introduction

Trauma resulting in spinal cord injury (SCI) is often associated with significant morbidity. More than half of all SCI patients develop complications during both the initial hospital stay and after discharge, with long-term problems including veno-thrombo embolism and pressure ulcers from decreased mobility, as well as a variety of pulmonary and gastrointestinal complications (Eckert and Martin 2017). Despite advances in supportive care for SCI, technologies that can directly facilitate spinal cord recovery have been limited. In this chapter we review the various implants and therapies that have been used to improve functional outcome in the SCI population.

Demographics

The annual incidence of traumatic spinal cord injury (SCI) in the USA is estimated at 54 cases per one million people, translating to approximately 17,700 new cases each year (National Spinal Cord Injury Statistical Center Updated 2018). Motor vehicle accidents are the most common cause of traumatic SCIs (Fig. 1), accounting for 38% of all injuries between 2010 and 2014, followed by falls (31%) and acts of violence (13%). Traumatic SCI occurs predominantly in men (78%) and its prevalence is disproportionately high among non-Hispanic blacks (Fig. 2). Notably, the incidence of SCI from falls has nearly doubled since the 1970s (Chen et al. 2016). The average age at time of injury has also increased, from 29 years in the 1970s to 43 years old in 2018. Most injuries occur at the level of the cervical spinal cord (59%), followed by thoracic (32%) and lumbosacral (9%) spine (Ahuja et al. 2017b).

Economic Burden

SCI afflicts devastating physical, psychosocial, and economical consequences on its patients and their families. After discharge from acute hospitalization, the most common outcome is incomplete quadriplegia (Fig. 3). Approximately one-third of all patients with SCI are re-hospitalized in any given year, most often for infections of the skin and genitourinary system (National Spinal Cord Injury Statistical Center Updated 2018). This and other health ramifications lead to staggering costs, ranging from 2 to nearly five million dollars over the course of a patient's lifetime (Fig. 4). In addition, less than one-fifth of SCI patients are employed at 1 year after injury, adding

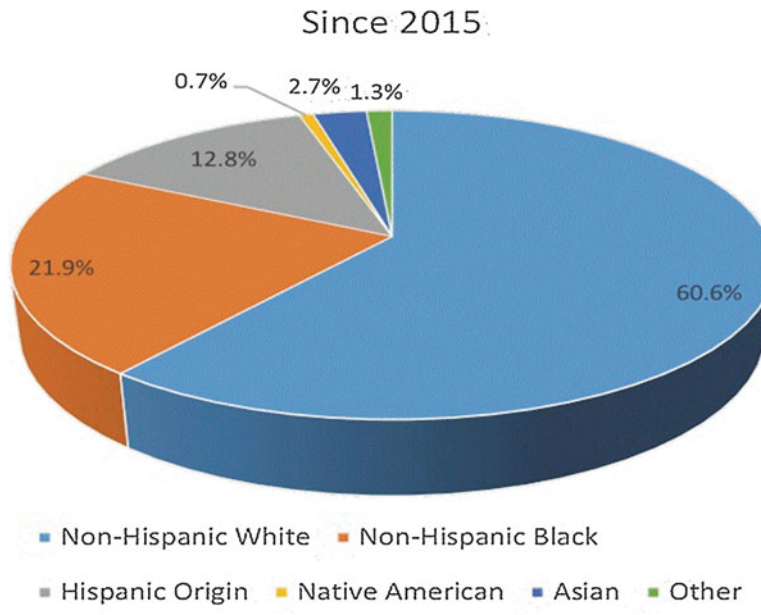


Fig. 1 Most common causes of SCI in the USA from 2015–2018. (National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, 2018. Redrawn with permission)

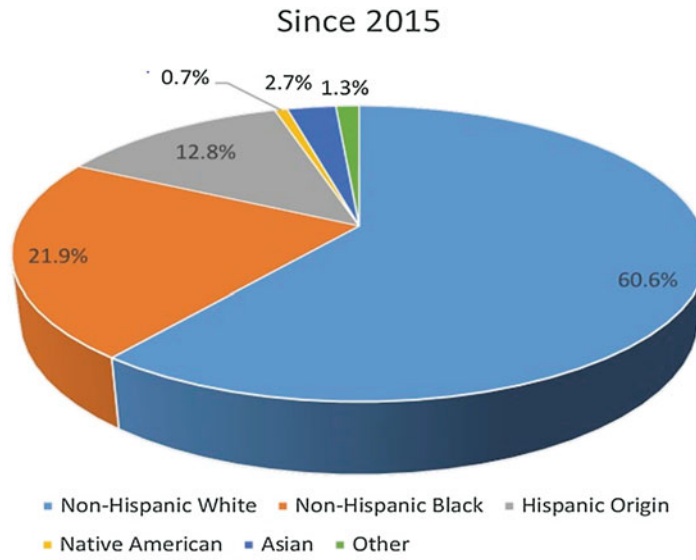


Fig. 2 Distribution of race/ethnicity in SCI cases in the USA from 2015–2018. (National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, 2018. Redrawn with permission)

on additional indirect costs from lost wages and benefits. Patients with SCI have persistently higher mortality rates when compared to age-matched controls (Fig. 5), with pneumonia and septicemia as the leading causes for the reduced life expectancy of these patients (Krause et al. 1997). The prognosis of restoring spinal cord function is largely dependent on the severity of injury (as measured by admission American Spinal Injury Association Impairment Scale [ASIA] grade, Frankel grade, or injury completeness) and the level of injury, as these two factors play important roles in the success of rehabilitation and regeneration (Wilson et al. 2012). Given the high morbidity and mortality associated with this population, there is a critical need for the development of new treatments and technologies to restore spinal cord function.

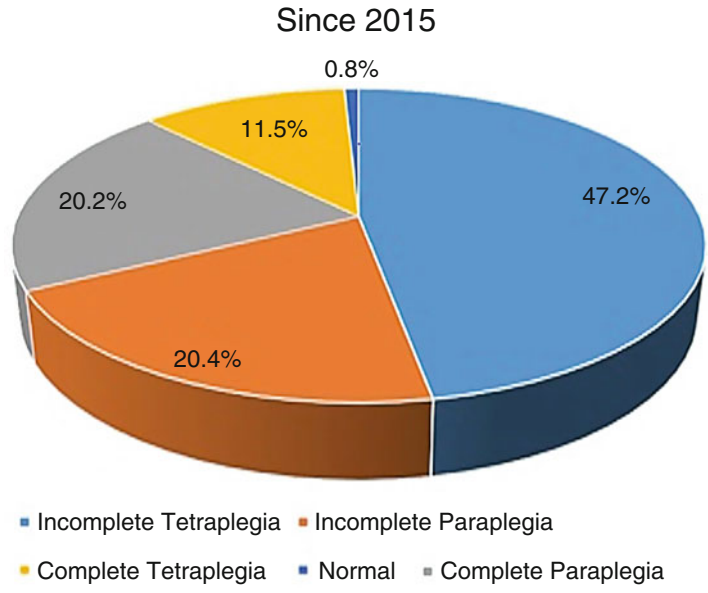


Fig. 3 Distribution of neurological injury in SCI cases in the USA from 2015–2018. (National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, 2018. Redrawn with permission)

Severity of Injury	Average Yearly Expenses (in 2017 dollars)		Estimated Lifetime Costs by Age at Injury (discounted at 2%)	
	First Year	Each Subsequent Year	25 years old	50 years old
High Tetraplegia (C1–C4) AIS ABC	$1,102,403	$191,436	$4,891,398	$2,688,229
Low Tetraplegia (C5–C8) AIS ABC	$796,583	$117,437	$3,573,960	$2,198,305
Paraplegia AIS ABC	$537,271	$71,172	$2,391,872	$1,569,714
Motor Functional at Any Level AIS D	$359,783	$43,700	$1,634,139	$1,153,420

Fig. 4 Costs of SCI patients in the USA. (National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, 2018. Redrawn with permission)

Age at Injury	No SCI	Life Expectancy (years) for Post-Injury by Severity of Injury and Age at Injury								
		For Persons Who Survive the First 24 Hours					For Persons Who Survive the First 24 Hours			
		AIS D—Motor Functional at Any Level	Para	Low Tetra (C5–C8)	High Tetra (C1–C4)	Ventilator Dependent Any Level	AIS D—Motor Functional at Any Level	Para	Low Tetra (C5–C8)	High Tetra (C1–C4)	Ventilator Dependent - Any Level
20	59.6	52.9	45.7	40.3	34.0	11.3	53.2	46.2	41.2	35.2	19.0
40	40.7	35.2	29.7	24.9	20.9	8.7	35.4	30.2	25.7	22.1	13.3
60	23.2	19.5	16.1	13.2	11.1	3.7	19.7	6.5	14.0	12.5	7.9

Fig. 5 Life expectancy of SCI patients in the USA. (National Spinal Cord Injury Statistical Center, Facts and Figures at a Glance. Birmingham, AL: University of Alabama at Birmingham, 2018. Redrawn with permission)

Grading Systems in SCI

To accurately characterize the level and extent of cord injury, five main grading systems have been developed and used (Tator 2006). In 1967, the Frankel system was the first to be developed and included five grades of severity. Although it was easy to use and understand, the Frankel system could not quantify recovery and definitions of each grade were imprecise. The Sunnybrook system was developed in 1982, which expanded the repertoire of severity grading and neurologic changes, allowing for increased precision in the clinical evaluation and quantification of recovery in a SCI patient. One major drawback of the Sunnybrook system is its lack of numerical scores

of motor and sensory function. In 1982, the American Spinal Injury Association published the International Standards for Neurological Classification of Spinal Injury (NASCIS), a grading and classification system that would evolve into the current American Spinal Injury Association (ASIA) Impairment Scale (Roberts et al. 2017). Figures 6 and 7 depict the NASCIS scoring worksheet and ASIA Impairment Scale, respectively. Since then, the ASIA system has been refined many times, improving its precision and reproducibility in defining spinal cord injury and allowing for better understanding of the scale's therapeutic implications. The major advantages of the ASIA system include a more accurate definition of a complete SCI and improved methodology for determining motor and sensory scores. One of its major disadvantages is the ceiling effect of Grades C and D, in which patients seldom improve sufficiently to change to the next grade. Of note, the most recent classification system has been the Benzel system, but this system cannot be used in the acute phase of injury, rendering it inappropriate for use in clinical studies.

SCI Pathophysiology: Primary Versus Secondary Injury

Primary Versus Secondary Injury

Primary Injury

An understanding of the mechanisms underlying SCI is essential to develop new strategies for restoring spinal cord function. Traumatic SCI can be pathophysiologically divided into primary and secondary injuries and can be temporally divided into acute (<48 h), subacute (48 h to 14 days), intermediate (14 days to 6 months), and chronic (>6 months) stages (Ahuja et al. 2017b). The primary injury (i.e., the direct traumatic event) causes the immediate mechanical disruption and dislocation of the vertebral column, leading to compression or transection of the spinal cord. On the cellular level, this produces foci of glial and neuronal necrosis, alarmin release, disruption of the microvasculature, and breakdown of the blood–brain barrier (BBB) (Tran et al. 2018). These events together then directly trigger a prolonged secondary injury

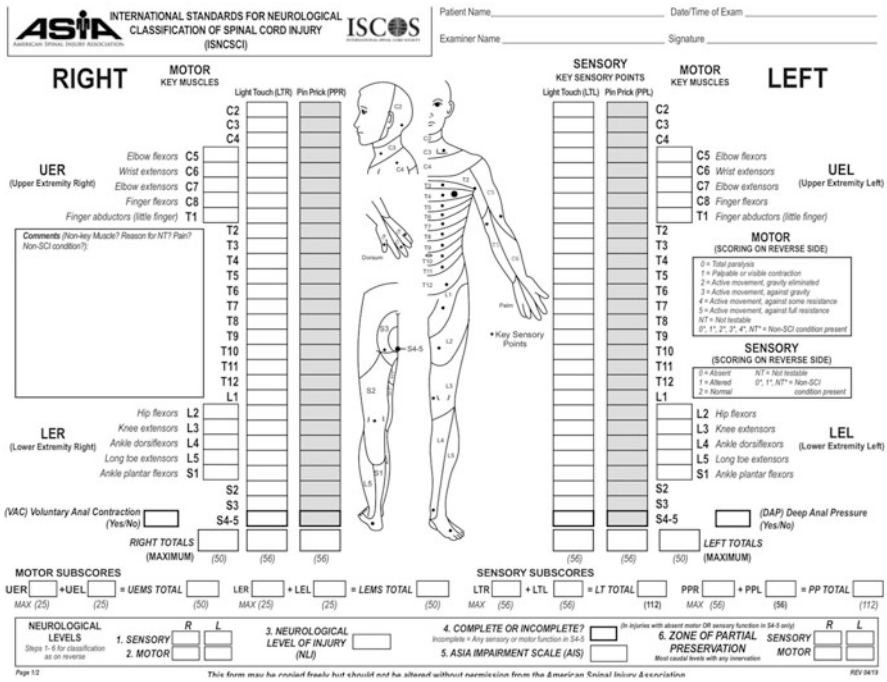
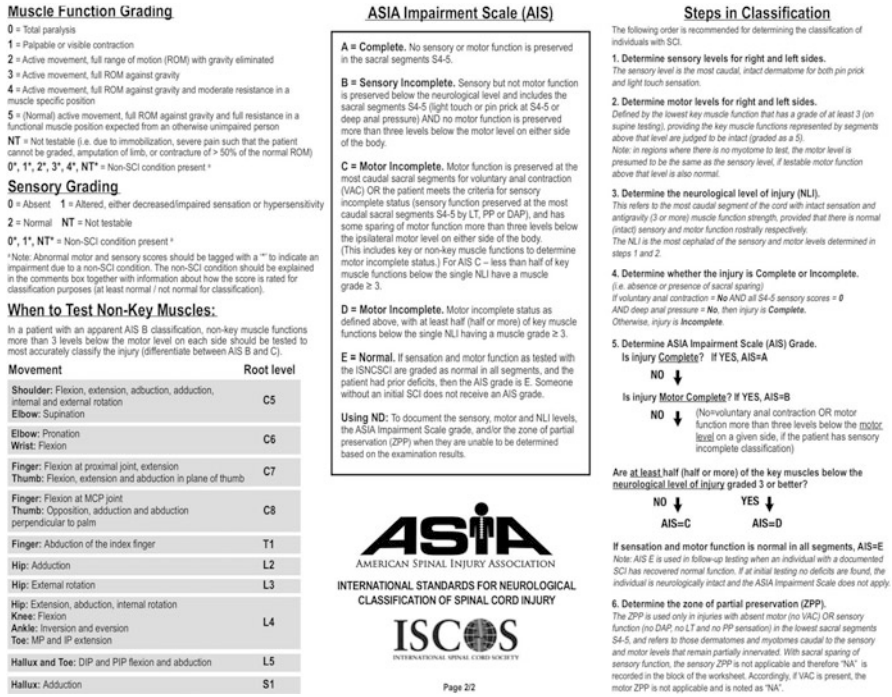


Fig. 6 International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and ASIA Impairment Scale (AIS) scoresheet



Muscle Function Grading

0 = Total paralysis
1 = Palpable or visible contraction
2 = Active movement, full range of motion (ROM) with gravity eliminated
3 = Active movement, full ROM against gravity
4 = Active movement, full ROM against gravity and moderate resistance in a muscle specific position
5 = (Normal) active movement, full ROM against gravity and full resistance in a functional muscle position expected from an otherwise unimpaired person
NT = Not testable (i.e. due to immobilization, severe pain such that the patient cannot be graded, amputation of limb, or contracture of > 50% of the normal ROM)
0*, 1*, 2*, 3*, 4*, NT* = Non-SCI condition present *

Sensory Grading

0 = Absent 1 = Altered, either decreased/impaired sensation or hypersensitivity
2 = Normal NT = Not testable
0*, 1*, NT* = Non-SCI condition present *

Note: Abnormal motor and sensory scores should be tagged with a "" to indicate an impairment due to a non-SCI condition. The non-SCI condition should be explained in the comments box together with information about how the score is rated for classification purposes (at least normal / not normal for classification).

When to Test Non-Key Muscles:

In a patient with an apparent AIS B classification, non-key muscle functions more than 3 levels below the motor level on each side should be tested to most accurately classify the injury (differentiate between AIS B and C).

Movement	Root level
Shoulder: Flexion, extension, adbuction, adduction, internal and external rotation **Elbow:** Supination	C5
Elbow: Pronation **Wrist:** Flexion	C6
Finger: Flexion at proximal joint, extension **Thumb:** Flexion, extension and abduction in plane of thumb	C7
Finger: Flexion at MCP joint **Thumb:** Opposition, adduction and abduction perpendicular to palm	C8
Finger: Abduction of the index finger	T1
Hip: Adduction	L2
Hip: External rotation	L3
Hip: Extension, abduction, internal rotation **Knee:** Flexion **Ankle:** Inversion and eversion **Toe:** MP and IP extension	L4
Hallux and Toe: DIP and PIP flexion and abduction	L5
Hallux: Adduction	S1

ASIA Impairment Scale (AIS)

A = Complete. No sensory or motor function is preserved in the sacral segments S4-5.

B = Sensory Incomplete. Sensory but not motor function is preserved below the neurological level and includes the sacral segments S4-5 (light touch or pin prick at S4-5 or deep anal pressure) AND no motor function is preserved more than three levels below the motor level on either side of the body.

C = Motor Incomplete. Motor function is preserved at the most caudal sacral segments for voluntary anal contraction (VAC) OR the patient meets the criteria for sensory incomplete status (sensory function preserved at the most caudal sacral segments S4-5 by LT, PP or DAP), and has some sparing of motor function more than three levels below the ipsilateral motor level on either side of the body. (This includes key or non-key muscle functions to determine motor incomplete status.) For AIS C – less than half of key muscle functions below the single NLI have a muscle grade ≥ 3.

D = Motor Incomplete. Motor incomplete status as defined above, with at least half (half or more) of key muscle functions below the single NLI having a muscle grade ≥ 3.

E = Normal. If sensation and motor function as tested with the ISNCSCI are graded as normal in all segments, and the patient had prior deficits, then the AIS grade is E. Someone without an initial SCI does not receive an AIS grade.

Using ND: To document the sensory, motor and NLI levels, the ASIA Impairment Scale grade, and/or the zone of partial preservation (ZPP) when they are unable to be determined based on the examination results.

ASIA
AMERICAN SPINAL INJURY ASSOCIATION
INTERNATIONAL STANDARDS FOR NEUROLOGICAL CLASSIFICATION OF SPINAL CORD INJURY
ISCOS
INTERNATIONAL SPINAL CORD SOCIETY

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Steps in Classification

The following order is recommended for determining the classification of individuals with SCI.

1. Determine sensory levels for right and left sides.
The sensory level is the most caudal, intact dermatome for both pin prick and light touch sensation.

2. Determine motor levels for right and left sides.
Defined by the lowest key muscle function that has a grade of at least 3 (on supine testing), providing the key muscle functions represented by segments above that level are judged to be intact (graded as a 5).
Note: in regions where there is no myotome to test, the motor level is presumed to be the same as the sensory level, if testable motor function above that level is also normal.

3. Determine the neurological level of injury (NLI).
This refers to the most caudal segment of the cord with intact sensation and antigravity (3 or more) muscle function strength, provided that there is normal (intact) sensory and motor function rostrally respectively.
The NLI is the most cephalad of the sensory and motor levels determined in steps 1 and 2.

4. Determine whether the injury is Complete or Incomplete.
(i.e. absence or presence of sacral sparing)
*If voluntary anal contraction = **No** AND all S4-5 sensory scores = **0** AND deep anal pressure = **No**, then injury is **Complete**.*
*Otherwise, injury is **Incomplete**.*

5. Determine ASIA Impairment Scale (AIS) Grade.
Is injury Complete? If YES, AIS=A
NO ↓
Is injury Motor Complete? If YES, AIS=B
NO ↓ (No=voluntary anal contraction OR motor function more than three levels below the motor level on a given side, if the patient has sensory incomplete classification)
Are at least half (half or more) of the key muscles below the neurological level of injury graded 3 or better?
NO ↓ AIS=C
YES ↓ AIS=D
If sensation and motor function is normal in all segments, AIS=E
Note: AIS E is used in follow-up testing when an individual with a documented SCI has recovered normal function. If at initial testing no deficits are found, the individual is neurologically intact and the ASIA Impairment Scale does not apply.

6. Determine the zone of partial preservation (ZPP).
The ZPP is used only in injuries with absent motor (no VAC) OR sensory function (no DAP, no LT and no PP sensation) in the lowest sacral segments S4-5, and refers to those dermatomes and myotomes caudal to the sensory and motor levels that remain partially innervated. With sacral sparing of sensory function, the sensory ZPP is not applicable and therefore "NA" is recorded in the block of the worksheet. Accordingly, if VAC is present, the motor ZPP is not applicable and is noted as "NA".

Fig. 7 International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) and ASIA Impairment Scale (AIS) grading and classification guide. (https://asia-spinalinjury.org/wp-content/uploads/2016/02/International_Stds_Diagram_Worksheet.pdf. International Standards for Neurological Classification of SCI (ISNCSCI) Worksheet, Updated April 2019. © 2019 American Spinal Injury Association. Reprinted with permission)

cascade, which may viciously cycle for weeks until the glial scar is formed.

Surgical stabilization and decompression is the essential cornerstone of acute treatment for patients during the primary injury. Overall, the goal of surgery is to realign the spinal column and reestablish spinal stability as to relieve compression on the spinal cord. Typically surgery involves open reduction, decompression, and instrumented fusion to bring the spinal column back into anatomical position. By correcting the mechanical disruption, surgery aims to reverse or avert any further primary injury and prevent secondary injury. Although clinical class I randomized evidence supporting the efficacy of early surgical decompression is still needed, several prospective, nonrandomized studies have supported the safety and efficacy of early surgical intervention in traumatic SCI. The prospective, multicenter, cohort-controlled Surgical Timing in Acute Spinal Cord Injury Study (STASCIS; N = 313) compared patients with cervical SCI receiving either early (<24 h) or late (>24 h) decompression. They noted an increased odds of 2 grade improvement in the American Spinal Injury Association (ASIA) Impairment Scale with early decompression (within 24 h) as compared to late decompression (>24 h) (Fehlings et al. 2012). Another study showed that very early decompression (within 8 h) was associated with better motor recovery and improved ASIA grade at 1 year post-injury (Ahuja et al. 2017b). Additionally, several studies have shown an association between early decompressive surgery and greater motor scale recovery, reduced length of stay, lower complication rates, and shorter length of hospital stay.

Secondary Injury

The hallmark of secondary injury is cord damage beyond the initial site of injury. In the simple sense, cell death begets additional cell death in

the secondary cascade. On the cellular level, disruption of the cord microvasculature leads to cell permeability, pro-apoptotic signaling, and ischemic injury, all of which potentiates additional cell death (Ahuja et al. 2017b). Incompetence of the BBB permits the unchecked entry of peripheral immune cells, toxic metabolic products, and other inflammatory substances into the central nervous system (CNS), called forth by alarmin release from necrotic cells. The ongoing necrosis of neurons and glial cells activates additional microglial cells, escalating the inflammatory response around the site of injury. This produces an overwhelming inflammatory response that inflicts damage to nearby cells by driving up oxidative stress, lipid peroxidation, and protein aggregation. Homeostatic imbalance, including the dysregulation of sodium and calcium channels and the overrelease of glutamate from dying cells, induces excitotoxic cell death, causing the release of additional glutamate and alarmin. As injured blood vessels lose their capability for autoregulation, the ensuing ischemia can persist for days to weeks after injury, extending further damage. All of these factors contribute to a harsh post-injury microenvironment that cyclically propagates and magnifies the original injury. In addition, disruption of the BBB in conjunction with the inflammatory response causes cord swelling, leading to further mechanical compression of the spinal cord.

Challenges for Recovery: Cervical Versus Thoracic SCI, Incomplete Versus Complete

Current strategies for neuroprotection and rehabilitation have focused primarily on preserving injured tissue and reducing the secondary injury. These approaches look to curb the inflammatory response and promote neural repair and regeneration after the primary insult. Without interventions to address the primary injury, inherent challenges in restoring SCI function vary depending on the level and completeness of cord injury.

Cervical Versus Thoracic SCI

Restoration of SCI function depends on the level of neurologic injury. A neurologic level of injury is defined as the most caudal spinal cord segment with intact sensation and Grade 3 or greater motor function (Roberts et al. 2017). For dermatomes not covered by muscles (C1-C4, T2-L1, and S1-S4-S5), the sensory level is used to delineate the level of injury.

Cervical SCI

For patients with cervical SCI, C6, and C7 are known to be the critical levels for achieving independence in most daily activities (Welch et al. 1986). The presence or absence of functional triceps is a critical determinant for functional independence in self-care tasks. A strong triceps permits stabilization of the elbow in extension, so that the shoulder depressors can act through the elbow in lifting the body weight, achieving independence in changing from lying to sitting position and in transferring to and from a wheelchair. Though patients with C6 injuries lack an intrinsic grasp, operating a motorized wheelchair is possible at this level through taking advantage of elbow flexion and shoulder abduction and flexion. Sparing of C7 allows for finger extension and flexion, affording even more independence with operating a wheelchair. Almost all cervical SCI patients will still need assistance with lower extremity dressing, bowel and bladder care, and driving. True functional ambulation is nearly impossible without truncal stability provided by thoracic musculature, though neuromodulation efforts have resulted in some success (discussed later in this chapter).

Compared to thoracic SCI, cervical SCI involves a mixture of damage to both central and peripheral nervous systems. Therefore, cervical SCI training approaches and chances of success is dependent on not only the injury of the spinal tracts but also on the damage of the motor neurons and roots, which can cause up to 70% of the paresis seen in C5 to C7 lesions (Dietz and Fouad 2014). The complexity and variability of cervical lesions makes the restoration of cervical cord function much more challenging. Patients with cervical

injuries are also at a higher risk for lifelong ventilator dependency compared to patients with thoracic injuries, restricting rehabilitation capacity and long-term independence (Winslow and Rozovsky 2003). Cardiovascular dysfunction leading to orthostatic hypotension is also more prevalent in cervical injuries (West et al. 2012).

Thoracic SCI

With the assistance of leg braces and pelvic band, the ability to hold an erect position and stand upright is usually reached around T6. At these levels, truncal stability is achieved from innervation supplied to the long muscles of the back, upper intercostals, and transversus thoracis. To be able to ambulate, there must be sufficient pelvic control and at least grade 3/5 strength in both hip flexors and one knee extensor (Branco et al. 2007). Though there is no set level for ambulation, most authors agree that lesions at or below T10 allow for ambulation due to innervation of the thoracic musculature and secondary hip flexors, including the external and internal obliques and latissimus dorsi.

Complete Versus Incomplete SCI

A complete SCI is defined as the absence of all motor and sensory functions in the sacral segments S4–S5. An incomplete injury is defined as the partial preservation of sensory or motor function in the lowest sacral segments (anal sensation, including deep anal pressure and voluntary external anal sphincter contraction). Incomplete SCI can then be further divided into sensory and motor incomplete subcategories. The presence of deep anal sensation may be the only indicator of an incomplete SCI. The determination of a complete or incomplete SCI requires resolution of spinal shock. Spinal shock is characterized by an initial depolarization of axonal tissue immediately after injury and is a physiologic response to trauma. Spinal shock involves a transient period of flaccid paralysis during which the patient is areflexic. Notably, this includes the absence of the bulbocavernosus reflex, a spinal-mediated reflex involving S2–S4. After return of this reflex, the patient can be assessed accurately for completeness of cord injury.

Complete SCI

The zone of partial preservation is used only with complete injuries. The zone of partial preservation documents dermatomes and myotomes caudal to the neurologic level of injury that remain partially innervated and is recorded for motor and sensation for the right and left sides. Presence of a zone of partial preservation is associated with improved neurologic recovery (Wilson et al. 2012). Otherwise, prognosis for neurologic recovery in a patient with a motor/sensory complete lesion (ASIA Impairment Scale A) is grim. Complete quadriplegics are unable to ambulate and only 5% of complete paraplegics will have sufficient motor recovery to permit ambulation (Branco et al. 2007). Waters et al. (1992) and Waters et al. (1993) found that of complete lesions assessed 1 month after injury, 90% of those causing complete quadriplegia and 96% of those causing complete paraplegia remained complete. Schönherr et al. (1999) found that approximately 1 month after injury, 100% of those causing complete quadriplegia and 96% of those causing complete paraplegia remained complete. The most recent data from the National Spinal Cord Injury Statistical Center (NSCISC) report a much higher rate of conversion from complete to incomplete status in quadriplegics, with 30% overall conversion and 15% to motor incomplete (Marino et al. 2011).

Incomplete SCI

As the amount of spared spinal cord tissue determines the effectiveness of rehabilitation training, the presence of an incomplete injury, as compared to a complete injury, is consistently associated with improved neurological recovery. This is because the success of facilitating meaningful plasticity during training depends on the presence of certain physiological prerequisites. In order to produce a locomotor electromyography (EMG) pattern in patients with SCI, afferent input from load receptors is needed (Dietz 2009). For example, no meaningful leg muscle activation occurs in individuals with complete SCI during supported stepping if there is no loading of the sole of the foot. This makes obtaining significant muscle activation in patients with complete SCI much more challenging than in patients with incomplete SCI. An additional factor that may also contribute

to the smaller EMG amplitudes in patients with complete paraplegia is a loss of descending noradrenergic input to spinal locomotor centers (Dietz 2012).

Concepts: Functional Regeneration, Neuroprotection, Immunomodulation

Many promising strategies are being explored in an attempt to regain function after spinal cord injuries, with a strong focus on regeneration. In the literature, several comprehensive reviews have been conducted on the status of translational advances in spinal cord injury (Badhiwala et al. 2018; Venkatesh et al. 2019; Ahuja et al. 2017b). While there are a number of promising strategies for treating SCI, there are currently no effective and reliable treatments that have achieved regeneration in SCI. Two major principles in the field of regeneration have focused on neuroregeneration and neuroprotection. Neuroregenerative techniques have predominantly focused on stem cell lines that can restore lost neurons. For neuroprotection, research has focused on factors that both promote regeneration and limit inhibitory factors. Different stem cell lines have the potential to regenerate neural circuits, provide trophic support, modulate the inflammatory response, and remyelinate damaged axons. To support both endogenous and implanted stem cells, there has also been a strong focus on neurotrophic factors that promote neuron growth and reagents that block inhibitory factors such as the formation of scar tissue. These immunotherapies serve as an adjunct to promote spinal cord regeneration through increasing cell survival and engraftment (Ahuja et al. 2017a; Tsuji et al. 2019).

A parallel strategy focuses on biomaterials that can mimic the physiological extracellular matrix and provide support and structure to regenerating neural structures. Biomaterials can be used to make scaffolds that provide guidance for existing damaged neurons and allow implanted cells to propagate and differentiate. Another goal of scaffolds has been to minimize secondary injury after SCI through inhibiting apoptosis and necrosis, limiting the formation of glial scar and serve as a vehicle for the delivery of immunomodulators and cell therapies (Liu et al. 2019).

A separate strategy for restoring SCI function is through neuromodulation with electrical interfaces. Neuromodulation is currently successfully in use for many neurological disorders, including deep brain stimulation for Parkinson's disease and epidural stimulation for pain. In the setting of SCI neurostimulation has already been used to help with respiratory pacing, bladder control, and restoring volitional movements through peripheral stimulation. New research suggests that spinal cord stimulation may also promote regeneration. Neuromodulation can also be adapted to restore motor and sensory function by creating an interface that connects the central nervous system with peripheral extremities. Through brain–machine interfaces, a tetraplegic patient has been able to perform reach and grasp movements. As technological advances continue, the field of neuromodulation will continue to increase in potential (James et al. 2018).

While there have been significant steps toward restoring function in SCI patients, to date there is no widespread and effective therapy available for regeneration or technology that restores function. In the following sections of this chapter, we review the current advances made, as well as challenges encountered in the different focuses of ongoing research. As the field continues to advance, an effective therapy will likely emerge from a combination of the various strategies already in development.

Results from Acute SCI Interventions: Stem Cells, Pharmacologics, Hemodynamic Strategies, CSF Drainage, Bio-Scaffolds, and Neuromodulation

Stem Cell Therapies

A wide variety of stem cell types have been explored with the goals of neuroprotection and neuroregeneration. Extensive research has shown promise in restoring function in SCI animal models (Hong et al. 2018). Cell therapies have been proposed to provide functional benefits

in SCI through several proposed mechanisms: neuroprotection, immunomodulation, axon sprouting and/or regeneration, neuronal relay formation, and myelin regeneration (Assinck et al. 2017). Stem cells for transplantation originally were developed from embryonic stem cells (ESCs), however given ethical and supply issues, induced pluripotent stem cells (iPSCs) have gained traction as favorable alternative. iPSCs have been successfully induced into specific neurons and glial cells, providing a more feasible source of cells to study. Studies have found success in integrating these stem cells into host circuitry in animal models. Neuronal stem cells (NSC) have been shown to enhance neurotrophic signaling, promote remodeling of neural circuitry, improve remyelination, and modify the extracellular matrix.

Supportive cell types are just as important as neurons themselves. Oligodendrocyte precursor cells (OPCs), mesenchymal stem cells (MSCs), olfactory ensheathing cells (OECs), and Schwann cells have thought to promote neuroprotection through several mechanisms. OPCs can secrete neurotrophic factors and remyelinate denuded axons. MSCs aim to regenerate damaged connective tissue and modulate inflammation. OECs have also been shown to induce regeneration and endogenous remyelination. Schwann cells are robust structural scaffolds in the peripheral nervous system that have been shown to modify astrogliosis in a way that facilitates remyelination and regeneration (Ahuja et al. 2017a; Badhiwala et al. 2018).

Cell therapy effectiveness will depend highly on the specific cell type, route of administration (IV, intrathecal and intraparenchymal), and timing. Ongoing trials explore and optimize each of these variables, with many different types of stem cells. The injection of MSCs, OPCs (AST-OPC-1), and autologous Schwann cells have all been been explored safely in phase I trials in SCI patients (Anderson et al. 2017; Priest et al. 2015; Jin et al. 2019). Despite successful preliminary trials, multiple late-stage trials have hit significant challenges, both scientific and financial. The Geron Corporation had launched a clinical trial of embryonic stem cells for SCI in 2010, citing "capital scarcity and uncertain economic conditions"(Lukovic et al. 2014). Another clinical trial by Stem Cells Inc. (Newark, CA) showed positive safety profiles in human fetal–derived NSC transplants into cervical and thoracic spinal cord injury sites. Further trials however did not show a significant response with clinically derived stem cell lines and studies have been terminated (Anderson et al. 2017). Despite failed trials, there continues to be a strong effort in clinical studies of cell therapies. The first human trial using iPSC has recently been approved to start (Tsuji et al. 2019).

Other than specific stem cells, other cells including macrophages and whole bone marrow have been thought to have potential to improve the microenvironment for neurological recovery. The bone marrow cells include hematopoietic stem cells, macrophages, lymphocytes, and marrow stromal cells. The bone marrow cells may secrete important cytokines as well as other essential factors for the survival and differentiation of neuronal cells.

While cell therapy is promising, there are also significant risks as with any new technology. A case of OEC implantation in the site of a chronic T10–11 complete SCI was found 8 years after implantation to have developed into an intramedullary spinal cord mass requiring resection (Dlouhy et al. 2014). This report raised concerns about the safety surrounding implantation of stem cells and highlights the importance of long-term monitoring. While the majority of stem cell trials have not reported significant adverse events, the follow-up time period for these trials has been limited to a few years. These reports should not deter the advancement of stem cell research but provide scientists with more information on how to safely proceed.

Pharmacologics

Steroids

Methylprednisolone sodium succinate (MPSS) was used in early spinal cord injury trials for its immunomodulatory and anti-inflammatory roles, both reducing neutrophil and macrophage

migration while also playing an important role in reduction of membrane peroxidation. The (National Acute Spinal Cord Injury Study) NASCIS I was a double-blind, randomized controlled trial performed comparing low-dose and high-dose administration in acute SCI. Results showed no difference between groups and the trial was stopped early. The NASCIS II trial was conducted with higher dose MPSS and compared with naloxone and placebo. Analysis was stratified based on timing of administration (<8 versus >8 hrs) and adjusted for the severity of injury (Bracken et al. 1990). Results demonstrated improvement in motor and sensory function in those patients who received MP within 8 hrs and no significant differences in either treatment arm greater than 8 hrs from injury. Wound infections and GI bleeding was observed with greater frequency in the MP group. Lastly, the NASCIS III trial was designed to compare 24 h MPSS infusion to a 48-h MPSS infusion. These two dosing schedules were compared with a 48-h infusion of a third drug, tirilazad mesylate, an inhibitor of lipid peroxidation. Results suggested that patients who received MPSS infusion as a 48-h infusion had improved motor function at 6 weeks and 6 months. Preplanned subanalysis demonstrated those who received MPSS between 3 and 8 h post-injury were more likely to improve at 6 months, though with increased risk of severe sepsis and pneumonia (Bracken et al. 1997). As a result, published guidelines offer a Level I recommendation against the use of MPSS in acute SCI, though the debate continues and recommendations are to continue evaluation in future higher-quality studies (Donavan and Kirschblum 2018).

Hemodynamic Intervention

Prevention of secondary ischemia and spinal cord hypoperfusion is paramount in the management of acute SCI. Cervical and upper thoracic SCI carry a risk of spinal shock due to variable interruption of the sympathetic outflow from cell bodies residing in the thoracic spinal cord. As such, strict hemodynamic monitoring and blood pressure (BP) parameters have been advised, though the recommendations have been controversial. Loss of supraspinal sympathetic regulation permits hypotension, bradycardia, and arrythmias. Post-mortem histological analysis of SCI patients with severe cardiovascular dysfunction shows more severe white matter and axonal degeneration in those patients who have severe cardiovascular dysfunction after SCI (Furlan and Fehlings 2008). Maintenance of mean arterial pressure (MAP) 85–90 mm Hg for the first week after acute SCI currently carries a Level III recommendation, according to published guidelines (Walters et al. 2013). While there is no universal agreement as to the vasopressor of choice, some studies have indicated that norepinephrine may be preferable to dopamine (Altaf et al. 2017).

CSF Drainage

Similar to the principles of TBI management, swelling and edema after SCI can have deleterious effects on local tissue perfusion. Surgical decompression, followed by efforts to prevent hypotension, hypoxia, and other secondary insults, is paramount in the management of acute SCI. Prevention of spinal cord ischemia can be accomplished by increasing perfusion and/or reducing intrathecal pressure by way of CSF drainage. This has been well described in vascular surgery where it is routinely employed after thoracoabdominal aortic aneurysm repair. A prospective randomized trial of 22 patients (ASIA A-C, inclusive of C3-T11 injury levels) was performed to evaluate the effect of 72 h of CSF drainage on peak intrathecal pressure (ITP) and correlated with neurological recovery after acute SCI (Kwon et al. 2009a). Though the study was not powered to detect differences in neurological outcome, there were no significant associated adverse effects reported in the study arm and spinal cord perfusion pressure was consistently higher during the duration of the study. An ongoing multicenter Phase IIb randomized controlled trial (NCT02495545) comparing the efficacy of CSF drainage and MAP elevation to MAP elevation alone is currently enrolling patients through the December 2019.

Growth Factors

Several important growth factors, have been identified and gained attention as neurotrophic agents in the central nervous system. Conversely,

inhibitory factors that inhibit neuronal growth have also been explored to understand the barriers to regeneration. All of these are being explored for their potential to be medications in treating SCI. By optimizing the microenvironment, these medications have the potential to enhance the regeneration of both endogenous cells and implanted stem cells.

Hepatocyte growth factor (HGF) is a c-Met receptor ligand that has been shown exert regenerative effects, including angiogenesis, after tissue injury in many epithelial organs. Studies in rodent models have shown that HGF in the central nervous system promotes angiogenic activity, prevents disruption of the blood–brain barrier, and promotes the survival of neurons after cerebral ischemia. Preclinical SCI studies investigating the use of intrathecal HGF in nonhuman primate models found improved ventral motor neuron survival and better motor outcomes, with significant improvements in upper limb recovery (Badhiwala et al. 2018; Kitamura et al. 2011). While most pharmacologics have been investigated through IV administration, a handful has been used intrathecally during the time of initial injury. In one human trial, HGF has administered as intrathecal injection at the time of injury and repeated weekly. Study results are still pending (Warita et al. 2019).

Granulocyte colony stimulating factor (G-CSF) is a small glycoprotein that has shown potential for enhancing cell survival and modulating inflammatory cytokine pathways. It is expressed on microglia and promostes expression of neurotrophic factors while inhibiting pro-inflammatory markers. G-CSF has been shown in mouse models to enhance neurogenesis and reduce apoptosis, with associated improvements in hind limb function (Koda et al. 2007). A randomized controlled trial in Iran showed that subcutaneous administration of G-CSF showed subtle but significant improvements in motor and sensory function compared to a placebo group in a population of incomplete subacute SCI (Derakhshanrad et al. 2018). Another group in Korea has experimented with G-CSF and isolated bone marrow cells injected during surgery at the site of contusion in six patients within 7 days of SCI. While the patients showed some neurologic recovery, the study mainly demonstrated the safety of the procedure (Park et al. 2005). Further multicenter trials will be needed to reinforce these findings.

Fibroblast growth factor (FGF) protects against excitotoxic cell death and reduces free radical generation (Badhiwala et al. 2018). FGF has been shown in several animal models to promote regeneration of spinal tracts (Cheng et al. 1996). This was first translated to human studies in 2004 when surgeons applied sural nerve grafts and fibrin glue infused with a closely related FGF: acidic FGF (aFGF) in a SCI patient, with improvement from wheelchair bound to ambulating with a walker (Cheng et al. 2004). Two further trials of aFGF administered during laminectomy without the nerve grafting have been done with additional doses of aFGF/fibrin through lumbar puncture at 3 and 6 months post-surgery. No significant adverse events were reported and ASIA motor and sensory scores showed significant improvement 24 months after treatment (Wu et al. 2008, 2011). The studies however did not have control arms, and further large-scale randomized controlled trials are currently enrolling.

Rho Signaling

The Rho signaling pathway regulates axon growth and is upregulated after SCI. Activation of the GTPase Rho A leads changes in the actin cytoskeleton and collapse of regenerating axons, neurite retraction, and increasing apoptosis (Nori et al. 2017). Medications that inhibit the Rho pathway have the potential to relieve the inhibition on axonal growth. C3 transferase is a toxin produced by clostridium botulinum and can block the Rho pathway. VX-210 aka Cethrin is a C3 transferase that has been used in clinical trials dosed in a fibrin sealant and administered during planned decompression/stabilization surgery after SCI (Fehlings et al. 2018, 2011). However an interim analysis of phase IIb/III trial suggested futility, and studies have been halted.

Neurite growth inhibitor A (NOGO-A) is a myelin-associated protein that functions through NOGO receptors and forms co-receptor complexes with the TNF receptor family proteins to activate the GTPase Rho A. This activates the Rho

pathway as discussed above and leads to inhibition of axon growth. A NOGO-A inhibitor (ATI355) has gone through a phase I clinical trial in 52 patients with SCI with acute SCI injury (4–60 days post-injury). The medication was administered via continuous intrathecal infusion over 24 h to 28 days. The published results confirmed safety and tolerability after 1-year follow-up with minimal adverse events, and no major adverse events attributable to ATI355. Future efficacy trials are still pending (Schwab and Strittmatter 2014; Kucher et al. 2018).

Excitotoxicity

Once the spinal cord is injured, the damaged cells release excess glutamate and leads to excitotoxic damage. Numerous medications have been explored in treating SCI with the targeted effect of limiting inflammation and excitotoxicity. Riluzole is a benzothiazole anti-epileptic that can reduce excitotoxicity though sodium blockade and reduction of presynaptic release of glutamate. This medication is already approved for neurodegenerative disorders including amyotrophic lateral sclerosis, and has been shown to reduce neurodegeneration and effects of traumatic injury by modulating excitotoxicity. The Riluzole in Spinal Cord Injury Study (RISCIS) trial has shown safety of oral administration of Riluzole in acute SCI. Phase II/III trials are now pending (Siddiqui et al. 2015).

Minocycline, a tetracycline antibiotic, also has been found to have anti-inflammatory, anti-oxidant, and anti-apoptotic properties. It has been shown to minimize N-methyl-D-aspartate (NMDA)-induced excitoxicity. Its effects may stem from its ability to modulate inflammatory effects of microglia (Shultz and Zhong 2017). Given its clinical availability and established safety as an antibiotic, it has been an attractive drug for clinical trials and is currently pending Phase III trials.

Gacyclidine is a noncompetitive NMDA recept antagonist that has targeted effects of reducing inflammation and excitotoxicity. Animal models showed possible attenuation of spinal cord damage. Early-stage SCI trials in humans have been completed but efficacy has yet to be shown (Donavan and Kirschblum 2018). Similarly, Magnesium also antagonizes NMDA receptors and has been explored for its potential to reduce inflammation and excitotoxicity. It has been used together with scaffolds, discussed in a later section, to treat SCI. To date, none of the medications have shown a clear benefit in the treatment of SCI.

Previously Explored Pharmacologics

A number of trials have shown negative results without further research. Thyroid releasing hormone (TRH) has been shown to antagonize many aspects of secondary injury. It was studied in a small clinical trial in 1995 in acute SCI with negative results (Lehrer 1996). Opioid antagonism has also been explored given the potential neurotoxic effects of endogenous opioids in SCI. The NASCIS II trial included a trial arm of naloxone which showed negative results. Gangliosides are glycolipids abundant in nervous tissue. In vitro experiments have shown potential benefit of gangliosides in enhancing axonal growth, and an experimental ganglioside GM-1 (monosialoate-trahexosylganglioside), also known as Sygen, had shown promise in animal models of SCI. Its efficacy however was not shown in a large RCT, and no future studies have been planned.

Bio-Scaffolds

Another strategy to facilitate regeneration focuses on providing support and guidance for damaged neurons through scaffolds that can both facilitate growth and inhibit antagonizing factors and the formation of glial scars. Many different natural materials have been used, including collagen, chitosan, alginate, and fibrin. Natural materials have advantages including biocompatibility, biodegradability, and low toxicity. Synthetic materials have also been developed, including various polymeric biomaterials, with the advantage of more controllable biodegradability and physicochemical and mechanical properties. Polyethylene glycol (PEG) is one synthetic biocompatible polymer that has shown potential to stimulate angiogenesis, reduce glial scar formation, and promote axonal regeneration through its ability to act as a

fusogen and stabilize compromised neuronal membranes. In animal models of SCI, PEG has been shown to improve hind limb function.

The potential of biological scaffolds can be augmented by seeding with pharmacologics, immunomodulators, and stem cell lines, providing an environment that provides both neuroprotection and positive growth factors. The addition of magnesium to PEG has been used in rat models of SCI and shown to provide tissue protection and improved locomotor recovery (Kwon et al. 2009b). While promising results have been demonstrated in animal models, the evidence in humans is limited (Liu et al. 2019). Few biological scaffolds have been translated from the research lab to clinical trials. Complications ranging from seroma formation to meningitis have been reported in human subjects (Liu et al. 2019).

The neuro-spinal scaffold (InVivo Therapeutics Corp, Cambridge, Massachusetts) is a porous polymer scaffold composed of poly(lactic-co-glycolic acid) covalently conjugated to poly-L-lysine that has been one of the few scaffolds to be used in humans. A preliminary study of one patient who sustained a spinal cord contusion at T11–T12 had the neuro-spinal scaffold placed during surgical decompression and fusion for the acute injury (Theodore et al. 2016). The patient preoperatively had a T11 AIS grade A complete injury, and 12 months postoperatively was noted to be L1 AIS grade C. Preliminary results from a larger study of 16 patients (INSPIRE study) showed that 7 (44%) reached the primary endpoint of ASIA Impairment Scale conversion at 6 months. While one patient was lost to follow-up, the remaining six patients who converted retained their improvements at the 12-month mark. Further large-scale studies as part of INSPIRE 2.0 are currently undergoing (Anon n.d.).

Neuromodulation

An alternative approach to SCI focuses on the development of electrical stimulation to augment or modify neuronal function. As technological advances in materials science and computing are made, the possibility of neuromodulation to restore spinal cord function becomes closer to reality. Stimulation can be applied direction to the muscle, peripheral nervous system, or even central nervous system to drive motor output (Fig. 8). Technologies have been explored in brain stimulation, brain–machine interfaces, spinal cord stimulation, and peripheral stimulation.

Peripheral Stimulation

Functional electrical stimulation (FES) involves the application of electrical stimulus to generate muscle contractions. By targeting specific muscles of interest, FES can induce controlled movements in the limbs and body. FES has successfully been used to improve ambulation in patients with incomplete SCI through generating contractions in the limbs (Badhiwala et al. 2018). While originally envisioned as a permanently worn device, FES may also be used as a clinical intervention with a limited number of training session. One case report describes how FES training allowed a patient to regain meaningful movement in his upper extremities (Popovic et al. 2016). Through the help of stimulation patients can potentially gain muscle strengthening as well as neuroplastic changes and cortical reorganization. This concept will be compared with conventional occupational therapy in an ongoing phase III multicenter trial.

Brain Stimulation

Brain stimulation has also been explored as an option to help SCI and explores the possibility of increasing the activity of residual pathways. Transcranial direct current stimulation (tDCS) and transcranial magnetic stimulation (TMS) are two noninvasive techniques that have been explored in combination with motor training to augment existing neurological pathways. As noninvasive procedures, both tDCS and TMS are considered safe and low risk, and have been researched extensively in the treatment of neuropathic pain in SCI with mixed results (Fregni et al. 2006; Wrigley et al. 2013; Gao et al. 2017). Several small studies have used multiple sessions of tDCS in small groups of patients in the chronic phase of SCI with some improvement in upper and lower extremity function (Gunduz et al.

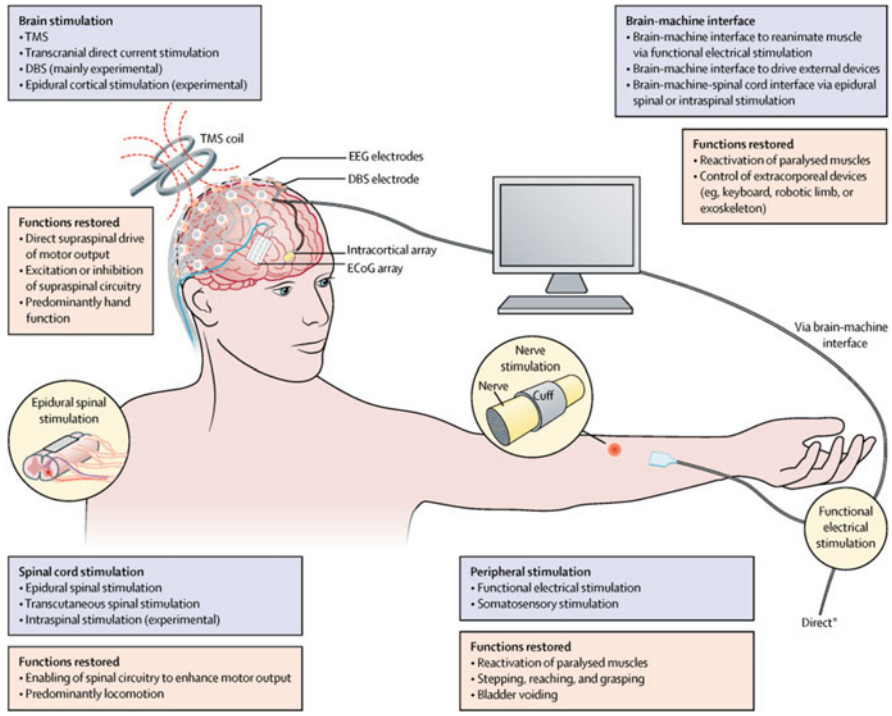

Fig. 8 Neuromodulation targets in SCI. https://ars.els-cdn.com/content/image/1-s2.0-S1474442218302874-gr1.jpg (Copyright requested through RightsLink). (Reprinted from Lancet Neurology Volume 17, Issue 10, Nicholas D James, Stephen B McMahon, Edelle C Field-Fote, Elizabeth J Bradbury, "Neuromodulation in the restoration of function after spinal cord injury," Pages 905–917, 2018, with permission from Elsevier)

2017). This therapy may be synergistic in conjunction with current rehabilitation therapies. tDCS in combination with direct motor cortex stimulation with epidurally implanted electrodes has also been shown to promote axonal sprouting and improve motor control in animal models. (Zareen et al. 2017)

Spinal Cord Stimulation

Epidural spinal cord stimulation has been implanted above the dorsal surface of the spinal cord extensively for chronic pain with a good safety record. This has allowed several initial SCI case studies to be completed where epidural stimulation of the lumbosacral spinal cord augmented recovery in chronic, motor-complete paraplegic SCI patients (Rejc et al. 2017; Grahn et al. 2017). In lumbosacral epidural electrical stimulation, a 16-electrode array is implanted over spinal segments L1–S1. Recovery of voluntary movement with epidural stimulation was observed in motor-complete patients 2 years post-injury (Angeli et al. 2014). There are two proposed mechanisms for this late recovery. First, there is activation of previously "silent" anatomical connections from epidural stimulation. These few remaining descending connections have been present since the time of injury but were insufficient to activate motor pools until epidural stimulation enhanced central excitatory drive by altering spinal cord circuitry. Stimulation may facilitate excitation of propriospinal interneurons, which support propagation of voluntary command to the lumbosacral spinal cord. Second, the continued improvement of voluntary movement with repetitive epidural stimulation and training suggests plasticity with the recruitment of novel neuronal pathways and synapses with time. These results suggest the ability of the spinal networks to learn with task-specific training and improve motor pool recruitment to promote force generation and accuracy.

Epidural stimulators have also been explored in chronic cervical injury and results suggest improvement in grip strength (Lu et al. 2016). In cervical epidural stimulation, two 16-contact percutaneous epidural leads are placed spanning C4–T1. Immediate improvements in maximal hand strength and control were seen in chronic, motor-complete tetraplegic SCI patients within one testing session and incremental, sustained improvements were observed after repeated stimulation. These results suggest that epidural stimulation facilitates the recruitment of viable, but previously nonparticipating, cervical interneuronal networks projecting to motor pools, similar to is observed with epidural stimulation to the lumbosacral spinal cord.

A number of clinical trials have also been investigating transcutaneous spinal cord stimulation (tcSCS) with a similar conceptual goal. tcSCS is less accurate but is noninvasive and inexpensive. However clinical trials of both direct SCS and aSCS are small, and larger clinical trials will need to be done to confirm initial findings.

Brain Machine Interfaces

Brain machine interfaces (BMI), also referred to as brain computer interface (BCI), have been a popular and exciting research topic. The technique allows the recording and decoding of brain activity and translates the information to generate functional output. This concept has shown promise in individual case studies (Bouton et al. 2016; Ajiboye et al. 2017). Recording devices range from noninvasive scalp surface EEG electrodes to invasive subdural or epidural implanted electrocorticography electrode arrays (ECoG) and intraparenchymal microelectrode arrays. The invasive devices have predominantly been implanted on the cortical surface gyri, often in the motor cortex. Neural activity is captured from these devices and decoded by a computer with the goal of interpreting movement plans. Noninvasive devices have a lower signal quality, while invasive recording devices are much more sensitive. The decoded signals are translated into commands that can be used to control an external device, such as prosthetic robotic limb or a cursor on a computer screen (Lee et al. 2013). One of the first implantations of BMI in humans was done by the BrainGate group at Brown University, where a small array implanted in the motor cortex allowed continuous control of a computer cursor in patients with severe SCI (Hochberg et al. 2006; Kim et al. 2008). Application of this technology goes beyond rehabilitation for SCI or stroke patients. Both the Department of Defense and commercial companies have funded efforts to master the ability to decode brain signal with the goal of human enhancement.

There are several barriers that will need to be addressed prior to widespread clinical applications of BMI. The technology currently requires a large amount of highly advanced and specialized technology, which has high costs that would make such a therapy inaccessible and unaffordable. Current participants are still required to be connected to a computer interface, which would not translate well to daily function. Implanted electrode arrays also are prone to gliosis and physical damage, resulting in loss of recordings. As the technology advances to become more portable, affordable, and durable, it will continue to expand in potential uses.

Challenges: Translational Studies, Timing of Intervention, Ethical and Economic Considerations, and Considerations in Clinical Trial Design

Consistency of Results

As with any research, the translation of research from the bench to patient care carries significant challenges. Animal models vary greatly from humans in body size, anatomy, and their response to severe SCI. While we try to control the variability in experimental models, patients carry significant heterogeneity in their individual characteristics and the type of SCI endured. This highlights the importance for early experiments to show a clear and significant benefit before moving on to higher-level trials, and likewise early-phase clinical trials will need to show the same to justify the cost of recruiting a larger population that is likely more heterogeneous.

Risks

While stem cells have been extensively studied in the laboratory, our experience with their use in humans is relatively limited, and we may not know the full range of potential side effects and complications associated with this therapy. As previously discussed, the use of olfactory nasal ensheathing cells for spinal transplantation led to the unwanted growth of a multicystic mass (Dlouhy et al. 2014). Conversely, immunotherapies that block the innate immune responses may prevent scar formation, but may also block protective processes and adversely affect spontaneous recovery (Putatunda et al. 2018). Government regulatory policies may help ensure the safety of translational research, but can also introduce further challenges by blocking potentially effective variations, such as adjustments in dose amount or number.

Timing

As the field of spinal cord injury moves into translational research, challenges surrounding clinical studies arise. One of the most important challenges is determination of timing of therapeutic intervention, which affects both recruitment strategy and potential treatment effects. A window of opportunity may exist for SCI patients in which a response to treatment is only possible for a limited time period after acute injury. This would limit studies to focus on patients in the acute or subacute phase of injury.

Studies that focus on acute injury face issues with accessing individuals within a few hours of presentation, requiring a developed infrastructure in trauma centers. In the acute setting, treatment effects are also more likely to be confounded by spontaneous neurologic recovery or other injuries and complications. The patients that are most likely to benefit from experimental treatments are sometimes also the most likely to spontaneously improve, which makes treatment effects very difficult to detect. While chronic SCI studies may be easier to recruit, patients showing high potential for recovery may not want to take on the risk an experimental approach carries. The burden of extensive follow-up and testing can also lead to difficulty in following the progress of studied patients (Blight et al. 2019; Blesch and Tuszynski 2009).

With respect to completed trials examining the effects of timing of surgical decompression, initial results from surgical trials (Vaccaro et al. 1997) showed no difference in ASIA motor score or grade in patients undergoing early (<72 hrs) versus late (>5 days) surgical decompression and 1-year average follow-up. All of these patients received high-dose methylprednisolone. The question of optimal surgical timing remained unanswered and gave rise to the Surgical Treatment of Acute Spinal Cord Injury Study (STASCIS) trial, which was intended to compare the efficacy of early (<24 hrs) versus late (>24 hrs) surgical decompression on 6-month outcomes in cervical SCI patients (Fehlings et al. 2012). All patients were aggressively medically managed with MAP goals >85 and 60% of enrolled patients received methylprednisolone as determined by each study team. Multivariate regression analysis, when controlled for methylprednisolone and type of injury (complete versus incomplete), demonstrated patients undergoing early surgical decompression were 2.8 times more likely to improve at least two grades in AIS (ASIA Impairment Scale) grade at 6 months. Several prospective cohort studies since have shown a benefit of early decompression. Subsequent retrospective studies have also shown significant improvement in 1-year SCIM (Spinal Cord Independence Measure) scores, AIS grade improvement, and AIS grade conversion in patients undergoing ultra-early decompression (<8–12 hr) after traumatic cervical SCI (Grassner et al. 2016; Burke et al. 2018).

Ethical Challenges

While a cure for SCI would transform the lives of affected patients, it is paramount to ensure that the research to achieve this goal is done ethically. The use of stem cells derived from embryos sparked intense ethical debate, with concern of whether

embryos should be considered "persons." As a result of this concern governments worldwide have strictly regulated the use of embryonic stem cells in research. The advent of induced pluripotent stem cells (iPSCs) through genetic reprogramming of somatic cells provided a useful alternative to embryonic stem cells and has significantly minimized this ethical controversy. There are also ethical concerns surrounding animal models of SCI, as lesions of the spinal cord significantly impact the quality of life of an animal. Animal use protocols should ensure the well-being of any animals experimented on.

Once a promising therapy is demonstrated in an animal model, a difficult question is when this should be translated into human trials. Experimental interventions of the spinal cord carry significant risk, as their effects in animals do not always perform the same in humans. Given that recovery in the early stages of injury is difficult to predict, it is a concern that a new therapy could inhibit or negatively affect spontaneous recovery. It is important for researchers and governing research and ethics review boards to carefully ensure the scientific validity, favorable risk–benefit ratio, and respect for human rights. Additionally studies should be designed to maximize safety while ensuring the best care for the patient. An additional ethical challenge arises in patient selection. Patients that have the most severe injury need the most help; they are also the least likely to recover. Ultimately, the high costs of human trials limit the number of participants with strict inclusion criteria that maximize the potential to detect a possible therapeutic benefit (Rosenfeld et al. 2008).

Costs

It is predicted that by 2025, global spending on clinical trials will reach $68.9 billion a year (May 2019). The estimated costs for preclinical studies alone can costs hundreds of millions of dollars (Trounson and McDonald 2015). Stem cell lines can cost thousands of dollars to produce. While rodent models of SCI are widely available and accessible, they do not reflect humans in an anatomical and physiological way. Larger animal models, such as primates, greatly increase in costs as well as regulation. These costs are nominal compared to human clinical trials, and costs continue to increase for late-stage trials as the number of patients required increases and the study becomes more complex. The high financial burden makes careful planning and patient selection imperative to achieve the highest likelihood of identifying effective therapies.

Challenges and Considerations in Designing of Clinical Trials

Various surgical and therapeutic trials have been conducted over the last several decades with the goal of improving functional outcomes for the spinal cord–injured population. Some have been randomized controlled trials (RCT) while others have primarily been cohort studies. Extensive reviews of the trials in SCI can be found in the literature (Tator 2006; Hawryluk et al. 2008; Donavan and Kirschblum 2018). In order to conduct effective and efficient future trials, it is imperative to review the important lessons learned from previous experiences.

One must appreciate the unique challenges in studying this population as well as the areas of possible conflict that can impact results and affect the success of measured outcomes. As outlined eloquently in his review of human SCI trials, Dr. Tator addresses the important shortcomings in SCI research and trial design (Tator 2006). Spinal cord injury itself is a heterogenous disease process. Not only are cervical and thoracic SCI populations quite different in their injury pattern and propensity to regain function, but complete and incomplete populations are also crucially different. Incomplete SCI patients have more capacity to recover than those with complete injury but the myriad pathophysiological mechanisms at place are difficult to control for in any given trial. As alluded to earlier, the complete SCI population is more homogeneous and therefore may be a better population to study, despite the fact that potential for recovery is less than the former. Though it makes good sense to design trials

based upon level of injury, thoracic ASIA grade A patients comprise less than 15% of the SCI population, for example, making trial accrual challenging. There are also limitations to our currently used ASIA grading system. For example, a ceiling effect exists for Grades C and D, making it difficult for patients to move out of one category to the next level of improvement. Spontaneous recovery presents a unique but omnipresent phenomenon. It was estimated by Burns et al. that approximately 60% of ASIA grade B through D patients move to a higher grade. Since these grades account for over 50% of patients with SCI, they must be included in trials. However, efficacy of a given intervention may be difficult to distinguish from the natural history in these patient populations. Further, combined upper and lower ASIA motor scores can be similar yet indicate vastly different cervical and thoracic SCI populations with varying degrees of injury and prognosis for recovery. As such, there has been an effort to stratify patients at trial entry into different levels and severities to more accurately quantify recovery. Lastly, and as is certainly the case for surgical trials, difficulty with blinding and timing of intervention provide unique challenges. It is of critical importance that examiners be blinded to treatment groups to minimize bias. This may require mandatory bandaging of surgical and "sham" sites or cooperation on the part of the patient to conceal their treatment group. Optimal timing of intervention has not been well established, though it has been hypothesized that neuroprotection be initiated early while subacute to chronic injury may be optimal for trials aimed at assessing regenerative capacity. These are only a few of the important points to consider when designing or evaluating results in SCI trials.

Currently no one effective therapy exists for restoring function in SCI. This emphasizes the need for continued research and translational studies. Despite the many challenges that exist in the research pathway, many translational human studies are underway. Both successes and failures will aid in our understanding of SCI and pave the road toward developing promising therapies. Throughout the process, it is equally important to ensure that ethical standards are adhered to. Through guidelines and careful review of each step, ethical challenges can be minimized to ensure the safety of all patients.

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Biologics: Inherent Challenges

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Charles C. Lee and Kee D. Kim

Contents

Abstract

A biologic product is derived from a biological system and may include osteogenic, osteoinductive, and/or osteoconductive properties that are required for efficient bone regeneration. Current biologics include autologous or allogenic bone products, growth factors, and bone graft substitutes. Each of these therapeutic approaches presents unique advantages and challenges that require further development. Due to known, inherent challenges of current biologics, a single approach may not be sufficient to address complex issues presented in patients with significant issues in the spine, especially those at high risk for nonunion. While a combinatory approach is certainly

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interesting, a new therapeutic modality that combines different aspects of bone repair and regeneration may be needed. Stem cell and gene-based approaches have been investigated to address unmet clinical needs, which may include systemic issues and/or suboptimal microenvironment at the site of implantation. Intricate interactions and molecular cross-talks between osteogenic, osteoinductive, and osteoconductive biologics that are required for successful bone fusion are still under investigation.

Keywords

Autograft · Allograft · Growth factors · Stem and progenitor cells · Gene therapy · Spine therapeutics · Spine biologics · Challenges · Microenvironment · Bone graft substitutes

Introduction

Two or more vertebrae may be fused to stabilize the spine for a variety of clinical conditions such as degenerative disc disease, vertebral fracture, scoliosis, and other conditions that cause instability of the spine. The height of an intervertebral disc may be up to 16 mm (Zhou et al. 2000) and represents the distance between two adjacent vertebrae that needs to be filled with new patient bone for a successful interbody fusion. In the absence of a true, effective osteogenic element in the treatment modality, this distance may present a significant challenge for the right type of cells on either side to migrate out from their native environment and bridge the bony gap, especially in patients with risk factors such as diabetes, aging, and smoking. As an example, a significant difference was observed in nonunion rates between nonsmokers and smokers (14.2% vs. 26.5%) (Glassman et al. 2000). Thus, a proper understanding of various therapeutic modalities, size and type of bony gap (or defect), and microenvironment, where bone regeneration must take place, is critical for a successful fusion.

A biologic medical product (or biologic) refers to a therapeutic modality that is derived from a biological system (e.g., animals, humans) and used to address a clinical condition. For bone fusion, it includes any biological elements that have osteogenic, osteoinductive, and/or osteoconductive properties, which participate in regeneration of bone in a clinical setting. An intricate interaction or molecular cross-talk between these properties may be necessary for efficient bone regeneration. The osteogenic component may include stem and progenitor cells (e.g., mesenchymal stem cells [MSC]), bone marrow-derived products (bone marrow aspirate), and autograft/allograft. It is typically referred to viable cells that can directly contribute to repair and regeneration of bone at the affected site. Exogenous (transplanted) or endogenous (native) cells that can proliferate and differentiate into mature bone cells may be considered osteogenic. An osteoinductive factor participates in differentiation of bone precursors toward the terminal lineage. It can modulate local microenvironment to promote tissue healing post-injury. Osteoinductive factors include bone morphogenetic proteins (BMPs), fibroblast growth factor-2 (FGF-2), and platelet-derived growth factor (PDGF) (Khorsand et al. 2017; Kim et al. 2015). An osteoconductive element provides a scaffold that can support the function of osteogenic cells and osteoinductive factors structurally to regenerate, fill, and bridge bony void or defect with new bone. It may be derived from a biological system or produced synthetically. In this chapter, current clinical uses of each of these components that participate in bone repair and regeneration and their inherent challenges are discussed.

Autologous Bone

Currently, technologies addressing the need to repair bone defect or void are extensive, but none currently offer the benefit of a personalized approach that is safe, relatively noninvasive, and anatomically defined for autologous bone formation. As described above, an ideal bone product would be osteoconductive, osteoinductive, and osteogenic. Autologous bone (autograft) meets the above criteria and is considered the “gold

standard" for bone repair and regeneration. Local autologous bone is often inadequate. Therefore, it is important to consider many factors such as potential morbidity due to the harvesting procedure, tissue condition at the harvest site, mechanical and structural implication of graft harvesting, and patient condition among others. Autologous bone is traditionally harvested from the iliac crest but can also be collected from other sites such as the rib, vertebral body, and fibula. The iliac crest has been considered the "gold standard" source since the amount of bone available for harvesting is relatively large compared to the other sites. A wide variety of harvesting techniques are available depending on the type of bone subject to harvesting and the approach used, including trapdoor (bone flap), window (removal of segmental bone), splitting (fissure in the iliac crest), and trephine extraction ("minimally invasive") techniques. Overall, there has not been consensus as to which technique results in a better clinical outcome, especially the risk of complication and morbidity associated with the harvest procedure of choice. While the use of autologous bone graft has shown exceptional efficacy, regardless of the type of harvesting methods or sites used, with a fusion rate greater than 94% (Sawin et al. 1998), donor site morbidity still presents a significant problem. Pain at the donor site was reported in 16% of patients who reported a worse pain at the donor site (iliac crest) than the primary surgical site in addition to difficulty walking (15.1%), employment (5.2%), recreation (12.9%), household chores (7.6%), sexual activity (7.6%), and irritation from clothing (5.9%) at 1 year follow-up (Kim et al. 2009). Similar findings were observed in other studies with a longer follow-up period (Sasso et al. 2005; Schwartz et al. 2009). Although there have been efforts to reduce donor site morbidity including restricting the area for harvesting and use of a suction drain (Kurz et al. 1989), the clinical outcome of using autologous bone is still less than optimal due to donor site morbidity, increased blood loss and frequent need for blood transfusion, prolonged operative time, risk of nerve damage, and a revision in many cases (Mulconrey et al. 2008).

Allogeneic Bone

Allogeneic bone (allograft) is considered an alternative source of graft material and eliminates the donor-site complications associated with autologous bone harvest procedures (Ehrler and Vaccaro 2000). It is harvested from cadaveric and living donors and is typically stored in a bone tissue bank. Fresh-frozen allografts, freeze-dried allografts, and demineralized bone matrix are the most commonly used forms of allogenic bone, and each preparation method brings certain advantages and disadvantages to a bone grafting procedure (An et al. 1995). Across all methods of preparation, allograft is more immunogenic and displays a decreased rate of graft integration in comparison to autograft (Ehrler and Vaccaro 2000). Fresh-frozen allografts are treated with antibiotics after harvesting and must be frozen below −70 °C to preserve the quality and viability of the graft material (Laitinen et al. 2006). The composition and structure of fresh-frozen allograft is most similar to those properties of autologous bone. Fresh-frozen grafts retain the most structural integrity of any processed allograft, which provides an optimal matrix for osteogenesis at the graft site. This preparation method also preserves a significant amount of endogenous BMPs known to be osteoinductive. However, the presence of cellular debris activates a host immune response and leads to increased risk of graft-site inflammation, delayed bone regeneration, and higher failure rate (An et al. 1995; Laitinen et al. 2006). Freeze-dried allografts are prepared similarly to fresh-frozen grafts with the addition of a dehydration process. Dehydration renders the graft material shelf-stable at room temperature and thus more readily stored for future use (Ehrler and Vaccaro 2000). Freeze-dried allografts carry a decreased risk of infection and immunogenicity at the graft site. This allograft type contains no live cells and fewer viable growth factors, but the mineralized portion may still provide a significant osteoinductive effect (Mellonig 1995). A potential drawback of freeze-dried allograft is decreased mechanical stability and structural strength, rendering the graft more brittle and prone to fracture (Cornu et al. 2000).

Demineralized bone matrix (DBM) is more extensively processed than fresh-frozen and freeze-dried allografts. Acid treatments are used to remove the inorganic, mineralized components of bone leaving behind the organic collagen matrix composed of type I collagen, non-collagenous proteins, and various growth factors (Lee et al. 2005). DBM is sold in numerous commercial formulations and is subject to a great deal of variability in processing techniques. Differences in acid solutions, temperature, particle size, terminal sterilization, and demineralization time result in lot-to-lot variability, yielding inconsistencies in BMP content and osteoinductive potential (Lee et al. 2005; Wang et al. 2007). DBM does not provide structural support as the mechanical properties of bone are significantly diminished secondary to the demineralization process (Pacaccio and Stern 2005). Generally, DBM is indicated for use as a bone graft extender and is not thought to be sufficient as a stand-alone bone graft substitute for reconstructive orthopedic procedures. Allograft materials made of minimally or highly processed allogenic bone are relatively abundant in supply and are effective in regenerating bone. Overall, the structural integrity and osteoinductivity of fresh-frozen allograft is preferred over freeze-dried allograft and DBM products, despite the risk of immunogenic complications.

Growth Factors

BMP-2

Bioactive agents including growth factors with osteoinductive functions are administered for spinal fusion as a means to promote endogenous bone formation and healing. BMPs are a family of osteoinductive growth factors with important roles in development and are known to stimulate osteoblastic differentiation of stem cells. BMP-2, or recombinant BMP-2 (rhBMP-2) produced in vitro by mammalian or bacteria cells, is the most widely studied and has been approved by the FDA for anterior lumbar interbody fusion (ALIF) in 2002 (US Food and Drug Administration 2019a). rhBMP-2 is typically administered with a carrier such as demineralized bone matrix or biodegradable collagen sponges at doses in the range of 3.5–20 mg (Duarte et al. 2017). A commercially available product for ALIF, Infuse™ Bone Graft (Medtronic), contains rhBMP-2 with an absorbable collagen sponge carrier inserted in a titanium cage to provide mechanical support. Early clinical studies demonstrated the Infuse™ product to be superior to iliac crest bone graft with 94% versus 88.7% fusion, respectively (Burkus et al. 2002a, b). Radiographs and computed tomographic (CT) scans provided evidence of rhBMP-2 driven osteoinduction in the interbody cages within 6 months of surgery and new bone formation in the surrounding disc space by 24 months post-surgery in all patients (Burkus et al. 2003). Follow-up studies compared cortical allograft dowels with or without rhBMP-2 for single level ALIF. All patients receiving the allograft with rhBMP-2 showed radiographic evidence of fusion by 12 months which remained stable through 24 months ($n = 79$, 100% fusion) compared with controls ($n = 52$, 89% and 81.5% fusion at 12 and 24 months, respectively) (Burkus et al. 2005, 2006). In addition to improving bone formation, the use of Infuse™ is simple with reduced operation times, length of hospital stay, and volume of blood loss compared to bone graft therapy (Burkus et al. 2002a). FDA has granted additional approvals for Infuse™ in polyetheretherketone supports for ALIF and oblique lateral interbody fusion (OLIF, US FDA 2019b).

The use of rhBMP-2 with the Infuse™ product was widely adopted for ALIF (on-label) as well as many off-label applications. In 2010, off-label use of rhBMP-2 was reported to be as high 85% including primary cervical, primary thoracolumbar, posterior lumbar, transforaminal lumbar, and posterolateral spinal fusions (Ong et al. 2010). When used as directed for ALIF, industry-sponsored clinical study publications reported efficacy rates superior to allogenic or autologous bone with adverse events rarely observed. Follow-up publications and review of FDA data summaries focused attention on a number of complications and adverse events including implant displacement, subsidence, osteoclast-mediated bone

resorption, ectopic bone formation, inflammation, life-threatening cervical swelling, urogenital complications, and possible increased risk of tumor formation (Carragee et al. 2011a; Savage et al. 2015; Faundez et al. 2016).

In addition to osteoinductive properties, rhBMP-2 enhances osteoclast activity which has been linked with subsidence or abnormal bone resorption. Localized areas of bone remodeling were noted at 12 months post-surgery by CT scan in 18% of patients receiving cortical allograft dowels with rhBMP-2 (Burkus et al. 2006). These regions resolved by 24 months in follow-up CT scans. Patients treated with rhBMP-2 within the disc space during transforaminal lumbar interbody fusion were observed with 69% vertebral bone resorption and 74% graft subsidence (McClellan et al. 2006). Radiologic analysis of interbody fusions in the cervical or lumbar spine performed with a polyetheretherketone cage and rhBMP-2 demonstrated endplate resorption in all cervical and most lumbar fusions with concomitant cage migration and disc space subsidence (Vaidya et al. 2008). Ectopic bone formation beyond the implant site has also been reported and is thought to be a consequence of leakage of rhBMP-2 from the collagen sponge due to pressure during the placement procedure or the use of irrigation or suction near the graft site (James et al. 2016). Leakage occurring in the epidural space may result in nerve root compression and is noted more frequently in transforaminal lumber interbody fusion (Rihn et al. 2009).

Use of rhBMP-2 in cervical fusions has resulted in severe, life-threatening swelling in the head and neck leading to dyspnea and dysphagia (Shields et al. 2006). Procedure-related swelling around the cervical spine contributes to constriction of airways and nerves that lie in close anatomical proximity. The life-threatening nature of these complications may require interventions such as intubation, anti-inflammatory medications, tracheotomies, or additional surgeries (Smucker et al. 2006; Fineberg et al. 2013). Seroma formation was also noted when the Infuse bone graft was used for occipitocervical fusion (Shahlaie and Kim 2008) with elevated levels of inflammatory cytokines including IL6, IL8, and TNFα reported in seroma fluid (Robin et al. 2010). The severity of inflammatory complications related to rhBMP-2 use in the cervical region prompted FDA to issue a public health warning regarding the use of this product in the cervical region in 2008 (Crawford et al. 2009). Use of rhBMP-2/Infuse™ products in pediatric spinal fusions is also contraindicated (Epstein 2013). No differences in infection rates were noted in spinal fusions with and without rhBMP-2 in a retrospective study by Williams et al. (2011) suggesting swelling events to be related to hypersensitivity rather than infection.

A number of urogenital complications have been reported including retrograde ejaculation and bladder retention with incidence rates up to 6.3% and 9.7% respectively, although in most studies these events were not statistically greater than observed in control groups (Carragee et al. 2011b). Further studies of 10-year outcomes following rhBMP-2/Infuse™ for ALIF suggest these complications may be related to concomitant prostatic disease with specific correlation to rhBMP-2 difficult to establish (Comer et al. 2012). Other studies suggest transperitoneal and laparoscopic approaches increase risk of urogenital adverse events in comparison to a retroperitoneal approach (Burkus et al. 2002a; Than et al. 2011).

BMPs have developmental and regenerative roles in many organ systems and are known to regulate cell growth and differentiation as well as stem and progenitor cell functions. Members of this family of proteins are frequently upregulated in tumors of diverse organ systems and the spine is a common site for tumor metastases leading to concerns that rhBMP-2 use in spinal fusions may increase tumor risk (Carragee et al. 2013). Retrospective analysis by Devine et al. (2012) did not find evidence of increased cancer risk when rhBMP-2 was used as approved. Higher doses of rhBMP-2 (40 mg) were linked to small increases in cancer risk, as was the use of rhBMP-7. In agreement with these findings, retrospective studies of cancer incidence in Medicare patients receiving rhBMP-2 over a 5-year period were not associated with an increase in cancer risk (Kelly et al. 2014; Beachler et al. 2016). Likewise,

an analysis of database studies of rhBMP-2 in spinal fusion was unable to detect a significant increase in local or distant site tumor formation (Cahill et al. 2015).

OP-1 (BMP-7)

Osteogenic protein 1 (OP-1), also known as BMP-7, is another member of the family of BMPs with osteoinductive potential. In spinal fusion, rhBMP-7 is delivered in a collagen putty (Olyppus Biotech). When compared with autograft bone for noninstrumented posterolateral lumbar fusion, the OP-1 implant was similar, but not superior to autograft bone (Johnsson et al. 2002). FDA approval, under an investigational device exemption, was granted in 2004 for OP-1 putty in posterolateral spinal fusion (Vaccaro et al. 2003, 2004). Radiographic and clinical outcomes were at least equivalent to the autograft cohort over the 2-year follow up period, with no adverse events reported (Vaccaro et al. 2005a, b). The OP-1 putty was also assessed as an adjunct to autograft bone for intertransverse process lumbar fusion in a small clinical trial (Vaccaro et al. 2003). Inclusion of OP-1 putty with the autograft bone was not shown to improve spinal fusion, although product safety was demonstrated with no adverse events reported. In a study with 4-year follow up, OP-1 putty was compared with iliac crest autograft and shown to be equivalent in promoting fusion and advantageous from a procedural view due to less blood loss and shorter operative times (Vaccaro et al. 2008a, b). In a randomized, multicenter trial, there were fewer fusions in the OP-1 cohort (54%) than in the iliac crest autograft groups (74%) (Delawi et al. 2016). More recent clinical trials are focused on the use of OP-1 in uninstrumented posterolateral fusions (Olympus Biotech, http://www.clinicaltrials.gov/ct2/show/NCT00679107). The safety profile of OP-1 in terms of adverse events appears to be superior to rhBMP-2; however, this should be interpreted with caution until larger OP-1 trials are completed. In terms of effectiveness, OP-1 has not been shown to be superior to autograft bone and direct comparisons with rhBMP-2 have not been conducted.

NELL1

Other growth factors have shown potential in spinal fusion studies in animals. Neural EGFL like 1 (NELL1) is an osteoblast-specific growth factor which acts in bone maintenance and repair to promote expansion of a progenitor population (James et al. 2017). When delivered in a demineralized bone putty carrier, NELL1 was found to be effective for spinal fusion in rats (Li et al. 2010). In a sheep spinal fusion model, NELL1 delivered in demineralized bone matrix promoted 100% fusion by 3 months with advantages in bone volume and mineral density compared to demineralized bone alone (Siu et al. 2011). Studies by Yuan et al. (2013) compared NELL1 in demineralized bone matrix with the BMP-2/Infuse™ bone graft product in a rat spinal fusion model. Fusion rates were similar in both groups (100%). Histological analysis demonstrated the presence of adipocytes and cyst-like bone formation in the rhBMP-2 graft cohort and increases in bone formation, ossification, and vascularization in the NELL1 group (Yuan et al. 2013).

Growth Factor Combinations

Combinations of growth factors have also been tested in animal spinal fusion studies including angiopoietin 1 (ANG1) and cartilage oligomeric matrix protein (COMP). ANG1 is a secreted factor with important roles in vascular development and angiogenesis. COMP is a BMP-binding protein expressed during endochondral ossification and shown in vitro to enhance BMP-2 activity (Ishida et al. 2013). A recombinant chimeric protein composed of COMP and ANG1 delivered in a collage sponge for lumbar fusion was shown to be effective (89.5% vs. 38.5% in sham-treated controls) in rats (Park et al. 2011). Greater bone volume, mechanical strength, and vascularity were also reported in fusions with the COMP-ANG1 chimeric protein. Endogenous BMPs are soluble factors thought to be present in nanogram concentrations, but supraphysiological doses of 3.5–20 mg are commonly utilized in spinal fusion

applications (Ishida et al. 2013). In an effort to reduce rhBMP-2 dosage and therefore improve product safety, co-administration of COMP and rhBMP-2 was shown to induce equivalent bone formation at lower doses than rhBMP-2 alone in a rat model of spinal fusion (Refaat et al. 2016).

Other growth factors studied in animal models for spinal fusion include AB204 (Activin A/BMP-2 chimera), calcitonin, FGF-2, growth differentiation factor 5, insulin-like growth factor 1, transforming growth factor β, noggin, peptide B2A, and secreted phosphoprotein 24 (Cottrill et al. 2019). In general, these studies suggest that growth factors alone or as an adjunct to bone autografts enhance spinal fusion efficacy. Adverse events associated with rhBMP-2 administration at pharmacological doses raise valid concerns about the safety of growth factor therapies with this family of proteins. Combinatorial approaches or methods to reduce dosage to physiological levels may provide safer, less expensive options. Growth factors such as NELL1, with greater specificity of action, may improve safety and efficacy but clinical trials have not yet been reported.

Stem and Progenitor Cells

An ideal population of cells for bone repair and regeneration must be able to self-renew and proliferate to provide a long-term reservoir of cells available to respond to biological cues. Also, they must be able to differentiate toward mature osteocytes without resulting in fibrosis. In a strict sense, a true stem cell must be able to self-review and differentiate toward multiple lineages clonally at the single-cell level. Progenitor cells have a limited capability to self-renew, proliferate, and differentiate. Stem and progenitor cells that participate in osteogenesis may reside in and near bone or at another location such as adipose tissue. Similar to the hematopoietic system, osteogenic stem and progenitor cells must also be capable of maintaining healthy, long-term homeostasis of the skeletal system. Single human bone marrow-derived high proliferative potential-mesenchymal colony-forming cells (HPP-MCFC) have been investigated for their ability to give rise to another generation of HPP-MCFC and differentiate into multiple lineages clonally (Lee et al. 2013). HPP-MCFC are present at a frequency of about 7% in typical bone marrow mesenchymal cell cultures and show a significant osteogenic activity when induced with osteogenic growth factors. Although controversies still exist, these proliferative and multipotent cell populations derived from different tissue sources are referred to as MSC. MSC have been identified in bone marrow, bone, fat, muscle, and umbilical cord (UC). However, most of studies on MSC are not performed clonally, and it is difficult to conclusively claim their "stem-cell-ness." MSC that have been isolated in culture show expression of different surface markers such as CD29, CD44, CD90, CD49a-f, CD51, CD73 (SH3), CD105 (SH2), CD106, CD166, and Stro-1 and lack of expression of CD45, CD34, CD14 or CD11b, CD79a or CD19, and HLA-DR in addition to plastic adherence and potential to differentiate toward multiple lineages (Dominici et al. 2006; Maleki et al. 2014). STRO-3+ mesenchymal precursor cells have shown an ability to partially reconstitute extracellular matrix (ECM) at 6 months following intradiscal administration into degenerate discs in sheep (Ghosh et al. 2012). Other cell types with similar phenotypic and functional properties have been described including adipose-derived stem cells (ASC) (Minteer et al. 2013), MSC isolated from different locations in umbilical cord (Nagamura-Inoue and He 2014), long bone (Toosi et al. 2017), and dental pulp (Kawashima et al. 2017).

Healthy bone is maintained through formation by osteoblasts and resorption by osteoclasts. An intricate balance between osteoblastic and osteoclastic activities determines the health of bone. The lifespan of osteoblasts (~2–100 days) and osteoclasts (~12 days) are relatively short, and these cells must continually be replenished by stem and progenitor cells. For example, bone marrow-derived MSC have been shown to proliferate and differentiate toward the osteogenic lineage, regulated by numerous signaling pathways such as β-catenin-dependent Wnt (D'Alimonte et al. 2013), Hedgehog (Salem et al. 2014), NELL1 (Lee et al. 2017b), and BMP signaling. Osteogenesis involves several steps that includes ECM

production (organic phase) and mineralization by hydroxyapatite (inorganic phase), followed by differentiation of osteoblasts into osteocytes through embedding in bone matrix and subsequent apoptosis. Osteoclasts have also been shown to participate in osteogenesis by inducing expression of Wnt 1 through the release and activation of TGF-β (Ramasamy et al. 2014). Thus, the microenvironment for bone stem and progenitor cells would include several factors as described above. A deficiency in any component of the microenvironment may result in an aberration in osteogenesis, similar to the hematologic aberrations noted with hematopoietic microenvironment changes. Also, self-renewal and differentiation of stem cells that participate in bone regeneration can be affected directly by specific epigenetic changes, leading to aberration in gene expression and metabolic bone disease (Pérez-Campo and Riancho 2015). It is entirely possible that unnatural or adverse microenvironment provided by a bone graft substitute may have a negative impact in bone repair and regeneration, regulated by proliferation and differentiation of stem and progenitor cells. Thus, the stem and progenitor cell microenvironment need to be considered carefully when transplanting these cells for clinical applications.

MSC are very responsive to their microenvironment (Lander et al. 2012). However, a database of approximately 700 clinical trials on MSC registered in ClinicalTrials.gov as a therapeutic agent indicates that the majority of these trials either did not use any carrier by injecting MSC directly into patients or used ceramic-based carriers (unpublished observation). While an increasing number of preclinical studies focus on MSC and their microenvironment, no clinical trials have considered the effects of the microenvironment on stem cell function. The clinical effectiveness and efficacy of MSC remain inconclusive, although these cells are investigated extensively as shown above, and there have not been any MSC-based therapies approved by the US Food and Drug Administration. Another comprehensive review on the use of MSC in close to 500 clinical trials revealed that the beneficial effect of MSC-based treatment could be principally due to their immunomodulation and regenerative potential (Squillaro et al. 2016). However, issues such as MSC heterogeneity, lack of standard isolation methods, donor heterogeneity, immunogenicity, and cryopreservation bring complexity to the interpretation of clinical data. In addition, in most cases, the host microenvironment may not have been ideal for long-term survival and desired function of transplanted cells.

Gene Therapy

Gene therapy is one strategy to optimize the tissue environment for bone healing or regeneration through delivery of genes encoding for osteoinductive or osteogenic factors. Treatment with a therapeutic osteoinductive factor typically requires large doses of recombinant proteins. In contrast, the use of regional gene therapy to modify native or implanted cells to produce the same protein of interest is potentially more physiologically relevant and cost effective (Phillips et al. 2005). Typically, a gene of interest is delivered to cells which then produce and secrete the target protein into the extracellular environment in a sustained pattern mimicking physiological secretion. The transgene may be introduced in vivo via local injection into patient tissue or in conjunction with transplants of stem or progenitor cells with the gene of interest introduced ex vivo. Local in vivo injection methods are comparatively simple and may provide a readily available, off-the-shelf product, although precise control of transgene delivery to cells in vivo remains a major challenge. Advantages of the ex vivo transduction approach include the ability to expand cells in culture to sufficient numbers essential for bone repair and the capability to quantify target protein production. Some of the challenges include the time and labor necessary for cell expansion and transduction, and risk of inflammatory response due to viral proteins (Baltzer and Lieberman 2004).

Many studies have explored the use of BMPs in gene therapy applications for spinal fusion (Barba et al. 2014). Early attempts at direct percutaneous in vivo gene delivery demonstrated that adenoviral

vectors containing BMP-2 promoted bone formation (Musgrave et al. 1999; Alden et al. 1999). Later studies explored various cell types for ex vivo gene modification followed by transplantation at the fusion site. An ideal cell type for this application should be readily harvested, easy to expand in culture, amenable to gene modification, and have inherent osteogenic and osteoinductive properties. MSC, which can be harvested from bone marrow and are known to differentiate toward osteogenic, chondrogenic, and adipogenic lineages, are a logical choice and have been widely studied as a source of autologous cells for this purpose. MSC genetically modified with BMP-2 were implanted by direct injection into thoracic disc spaces (Riew et al. 2003) or lumbar paraspinal muscles (Hasharoni et al. 2005) and resulted in bridging bone formation in pigs and mice, respectively. Biomechanical tests demonstrated BMP-2-modified MSC-mediated spinal fusion and were as effective as bilateral fusion with stainless steel pins in a mouse model (Sheyn et al. 2010). To improve efficacy, BMP-2-modified MSC were implanted on collagen sponges or demineralized bone carrier matrix and shown to promote abundant bone formation and fusion rates superior to administration of BMP-2 alone (Wang et al. 2003). Additional studies in the rat model of lumbar fusion drew similar conclusions (Peterson et al. 2005; Miyazaki et al. 2008a). In follow-up studies, Miyazaki et al. (2008b) found adipose-derived MSC, which are easier to isolate from patients, to be comparable with bone marrow MSC in this model. Adenoviral-mediated BMP-2 modification of fibroblasts prior to injection along the paraspinous musculature induced heterotopic ossification, new bridging bone, and greater than 90% fusion by 4 weeks in both immune-competent and immune-deficient mice ($n > 40$ per group, Olabisi et al. 2011). Other members of the BMP super-family explored in spinal fusion studies include BMP-4 (Zhao et al. 2007), BMP-6 (Laurent et al. 2004), BMP-7 (Hidaka et al. 2003), BMP-9 (Helm et al. 2000; Dumont et al. 2002), and combinations of BMP-2 and -7 (Zhu et al. 2004; Kaito et al. 2013) with most studies reporting high rates of fusion in rodent or rabbit studies. Despite promising preclinical results in small animal models, the translation of BMP-directed adenoviral mediated gene transfer for spinal fusion to human patients faces challenges including the presence of neutralizing antibodies from previous exposures to adenovirus (greater than 80% of adults are seropositive) which limit effectiveness (Kim et al. 2003), systemic toxicity, and regulatory barriers to clinical trial approval (Wang 2011).

Ideal viral vectors for gene delivery in spinal fusion applications should be capable of delivering the desired transgene efficiently to initiate the bone formation required for the fusion process, but also self-limiting to avoid excessive or abnormal bone formation. Non-integrating, adenoviral vectors induce high, yet transient, levels of gene expression and are the vector of choice for most spinal fusion studies as outlined previously. Lentiviral vectors, which may infect nondividing cells and are known to insert within the host cell genome, have also been studied for this application. Rat MSC transduced with a lentiviral-BMP-2 vector were implanted in hind limb muscle pouches and observed to induce robust bone formation (Sugiyama et al. 2005) in a proof-of-principle study. Bone marrow MSC transfected with lenti-BMP-2 were implanted in collagen sponges and shown to induce spinal fusion in rats (Miyazaki et al. 2008b). Direct comparisons of adenoviral or lentiviral BMP-2 ex vivo gene therapy in MSC seeded on collagen sponges for implantation suggest improved bone formation with lentiviral delivery (Miyazaki et al. 2008c) at 8 weeks post implantation. Longer studies will be necessary to assess safety and risks of insertional mutagenesis with lentiviral vector approaches. Nonviral gene transfer approaches including sonoporation, electroporation, and nucleofection are thought to be safer than viral delivery methods, but low transfection efficiency has limited their application in spinal fusion studies (Sheyn et al. 2008; Makino et al. 2018).

Other osteoinductive proteins studied for gene therapy applications in spinal fusion include NELL1, LIM mineralization proteins (LMPs), and SMAD family member 1 (SMAD1). Lu et al. (2007) utilized adenoviral-mediated NELL1 delivery in demineralized bone matrix to show improved bone quality and maturity at 6 weeks post implantation in a

rat spinal fusion model. In comparison to BMP-2 administration, goat MSCs carrying the NELL1 transgene promoted less bone mass but greater trabecular and chondroid bone formation (Aghaloo et al. 2007). LMP1 encodes an osteoinductive intracellular protein which promotes bone growth and skeletal organization. Initial studies of LMP1 for gene therapy in spinal fusion utilized bone marrow cells transfected with LMP1 cDNA with results demonstrating successful fusion (Boden et al. 1998) in rats. Bone marrow or buffy-coat cells transduced with adenoviral LMP1 for 10 min and implanted in demineralized bone or collagen-ceramic composite sponges were shown to induce posterolateral lumbar fusion in rabbits (Viggeswarapu et al. 2001). To improve ease and efficiency of cell isolation, autologous dermal fibroblasts from skin biopsies were transduced with adenoviral-LMP3 and shown to induce ectopic bone formation in muscle (Lattanzi et al. 2008). SMAD1, a downstream target of BMPs, is a key intermediary in expression of genes driving osteoblast differentiation and thus proposed to induce osteogenesis more specifically than BMPs. MSC transduced with SMAD1C and implanted on gelatin sponges were shown to support efficient new bone formation in a rabbit model of lumbar spinal fusion (Douglas et al. 2010).

Despite the promising results of preclinical gene therapy studies for spinal fusion, translation of these results to therapies for human patients has shown little progress. Variables which will need to be optimized to move gene therapy approaches forward include choice of vector, therapeutic gene, delivery method (in vivo or ex vivo), source of cells for ex vivo modification, and implantation or injection strategies. The risks associated with the viral vector-mediated delivery including systemic toxicity, insertional mutagenesis, and genomic instability constitute significant barriers to bringing such therapies into the clinic (Wang 2011). Regulatory approval for gene therapy approaches for spinal fusion, a procedure which may influence quality of life but for which the underlying pathology is typically nonlethal, may be difficult to achieve.

Microenvironment

In a therapeutic situation, it may be critical to consider the effects of the implant site on the fate of transplanted stem and progenitor cells and growth factors. It is entirely possible for a damaged or diseased implant site to have an unintended consequence on incoming cells and growth factors. For example, as described above, growth factors may leak out of the implant site and result in unintended consequences locally and systemically, especially if growth factors are introduced at a dose significantly higher than their physiological levels (as seen with BMP-2). In addition, in a healthy intervertebral disc, numerous factors such as cytokines, growth factors, endogenous cells, enzymes, and mechanical stimuli regulate the balance between the anabolic and catabolic processes. However, decreased proteoglycans and collagen II, increased proteinases and cytokines, and decreased (acidic) pH have been observed in a degenerating intervertebral disc (Huang et al. 2013), caused by aging, disease, trauma, or mechanical stress. These factors may comprise an unfavorable microenvironment and present a significant challenge when stem and progenitor cells are considered as a therapeutic option. Thus, it is imperative that biologics must be delivered within a carrier that can retain therapeutic elements and maintain a healthy microenvironment for tissue repair and regeneration.

A hostile microenvironment at a disc impacts directly on the success of any attempted interbody fusion. Anterior cervical discectomy and fusion (ACDF) is the most common fusion surgery in cervical spine. Interbody fusion is also often utilized in lumbar spine: transforaminal lumbar interbody fusion (TLIF), posterior lumbar interbody fusion (PLIF), direct lateral interbody fusion (DLIF), and anterior lumbar interbody fusion (ALIF). Without successful fusion, the patients may have persistent or new pain and the implants utilized for fusion may fail, possibly leading to another surgery. Posterolateral fusion is very common in lumbar spine, and it may pose even more challenging microenvironment. Successful fusion depends on a solid bony growth spanning the transverse processes with adjacent

ligament and musculature that may interfere with bone regeneration. As discussed previously, restoration of the microenvironment affected by various exogenous and endogenous, adverse physiological influences may be required prior to and/or at the time of stem and progenitor cell transplantation (Lee and Kim 2012).

Autologous bone harvesting and implantation result in transfer of not only stem cells that reside in the harvested bone but also their microenvironment. Undoubtedly, autologous bone harvested from a non-load-bearing site such as the iliac crest consistently results in a positive clinical outcome and is considered the "gold standard" for bone repair. As described above, transplanted bone marrow-derived MSC taken out of their native microenvironment and expanded do not result in clinical outcomes similar to implantation of bone. Thus, implantation of both stem and progenitor cells along with their native microenvironment ("autograft") is unarguably better than cells ("cell transplantation") alone. However, the clinical outcome when using the autograft approach is less than optimal due to donor site morbidity (especially pain), fracture, infection, increased blood loss, prolonged operative time, and risk of nerve damage. In addition, autograft is limited in quantity, and quality is suboptimal depending on the patient. Due to these risks and limitations, bone graft substitutes have been increasingly utilized instead of autograft. Bone graft substitutes are generally not indicated to be used with stem and progenitor cells but known to participate in bone regeneration, potentially reestablishing the microenvironment for bone stem and progenitor cells that are residing at the site of injury or transplanted.

Bone graft substitutes are discussed in ▶ Chap. 11, "Bone Grafts and Bone Graft Substitutes" in this book and broadly categorized into allografts, ceramics, polymers, and biologics. Several factors such as mechanical stress, vascularity, and surface characteristics of graft material have demonstrated to influence the stimuli and microenvironment of cells. These factors seem to have a collective influence on the osteogenic differentiation of stem cells through epigenetic/gene upregulation mechanisms. For example, mechanical stretch induced downregulation of GNAS (stimulatory G-protein alpha subunit) isoforms of mesenchymal cells and upregulation of osteogenic differentiation transcription in in vitro models (Vlaikou et al. 2017). In another study, mechanical stress in osteoblast precursor cells in 3D scaffolds experienced greater signaling through MAP kinase pathway (Appleford et al. 2007). Tissue engineered bone constructs of DBM and nanoscale self-assembling peptides provided with decreased pore size and increased charge field resulted in better enrichment of osteogenic cells (Hou et al. 2014).

Ceramic-based bone graft substitutes include calcium phosphate, calcium sulfate, hydroxyapatite (HA), β-tricalcium phosphate (β-TCP), and bioactive glass. HA scaffolds showed a greater degree of ectopic bone formation than β-TCP when implanted with MSC in rats (Denry and Kuhn 2016), but better attachment and spreading of MSC were observed with β-TCP while expressing G-protein coupled receptor (Barradas et al. 2013). Surface modification of calcium phosphate cement with arginine–glycine–aspartate (RGD) showed a significant improvement in attachment, survival, and proliferation of MSC (Chen et al. 2012), indicating that additional coating may be required to provide an optimal environment for MSC. Similarly, it has been postulated that the initial contact with blood primes the surface and prepares calcium phosphate ceramic scaffolds (CPS) for viable in situ cell seeding (Denry and Kuhn 2016). In addition, CPS show a very slow degradation rate (Bružauskaitė et al. 2016; Winter et al. 1981) and are not radiolucent, thus interfering with the visualization of new bone formation by radiographic evaluation.

Poly-lactic acid (PLLA) (Holderegger et al. 2015), polyglycolic acid (PGA) (Generali et al. 2017), and poly-DL-lactic-co-glycolic acid (PLGA) (Mendes Junior et al. 2017) have been proposed as a synthetic bone graft substitute. All of these synthetic materials show exceptional compatibility with MSC and support osteogenesis. However, PLLA, PGA, and PLGA degrade within 30 days (Generali et al. 2017) and may not be able to bridge a critical size bone defect,

considering natural bone regeneration over several months. Growth factors such as BMP-2 has received a significant attention due to its potent osteogenic properties and safety issues including adverse effects (e.g., life-threatening inflammatory complications), ectopic bone formation, osteoclast activation, and induction of adipogenesis (James et al. 2016). Other growth factors such as fibroblast growth factor-2 and insulin-like growth factor-1 have been shown to induce osteogenesis (Nagayasu-Tanaka et al. 2015; Guntur and Rosen 2013). However, as shown with BMP-2, patient safety must carefully be considered before clinical utilization.

ECM is an essential regulator of stem cell function and a critical component of stem cell microenvironment. ECM is primarily comprised of proteins (e.g., collagen, laminin, fibronectin, elastin) and carbohydrates (polysaccharides). While various proteins in ECM have been investigated for bone regeneration, the clinical utility of the polysaccharide component has not yet been explored fully. Carbohydrate-based, polysaccharide materials have been used to regenerate bone in preclinical settings including cellulose (Park et al. 2015), alginate (Hung et al. 2016), chitosan (Levengood and Zhang 2014), and glycosaminoglycans (Mathews et al. 2014). Carbohydrate-based materials have a long history of use in various medical applications and are nontoxic, biocompatible, soluble, and biodegradable. These properties make carbohydrate-based polymers an excellent scaffold for tissue engineering. A recent study reported that supramolecular sulfated glycopeptide nanostructures with a trisulfated monosaccharide on the surface amplified signaling of BMP-2, resulting in enhanced bone formation (Lee et al. 2017a). Thus, carbohydrate-based polymers may play a key role in developing novel therapeutic approaches and addressing the microenvironment issue in near future as shown in recent studies on stem cells (Batchelder et al. 2015b), tumor heterogeneity (Batchelder et al. 2015a), and cardiac tissue regeneration (Baio et al. 2017).

These therapeutic approaches using bone graft substitutes aim to generate bone by providing an osteoconductive environment for endogenous cells and factors and/or inducing osteogenesis and migration of host cells into the target site, reestablishing the microenvironment conducive to tissue regeneration. Bone regeneration and repair are fairly successful in healthy individuals, but high-risk patient populations have been reported to show nonunion rates as high as 40% for bone fusion (Scott and Hyer 2013). In well-controlled preclinical studies, diabetes showed a significant negative effect on bone regeneration compared to healthy animals under the identical experimental conditions including bone graft substitutes (Camargo et al. 2017). Thus, it is clear that bone graft substitutes alone are not sufficient for bone regeneration in high risk patients.

Conclusions

Contrast to small defects that the body can heal spontaneously, critical bone defects (>25 mm) have a higher probability of nonunion (>50%) and require a therapeutic intervention (Haines et al. 2016). Current biologics available for bony fusion address one or two components of complete bone repair and regeneration: osteogenicity, osteoinductivity, and osteoconductivity. A product or combination product that possesses all of these properties may be needed to close or bridge a critical bone defect in a functionally meaningful manner, especially in patients with high risk factors, in addition to systemic or local environment (microenvironment) that may adversely influence the patient outcome.

Cross-References

▶ Bone Grafts and Bone Graft Substitutes

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Robotic Technology

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Abstract

With increasing numbers of patients requiring spine surgery, there has been an emphasis on technological advances designed to enhance surgical outcomes and improve patient safety. In particular, the number of elective spinal fusion surgeries in the USA continues to increase. Instrumentation of the spine with pedicle screws is frequently used for indications including deformity and instability. With neurovascular structures near the pedicle, accurate screw placement is of paramount importance to ensure good outcomes. Reported complications related to pedicle screw malposition range from 1% to 54% (Molliqaj et al., Neurosurg Focus 42(5): E14, 2017). Currently, there are several techniques described for inserting pedicle screws, including freehand manual insertion based on anatomic landmarks and fluoroscopy, manual insertion with navigation assistance systems, and robotic-assisted methods.

Keywords

Robot · Navigation · Spine · Surgery · Pedicle · Screw

Introduction

With increasing numbers of patients requiring spine surgery, there has been an emphasis on technological advances designed to enhance surgical outcomes and improve patient safety. In particular, the number of elective spinal fusion surgeries in the USA continues to increase. Instrumentation of the spine with pedicle screws is frequently used for indications including deformity and instability. With neurovascular structures near the pedicle, accurate screw placement is of paramount importance to ensure good outcomes. Reported complications related to pedicle screw malposition range from 1% to 54% (Molliqaj et al. 2017). Currently, there are several techniques described for inserting pedicle screws, including freehand manual insertion based on anatomic landmarks and fluoroscopy, manual insertion with navigation assistance systems, and robotic-assisted methods.

The goal of this review is to focus on robotic-assisted surgical platforms used for the insertion of pedicle screws by highlighting their history and reviewing the literature regarding the current state of robotic platforms in spine surgery. In addition to detailing the history of robotics in spine surgery we will discuss terminology and definitions as well as reported benefits and costs associated with their use.

To better understand the basic concepts of robotics, it is important to understand or define the terminology that is used to describe robotics pertaining to surgical platforms. By definition, a robot is a machine capable of automating one, or a series of actions or steps in a procedure (Urakov et al. 2017). According to the Robot Institute of America, a robot is defined as a reprogrammable, multifunctional manipulator designed to move material, parts, tools, or specialized devices through various programmed motions for the performance of a variety of tasks (Jacofsky and Allen 2016). Robots should play an integral role in surgery to be classified as "surgical robots." There are several different ways to categorize robotic platforms, but their actions are classified as being either direct or indirect. Robots act directly when they cut tissue or mill bone into a predetermined and final desired shape, or indirectly by holding cutting jigs or drill guides (Chen et al. 2018). Furthermore, both direct and indirect surgical robotic platforms are further classified as passive, semi-active, and active systems (Jacofsky and Allen 2016).

Passive, Semi-Active, and Active Systems

Passive systems are used to complete a portion of the surgical procedure under direct, continuous control of the operating surgeon. The robotic instrument acts as an extension of the surgeon's hand and is unable to function without an operator engaging the device. Examples of passive systems include the OMNIbotics (OMNI) and the da Vinci surgical robot (Intuitive Surgical) (Chen et al. 2018).

Semi-active systems require surgeon involvement but provide feedback in the form of haptics (tactile, auditory, or visual) that restrict what can be done surgically to prevent the user from operating outside of a predetermined boundary. Semi-active systems can theoretically enhance the surgeon's control of the robotic instruments and increase surgical safety by preventing the surgical instruments from entering a "no-fly zone" as determined by the surgical plan. Current examples of semi-active systems include the Mako robotic arm–assisted surgical platform (Stryker) for total knee arthroplasty and the Navio surgical system (Smith and Nephew) used in unicompartmental knee arthroplasty.

Finally, active systems can perform a task entirely independently through the use of preprogrammed algorithms and predetermined parameters for surgical resection of tissue without direct manipulation by a surgeon or operator. Active systems allow for surgeons to initiate and stop the robot's activity but do not allow for continuous control, or the ability to alter the robot's actions intraoperatively (Chen et al. 2018). Current examples of active systems which are fully autonomous include the ROBODOC Surgical System and TSolution One (Think Surgical) (Chen et al. 2018).

Supervisory-Controlled, Telesurgical, and Shared-Control Systems

Additionally surgical robots have been classified into three main categories of systems, according to Kochanski et al. which are supervisory-controlled systems, telesurgical systems, and shared-control systems (Kochanski et al. 2019).

Supervisory-controlled systems are designed so that the surgeon can plan the robotic portion of the case before beginning the procedure. The surgeon initiates the procedure, then allowing the robot to perform its portion of the case autonomously under the direct supervision of the surgeon, making it an active system. Telesurgical systems, which are passive, offer the surgeon complete control of the robot at all times. Examples of telesurgical systems include the Georgetown robot and the Spine Bull's-Eye robot, both designed for use in spine surgery and the da Vinci surgical robotic system (intuitive surgical) which is widely utilized in various surgical specialties. Lastly are the shared-controlled systems, which allow for the robot and surgeon to share control of surgical instruments concurrently. Notably, most spine surgical robots on the market today such as the Mazor X, Excelcius GPS, and the ROSA spine robot are classified as shared-control systems. These systems require either preoperative or intraoperative CT or fluoroscopic imaging and use proprietary software to plan trajectories for pedicle screw placement. Once the preoperative plan is confirmed, the surgeon manually inserts the pedicle screws using the robotic instruments as a guide.

Image-Based Systems

Currently, most orthopaedic and spine robotic systems require a preoperative plan and computer model on which to base the surgical procedure. Having a preoperative plan to execute is one aspect of orthopaedic and spine robotic systems that differentiates it from other surgical robots, such as the da Vinci. Having a specific reproducible plan, which allows the surgeon to preoperatively or intraoperatively analyze and predict the desired result before any tissue is resected is a significant advantage of these systems (Jacofsky and Allen 2016).

The patient's anatomy must be registered via mapping points on the bone with a navigated tool during the registration process or via intraoperative scan in both system types so that the robot knows where the instruments are in space relative to the patient's anatomy. In image-based systems, this

Fig. 1 Intraoperative CT scan used for imaged-based planning to map the patient's anatomy in the prone position and register instruments used in lumbar fusion

registration is referenced to the preoperative imaging. Currently, preoperative CT or an intraoperative CT scan is used (Fig. 1). Intraoperative CT limits the need for bony registration as the navigation arrays are typically included in the scan. Potential disadvantages of image-based systems include increased cost, patient inconvenience, and increased radiation exposure to the patient during CT (Jacofsky and Allen 2016). Potential advantages include extremely accurate mapping of the patient's anatomy, which increases the precision of implant placement.

History of Robotics in Surgery

Robotic surgical platforms are used in many surgical specialties, including gynecological, urological, thoracic, orthopaedic, and general surgery over the last two decades. According to early reports, the use of the UNIMATION PUMA 200 (Programmable Universal Manipulation Arm, Nokia) during a neurosurgical biopsy performed in 1985 marked the first documented robotic-assisted surgical procedure (Chen et al. 2018). That same system was repurposed and used for the transurethral resection of prostate tissue, which eventually lead to the development of the ProBot, which was designed explicitly for prostate surgery (Jacofsky and Allen 2016). With a growing body of evidence supporting their safe and predictable implementation, the field of robotic surgery began to proliferate. Since then, the integration of robotics in the operating room has steadily increased across a variety of surgical specialties.

Robotic surgery began to gain momentum in the year 2000 when the da Vinci surgical robotic system (intuitive surgical) was approved for use in urologic, gynecologic, and general laparoscopic procedures by the US Food and Drug Administration (Perez-Cruet et al. 2012). The da Vinci is a robotic system that offers surgeons the ability to perform a variety of soft tissue procedures with more minimally invasive technique (Jacofsky and Allen 2016).

The first applications of the da Vinci platform were directed towards soft tissue procedures such as laparoscopic prostatectomies and gynecological surgeries that were readily adopted. In fact, in 2012, 85% of prostatectomies in the USA were performed with robotic assistance (Chen et al. 2018). The da Vinci surgical robot is a telesurgical platform that allows the surgeon to control the docked surgical robot from a remote station that is outside the sterile field yet within the same operating room as the patient. This ability allows the surgeon to visualize the patient and surgical field in an augmented three-dimensional view, provided by endoscopic cameras, which allows

for real-time decisions to be executed with unparalleled precision while minimizing soft tissue trauma typically experienced by the patient. The da Vinci articulating robotic arms serve as extensions of the surgeon's instruments and are under complete control of the operating surgeon at all times.

While the da Vinci robot has not been as widely adopted by spine surgeons for routine surgical techniques, it has been reported to be used for the resection of paraspinal tumors, transoral odontoidectomy, and in laparoscopic-assisted anterior lumbar interbody fusion (D'Souza et al. 2019). For the treatment of spine trauma, the da Vinci robot was recently used in a minimally invasive retroperitoneal approach for the treatment of an L3 fracture with corpectomy and expandable cage implantation with a good clinical outcome (Lippross et al. 2020).

Robotics and Computer-Assisted Navigation

Historically, robotics and image-guided navigation systems used in spine surgery have been considered mutually exclusive technologies. However, both technologies fundamentally rely upon radiographic imaging and stereotaxic principles in order to provide precision and accuracy during spine surgery (Ganz 2011). Stereotaxy refers to the use of instruments that relate anatomical targets within the body with radio frequency markers using a cartesian coordinate system. This can provide the surgeon with haptic feedback when accessing areas of the surgical field that are difficult to appreciate visually (Ganz 2011).

Stereotactic techniques have since been applied to the field of spine surgery and lead to the development of the intraoperative CT with Stealth Station navigation (Medtronic Inc.). The robotic systems described in this chapter involve the automated performance of various portions in the operation. However, image-guided systems have the benefit of providing real-time haptic feedback to the surgeon, who then uses that information to perform those portions of the case manually.

Both image-guided navigation and robotics systems that have historically been used in spine surgery are fundamentally based upon stereotactic principles coupled with pre/intraoperative patient imaging and registration (Fig. 2). Similar to navigation-assisted techniques, robotic systems also rely on radiographic imaging and stereotaxis for trajectory planning and drilling of pedicle screw bone tunnels and screw insertion (Kochanski et al. 2019). Historically robotic systems have lacked the real-time navigation that image-guided systems utilize. However, newer robotic systems such as the Excelsius GPS (Globus Medical), ROSA Spine (Zimmer-Biomet), and Mazor X Stealth (Medtronic) allow for real-time image guidance coupled with the precision and accuracy of an automated robotic arm to ensure a proper trajectory when inserting pedicle screws (Kochanski et al. 2019).

History of Robotics in Spine Surgery

Robotics have been implemented throughout the majority of surgical specialties, and spine surgery is no exception. To date, the use of robots in spine surgery has primarily been limited to using a planning platform to assist with pedicle screw placement which is often used to stabilize the vertebral column in spinal fusion surgery (Urakov et al. 2017). Metallic screws are inserted into each pedicle involved at each vertebral level involved in an operation, and then rods are inserted through the heads of all screws on each side in order to support the vertebral column. Accurate positioning of the pedicle screw is essential given the proximity of the neurovascular structures, including the spinal cord, spinal nerve roots, and major blood vessels. The goal of modern robotics systems in spine surgery is to assist surgeons in consistently placing pedicle screws with accuracy and precision based on advanced imaging and guidance software. Currently, there are only three manufacturers with five robots approved by the FDA indicated for instrumentation of the spine in the USA. These include Mazor's three generations of robots: the SpineAssist, the Renaissance Guidance System, and Mazor X (Mazor

Fig. 2 Spine surgeon inserting pedicle screws under navigation with instruments registered via intraoperative CT scan

Robotics), the ROSA Spine robot (Zimmer Biomet), and the Excelsius GPS (Globus Medical).

Mazor Robotics

Mazor Robotics was founded in 2001 in Israel. The company brought the first commercially available robot for spine surgery to market. Starting with the FDA approval of SpineAssist in 2004, the company's technology continued to evolve with the launch of the Renaissance Guidance System in 2011, and eventually the Mazor X which was released in the USA in 2016. As Mazor is the longest standing company to produce approved spine surgical robots, the majority of the published literature has focused on these systems.

Mazor: SpineAssist

The first robotic-assisted platform to reach the US market, with applications specifically designed for use in spine surgery, arrived in 2001 with SpineAssist (Mazor Robotics). SpineAssist was approved for use in the USA in 2004 and became the first commercially available mechanical guidance system used for the placement of pedicle screws in thoracolumbar surgery (Theodore et al. 2018). SpineAssist, which is the spinal application of its predecessor SmartAssist (Mazor Robotics), is a shared-control semi-active platform that is rigidly attached to the patient's iliac crest or spinous process, unifying the patient and robot. This ensures that patient movement due to positional changes or respirations does not interfere with the position of the robot relative to the patient, thus potentially providing higher accuracy with the placement of pedicle screws. SpineAssist was designed to accurately guide and assist the surgeon in drilling and placing spinal implants such as pedicle screws, however, the actual instrumentation of the patient's spine is performed by the surgeon and not the robot itself.

The SpineAssist System consists of two units: a small hexapod robot that can move with six degrees of freedom and a separate computer workstation with a graphic user interface. Using the workstation, the surgeon plans the trajectory for pedicle screw placement at any time prior to the start of the case (Shoham et al. 2007). During

the operation, the robot's base platform is mounted on the vertebrae using a disposable sterile clamp system. The coordinates of the desired screw insertion trajectory are obtained from preoperative plans made by the surgeon using a reconstructed CT image, which is obtained pre- or intraoperatively. Following a registration process that involves matching two intraoperative fluoroscopic images with the preoperative CT scan, the planned coordinates are then translated to each of the robot's six articulators to create the required motion. The computer system controls the movement of the robot to the desired position where the guide arm is then activated to move into the preplanned trajectory. The surgeon performs the manual drilling and screw insertion via an open or percutaneous technique according to the patient's needs (Shoham et al. 2007).

Mazor: The Renaissance Guidance System

Mazor Robotics' second-generation robot and successor to SpineAssist is the Renaissance Guidance System. The Renaissance is a miniature robotic platform that acts as a mechanical guidance unit that can be mounted directly to the patient via bone-anchored attachments to the spine or pelvis or the operating table (Malham and Wells-Quinn 2019). A three-dimensional marker is attached to the platform before the intraoperative CT scan is performed using an intraoperative CT with the patient prone on the operating table. The images are uploaded into the Renaissance System's interface, and the surgeon uses the information to plan the procedure using the system's software. The patient's anatomy can be reviewed in coronal, axial, and transverse planes to ensure that the proper trajectory is planned before instrumentation. Once the plan is complete, the robot's guidance system is mounted to the platform and automatically sent to the preplanned trajectory where the surgeon can use the system to place K-wires that are then used to guide the insertion of cannulated pedicle screws. The Renaissance Guidance System has been used in approximately 30,000 cases.

Mazor: Mazor X

Newer robotic platforms such as the Mazor Robotics' third-generation spine surgical robot, the Mazor X (Fig. 3), which was released in the USA in 2016, utilize an automated mechanical arm fixed with a drill guide which assists in drilling and pedicle screw insertion, with or without K-wire placement. This feature requires surgeons to introduce instruments using the robotic arm, which provides haptic feedback if tools deviate from a preplanned trajectory. The surgical robot is either mounted to the operating table or the floor and is connected to the patient similarly using bone anchors as with the Mazor Renaissance System (Malham and Wells-Quinn 2019). There is an associated computer station with a user interface that contains the planning software that allows for planning of screw

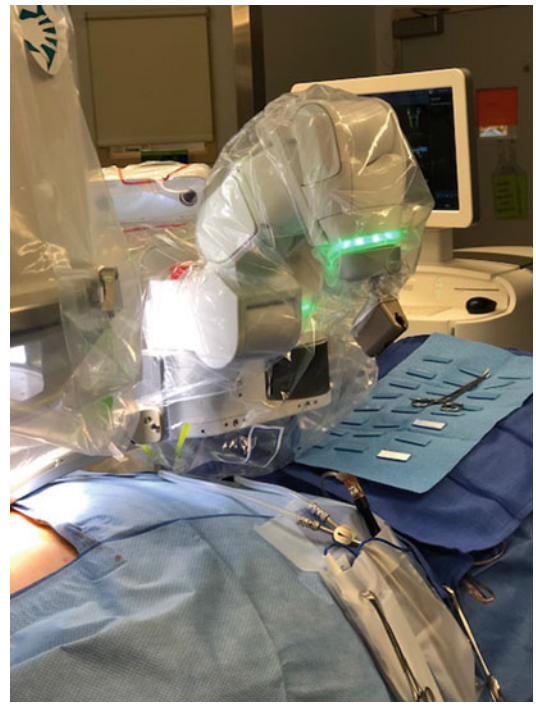

Fig. 3 Mazor X robotic arm used in posterior lumbar instrumented fusion

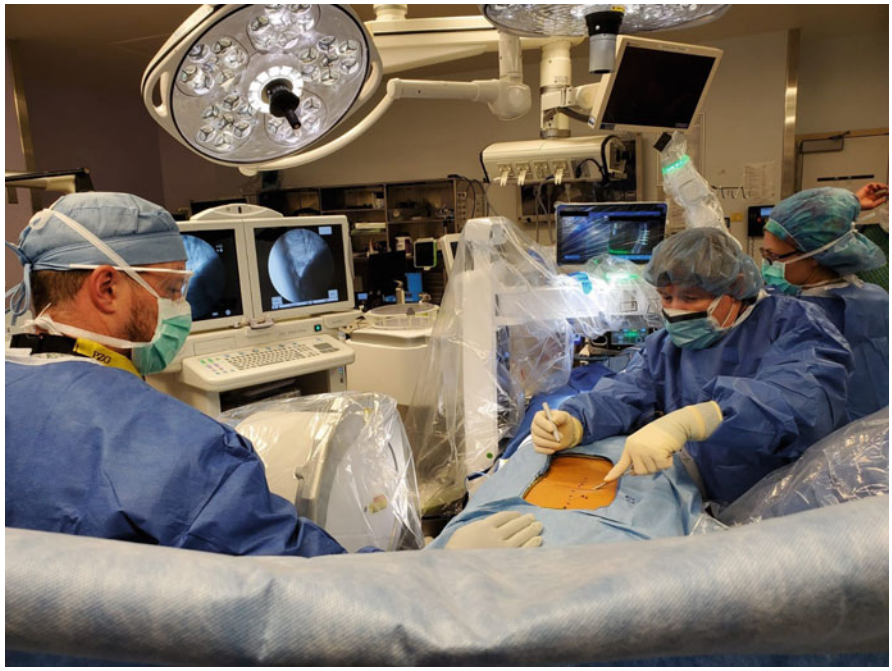

Fig. 4 Spine surgeons localizing appropriate levels using fluoroscopy for treatment of the lumbar spine with the Mazor X Robotic platform

trajectories based on the patient registration process. The automated robotic arm, which is controlled by the user interface and directed by the surgeon, can move between preplanned screw trajectories at various levels quite rapidly, allowing the surgeon to drill while providing tactile feedback to ensure adequate purchase as instruments enter the bone. Once the setup and registration process are performed, the automatic movements of the robotic arm between various levels allow for rapid and accurate insertion of pedicle screws potentially decreasing total surgical time. The Mazor X system retails at approximately $1000,000 with disposable costs ranging from $1000–$1500 per case according to recent market reports (Fig. 4).

Mazor Robotics' newest addition to their robotics line combines its navigation technology with Robotics to form the Mazor X Stealth robotic-assisted surgical platform. Mazor X Stealth received its FDA approval in2018 and was used in its first cases in early 2019 just after the acquisition of Mazor Robotics by Medtronic (Minneapolis, MN). The Mazor X Stealth allows for the union of the computer navigation software, and the Mazor robotic-assisted surgical platform to improve accuracy and precision of pedicle screw placement in spine surgery. By combining these two technologies, surgeons can use software to formulate their preoperative plan based on a 3D analysis of the patient's anatomy. This allows surgeons to place pedicle screw trajectories accurately with the assistance of the robotic arm and receive navigation feedback in real time to ensure that trajectories match the preoperative plan.

ROSA Robot

The ROSA Robot, which stands for Robotic Stereotactic Assistance, was initially developed in 2007 by MedTech in Montpellier, France (now Zimmer-Biomet), for use in cranial surgery in Europe. The company expanded its applications for the platform and developed ROSA Spine which was cleared for use in the USA by the FDA in early 2016. ROSA Spine combines navigation technology with robotic assistance to aid surgeons in placing pedicle screws according to

preplanned trajectories, and performance of transforaminal lumbar interbody fusions (Chen et al. 2018; Lonjon et al. 2016). With the patient in the prone position on the operating table, the ROSA Robot's floor-mounted platform is brought into position at the side of the table, while the separate navigation camera is placed at the foot of the patient. A referencing marker is rigidly mounted to the patient's iliac crest, which monitors the patient's movements, either respiratory or due to manipulation by the surgeon. Intraoperative fluoroscopic images are obtained using a specific registration pattern held by the robotic arm. The images are then uploaded directly to the user interface where the surgeon can begin using the planning software to plan the ideal trajectory for each screw. Once the trajectories have been planned, the articulating robotic arm can handle marked instruments that are confirmed by the navigation camera to enable accurate placement of instruments according to the preplanned trajectories. This allows for real-time adjustments to be made to account for the patient's respiratory movements, which are continuously monitored by the navigation cameras (Lonjon et al. 2016). The ROSA Spine Robot, which retails for just over $600,000, is the least expensive of the three leading systems with automated robotic arms available in the market.

Excelsius GPS

The Excelsius GPS released by Globus Medical (Audubon, PA) in 2018, received FDA approval for use in spine surgery in 2019. This system uses proprietary software for planning pedicle screw trajectories and an automated robotic arm to guide instruments simultaneously with navigation technology and has proved to be safe and effective as a means for inserting pedicle screws (Galetta et al. 2019). A recent single institution study demonstrated a 99% rate of successful pedicle screw placement out of 562 screws placed using the Excelsius GPS system in minimally invasive lumbar spine surgery using a variety of approaches (Huntsman et al. 2020). One advantage of this system is the ability for robotic-assisted insertion of pedicle screws without the use of K-wires. By using real-time image guidance, the surgeon is able to manipulate a variety of compatible surgical instruments according to the preoperative plan via the robotic–navigation interface. Excelsius GPS is indicated for spinal instrumentation from C1-pelvis and is compatible with most imaging systems using preoperative or intraoperative CT or fluoroscopy. The Excelsius GPS costs approximately $1,200,000, with an average cost of $1000 per procedure in disposables required for its use.

Benefits of Robotic-Assisted Spine Surgery

There have been many benefits reported in the literature attributed to the use of robotic-assisted spine surgery including minimally invasive applications, improved accuracy, reductions in radiation to OR staff, decreased blood loss, faster pedicle screw insertion time, reduction in human error due to tremor or fatigue, and decreasing the learning curve associated with pedicle screw insertion technique among resident and fellow trainees (Li et al. 2020; Siddiqui et al. 2019). Of which, pedicle screw placement accuracy and reduction in radiation exposure to surgeons and operating room staff have been the most widely reported.

Benefits: Improved Accuracy of Robotic-Assisted Pedicle Screw Placement

In many studies, the accuracy of pedicle screws is evaluated using postoperative CT scans, which are used to confirm the trajectory of the screw within the cortical bone of the pedicle. These images are graded based on the Gertzbein-Robbins classification, where the deviation of the screw is measured against the "ideal" trajectory of the screw. According to this classification system, Grade A is an interpedicular screw without a breach of the cortical layer, a Grade B screw breaches the cortex but is deviated <2 mm laterally from the pedicle, and Grade C and D are breaches of <4 and <6 mm,

respectively (Solomiichuk et al. 2017). While theoretically, a more displaced screw may have a higher chance of postoperative complications, the clinical significance of this radiographic definition in the absence of clinical symptoms is not well described (Kochanski et al. 2019). The majority of screws with a minor breach of the pedicle cortex may still maintain excellent biomechanical properties and are unlikely to require revision. Thus, in the absence of clinically apparent neurologic of vascular symptoms or biomechanical instability, a minimally displaced screw is unlikely to cause unwanted complications. However, clinically significant misplacement of pedicle screws can cause fractures, neurologic or vascular impairment, injury to the dura, and biomechanical instability (Solomiichuk et al. 2017).

A multicenter retrospective review evaluating the accuracy of pedicle screw placement using SpineAssist (Mazor Robotics) in the placement of 3271 pedicle screws was performed by DeVito et al. Pedicle screws were placed using the robotic platform and then evaluated and graded using post-op CT. They found 98% of robotic pedicle screws placed to be clinically acceptable when evaluated using fluoroscopic X-rays before leaving the operating room. One hundred and ninety-eight patients underwent postoperative CT analysis, and 98.3% of the screws placed were found to be within 2 mm of the pedicle cortex. Only 1.7% of the screws placed had a pedicle wall breach greater than 2 mm (Kochanski et al. 2019). This study was consistent with previously published literature demonstrating that robotic-assisted techniques are a safe and effective option for the insertion of pedicle screws.

In a retrospective series performed by Molliqaj et al., 439 thoracolumbar pedicle screws were inserted using SpineAssist (Mazor robotics), and 441 screws were inserted using a freehand fluoroscopic-guided technique by experienced spine surgeons. The accuracy of screw placement was determined by neuroradiologists who were blind to the treatment group. Each screw was independently evaluated and graded based on the Gertzbein-Robbins criteria. In the robot-assisted group, 366 (83.4%) of screws placed were found to be perfectly intrapedicular (Gertzbein-Robbins Grade A) vs. 335 (76%) in the freehand group. Additionally, 93.4% of robotic-assisted pedicle screws were classified as nonmisplaced, defined as Gertzbein-Robbins Grades A and B, compared to 88.9% of the screws in the freehand fluoroscopy ($p = 0.005$) (Molliqaj et al. 2017).

The Renaissance system (Mazor Robotics) was evaluated for accuracy and safety for use in lumbar spinal fusion surgery by Kim et al. The study compared robot-assisted posterior lumbar interbody fusion (Robot-PLIF) vs. a conventional freehand open approach (Freehand-PLIF). A total of 37 patients were treated using the robotic-assisted platform, and 41 patients were treated with the conventional freehand approach. Of the pedicle screws inserted using the Robot-PLIF approach, 93.7% were Grade A, with 5.7% Grade B, and 0.6% Grade C breaches, respectively. All breaches occurred in the lateral wall of the pedicle in the Robot-PLIF group. In the Freehand-PLIF group, 91.9%, 7.6%, and 0.6% of pedicle screws placed were classified as Grade A, B, and C breaches, respectively. The Grade C breach was an inferior wall violation resulting in a subsequent nerve root irritation that required revision. Additionally, it was noted that none of the 74 screws in the Robot-PLIF group violated the proximal facet joint, while 13 of the 82 Freehand-PLIF groups violated the proximal facet joint ($P < 0.001$) (Kim et al. 2017).

Hu et al. investigated the accuracy of robotic-assisted pedicle screw placement as well as learning curve associated with spinal instrumentation using the Mazor Renaissance platform. They found that over the course of 150 cases performed by a single surgeon there was an overall increase in the accuracy of pedicle screw placement that was associated with the increasing number of cases performed using the robot. By dividing patients into groups of 30, the investigators analyzed pedicle screw accuracy when placed by the robot, the rate at which pedicle screws had to be converted to manual insertion due to malposition, and the overall rate of malposition of screws placed robotically. They found that when analyzed by intraoperative fluoroscopy and post-op radiographs, there was a greater than 90% success rate in pedicle screw placement after the first 30

cases using the robot (82% in the first group of 30 cases, 91–95% in the following 120 cases). Additionally, the number of screws that had to be converted to manual insertion decreased from 17% in the first 30 cases and 7% in the last 30 cases in the study. Screw malposition using the robot also decreased with increased surgeon experience notably from 1.4% in the initial group and 0% in the last group. The authors concluded that improved accuracy, decreased rates of screw reinsertion, and decreased rates of screw malposition could be achieved after the surgeon completes the initial 30 cases using the robot. These findings were consistent with other published reports, and have been replicated with another surgeon evaluated outside of the study (Hu et al. 2014).

These studies suggest that robotic-assisted techniques can consistently, safely, and accurately be used to insert pedicle screws that are at least as acceptable as the current conventional techniques. Further research is needed to determine if robot-assisted techniques are both statistically and clinically significantly superior than the current standard in terms of safety and accuracy of pedicle screw insertion.

Benefits: Decreased Radiation Exposure

Intraoperative fluoroscopy has been widely used in orthopaedic surgery and is particularly helpful in minimally invasive spine surgery such as percutaneous pedicle screw placement. Radiation safety, including limiting dose and exposure, to patients, surgeons, and staff, is of significant concern and has been receiving increased attention in published literature. There are several ways to standardize and quantify radiation exposure. The Gray (Gy), which is used to express an absorbed dose of radiation, is the actual physical quantity of one joule of radiation energy per kilogram of matter. The sievert (Sv) represents the biological equivalent of an effective dose on tissue and can be used to measure the cumulative dose of radiation absorbed by tissue over time. For healthcare workers, an upper limit of 20 millisieverts (mSv) of radiation exposure per year has been established by the international commission of radiological protection (Hayda et al. 2018).

Radiation exposure among spine surgeons varies considerably and assessing radiation exposure in spine surgery can be challenging due to a lack of standardized reporting. For instance, some studies report radiation exposure in time (seconds) per screw, whereas others report total radiation generated throughout a case using an entirely different scale or measurement (Malham and Wells-Quinn 2019). As such, implementing new technologies such as robotic surgical systems that can potentially decrease the risk of this occupational hazard in spine surgery would likely be beneficial to OR staff.

One of the proposed benefits of robotic-assisted surgical systems is that they can potentially limit radiation exposure to operating room staff. CT imaging can be performed before the day of surgery or using an intraoperative CT scan with the surgical staff outside the operating room. In a study performed by Mendelsohn et al., patients undergoing intraoperative CT-assisted lumbar spine surgery were found to be exposed to 2.77 times more radiation (5.69 mSv) than patients in a fluoroscopic-assisted control group. However, the surgeon and OR staff were exposed to approximately 2.5 times less radiation in the intraoperative CT group when compared to the fluoroscopy group (Hayda et al. 2018). In another study by Costa et al., patients undergoing CT-based navigation-assisted lumbar spine surgery were exposed to a mean of 5.15 mSv of radiation, whereas the surgeon and staff who were outside the operating room at the time of the scan were reported as having no radiation exposure. Both studies confirm that the use intraoperative CT increases radiation exposure to the patient by approximately 7.5 mSv, which is less than that sustained during a routine lumbar CT. Additionally, radiation exposure to the surgeon and staff were reported to be decreased in both studies (Hayda et al. 2018).

A review of literature demonstrated promising results when evaluating radiation exposure measured in seconds of fluoroscopy time comparing robotic-assisted vs. traditional freehand insertion

of pedicle screws. A study performed by Kandlehardt et al. demonstrated an average radiation exposure time of 34 s per screw in the robotic-assisted group vs. 77 s per screw in the fluoroscopic-assisted freehand group (Kochanski et al. 2019). Likewise, Schoenmayr and Kim reported a decrease in radiation exposure by 40% when comparing robotic systems to traditional techniques. Additionally, Roser et al. found an average fluoroscopy time of 31.5 s per screw for using traditional freehand technique vs. 15.98 s per screw in the robotic-assisted cohort in a prospective randomized study evaluating the two groups (Kochanski et al. 2019). These studies demonstrate positive results and support the proposed benefits of reductions in total radiation exposure associated with robotic-assisted spine surgery. However, further research is likely needed to determine the impact of robotics systems on total radiation exposure to both surgeons and patients due to differences in surgeon experience, operative technique, and imaging protocols for robotics systems used between these studies and others like them (Kochanski et al. 2019).

Costs

Introducing robotic-assisted techniques may potentially improve precision and accuracy in the operating room, but the ultimate acceptance of robotic surgery into mainstream surgical practice will be heavily dependent on its cost-effectiveness. According to a 2019 market analysis, the average upfront cost of a spine surgical robot can be anywhere from 600,000–1,300,000 dollars depending on the model and purchasing agreement for a health system. Additionally, there is typically an annual service contract that can cost as much as $100,000 to service and maintain the robot (Ahern et al. 2020). Over time the total costs to operate, service, and maintain each robot accumulate and thus increase the total cost of each surgical procedure in which the robot is used. As such, the added upfront costs, added surgical time, and training of the surgeon, and OR staff must be considered and weighed against the potential benefits of robotic-assisted surgery. According to a review by Ahern et al., these added upfront costs could be offset if robotic-assisted spine surgery can continue to decrease operating room time, hospital length of stay, and rates of revision surgery (Ahern et al. 2020). Although the learning curve for robotic-assisted surgery is steep and volume dependent, once surgeons become familiar with their use, operating room times may decrease leading to more operating room efficiency (Ahern et al. 2020). Additionally, costs may be recouped by capturing a greater portion of patients who desire robotic-assisted procedures.

Limitations

Despite the reported benefits, there is still a lack of published data demonstrating conclusive evidence that suggests that long-term clinical outcomes in spine surgery are significantly improved with robotic-assisted techniques when compared to traditional methods. More extensive studies are needed to investigate further if robotic-assisted techniques in spine surgery are beneficial enough to justify the upfront and maintenance costs associated with their use.

Discussion

The goals of spine surgery are to improve patient functioning and reduce morbidity associated with disease of the spine. Over the last two decades, robotic-assisted technologies for use in spinal instrumentation have evolved rather quickly. The rapid growth and integration of imaging, navigation, and robotics in spinal surgery provide surgeons and health systems with an increasing number of options in spine surgery. Robotic techniques have been shown to be safe and effective in treating instability and deformity caused by degenerative spine disease or trauma as well as in other complex cases where patient anatomy may be distorted such as revision or tumor surgery. It is important to note that over the long term, most industries that have implemented robotic technology have demonstrated increased

production capacity, improved precision, and decreased costs.

There are many reported advantages of robotic-assisted spine surgery including minimally invasive applications, improved accuracy of pedicle screw placement, and decreased radiation exposure to the surgeon, and operating room staff. While the reported advantages and potential benefits of using robotic-assisted techniques are promising, they must be weighed against the increased direct costs associated with purchasing and maintaining the surgical robot, added surgical time, and the ongoing education and training of the surgeon and operating room staff on the robot's use.

While it is not the goal of this review to argue in favor or against the use of robotics in spine surgery, robotics in the operating room are likely here to stay. In spine surgery, technologies such as computer navigation and robotic-assisted techniques continue to evolve in an effort to improve patient outcomes, decrease complications, and increase patient safety. As such, more high-quality studies are needed to investigate improvement outcomes, efficiency, and reductions in total costs of care in order to provide the information that spine surgeons and health systems will need to decide if they will implement robotics into their practice.

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