Pathophysiology of Spinal Pain

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Key Points

- Spine pain is a costly and prevalent problem in the United States and worldwide.
- Risk factors for back pain include age, obesity, smoking, and workplace stress and dissatisfaction.
- Disc herniations occur anywhere in the spine but mostly in the lower lumbar and cervical spine leading to radicular symptoms in the distribution of the affected nerve root(s).
- Discogenic pain derives from injury to the intervertebral disc but has complex molecular underpinnings that involve changes in vascularization and innervation.
- Spinal stenosis occurs most commonly in the lumbar region and secondary to degeneration, causing extremity paresthesias, weakness, and neurogenic claudication.
- Facet joints can be a common source of spine pain that typically develops after cumulative lifetime stress, leading to inflammation.
- The sacroiliac joints are richly innervated, both in the joint capsule and the extra-articular ligaments; sacroiliac joint pain can be associated with leg length differences, low-grade trauma, and pregnancy.
- Cancer and inflammatory conditions are unique pathophysiological states which can produce spinal pain.

Epidemiology of Spinal Pain

Disorders of the spine constitute a majority of chronic pain complaints, with the lifetime prevalence of spinal pain reported to range from 54% to 80% [1]. Among spinal pain conditions, annual prevalence estimates range from 30% to 50% for neck pain, 15% to 45% for chronic low back pain, and 3% to 23% for thoracic pain [1]. The socioeconomic burden of spinal pain, and in particular back pain, is tremendous, cutting across developed and developing countries alike. In the United States, spinal pain is the leading cause of activity limitation in people younger than 45 years of age and the fifth most common cause for all physician visits, at an estimated annual cost of $86 billion in 2005 [2–5]. National expenditures for spinal pain have steadily increased an average of 7% per year from 1997 to 2006 [2]. Further, it appears that the prevalence of low back pain may be increasing. In one study, the prevalence of low back pain was found to have increased from 3.9% in 1992 to 10.2% in 2006 [6]. Calculated at roughly 1% of the gross domestic product in 1998, health-care expenditures for back pain are astounding [7].

Several risk factors for back pain have been reported. Age is one of the more common risk factors. The incidence of back pain is highest in the third decade, increasing with age until 65 years, before gradually decreasing [8]. Other factors such as obesity, smoking, and lack of exercise and workplace

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factors such as job dissatisfaction, monotony, lack of social support, and stress have also been reported to be associated with an increased incidence of back pain [9–11].

Brief Anatomy of the Human Spine

The human spine is a complex structure comprised of 7 cervical, 12 thoracic, 5 lumbar, 5 (fused) sacral, and 4 coccygeal bony units termed vertebrae. These vertebrae are arranged in a linear column, connected by ligaments, intervertebral discs (IVDs), cartilage, and muscles. The fundamental anatomical unit of the spine is composed of paired facet joints and the intervertebral disc, referred to as the three-joint complex. Each of the elements contributes to strength and function of the spine but is also a potential source of pain in the event of injury or pathology. Each of these general regions (cervical, lumbar, etc.) is exposed to different insults and disturbances, thus having predilections for different pathological states. Common causes of lumbar back pain include radicular pain due to disc herniation or spinal stenosis, discogenic pain, facet joint pain, myofascial pain, and sacroiliac joint pain. Table 5.1 summarizes features of these clinical syndromes.

Disc Herniation

Intervertebral discs (IVDs) are complex structures, composed of a central nucleus pulposus (NP) that is encased by the annulus fibrosus (AF) and bordered superiorly and inferiorly by cartilaginous endplates (EP) (Fig. 5.1). The NP is a gelatinous structure that is composed of proteoglycans con-

Table 5.1 Clinical evaluation of lumbar pain [77, 97, 106, 133–144]

Source of pain	Risk factors	History	Clinical signs	Physical exam
Radicular				
Disc herniation	Advanced age Genetics Obesity Diabetes Smoking Strenuous labor	Acute onset	Back pain Radiating LE pain, weakness, paresthesias in dermatomal and myotomal distribution Exacerbated by bending forward, sitting, coughing, straining Relieved by lying down, walking	Straight leg raise (SLR) test: 92% sens, 10–100% spec for lower lumbar and sacral pathology Crossed SLR test: 28% sens, 90% spec Femoral nerve stretch test: 50% sens, 100% spec for L2–L4 (mid to upper lumbar radiculopathy)
Spinal stenosis	Advanced age Congenital narrowing Trauma (e.g., fractures or post-surgical)	Insidious onset	Back pain LE sensory loss, weakness Neurogenic claudication Exacerbated by walking, standing Improved by forward bending	Neurological exam often normal, unless severe or prolonged course Wide-based gait, positive Romberg in setting of LBP has 90% spec
Axial				
Facet joint	Motor vehicle accident Trauma (e.g., sports, fall) Advanced age Obesity Female sex	Insidious or acute (less frequent) onset	Localized back pain Referred pain does not typically extend past knee	Paraspinal tenderness Pain worsens with various movements including lateral flexion, flexion and extension No neurological deficits
Sacroiliac joint	Leg length discrepancy Scoliosis Gait abnormalities Persistent low-grade trauma Pregnancy	More likely to be associated with an inciting event than other sources of axial pain	Variable presentation Buttock pain extending into posterolateral thigh most typical referral pattern Pain radiating to groin	Numerous exam maneuvers, individual utility debatable >3 positive provocative tests have reasonable sens (77–94%) and spec (57–100%) in identifying positive response to diagnostic joint injections
Intervertebral disc	Smoking Advanced age Trauma	Insidious onset	Localized back pain Paraspinal muscle spasms	Midline tenderness, reduced ROM Centralization phenomenon 64% sens, 70% spec; bony vibration test utility debated
Myofascial pain	Postural habits Sleep disorders Exercise deficiency or overuse injury Trauma	Chronic, localized symptoms	Can mimic other conditions due to heterogeneity of symptoms Muscle tightness and imbalance which can be associated with stress, anxiety	Imbalance, gait abnormalities Palpation: taut bands and tender points in muscles of interest Imaging: ultrasound with Doppler flow, magnetic resonance elastography

Abbreviations: *sens* sensitivity; spec, specificity, *LE* lower extremity, *LBP* lumbar back pain, *ROM* range of motion

tained in a loose network of type II collagen and is primarily responsible for the ability of the IVD to withstand substantial axial loading. The AF is a thick and dense outer ring that is commonly divided into the inner and outer annulus. The outer annulus is made of highly organized, concentric lamellae that are composed of fibroblast-like cells that make type I collagen, giving it high tensile strength. The inner annulus is a transitional zone between the AF and NP, which consists of different proteoglycans and both type I and type II collagen. The EP is made of a 0.6-mm-thick layer of hyaline cartilage and has a capillary network that may extend into the outer AF, providing nutrients to the otherwise avascular IVD [12, 13].

The IVD functions to stabilize the spine, absorb shock, and allow for movement and flexibility of the otherwise rigid spine. It must withstand the biomechanical demands of the spectrum of human movement, including axial and rotational forces, flexion, extension, and lateral bending motions. These demands, coupled with its relatively avascular composition and limited ability to remodel, contribute to the natural degenerative process of IVDs and predispose it to pathologies such as disc herniations [12].

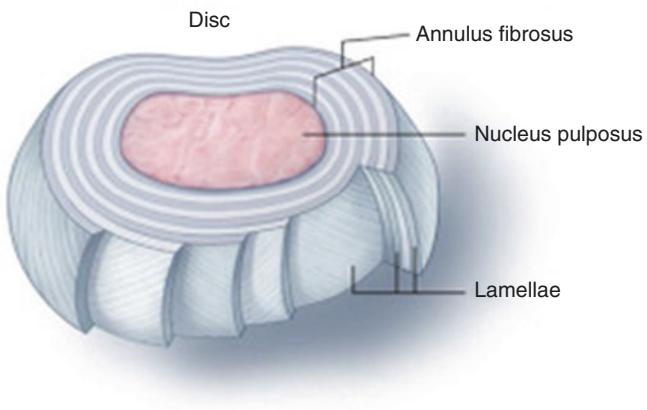

Fig. 5.1 Intervertebral disc structure. (Reprinted with permission from Hooten and Cohen [145])

According to the recommendations of the North American Spine Society, American Society of Spine Radiology, and American Society of Neuroradiology, the consensus definition of a disc herniation is a "localized or focal displacement of disc material beyond the limits of the intervertebral disc space" [14]. Disc herniations can be divided into three classifications, based on structural damage. *Protrusions* are wide-based herniations in which the outer annulus remains intact. *Extrusions* are narrow-based herniations with rupture of the outer annulus. Lastly, sequestrations are herniations that are completely detached from the rest of the IVD [12]. Figure 5.2 shows the potential consequences of disc protrusion on traversing and exiting nerve roots.

Whereas disc herniations can occur anywhere along the spine, the majority occur in the lumbar spine (L4–L5 or L5–S1), followed by the cervical spine (C5–C6 or C6–C7) [15, 16]. Lumbar disc herniations have highest prevalence among people aged 30–50 years and are more common in men. Several risk factors have been identified, including obesity, diabetes, hyperlipidemia, and smoking [12]. The mechanisms by which these comorbidities increase the risk for disc herniation is unknown, although it has been proposed that they may promote annular degeneration through altering microcirculation and cytokine expression [17, 18]. Other risk factors include strenuous labor, especially that requiring a combination of axial load with flexion or torsion [19, 20]. Lastly, positive family history (i.e., genetics) appears to impart an increased risk of developing lumbar disc herniation [21].

Disc herniations can result from acute trauma or progressive degenerative changes. Degenerative changes start early in life and include small clefts in the AF, decreased cell density of the NP, and decreased capillary supply to the AF [22, 23]. Changes to the AF play a crucial role in the development of disc herniations. With age, the number and severity of

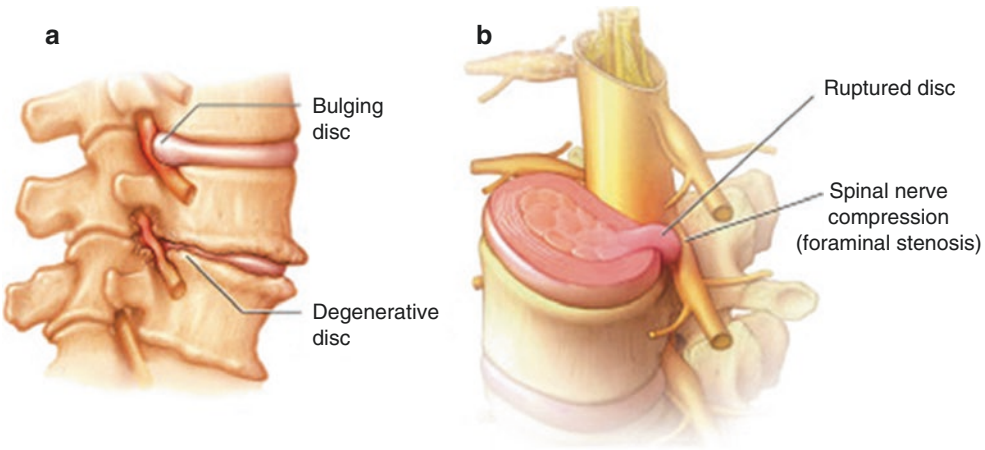

Fig. 5.2 (**a**) Lateral view of the potential effects of disc herniation and degenerative changes on spinal nerve roots. (**b**) Axial view of a ruptured lumbar intervertebral disc. (Reprinted with permission from Hooten and Cohen [145])

annular clefts increase, the boundary between the AF and NP fades, and the integrity of the outer layer of the AF becomes compromised [24]. Lumbar disc herniations most often occur posterolaterally, where the AF is relatively thin and not reinforced by the posterior or anterior longitudinal ligament [12]. In contrast, herniations in the cervical spine are more likely to occur laterally.

Pain is often characterized as sharp and stabbing, with a radicular component. Radicular pain is commonly attributed to either mechanical compression of the traversing nerve root or spinal canal or to chemical irritation [25]. Mechanical compression not only deforms the nerve root but can impinge on the microcirculation and lead to ischemia and radicular symptoms [12]. Further, studies have demonstrated that while disc herniation stimulates an inflammatory cascade that has a role in stimulating the resorption of the disc, this same cascade can also lead to chemical irritation of the nerve root and radicular symptoms, even in the absence of compression [26–29]. The observations that over 10% of patients who undergo discectomy for refractory pain experience unsatisfactory results months or years after and that there is no apparent correlation between lumbar decompression outcomes and radiological evidence of persistent herniation point to an underlying pain mechanism that is not purely related to mechanical compression but rather perpetuated by upregulation of inflammatory mediators such as TNF-alpha [30, 31].

Discogenic Pain

Approximately 39% of patients with mechanical lower back pain suffer from primary pathology of the intervertebral disc [32], with the proportion of individuals with positive discograms varying widely based on selection criteria (i.e., more liberal criteria will result in a lower proportion of positive results). Discogenic pain can be difficult to diagnose, and the pathophysiological components of disc degeneration have molecular, anatomical, and physiological aspects. As previously discussed, the intervertebral disc is composed of a tough and ring-like annulus fibrosus surrounding a gelatinous nucleus pulposus [33]. The annulus fibrosus is composed of concentric rings (lamellae); there are 15–25 layers depending on the location of the disc within the spine [34]. The annulus fibrosus surrounds the gelatinous nucleus pulposus [24, 33]; both of these structures are flanked superiorly and inferiorly by cartilaginous endplates. The innervation of the disc is complex but is thought to be composed of sinuvertebral nerves which derive from the dorsal roots [33, 35] and from sympathetic fibers ventrally. Normally, there is only minimal neural penetration of the annulus fibrosus [36].

The pathophysiology of discogenic pain can be viewed from the perspective of distinct pathological lesions which are found to correlate with painful symptoms or from the molecular and histological changes which have been found in tissue. The physiological causes of discogenic pain are commonly divided into torsion injury, internal disc disruption, and infection [37]. Internal disc disruption is the most common attributed cause of discogenic pain, resulting from radial tears to the disc and degradation of the nucleus pulposus. Radial fissures extend from the nucleus pulposus outward to the annulus fibrosus; other types of fissures include transverse fissures, which extend horizontally outward and involve the peripheral annulus and circumferential fissures, which resemble separation between the concentric rings of the annulus. These can form from compression injury or endplate deficits. Additionally, painful symptoms have been reported to occur more frequently in patients with high-grade annular disruptions.

Torsional injuries to the disc can result from forcible rotation about the zygapophyseal (facet) joint and lateral stress to the annulus fibrosus [37]. Based upon ex vivo studies, Farfan et al. showed how torsion could produce tears of the annulus [38]. Subsequent study has shown that torsion has a greater propensity to produce damage when combined with flexion [39].

More mechanistic details regarding discogenic pain have also been ascertained by ex vivo studies of degenerated discs. Changes in innervation and vascularization seen in harvested intervertebral discs from patients with discogenic pain and disc degeneration have shown more extensive spread of nerve fibers and granulation, which extend further into the annulus fibrosus and even into the nucleus pulposus [35, 40]. Freemont et al. showed that nerve growth factor (NGF) expression correlated with microvascular and nerve fiber ingrowth into the annulus fibrosus and nucleus pulposus, suggesting how molecular signaling reflects histological changes [41]. Increased expression of inflammatory markers such as TNF-alpha has also been found to be enriched in cadaveric samples of intervertebral discs from patients with clinical symptoms [42].

Spinal Stenosis

Spinal stenosis is a clinical entity defined by narrowing of the spinal canal, leading to cord or nerve root impingement that can result in radiculopathy and neurogenic claudication. Spinal stenosis can occur throughout the spine, but at an estimated annual incidence of 5 cases per 100,000 individuals, lumbar spinal stenosis (LSS) is 4 times more common than cervical spinal stenosis [43]. LSS is often classified by etiology and anatomy. Primary LSS results from congenital abnormalities (e.g., short pedicles) that narrow the spinal canal, while secondary LSS results from an acquired insult, most commonly from progressive

degenerative changes [44]. Other etiologies of secondary LSS include metabolic causes such as epidural lipomatosis, infectious causes such as osteomyelitis and discitis, rheumatologic conditions, cancer, and post-traumatic stenosis such as with fractures or surgeries [45]. Anatomically, LSS can be classified as involving the central canal, lateral recesses, neural foramina, or any combination of the three. Attempts have also been made to classify LSS based on the anterior-posterior diameter of the spinal canal, although this has not been clinically validated. A spinal canal diameter <10 mm is considered absolute LSS and is often symptomatic, while a spinal canal diameter of 10–12 mm is considered relative LSS and is usually asymptomatic. LSS most commonly affects the lower three levels, with L4–L5 most frequently affected, followed by L3–L4, L5–S1, and then L1–L2 [45]. In the cervical region, C5–C6 is the most frequently affected segment.

Degenerative LSS, the most common form of LSS, develops through multifactorial processes that can act in concert to propagate the disease. Thickening of the ligamentum flavum (LF), which covers a significant portion of the posterior and lateral walls of the spinal canal, is believed to play a major role in the pathogenesis of LSS. Whether thickening occurs by "buckling" of the LF into the spinal canal due to loss of intervertebral disc height or by hypertrophy of the LF in the absence of disc space narrowing, the diameter of the spinal canal is reduced, causing mechanical compression of the nerve root, cauda equina, or dural sac, leading to a variety of symptoms that may include back pain, leg pain, and gait disturbance [46]. LF hypertrophy is believed to be a multifactorial process, associated with aging, mechanical stress, activity level, and genetics. It is postulated that stress-induced tissue damage triggers an inflammatory response that causes scarring, the repeated accumulation of which results in the development of LF hypertrophy [47, 48]. Spinal instability has also been postulated to play a role—increased segmental range of motion has been shown to be an independent risk factor for LF thickening [46]. Whereas normal LF is composed primarily of elastic fibers, hypertrophied LF is characterized by disorganized and decreased elastic fibers as well as increased fibrosis, especially along the dorsal aspect of the LF, which is subject to higher stress [49]. Hypertrophied LF is thus stiffer and more vulnerable to the constant flexion-extension movements required, potentially leading to a feed-forward cycle of further scarring and repair [46]. The molecular mechanisms of LF hypertrophy are not fully understood, but LF hypertrophy has been shown to be associated with increased expression of matrix metalloproteases (MMPs), tissue inhibitors of matrix metalloproteases (TIMPs), connective tissue growth factor (CTGF), bone morphogenetic protein (BMP), platelet-derived growth factor-BB (PDGF-BB), and various inflammatory cytokines, including TGF-β [49–57].

In addition to LF hypertrophy, other degenerative processes occur that predispose to the development of LSS. As the intervertebral disc degenerates, disc protrusions can develop that cause ventral narrowing of the spinal canal, resulting in central stenosis. Disc degeneration also results in a loss of height of the intervertebral space, resulting in not only potential buckling of the LF into the dorsal spinal canal as aforementioned but also narrowing of the lateral recesses and foraminal stenosis. Disc degeneration also adds increased strain on the facet joints. This increased load can result in facet arthrosis, joint capsule hypertrophy, and joint cysts, leading to lateral and foraminal stenosis as well as increased spinal instability, which promote further deleterious hypertrophic changes [45]. These degenerative changes ultimately result in potential compression of nerve roots, dura, intraspinal vessels, and the cauda equina, leading to a heterogeneous array of symptoms.

Common symptoms of LSS include lumbago, neurogenic claudication, leg hypesthesias and paresthesias, ataxia, and leg weakness or heaviness. Neurogenic claudication is considered the classic clinical presentation. This term was coined by Dejerine in 1911 and first defined by von Gelderen in 1948 as "localized, bony discoligamentous narrowing of the spinal canal that is associated with a complex of clinical signs and symptoms comprising back pain and stress-related symptoms in the legs (claudication)" [45]. Neurogenic claudication is comprised of lumbar back pain that radiates toward the gluteal region, groin, and legs, often in a radicular pattern, with associated sensorimotor deficits such as paresthesias, weakness, and cramping. It is typically exacerbated by activities like standing and walking that transiently extend the spine, increasing lordosis and the degree of stenosis. Conversely, pain is eased by activities like stooping and sitting that cause flexion of the spine, opening the spinal canal. Means to distinguish neurogenic from vascular claudication include longer time to offset, pain relieved by sitting, a positive "shopping cart sign" or pain not worsened when walking uphill, more prominent neurological symptoms (e.g., numbness or neurological weakness), and a normal ankle brachial index [58].

The reproducibility of symptom onset and offset with postural changes highlights the importance of dynamic factors in the pathogenesis of neurogenic claudication. Epidural pressure has been shown to vary significantly with lumbar flexion and extension, increasing with walking and decreasing immediately after stopping [59]. Although these pressure variations, ranging from 15 to 18 mmHg during flexion to 80–100 mmHg during extension, are not enough to interrupt arterial flow, they may play a significant role in the development of venous congestion, as well as intermittent compression of nerve roots that results in impairment of nerve conduction. Indeed, neurogenic claudication is believed to result from either direct mechanical compression of nerve

roots or indirect vascular insufficiency from reduced arterial blood flow or venous congestion. With spinal extension, exacerbation of the stenosis occurs, causing mechanical compression of the cauda equina and nerve roots, leading to tissue injury and degeneration of nerve fibers. In addition, there is occlusion of the subarachnoid space, leading to venous stasis. The relationship between extensor postures, increased intraspinal pressure, vascular engorgement, and decreased venous drainage has been demonstrated in multiple studies [60–63].

Venous stasis is deleterious in several ways. Venous stasis has been shown in a rat model of LSS to elicit ectopic firing, which is thought to emanate from the dorsal root ganglia, with propagation in both directions, potentially playing a role in the origination of radicular pain as well as the development of paresthesias [64]. Further, venous stasis results in elevated capillary pressures, which can lead to intraradicular edema. Intraradicular edema is also thought to result from mechanical compression, which has been shown to increase permeability of the endoneurial capillaries, causing an inflammatory response with macrophage and mast cell infiltration [65]. Intraradicular edema is thought to be closely related to the development of radiculopathy.

Facet Joint Pain

Facet, or zygapophysial, joints are important sources of acute and chronic spine pain, due to their rich innervation. The facet joints form the posterolateral articulations between adjacent vertebral arches, with the superior articular facet facing upward and articulating with the inferior articular facet of the above vertebra (Fig. 5.3). This three-joint complex formed by the intervertebral disc and the paired facet joints functions to stabilize the spine and limit excess motion [66]. The facet joints also assist the intervertebral discs with weight-bearing, with the percentage of axial burden increasing with aging, disc generation, and facet arthritis [67]. Structurally, facet joints are true synovial joints, comprised of hyaline cartilage overlying subchondral bone, a synovial membrane, a fibrous joint capsule, and a joint space that can accommodate 1–2 mL of fluid [68]. Each facet joint receives dual innervation from the medial branch of the posterior primary rami at that level and from the level above. Thus, the L4–L5 facet joint receives innervation from the L4 medial branch (corresponding segment) and the L3 medial branch (the level above). The medial branches of the L1–L4 dorsal rami travel across the top of the transverse process, through the dorsal leaf of the intertransverse ligament at the base of the transverse process. Each nerve then travels in the groove between the transverse process and superior articular process, before curving medially around the base of the superior articular process. As it crosses the lamina, it then divides into multiple branches that innervate not only the facet joints but also the multifidus muscle, the interspinous muscle and ligament, and the periosteum of the neural arch [66, 69]. Although unproven, some studies suggest that the facet joints may also receive additional innervation from the dorsal root ganglion, the medial branch below the facet joint, and the paravertebral sympathetic ganglia [70–73]. Histologic studies of facet joints demonstrate the presence of encapsulated and free nerve endings, as well as nerves containing substance P and calcitonin gene-related peptide [74, 75]. Nerve fibers have also been found in structures outside the joint capsule, including subchondral bone, which may contribute to pain [76]. This rich innervation of the facet joint capsule and surrounding structures makes it an important pain generator.

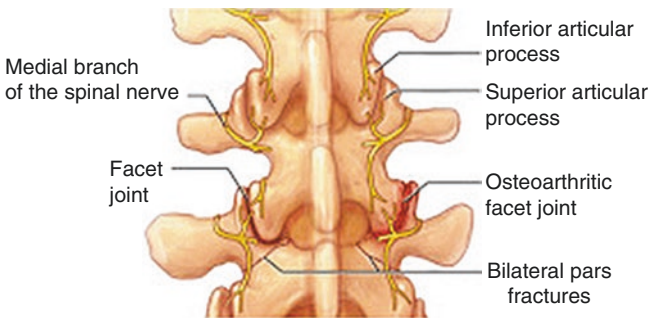

Fig. 5.3 Anatomy and innervation of the lumbar facet joint. Also depicted are bilateral fractures of the pars interarticularis (pars defect) and an osteoarthritic facet joint. (Reprinted with permission from Hooten and Cohen [145])

Although the development of facet joint pain can sometimes be traced to an inciting event [77], the majority of cases are the result of cumulative stress over a lifetime [66]. Studies have shown that the upper three lumbar facet joints are maximally strained with lateral bending, while the lower two lumbar facet joints are maximally strained during forward flexion [78]. Further, disc degeneration can alter the biomechanics of the three-joint complex, resulting in increased stress on the facet joint and hypertrophic changes in the capsule [79]. Repetitive stress is associated with synovial release of inflammatory mediators, leading to facet joint effusion and subsequent capsular distension. This capsular distension activates synovial and capsular nociceptors, resulting in pain [80]. The mechanism by which this can lead to persistent pain has been demonstrated in several animal studies. In goats, excessive capsular strain activates nociceptors and can lead to persistent neural after-discharges [75]. This persistent nociceptive input leads to peripheral sensitization, which may lead to central sensitization and neuroplasticity [81]. At even higher degrees of capsular strain, signs of capsular axonal injury were present, as demonstrated by axonal swelling and retraction balls, which can lead to

axonal hyperexcitability and spontaneous firing and hence may play a role in the generation of neuropathic pain [75]. In a series of other animal studies, the application of inflammatory mediators such as substance P and phospholipase A_2 was shown to lead to vasodilation, venous congestion, and polymorphonuclear leukocyte aggregation in the lumbar facet joint and surrounding tissues [82–84]. Inflammation also resulted in neuronal sensitization, as demonstrated through decreased thresholds of nerve endings, increased basal discharge rates, and recruitment of previously silent units [85].

In addition to capsule distension, other mechanisms of pain generation have been postulated. Chronic inflammation can lead to facet hypertrophy and foraminal narrowing, which can cause impingement of nerve roots, leading to radicular symptoms [86, 87]. Nerve entrapment can also occur with calcification of the mamilloaccessory ligament and is especially common at L5 (20%) and L4 (10%) [88]. Lastly, irritation of the facet joint capsule may result in reflex spasm of the paraspinal muscles [89, 90].

Sacroiliac Joint Pain

The sacroiliac joint (SIJ) is the largest axial joint in the body and is estimated to be the source of approximately 15–25% of axial lumbar back pain cases in carefully screened patients (i.e., non-neuropathic pain predominantly below L5) [91–93]. Although the SIJ is often characterized as a diarthrodial synovial joint, the posterior two-thirds of the joint interface lacks a capsule and is connected through an extensive network of ligaments [94]. The SIJ is also reinforced by numerous myofascial attachments that impart joint stability and influence movement, including the thoracolumbar fascia, gluteus maximus, piriformis, and biceps femoris [95, 96]. Innervation to the SIJ is complex and the subject of debate. The posterior joint is believed to receive its major innervation from the lateral branches of the dorsal rami of S1–S3, with variable contributions from L5 to S4 in some individuals [97, 98]. Innervation to the anterior joint is even less well understood, with studies suggesting innervation from the L5 to S2 ventral rami, with possible contributions from L4 [99, 100].

Numerous histological studies have suggested that the SIJ is capable of transmitting proprioception and nociception [101–103]. In cadaver studies, substance P and calcitonin gene-related peptide (CGRP)-positive nerve fibers have been found to be present in the superficial layers of sacral and iliac cartilage, as well as the surrounding ligamentous structures, supporting the idea that the SIJ is capable of nociception [104]. Furthermore, as several pathways of communication have been demonstrated between the SIJ and nearby neural structures, it is possible that inflammatory mediators extravasate in the setting of capsular disruption, leading to symptoms of sciatica. In one study, ventral capsular tears were observed in 21% of patients based on contrast injection patterns [92]. On post-arthrography CT, the most common patterns of extracapsular contrast extravasation from the SIJ to nearby neural structures include posterior spread into the dorsal sacral foramina, superior recess spread into the L5 nerve root sheath, and ventral spread into the lumbosacral plexus [105]. Thus, injuries to the various components of the SIJ and surrounding structures, whether by distension, compression, shearing forces, altered mechanics, or inflammation, can all be sources of pain [106]. Mechanistically, these can be simplified into intra- and extra-articular sources of SIJ pain. Extra-articular causes include enthesopathies, ligamentous and muscular injuries, and fractures. Intra-articular causes are less common and include arthritis and infection [106].

Several predisposing factors for developing SIJ pain have been reported [106]. These include factors that increase SIJ burden, such as leg length discrepancy and scoliosis, which can both increase pelvic obliquity, leading to abnormal bilateral alignment of the SIJ and increased stress through the joint [107, 108]. In a finite element model of SIJ loading, as little as 1 cm of leg length discrepancy increases the load across the SIJ during lateral bending by almost five-fold [109]. Other factors that increase SIJ burden include gait abnormalities, vigorous exercise, and other forms of persistent low-grade trauma [110, 111]. Lumbar and lumbosacral fusion have also been shown to increase the risk of SIJ pain, especially as the number of operative segments increases, presumably through ligamentous weakening, disruption of the joint cavity, and postoperative hypermobility [112–115]. Lastly, pregnancy increases the risk of SIJ pain through a combination of weight gain, increased lordosis, hormone-induced ligamentous laxity, and trauma associated with parturition [116]. MRI changes of the SIJ during the peripartum period include bone marrow edema, capsulitis, and enthesitis [117].

Compared to facetogenic and discogenic pain, which tend to be more insidious in onset, SIJ pain is more likely to be associated with an inciting event [97, 118]. In one study evaluating patients with injection-confirmed SIJ pain, most (44%) recalled a specific traumatic event (e.g., motor vehicle accident, fall, or pregnancy), while 35% had idiopathic onset, and 21% were considered to have had cumulative trauma [118]. The mechanism of SIJ injury is described as a combination of axial loading with abrupt rotation [106]. Specific mechanisms of acute injury include direct fall on the buttocks, sudden heavy lifting, rear-end motor vehicle accident with the ipsilateral foot on the brake, and stepping into an unexpected hole [95, 106, 119, 120]. Other chronic mechanisms include repetitive shear or torsional forces, such as with golfing and bowling [121] .

Inflammatory Disorders and Cancer

There are a number of less common conditions that can also cause spinal pain. Inflammatory disorders such as ankylosing spondylitis and metastatic disease can contribute to spinal pain, involving complex mechanisms that deserve special mention. Their pathophysiological involvement of the elements of the spine can often present a mixed pain syndrome with both nociceptive and neuropathic features.

Ankylosing spondylitis is a seronegative spondyloarthropathy with a strong association with HLA-B27, which can lead to a syndrome of sacroiliitis, thoracolumbar, and even cervical pain [122, 123]. Inflammatory back and pelvic pain that is dull and deep, with nocturnal exacerbations, is the most common clinical presentation [124], although studies have also suggested that some patients report neuropathic pain and sensorimotor symptoms [125]. Pathogenesis of this arthropathy involves aggregation of inflammatory T-cells, B-cells, macrophages, and osteoclasts at the insertions of ligaments (entheses) [122]. Gradually, patients develop dysregulation of cytokines such as TNF-alpha or IL-17, also considered important in the genesis of this disease; as a useful corollary, disease-modifying agents targeting TNF-alpha have been helpful in the amelioration of symptoms. At a structural level, damage through bone erosion followed by bone formation [126] and gradual fusion and loss of mobility of joints [127] contribute to disability and loss of mobility. Thus, a complex and poorly understood process with immunological overtones presents a unique syndrome of spine pain.

Metastatic cancer represents another important cause of spinal pain with up to 70% of cancer patients showing signs of tumor infiltration to the axial spine on postmortem examination. Spinal metastases occur most commonly in the thoracic spine (60–80%), followed by the lumbar spine (15–30%), and finally the cervical spine (<10%). The most common cancers to metastasize to the spine are breast, lung, and prostate cancers, although renal, thyroid, and gastrointestinal sources of malignancy are also observed [128]. Additional information will be provided in other chapters in this book.

Cancer-associated bone pain is complex, has been found to involve unique mechanisms on molecular and physiological levels, and can demonstrate aspects of both nociceptive and neuropathic pain. Studies have shown that patients with cancer-associated bone pain frequently describe neuropathic symptoms [129], which can result from direct compression on nervous structures or central sensitization [130]. Pain can result from tumor cell-driven infiltration, compression of peripheral nerves, or stretching of bone. Central sensitization also occurs from chronic inflammatory or neuropathic injury from bone cancer, with studies revealing neurochemical changes which can be seen in the spinal cord as demonstrated in animal models of cancer pain [131, 132]. Thus, there are multiple mechanisms that can contribute to the uniquely devastating symptoms caused by metastatic spread of cancerous disease to the axial spine.

Summary

There is a wide range of pain syndromes that affect the spine, each with distinct molecular, cellular, and anatomic abnormalities, leading to their respective symptoms. It is crucial for the pain practitioner to understand the underlying pathophysiology of spinal disease in order to efficiently utilize helpful therapeutic approaches. Perhaps most important, continued study into the basis of a specific syndrome may guide development of more beneficial future therapies.

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