Diagnosis and Management of Hip Disease

Biological Bases of Clinical Care

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To Judy, David, and Daniel who have animated my life and given it its meaning

Preface

The diagnosis and treatment of diseases of the hip have substantially advanced in recent years. While previous advances were largely due to the development of therapeutic devices and concomitant development of biocompatible materials, more recent advances have been the result of an improved understanding of the biology of the hip. In this context, biology is interpreted broadly to include kinematics, biomechanics, anatomy, and metabolism.

The title of the book conveys the importance of advances in understanding biology as the basis for contemporary diagnosis and safe, effective treatments. This volume presents important advances in pathophysiology, pathologic anatomy, and diseases of the hip on the tissue and metabolic levels. The current emphasis on medical risk reduction in hip replacement is presented in three important chapters. The social and economic contexts in which hip diseases are treated and which affect treatment choices are discussed.

I have been extremely fortunate in being instructed in my residency training and mentored in my early years of clinical fellowship and practice by individuals who not only understood the importance of the biological basis of clinical practice but also developed it in the context of musculoskeletal disease in general, and of the hip in particular. I will always be grateful to William Harris, chief of the Hip Service and my thesis advisor at the Massachusetts General Hospital and to K. Frank Austen, chair of rheumatology, and Clement Sledge, chair of orthopedics, both at the Brigham. I could not overstate the impact that Henry Mankin, chair of orthopedics at Mass. General has had on my academic, medical orientation to clinical practice. Finally, my current chairman, under whom I was also a resident, Michael Ehrlich, has had profound influences on my professional life.

These original thinkers and generous gifted teachers created new modes of thought and provided the inspiration and the guidance to understand musculoskeletal disease and treatment in biological terms. To them, I owe the privilege of working at the interface of biology and clinical care. Any misunderstandings, errors, or omissions along the way are mine alone.

Providence, RI, USA — Roy Kenneth Aaron, MD

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Chapter 1
Health Care Organization and Its Impact on Care of Diseases of the Hip

Benedict U. Nwachukwu and Kevin J. Bozic

Introduction

Spending on healthcare delivery in the United States (U.S.) has long been a point of great concern [1–3]. The proportion of gross domestic product (GDP) used for healthcare expenditure is used as a benchmark against which nations are compared. According to World Health Organization (W.H.O.) statistics the U.S. spent 17.9 % of GDP on healthcare in 2011, the most of any nation, and based on historic trends healthcare expenditure is expected to rise to 20 % of GDP by 2017 [4]. Perhaps of even greater concern is that the large expenditures of the U.S. healthcare system are not producing superior health outcomes. The U.S. lags behind almost every other industrial nation in public health outcome parameters such as life expectancy and infant mortality [4]. Prior reports such as that in 2004 by the Institute of Medicine (IOM) have attributed lagging health outcomes to a lack of access to healthcare for many U.S. citizens. Specifically a prior report noted that the U.S. was one of the few industrialized nations that had not achieved universal healthcare or that guaranteed access to healthcare for its citizens [5].

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Table 1.1 Definition of key terms

Term	Definition
Accountable care organization	A healthcare network consisting of various physicians from different specialties, hospitals and other non-physician healthcare providers that are contracted to provide coordinated care to a group of patients
Bundled payment/Episode of care payment	A payment model for the global reimbursement of healthcare providers (hospitals, physicians, and non-physician providers) according to a clinically defined episode of care
Fee for service payment	A payment model in which healthcare providers are reimbursed according to each service provided (e.g., office visit, diagnostic test)
Patient centered medical home	A healthcare delivery model centered around primary care with a goal of creating better access to healthcare services, coordinating care and implementing prevention programs.
Pay-for-performance	A model of reimbursement in which healthcare providers are incentivized to achieve better outcomes through incentives for meeting certain quality markers
Population Health Model	An aspect of healthcare redesign focused on implementing prevention programs and maintaining the health of the health plan population, thereby decreasing the eventual need for surgical intervention

To address these concerns, significant strides have been made in the U.S. to reorganize how healthcare is delivered in order to contain costs and improve quality and access. In 2010, President Barack Obama passed the Patient Protection and Affordable Care Act (PPACA). As part of the legislation, healthcare coverage was offered to all Americans through healthcare exchanges and an individual mandate was issued requiring Americans to sign up for health insurance. In addition to expanding access to care, PPACA also introduced measures to change the system of healthcare delivery. In this chapter the changes in healthcare delivery most pertinent to the orthopedic surgeon treating hip diseases are introduced: accountable care organizations (ACOs), bundled payments, and patient-centered medical homes (PCMHs). Novel ways derived as part of healthcare reform for incentivizing providers to improve quality and contain costs are also explored (Table 1.1).

Delivery Models & Reimbursement

Overview of Organized Delivery Models

In order to allow for cost savings through coordination of care, healthcare delivery is transitioning towards centrally planned modes of care delivery [6]. ACOs and PCMHs represent two novel delivery models implemented as part of PPACA that will likely impact the care of diseases of the hip.

The PCMH is primarily a healthcare delivery model centered around primary care with a goal of creating better access to healthcare services, coordinating care and implementing prevention programs. PCMHs are similar in concept to ACOs, the difference between the two is best conceptualized by thinking of ACOs as comprised of many "medical homes" or as ACOs have been dubbed by some: a "medical neighborhood" [7].

An ACO is a healthcare network consisting of various physicians from different specialties, hospitals, and other non-physician healthcare providers that are contracted to provide coordinated care to a group of patients. The ACO is then typically accountable to a third party payer for the cost and quality of care provided to a population of patients. The Centers for Medicare & Medicaid Services (CMS) represent the largest ACO third party payer and are in the process of testing several ACO models. Medicare ACO programs include Medicare Shared Savings Program, Pioneer ACO model, and Advance Payment ACO model. The common goal in all ACOs is to find ways to improve quality and decrease overall costs. For example, as part of the CMS Shared Savings Program, Medicare fee-for-service programs are converted into ACOs that seek to lower their growth in health care costs while meeting performance standards on quality of care. These ACOs then share costs savings resulting from changes in practice with CMS.

In addition to implementing a financial reorganization, ACOs have also introduced a redistribution of healthcare delivery. Because there is increased provider accountability, ACOs incentivize a shift toward provider-led organizations and an orientation toward primary care, management and prevention of medical illness across the entire continuum of the care cycle. Thus, the fiscal responsibility in the management of hip osteoarthritis (OA), for example, may include aspects of the care cycle for which the orthopedic surgeon typically pays less attention such as pre-arthritic hip pain and prevention of progression to end stage hip OA. Similarly, for conditions like avascular necrosis of the hip that progress through a variety of degenerative stages prior to requiring orthopedic intervention, the orthopedic surgeon may begin to play more of an active (in concert with primary care physicians) in prevention of disease progression and disease management.

Incentives in Healthcare Reorganization

Central to the reorganization of how healthcare is delivered is a reorganization of how healthcare providers are reimbursed for their care of patients with certain disorders. Provider payment reform has long been considered a viable method for driving attention to the escalating costs of the U.S. healthcare system [8]. In this section, we outline payment methods resulting from healthcare delivery reorganization.

Traditionally, payment for orthopedic services has been based on a fee-for-service model. Such payment models created an orientation toward increasing the volume and intensity of service provided without necessarily rewarding the value of healthcare delivered. Thus pay for performance (P4P) incentive schemes evolved from

fee-for-service models. These P4P models adopted fee-for-service models and created quality of care related bonuses based on standardized metrics for different aspects of care.

As ACOs have become more widespread, there is now a shift toward "bundled payments" or episode of care payments. Under this payment structure, a single payer provides payment to all providers for all care related to the treatment of a condition, e.g. hip osteoarthritis requiring a total hip arthroplasty (THA). In this example, for a patient presenting with hip OA requiring a THA, providers may receive a fixed payment for an "episode of care," including pre-operative screening, in-patient admission, and the surgery itself as well as early post-operative (e.g., 30 days post-operatively) care, rehabilitation, and management of complications. The onus therefore is on the providers involved in these phases of care to maintain appropriate margins by providing care that is necessary and avoiding non-value-added interventions.

Early evidence for quality improvements and cost savings based on bundled payments has been promising. One of the earliest demonstrations for the impact of bundled payment on hip disease came from the Geisinger Health System (GHS) [9]. GHS physicians developed a program for implementing bundled payment for THA. GHS offered payers a guarantee that procedural and post-procedural costs (including costs related to re-admission) would be inculcated into a global payment scheme. After the introduction of their Provencare program, Geisinger reported a 3.6 % reduction in hospital length of stay, a 58 % reduction in 30-day re-admission, a 49 % reduction in deep venous thrombosis (DVT), and 67 % reduction in pulmonary embolism (PE) rate [8].

Changes in the Care of Hip Diseases

Increased Access to Care

PPACA is largely credited with addressing the large number of uninsured people in the U.S. As such, moving forward there will be a larger number of patients with health insurance seeking appropriate care and obtaining necessary orthopedic services. There is theoretical evidence to suggest that universal access to healthcare coverage leads to increased utilization of orthopedic services. For example, trend data for hip arthroplasty utilization suggests that THA utilization spikes at the point of healthcare eligibility—i.e., at age 65 upon reaching the age of Medicare eligibility [10]. However there is also a theoretical concern that in the new universal healthcare model, the provision of health insurance alone will not achieve the goal of optimizing the musculoskeletal health of the population. Specifically, the vulnerable and under-represented population segments may not benefit equally from expanded healthcare coverage. Disparities in the provision of healthcare services have been well documented [11–13], and there are myriad reasons why vulnerable population segments may not seek medical care even when the access is available [14]. Furthermore, there are other

possible reasons suggesting that even when these population segments seek care they may not receive the care that would otherwise be indicated for them. We briefly discuss some of the disparities in healthcare access for hip disease in order to outline how healthcare reorganization can help address some of these inequalities. Specifically, we use access to THA as a case example. Hip OA is a leading cause of disability in the U.S. and THA is an effective and safe procedure for alleviating pain and restoring physical function. Given the established efficacy, differential access based on race and/or socioeconomics represents a concerning disparity.

There is a well-established evidence base suggesting that there is an underutilization of THA for ethnic minorities and the socioeconomically disadvantaged [15]. Mahommed et al. used a Medicare database to analyze 61,568 patients who had had a primary THA and 13,483 who had a revision THA during a 1-year period. The authors found rates for primary THA were higher for whites than African Americans, and for those with a higher income [16]. Studies such as these suggest that beyond a lack of healthcare access, patient and provider specific reasons may represent potential reasons for consistently lower utilization of THA among vulnerable segments of the population. Patient specific reasons are thought to include lack of recognition of symptoms, a higher threshold for seeking care, ineffective communication of symptoms to providers, unfamiliarity with procedures and lower expectations of post-operative outcome. Some studies have suggested that many of these reasons for underutilization are related to a lack of access to a primary care physician who can play a role in initial referral and can facilitate trust by educating and communicating with patients in a culturally competent manner [15]. As such it is plausible that as healthcare reorganizes around a primary care model, disparities in underutilization of elective procedures may become addressed. However there is a significant onus placed on the primary care physicians, case managers, and care coordinators in this model to work with these populations in order to overcome aforementioned barriers to seeking care and understanding the disease process. Further, in light of the responsibility placed on these providers in the new healthcare models, it is crucially important that providers, payors, and healthcare deliver organizers understand that provider related biases affect patient utilization and access to healthcare services. One study found that both primary care physicians and orthopedic surgeons were less likely to offer joint arthroplasty to women when faced with standardized male and female actors [17]. Another study not directly related to orthopedics found that physicians were less likely to recommend cardiac catheterization to racial minorities who had the same medical history and symptoms as white counterparts [18]. Thus, as access to orthopedic care is expanded to a broader population, it is important to understand that ensuring equal access to care goes beyond enrollment in a health plan.

In addition to issues of underutilization, increased access to health insurance may raise the possibility of *overutilization* of elective procedures. Specific to the management of hip OA, this is an area of potential concern. With the introduction of more durable implants, there has been a recent trend toward increased utilization of hip arthroplasty among younger patients (age < 65 years) [19]. As such, with healthcare

reorganization there will be increased pressure for utilization management in order to judiciously indicate patients for procedures. Musculoskeletal conditions such as hip OA will require orthopedically driven metrics for the management of various stages of disease, e.g. appropriate use of diagnostic and therapeutic interventions, and well-defined criteria for referral to a surgical specialist (more on this in subsequent sections).

Supply Side Crisis

Studies published prior to the introduction of universal healthcare coverage suggested that based on population senescence trends alone that there could be a supply side crisis for joint arthroplasty, i.e. there would not be enough arthroplasty surgeons to respond to the demand for joint replacement [20]. There has yet to be a revised projection incorporating demand based on universal healthcare coverage. As part of any revised projection however the previously projected supply side crisis is likely to become more pronounced. Supply side issues may become even more evident in other non-arthroplasty fields of orthopedic surgery. For example, in conditions like femoroacetabular impingement, which is being increasingly recognized, hip arthroscopy has been utilized to treat this condition at increased rates. Plausibly there may be a future supply side crisis for hip arthroscopists.

The manifestation of supply side crises for hip conditions will likely be increased wait times for surgeon availability. The experience of some European nations may serve as an example, i.e. where significant wait times for specialty care is the norm. In these countries, patients become accustomed to living with chronic conditions until a specialist is available [21]. Further, the affluent population segments seek care out of the insurance system by paying out of pocket in order to gain more immediate access to care. This phenomenon may eventually lead to a socioeconomic tiering of specialty care.

Pressure for Cost Containment

Inherent in shared savings programs is a pressure to identify areas for cost containment, primarily through the elimination of non-value-added services. As such, the processes of healthcare delivery for musculoskeletal hip conditions will evolve to become more cost conscious. There is already a trend toward decreased length of stay (LOS) for many in-patient procedures. In order to decrease LOS for elective procedures requiring inpatient admission, multidisciplinary teams are involved in discharge planning even prior to patient admission. Further, because bundled payments incorporate payments for care provided after discharge, the cost and appropriateness of discharge destinations will become an increased focus of attention. For example, when a patient may appropriately receive post-discharge care at home with visiting services, this option is now more often exercised as opposed to discharging the patient to in-patient rehabilitation.

Beyond just decreasing LOS, some centers have moved toward avoiding an in-patient stay altogether in the management of certain hip conditions. Traditionally, surgeries of the hip have required in-patient hospitalization. However there are now reports of protocols and pathways for outpatient THA in selected patients. Berger et al. originally reported on a protocol for outpatient THA [22–24]. Berger developed and implemented a comprehensive perioperative management protocol that included pre-operative teaching, the use of regional anesthesia for improved pain control, and preemptive oral analgesia and anti-emetics. In addition, a dedicated nurse clinician was on staff to manage patients and respond to clinical issues such as nausea, hypotension, and oversedation that could potentially delay discharge. With the Berger protocol, patients are evaluated post-operatively according to strict criteria which patients are required to meet prior to discharge. Criteria mandate that patients are able to independently transfer into and out of bed to a standing position; patients are also required to rise from a chair to a standing position, walk 100 ft and ascend/descend a flight of stairs. In addition to these physical tasks, patients are required to have stable vital signs, tolerate a regular diet, and have adequate pain relief with oral analgesics alone.

Currently, outpatient THA is not the standard of care in the United States; however as bundled payments continue to spread and hospital systems look for areas of cost saving, there could be increased impetus for same day or brief-stay THA. Before adopting these practices, however, more work needs to be done to investigate the clinical safety and outcomes for these expedited pathways. One prior study by Parvizi and colleagues found that most of the fatal and near fatal complications associated with lower extremity arthroplasty occur during the typical three-day in-patient stay [25]. As such the authors cautioned against early discharge. More work needs to be done to understand the subset of THA patients that can be safely discharged on the day of surgery. Further, formal cost analyses may be warranted to investigate the cost efficacy of these pathways. As Berger concedes in discussion of the same day THA pathways, cost savings from decreased hospital stay may be transferred to personnel costs for intensive pre-operative and perioperative management [23].

Another potential target area for cost containment is an emphasis on the location in which surgical care is delivered. There has been a surge in the utilization of ambulatory surgery centers (ASCs). Procedures performed in ASCs are associated with less cost than those performed in the hospital due to lower overhead, operating expenses, and personnel requirement within ASCs [26, 27]. Thus, when appropriate there will be a pressure to perform hip procedures in ASCs.

Population Health Model

Inherent in the design of ACOs and PCMHs is an orientation toward a Population Health Model (PHM). Healthcare reorganization will introduce a PHM for orthopedic surgery. In theory PHM would work by developing prevention strategies

to maintain patient health and prevent the eventual need for a surgical intervention. We briefly use hip fractures and orthopedic intervention for hip fractures as an example of PHM. In a PCMH or ACO model, the goal would be to decrease the incidence of hip fractures among a group of enrollees. Thus, as part of this program, elderly patients and those deemed to be at high risk would undergo fall risk and bone-density screenings. Orthopedic surgeons, PCPs, and payors would create screening guidelines which would then be implemented by PCPs. Multidisciplinary care pathways to prevent falls and optimize bone density among high risk patients would be developed and implemented with the goal of reducing the incidence of hip fracture and the costs associated with hip fracture surgeries.

In addition to the prevention of illness, a component of PHM inherent in healthcare organization is utilization management. As part of PHM for orthopedics, surgeons and PCPs would collaborate with payors to better understand the source of claims and major cost drivers within a group of enrollees. Together, these parties would then identify claims that can be prevented through more coordinated care. Further, orthopedic surgeons will be called on to create evidence-based clinical practice guidelines and direct the management of musculoskeletal diseases at the primary care level. Orthopedic surgeons will play a greater role in defining appropriate use criteria for diagnostic and therapeutic interventions in musculoskeletal conditions. By developing these criteria, costs can be minimized by eliminating non-value-added diagnostic and therapeutic interventions.

Early Lessons from Real World Examples of Healthcare Reorganization

Several healthcare organizations and hospital systems have redesigned their clinical care pathways in anticipation of healthcare reorganization and changes in financial incentives. Hospital systems have sought to respond to pressures for reorganization through diversification of healthcare services and/or specialization. In this section we describe the healthcare reorganization for two hospitals in California; one focusing on specialization and the other on diversification. Both models of healthcare delivery are viable in the new healthcare environment. Specialization allows hospitals to focus on a few specialized services thereby maximizing efficiency and high quality. PPACA specifically encourages specialization through bundled and episode of care payments for specific service lines. On the other hand, diversification allows for integration and a coordinated approach whereby hospitals and medical groups are able to provide the services for all aspects of a patient's health.

The Hoag Orthopedic Institute (HOI) is a specialty hospital in California that is considered a regional center of excellence. HOI provides specialized care to patients who are already seeking a joint replacement. As such the health system deals less with the pre-arthritic and progressive OA patient population that would be seen in a PHM. This focus is in part because due to the organizational capabilities

of HOI, there is no reward for engaging in chronic disease management. As such healthcare reorganization at HOI focused on improving operational efficiency to maximize the number as well as the quality of procedures done by each surgeon. The secondary goal being to minimize wait time in order to allow for a growth in referral volume. HOI was able to achieve these goals however as noted by Robinson, specialization alone may be insufficient in the current healthcare environment and may require partnership in order to respond to the pressures of inherent in healthcare reorganization [28]. Hoag has now merged with a large multi-hospital system, thereby suggesting that care coordination is integral for the reorganization of healthcare.

In contrast to a specialized healthcare system, The Kaiser Permanente organization has over seven million enrollees in California and represents a highly diversified approach to healthcare delivery. In 2011 Kaiser Irvine was faced with increased wait times for elective surgery and as a result the orthopedics department developed the "Osteoarthritis care pathway" [28]. The pathway focused on patients with intermediate severity of osteoarthritis who were not yet candidates for surgery but who needed pain management, functional assistance, and prevention of disease progression (e.g., weight loss). These functions were considered primarily non-surgical in nature and thus out of the direct domain of the orthopedic surgeon. Kaiser's reorganized diversified clinical pathway thus emphasized the role of nurse practitioners, nurses, physical therapists, and wellness coaches. The overall goal from the health system perspective being to limit the need for surgery in non-end stage arthritics by delaying disease progression, managing symptoms, and limiting the involvement of surgeons in non-surgical processes. The impact of the program was highly positive and it helped to decrease wait times, improve surgeon efficiency, and establish a standardized flow of patients through the care cycle.

These early examples suggest that there are multiple ways in which to respond to the need for healthcare reorganization for the management of hip disease. Going forward, reorganization efforts will need to be institution/health system specific with continuous collaboration and interaction of allied healthcare providers.

Conclusion

ACOs, bundled payments, and PCMHs represent a reorganization of healthcare delivery and payment in the U.S. aimed at improving quality of care and decreasing costs. Orthopedic surgeons will play an integral role in the redesign of healthcare. Specific to conditions of the hip, orthopedic surgeons will be accountable for ensuring increased access, defining appropriateness criteria for both diagnostic and therapeutic interventions, and management of hip disease across an entire spectrum of disease. More than ever before, orthopedic surgeons will be called on to collaborate with primary care physicians, payors, and allied healthcare providers to optimize the value of care we provide to our patients.

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Chapter 2
Prevalence and Societal Burden of Hip Osteoarthritis

Jennifer R. Racine

Introduction

Between 1996–1998 and 2004–2006, the number of individuals reporting a musculoskeletal disease increased by nearly 14 million from the 76 million reported in 1996 [1]. Of the major subgroups of musculoskeletal diseases, arthritis and joint pain have the highest occurrence, reflecting the overall aging population [1]. Arthritis is the most common cause of severe long-term pain and physical disability, and can also affect the psychosocial status of afflicted people as well as their families and careers [2]. From 2007 to 2009 data show that one in nine, or 21 million U.S. adults, had arthritis-attributable activity limitations [3]. OA is the most common type of arthritis and frequently affects the hip. OA of the hips results in pain and stiffness and often leads to significant problems with mobility and disability requiring expensive total hip replacement [4]. OA causes pain and contributes to diminished function reflected in reduced muscle strength, range of motion, and joint instability. Patient-reported outcomes measures have described OA having a major impact on activities of daily living, leading to severe limitations in participation in physical activity, and a decreased quality of life for patients [5].

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Osteoarthritis of the Hip

Prevalence

The prevalence of OA is difficult to determine because *symptoms* of OA (joint pain, swelling, and stiffness) do not always correlate with the *pathology* of OA [6]. The occurrence of pain associated with joint degeneration varies widely among joints and among individuals [7]. The incidence of either radiographic or symptomatic OA increases considerably with age [8–10].

Individuals with advanced degeneration of the joints may have minimal pain and disability, and for this reason, investigations of the prevalence of OA based on evidence of joint degeneration, such as imaging studies or direct inspection of joints, yield larger numbers of affected individuals than do studies that require evidence of joint degeneration and joint pain together for the diagnosis of OA [11, 12]. Recent information on the epidemiology of OA originates from population-based radiographic surveys [13]. Population-based studies in the US suggest prevalence rates comparable to those in Europe, increasing from 1 % for severe radiographic disease among people aged 25–34 to 30 % in those aged 75 and above [13]. In 1997, a study in the Netherlands demonstrated that of the 1040 participants aged 55–65, only 135 (13 %) were free from radiographic evidence of OA [14].

While most studies have focused on information from radiographic OA, there is increasing interest in the prevalence of symptomatic OA. This is important in order to determine the healthcare needs and options for patients. Symptomatic OA affects nearly 27 million Americans and is the leading cause of disability in the US [15, 16].

Using the Johnston County Osteoarthritis Project (JoCo), a longitudinal population-based study of OA in North Carolina, Murphy et al. used a logistic regression analysis to evaluate the lifetime risk of symptomatic hip OA (defined as the proportion of individuals who developed symptomatic hip OA in at least one hip by 85, among those who lived to age 85). They found the overall lifetime probability for developing symptomatic hip OA was 25.3 % (total $n = 3068$, ineligible $n = 321$ women who were <50 years old, eligible $n = 2756$), suggesting that one in four Johnston County residents who live to age 85 are at risk of developing symptomatic hip OA [17]. In another JoCo study, Jordan et al. used weighted prevalence estimates to report contemporary evaluations for four hip outcomes; (1) Hip symptoms, which were assessed separately for right and left sides of the body by the following question: “On most days, do you have pain, aching, or stiffness in your (right, left) hip?” Hip symptoms were defined for analysis as an affirmative response to this question in at least 1 hip; (2) Radiographic hip OA, defined for analysis as Kellgren–Lawrence (K–L) grade of at least 2 in at least 1 hip; (3) Moderate/severe radiographic hip OA, defined as K–L grade 3 or 4 in at

least 1 hip; and (4) Symptomatic hip OA, defined as the presence of hip symptoms in at least 1 hip with corresponding radiographic hip OA in that joint [18]. Jordan et al. reported that of the 2997 participants in their study (total cohort = 3068, missing data $n = 71$), 1078 (36 %) reported hip symptoms, 827 (27.6 %) had radiographic hip OA, 291 (9.7 %) had symptomatic hip OA, and 75 (2.5 %) had severe radiographic hip OA [18]. The prevalence of these four outcomes was consistently and significantly higher for older age groups [18]. Three outcomes (hip symptoms, radiographic hip OA, and symptomatic hip OA) were significantly higher among women compared to men (Table 2.1) [18]. Two outcomes (radiographic hip OA, symptomatic hip OA) were significantly higher among African-Americans than among Caucasians [18]. The prevalence of three outcomes (radiographic hip OA, symptomatic hip OA, and moderate/severe radiographic hip OA) was higher in those aged 75 years or older and occasionally for those aged 65–74, compared to younger ages in both sex and racial groups [18]. Women had greater prevalence of hip symptoms than did men in both racial groups (Table 2.2) [18].

Table 2.1 Weighted prevalence for four hip outcomes, all participants and by selected demographic subgroups, Johnston County Osteoarthritis Project, 1991–1997[a]

Demographic subgroup	Hip symptoms		Radiographic hip OA		Symptomatic hip OA		Severe radiographic hip OA	
	%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
All participants	36.2	34.7, 37.8	27.6	26.3, 28.9	9.7	8.9, 10.6	2.5	2.2, 3.0
Age group								
45–54	30.7	28.5, 33.0	21.2	19.0, 25.1	8.9	7.5, 10.5	1.4	0.8, 2.4
55–64	35.9	33.6, 38.3	23.0	21.1, 25.1	8.9	7.5, 10.5	1.1	0.8, 1.6
65–74	40.7	38.1, 43.4	31.1	28.9, 33.4	10.8	9.4, 12.5	3.6	2.8, 4.6
75+	42.3	38.3, 46.3	42.9	39.2, 46.7	17.0	14.6, 19.6	5.7	4.3, 7.5
Sex								
Men	31.8	29.8, 33.8	25.4	23.6, 27.3	8.3	7.2, 9.5	2.6	2.0, 3.2
Women	39.5	37.7, 41.5	29.5	27.8, 31.3	11.1	9.9, 12.3	2.5	2.1, 3.1
Race/ethnicity								
Caucasian	36.0	34.3, 37.8	26.6	25.1, 28.1	9.2	8.3, 10.2	2.4	2.0, 3.0
African American	37.1	34.9, 39.4	32.1	29.9, 34.4	12.0	10.3, 13.9	3.1	2.5, 4.0

[a]Weighted to the 1990 target population. Radiographic data were available for women only age 50 years and older [Reprinted from Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. The Journal of rheumatology. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. 2009 Apr;36(4):809–15. With permission from The Journal of Rheumatology]

Table 2.2 Weighted prevalence for four hip outcomes, by race/ethnicity, sex, and age group, Johnston County Osteoarthritis Project 1991–1997[a]

Racial/ethnic group	Age	Hip symptoms		Radiographic hip OA		Symptomatic hip OA		Severe radiographic hip OA	
		%	95 % CI	%	95 % CI	%	95 % CI	%	95 % CI
Caucasian									
Men	All	31.7	29.6, 34.0	23.8	21.9, 25.9	7.6	6.4, 8.9	2.5	1.9, 3.3
	45–54	30.3	26.5, 34.3	20.9	17.8, 24.5	6.6	4.8, 9.0	1.7	0.9, 3.5
	55–64	29.7	25.7, 34.0	18.5	15.8, 21.7	5.7	4.2, 7.8	0.9	0.5, 1.8
	65–74	33.5	29.9, 37.4	32.0	27.9, 36.3	8.3	6.2, 10.9	5.8	4.3, 7.9
	75+	40.1	32.7, 47.9	30.9	24.6, 38.0	16.2	11.3, 22.7	1.6	0.8, 3.3
Women	All	39.4	37.1, 41.6	29.1	27.1, 31.2	10.8	9.5, 12.2	2.3	1.8, 3.0
	45–54	30.6	27.6, 33.7						
	50–54			18.5	15.5, 21.9	4.1	2.6, 6.2	1.1	0.4, 3.1
	55–64	39.7	36.3, 43.2	25.1	22.1, 28.3	10.1	8.1, 12.5	1.1	0.7, 1.8
	65–74	45.1	41.2, 49.1	28.7	25.5, 32.1	11.3	9.2, 13.9	1.5	0.8, 2.8
	75+	45.2	39.7, 50.9	47.4	41.8, 53.2	17.6	45.5, 21.2	7.1	5.0, 10.1
African American									
Men	All	32.0	28.5, 35.8	33.2	29.6, 37.0	11.7	9.1, 14.9	2.7	1.7. 4.2
	45–54	26.1	21.0, 32.0	29.3	23.7, 35.6	5.7	3.2, 10.0	0.9	0.4, 2.2
	55–64	35.3	28.4, 42.8	34.2	26.7, 42.6	14.7	8.9, 23.4	1.5	0.6, 3.6
	65–74	41.7	35.7, 48.0	34.1	28.2, 40.6	16.9	12.8, 22.0	5.3	3.4, 8.1
	75+	21.1	12.9, 32.5	43.0	33.3, 53.2	12.9	6.0, 25.5	5.8	1.3, 21.9
Women	All	40.3	37.7, 43.0	31.2	28.2, 34.4	12.2	10.3, 14.5	3.5	2.7, 4.6
	45–54	36.3	32.1, 40.7						
	50–54			21.3	16.0, 27.7	7.8	4.4, 13.4	0.9	0.3, 2.3
	55–64	42.1	37.4, 46.9	23.6	19.9, 27.8	11.6	8.6, 15.5	1.4	0.5, 3.9
	65–74	42.0	37.4, 46.9	37.1	30.8, 44.0	12.3	8.7, 17.2	5.3	3.7, 7.5
	75+	42.1	34.2, 50.5	45.7	39.5, 52.0	17.7	14.0, 22.0	7.3	4.8, 10.9

[a]Weighted to the 1990 target population. Radiographic data were available for women only age 50 years and older [Reprinted from Jordan JM, Helmick CG, Renner JB, Luta G, Dragomir AD, Woodard J, et al. Prevalence of hip symptoms and radiographic and symptomatic hip osteoarthritis in African Americans and Caucasians: the Johnston County Osteoarthritis Project. The Journal of rheumatology. [Research Support, N.I.H., Extramural Research Support, U.S. Gov't, P.H.S.]. 2009 Apr;36(4):809–15. With permission from The Journal of Rheumatology]

Hip Arthroplasty

The most common condition for which total hip arthroplasty is done is severe OA of the hip [19]. In 2011, the National Center for Health Statistics reported that of the 230,144 total hip replacements surveyed, 85.5 % were due to OA [20]. The primary indication for this procedure is severe pain and related restriction in activities of

daily living [19]. To relieve discomfort and increase function of severe symptomatic OA, a hip replacement is an effective and in some cases, an only option. Between 1990 and 2002 the rate of primary total hip arthroplasties per 100,000 persons increased by approximately 50 % [21]. In 2006, total hip replacements, including revision procedures, accounted for 37.6 % of nearly one million inpatient arthroplasty procedures performed [20].

Total hip arthroplasties have been performed in an aging population with end-stage-hip OA. In 2010, Singh et al. reported a correlation between increasing age and increasing incidence of total hip arthroplasty over time [22]. In their population-based study of trends using hip arthroplasty between 1969 and 2008, they found that ages 0- through 49, 50- through 59, and 60- through 69-year age groups, the rate of total hip replacement usage gradually increased. They also reported peaks of utilization in 2005–2008, increasing more than sevenfold, and almost doubling between 1997–2000 and 2005–2008 [22].

Partial Hip Replacement

Partial hip replacement, generally a hemiarthroplasty in which the femoral head but not in the acetabulum is replaced, is performed principally for hip fracture (76 % of cases) [20]. Women have been reported to have higher incidence of fractures due to a greater prevalence of osteoporosis [20]. In 2006, the number of partial hip replacement procedures was estimated to be about 138,000 and 73 % of partial hip replacements were performed on females [20].

Revision Hip Replacement

Revision total hip replacement consumes a disproportionate amount of cost and other resources and involves more morbidity than primary total hip replacement. Using the Healthcare Cost and Utilization Project Nationwide Inpatient Sample database of 51,345 revision total hip arthroplasty procedures performed between October 1, 2005, and December 31, 2006, Bozic et al. found that a greater number of revision total hip arthroplasty procedures were performed on females compared to their male counterparts; 29,252, and 21,979, respectively ($n = 51{,}231$) [23]. They also discovered that 10,370 (20.2 %) patients in whom revisions were done were <55 years old, while the highest number of revisions, totaling 13,858 (27.0 %), were patients 75–84 years old. The oldest age group, 85–99 years old, constituted only 4423 or 8.6 % of revisions ($n = 51{,}315$) [23]. Similarly, Dorey et al. found that younger patients, especially those who are active and place a greater demand on their hip replacements, require greater numbers of revision

surgeries compared to older patients [24]. Geographically, the South (Delaware, District of Columbia, Florida, Georgia, Maryland, North Carolina, South Carolina, Virginia, West Virginia, Alabama, Kentucky, Mississippi, Tennessee, Arkansas, Louisiana, Oklahoma, and Texas) had the highest revision rates 18,867 (36.7 %), compared to the Northeast (Connecticut, Maine, Massachusetts, New Hampshire, Rhode Island, Vermont, New Jersey, New York, and Pennsylvania), 8729 (17.0 %) ($n = 51{,}345$) [23]. The correlation between southern geographic location and higher revision rates could be due to profession, surgeon accessibility, and cost.

Socioeconomic Factors in Hip OA

Socioeconomic factors play a major role in the treatment of hip OA by total hip replacements. Previous investigations have suggested considerable differences among ethnic groups in the utilization of hip replacements, with rates of utilization being higher in whites than among minorities [25–28]. Escalante et al. found recipients of hip replacement less likely to be Hispanic than other hospitalized persons with a similar level of access to care [28]. They believed this under-representation involved factors such as access to health care and low socioeconomic status, among others [28]. According to Lavernia et al., however, African Americans and Hispanics are less likely to undergo a total hip arthroplasty for severe OA [29]. They suggested that minority populations are less likely to perceive any advantage of hip replacement and encounter barriers such as accessibility of surgeons, cost, etc. when considering total joint replacement [29, 30]. Compared to whites having THA or TKA, Hispanics and African Americans have worse preoperative function and an increased incidence of infection-related complications [29, 31, 32].

Educational level influences the prevalence of OA. Cleveland et al. analyzed data on 3087 individuals (68 % Caucasian and 31.8 % African American) from cross-sectional baseline data in the JoCo Project looking for an association between individual and community socioeconomic status (SES) measures with hip osteoarthritis (OA) outcomes based on educational attainment level. Of the 298 participants who had symptomatic hip OA, the mean age was 65.9, 60.1 % were female, 49.0 % had less than 12 years of education, and 54.4 % were considered the medium poverty level compared to the lower and higher poverty levels (18.8 % and 26.8 %, respectively) [33]. For this particular study, poverty was classified into three points of group poverty rates; low (referent), medium, or high community poverty rates [33]. The results of this study also support previous work showing a higher incidence of OA in females, a decrease in the age of patients with OA, and socioeconomic factors, such as education and poverty level correlating with the prevalence of OA.

Using data from the National Health and Nutrition Examination Survey (NHANES-I), Tepper et al. studied the relationship between years of education and radiographic hip OA. Although univariate logistic regression analyses suggested that higher educational level correlated with radiographic hip OA, a multivariate model determined that the relationship's statistical significance was marginal [33, 34]. However, a previous study in Norway reported a greater incidence of self-reported hip OA among those with fewer than 12 years of education [33, 35]. Also using the JoCo study, Murphy et al. suggested that participants with less than a high school education developed hip OA more than other participants [17].

Income has an influence on OA prevalence. According to the Health Care Utilization Project (HCUP), adults residing in high income communities had about 6000 more quarterly hospital discharges for primary hip replacement for OA than did those in the lowest income communities [36]. The greater hospital discharge rates for higher income communities could be multifactorial; ability to pay for surgery either out of pocket, or through insurance is higher with larger income families. Adults residing in the lowest income communities had about 7000 discharges per quarter in 2003, increasing to 12,500 discharges per quarter in 2010 [36]. In 2007, Agabiti et al. evaluated whether economic status affects the rate of having a total hip replacement using a multicity population-based longitudinal study. Analyzing hospital registries from four cities around Italy (Rome, Milan, Turin, and Bologna), they determined that low-income participants were less likely than high-income counterparts to have a total hip replacement, and low income was correlated with an increased risk of acute adverse medical events [37].

The average hospital cost for discharges of primary hip replacement for OA was similar for adults residing in the lowest and highest income communities, increasing from about $13,500 in 2003 to $16,500 in 2010 [36]. However, the average length of stay has decreased for both income levels. According to Steiner, the average length of stay for low income communities in 2003 was higher by 0.6 days than their higher income counterparts [36]. This could be due in part to a higher complication rate. The average length of stay for discharges with primary hip replacement in low income communities had decreased from 5.6 days in 2003 to 4.5 days in 2010, while higher income communities' average length of stay decreased from 5.0 days in 2003 to 4.0 days in 2010 [36]. Even though the length of stay has decreased for both income levels, the hospital cost for discharge has increased. This increase in costs could be due to inflation.

Projections

In 2007, Kurtz et al. performed statistical projections of the number of primary and revision total hip replacements between 2005 and 2030 based on historical Nationwide Inpatient Sample (NIS) data from 1990 to 2003. In 2003, 202,500

Table 2.3 Summary of sensitivity analysis of the projected number of hip and knee arthroplasties with use of models comparing variable prevalence (baseline) with constant prevalence

	Annual number of procedures (in thousands)[a]			
Type of procedure[b]	2005	2010	2020	2030
Primary total hip arthroplasty				
Variable	209 (193–225)	253 (232–273)	384 (339–435)	572 (481–681)
Constant	179 (156–202)	194 (169–219)	236 (205–268)	277 (240–315)
Revision total hip arthroplasty				
Variable	40.8 (34.9–47.0)	47.8 (40.3–56.1)	67.6 (54.0–83.9)	96.7 (72.1–130.0)
Constant	36.0 (29.5–42.6)	38.9 (31.8–46.0)	47.2 (38.3–56.0)	56.6 (45.8–34.5)

[a]The variable prevalence (baseline) and the constant prevalence are based on 1990 to 2003 data from the Nationwide Inpatient Sample

[b]The values are given as the projected value with the 95 % prediction interval in parentheses

[Reprinted from Kurtz S, Ong K, Lau E, Mowat F, Halpern M. Projections of primary and revision hip and knee arthroplasty in the United States from 2005 to 2030. The Journal of bone and joint surgery American volume. 2007 Apr;89(4):780–5. With permission from The Journal of Bone and Joint Surgery]

primary and 36,000 revision total hip arthroplasties were performed [38]. By 2030, the projections for primary and revision arthroplasty using the NIS data could range from two to five times greater than what Kurtz et al. projected (assuming constant surgery prevalence) (Table 2.3) [38]. According to Kurtz et al., the demand for primary total hip arthroplasty was estimated to grow by 174 %, from 208,600 in 2005 to 572,000 by 2030, while the number of revision arthroplasty procedures performed in 2005 was expected to grow from 40,800 to 96,700 in 2030 [38]. This affects both costs to the patient and the hospital.

Societal Impact

Cost of Care

OA is a major contributor to the total economic burden (1–25 % of the gross national product) of western nations [39, 40]. Leigh et al. placed the total annual costs of OA at $89.1 billion and estimated that between $3.4 billion and $13.2 billion of that expenditure was due solely to job-related OA, making job-related OA more costly than asthma and pulmonary diseases, and also more than renal and neurologic diseases combined [41, 42]. Job related injuries are defined as acute and repetitive injuries that are the consequences of job exposures [41].

OA contributes to a decrease in activities of daily living, and quality of life, and an increase in loss of workdays, all of which result in out-of-pocket costs to the patient. The World Health Organization (WHO) has estimated 10 % of the world's

population over 60 years old suffer from OA, 80 % of people with OA experience limitation of movement, and 25 % cannot perform major daily activities [43]. Estimated costs of hip OA are both direct and indirect.

Indirect Cost

The indirect cost refers to personal or family costs incurred such as lost wages, lost productivity, and expenditures resulting from the need for home care and childcare that would otherwise not be incurred [42]. Indirect costs are a large part of the overall economic burden of hip OA. In 2004, it was estimated that the annual indirect costs for OA was US$1760 per person (compared with US$3952 direct annual costs) [42, 44]. Information based on a claims database consisting of five million privately insured individuals put the indirect costs of OA at $4603 per person annually [42, 45]. Bitton reported one study that indicated that indirect costs amount to approximately one third of total costs [42, 44]. One observation reported that of 9933 participants from the Medical Expenditures Panel Survey (MEPS) who have OA, 92 % see physicians during the year, 34 % visit at least one OA specialist, 25 % see an orthopedist, 11 % a physical therapist, and 6 % a rheumatologist [39]. Another study found that OA accounted for 7.1 million (19.5 %) of all arthritis-related ambulatory medical care visits of which 4.9 million were female patients, while 2.2 million male [16]. These visits take time out of work for both the patient and the family member.

Direct Cost

Direct costs are expenses that are directly attributable to, in this case, OA, such as co-payments and fees for surgical treatment. Determining the results of direct costs of OA can be difficult due to diverse patient populations, different payers, different variables calculated, and different treatment locales [42]. One Canadian study from a government health plan found direct costs for OA patients were US$3952 per person per year based on 1999 and 2000 data in the province of Ontario [42, 44]. A study of claims filed with a US managed care plan between 1991 and 1993 compared the medical costs of OA patents with non-OA to determine the additional costs attributable solely to OA [42, 46]. They divided patients into two age groups: <65 years and >65 years [42, 46]. For the <65 years age group total annual costs were $5294, which was $2827 more than non-OA patients. OA patients 65 years or older had overall annual costs of $5704, which were $1963 higher than non-OA patients, suggesting together, OA costs are roughly double those of non-OA patients [42, 46].

Data from a managed care organization, over the course of 1 year starting in mid-1993, calculated direct costs as a combination of medication use, ambulatory care, and hospital care; the annual direct cost for 10,101 OA patients was just $543, while the total cost to the health maintenance organization was $4,728,425 [47]. Nearly half, $2,170,890 (46 %) was for hospital care and a third, $1,509,637 (32 %) was for medications [42, 47]. Treatment cost is higher for OA patients than RA patients due to the prevalence of the disease.

Hospitalization utilization greatly influences direct costs. Since 1992, the average length of stay (LOS) in the hospital following a total joint procedure has declined by 50 % [20]. Rates of discharge to home (routine), short-term/skilled nursing/intermediate care, or other discharge sites vary with age of the population and databases analyzed. According to one study, the mean hospitalization cost of hip and knee replacement procedures, not including charges not routinely billed by the hospital such as physician and prescription costs, increased between 1998 and 2007 by an average 109 % [20]. One-fourth of the growth was seen between 2004 and 2007, in spite of the reported shorter hospital length of stay for the procedures. Partial hip replacements (125 %) have shown the highest levels of increase [20]. Revision hip replacements with a mean increase of 86 % showed the lowest level of per procedure cost increase [20]. In recent years, the average hospital cost for discharges for primary hip replacement for OA has increased over time, from about $13,000 in 2003 to $16,500 in 2010 [36]. The increasing trend is projected to continue in 2011 and 2012, with the average hospital cost projected to be about $18,000 at the end of 2012. Using the Gross Domestic Product (GDP) price index, a cost of $13,000 in 2003 would be equivalent to a cost of $16,000 in 2010 [36]. Therefore, the average hospital cost through 2010 remained relatively constant and consistent with the cost expected by inflation alone [36].

Conclusion

Currently, there is no cure for OA. About 80 % of patients with OA have some degree of movement limitation; 25 % cannot perform major activities of daily living and 14 % require help with routine needs [48]. Treatment includes relieving symptoms and improving function, and can consist of a combination of patient education, physical therapy, weight control, use of medications, and eventually total joint replacement. The prevalence of OA is projected to increase. Females are at higher risk of developing OA, as well as patients who are obese, and socioeconomically disadvantaged. Minorities are more likely to have a higher complication rate after total hip replacement and less likely to have the surgery because of cost, healthcare disadvantages, and perceived barriers. The cost due to OA is also projected to increase. Even though the length of stay for a total hip replacement is decreasing, the direct and indirect costs of hip replacements are increasing for both low and high-income communities. As the societal and medical burdens of OA are growing in prevalence, so are the costs in treating and preventing it.

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Chapter 3
Metabolic Syndrome, Obesity, and Osteoarthritis

Charles Eaton and Roy K. Aaron

Introduction

Patients with OA exhibit a higher than expected prevalence of cardiovascular comorbidities including ischemic coronary disease, cerebrovascular and peripheral arterial disease, and venous thromboembolism [1, 2]. The coincidence of obesity, hypercoagulation, and inflammation in both OA and cardiovascular disease has suggested potentially important linkages between OA and the MS including both inflammatory and coagulation proteins [3]. Patients with OA have higher than average body mass indices and serum procoagulant and inflammatory proteins. Obesity and the MS have been linked to the prevalence and severity of OA including intraosseous vascular pathology, hypertension, atherosclerosis, type 2 diabetes, and insulin resistance. Several studies have suggested that the MS rather than obesity is a greater risk factor for the initiation and progression of OA [4–6]. Some metabolic parameters seen in OA are fairly well defined and are associated with obesity, e.g., insulin resistance and dyslipidemia while others, notably hypofibrinolysis associated with plasminogen activator inhibitor -1 (PAI-1), and inflammatory cytokines, are often not included in the definition of the MS but are probably related and may have particular importance with regard to OA. Relationships among coagulation and inflammatory proteins and articular damage have been well described [7].

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This chapter will review the epidemiologic evidence of an association between MS and OA, data implicating biologic pathways to both MS and OA, and emerging information on structural vascular pathology and OA.

Metabolic Syndrome and Epidemiologic Studies of Knee, Hand, and Hip OA

The MS, characterized by the aggregate of truncal obesity, impaired glucose homeostasis, dyslipidemia and elevated blood pressure, has been shown to predict additional risk of cardiovascular disease beyond traditional risk factors of age, smoking, hypertension, obesity, and diabetes [8]. The explanation for these findings has focused on systemic inflammation including pro-inflammatory cytokines such as tumor necrosis alpha (TNF-α), reduced insulin sensitivity and increased insulin resistance, and adipokines which in turn affect cholesterol efflux and apolipoprotein metabolism and result in elevation in triglycerides and low levels of high-density lipoprotein (HDL) cholesterol. Various definitions of MS have been used with the National Cholesterol Education Program (NCEP) and World Health Organization (WHO) criteria being the most common [9]. WHO criteria require evidence of insulin resistance either by elevated homeostatic model assessment of insulin resistance (HOMA-IR) index, elevated fasting insulin levels or elevated insulin levels in response to a glucose load, plus at least two of the following criteria: arterial blood pressure ≥140/90, plasma triglycerides ≥150 mg/dl, HDL cholesterol <35 in men, and <39 mg/dl in women, obesity defined as body mass index (BMI) >30 kg/m^2 or waist/hip ratio of >0.9 in men and >0.85 in women, urinary albuminuria defined as >20 μg/min [10]. The NCEP defines MS present if three of the following criteria are met: (1) abdominal obesity based on high waist circumference (>102 cm (>40 in) for men and >88 cm (>35 in) for women), (2) elevated blood pressure (≥130 mmHg systolic or ≥85 mmHg diastolic), (3) elevated fasting plasma glucose (≥100 mg/dl), (4) high serum triglycerides (>150 mg/dl), and (5) low HDL levels (<40 mg/dl for men and <50 mg/dl in women) [9].

In the OA literature, various definitions of MS have been utilized. Below is a summary of the studies evaluating MS and knee, hand and hip OA prevalence, incidence and progression and response to arthroplasty.

Cross-Sectional Studies

The occurrence and the progression of OA of the knee have been associated with components of the MS in a population-based study, Research on Osteoarthritis/Osteoporosis Against Disability (ROAD). In this study of 1384 Japanese individuals,

the odds ratio for both occurrence of knee OA increased in a dose–response manner (1 MS component 2.33, 2 MS components 2.82, ≥3 MS components 9.83) compared to no MS components. A similar finding was found for knee OA progression based upon change in Kellgren–Lawrence (KL) grade over 3 years with (1 MS component 1.38, 2 MS components 2.29, ≥3 MS components 2.80) compared to no MS components. Hip OA was not evaluated [6].

For hand OA, a recent cross-sectional study in the Netherlands Epidemiology of Obesity cohort of 6673 participants found weight and fat free mass to be strongly associated knee OA but metabolic factors to be more strongly associated with hand OA [11]. Knee OA was associated with weight and fat-free mass, adjusted for metabolic factors (OR 1.49, 95 % CI 1.32–1.68) and 2.05 (1.60–2.62), respectively. Evaluating only hand OA, MS, adjusted for weight was associated with prevalent hand OA (OR 1.46, 95 % CI 1.06–2.02).

We recently analyzed a cross-sectional sub-sample of $N = 212$ at baseline in the Osteoarthritis Initiative evaluating the association of MS and hand OA defined as a definite osteophyte on two finger joints on at least two different digits. We found MS (defined as three of the following: diabetes, dyslipidemia, hypertension, increased waist circumference) was associated with radiographic hand OA (OR = 1.91, 95 % CI 1.01–3.62) and abdominal adiposity was associated with hand OA with OR = 3.23, 95 % CI 1.01–10.2 after adjustment for BMI.

Prospective Studies

Recently, the Melbourne Collaborative Cohort Study evaluated the association of MS and its components with total knee and hip replacement for OA in 20,430 individuals [12]. With a mean duration of follow-up 6.8 years, there were 660 total knee replacements (TKR) and 562 hip replacements (THR). Each component of MS and presence of MS was associated with TKR, HR = 1.92, 95 % CI 1.59–2.32 for MS, with the strongest association found for central adiposity HR = 3.06, 95 % CI 2.48–3.77. All associations were attenuated once adjusted for BMI, however MS, central adiposity, and hypertension remained statistically significant with HR of 1.24, 1.59, 1.24, respectively. For THR, central adiposity (HR = 1.30, 95% CI 1.08–1.55) and trend for MS (HR = 1.19, 95 % CI 0.95–1.49) was noted. For THR, all associations were attenuated to non-significance once BMI was adjusted for.

The Malmo Diet and Cancer study evaluated 5171 subjects for knee OA defined by arthroplasty or high tibial osteotomy, or hip OA defined by arthroplasty with 12 years of follow-up [13]. They found 80 participants with knee OA and 120 with hip OA using these definitions. For knee OA, MS was associated with incident knee OA, HR = 2.3, 95 % 1.5–3.5 in age and sex adjusted models, with a stronger effect in women HR = 2.9, 95 % CI 1.7–4.9. These estimates changed little adjusting for C-reactive protein (CRP) HR = 2.1, 95 % CI 1.3–3.3, and for women HR = 2.5, 95 %

CI 1.5–3.4 but were significantly attenuated once adjusting for baseline BMI; HR = 1.1, 95 % CI 0.7–1.8, and for women HR = 1.4, 95 % CI 0.8–2.6. For hip OA, MS showed no association HR = 1.0, 95 % CI 0.6–1.5, and for women HR = 1.1, 95 % CI 0.6–1.9 but CRP showed a trend towards increased risk of hip OA; HR = 1.4, 95 % CI 0.8–1.7, and for women HR = 1.6, 95 % CI 0.9–2.9. Adjustment for BMI significantly attenuated these results.

We evaluated the association of MS with knee OA progression in the Osteoarthritis Initiative. MS and joint space width (JSW) were evaluated in 2168 individuals with KL-2 or greater knees. We defined MS score (0–4 at baseline) using gender specific cut points for central adiposity, elevated blood pressure as diagnosed hypertension or blood pressure >130/85 mmHg, presence of diabetes or impaired glucose homeostasis, and dyslipidemia requiring hyperlipidemia medications. The progression of knee OA was defined by repeated measures of medial JSW at a fixed point using a semi-automated computer algorithm. Increasing MS scores were associated with increased narrowing of JSW at 48 months in gender specific models. Least Square (LS) means of ΔJSW for 0, 1, 2, ≥3 MS elements were: 0.44, 0.57, 0.57, 0.66 mm in men (P trend = 0.006) and in women, LS mean of ΔJSW 0.47, 0.59, 0.57, 0.66 mm (P trend = 0.003). Adjustment of age, race, and baseline KL grade diminished these associations but remained significant for 2 or MS elements compared to none, but the test for trend became non-significant. Adjusted LS Mean ΔJSW by MS score were 0.30, 0.37, 0.46, 0.38 mm in men and in women, LS mean of ΔJSW were 0.28, 0.34, 0.41, 0.33 mm.

Response to Arthroplasty

The association of MS and functional outcomes after hip and knee replacement surgery has also been evaluated [14]. Ghandhi et al. evaluated 677 consecutive primary knee and hip replacements and found that increased numbers of MS risk factors were associated with worse Western Ontario and McMaster Universities Arthritis Index (WOMAC) scores at baseline and one year post operative but also found that individual metabolic factors to be stronger predictors. For hip OA, hypertension and obesity were predictors of worse outcomes while for knee OA, obesity was the strongest risk factor.

In summary, there is increasing evidence from the above epidemiologic studies of a complex relationship between MS, its components and OA that needs further investigation. Much previous work has been associated with obesity and its effect on mechanical loading of the joint, overuse patterns and development of OA, but more recent evidence suggests metabolic factors associated with obesity (adipokines, inflammation, altered innate immunity, insulin resistance, glucose toxicity, lipid peroxidation, oxidative stress, endothelial dysfunction, angiogenesis) are associated with a range of biologic pathways linked to cartilage, synovium and subchondral bone are equally important in the pathogenesis of OA. Below we describe these biologic pathways and present evidence for these associations.

Animal and Human Studies of Biologic Pathways Linking MS and Its Components with OA

Chondrocyte Biology

OA is characterized by alterations in chondrocyte proliferation and differentiation as well as synthesis of extracellular matrix (ECM) components. In early OA, there is evidence of increased chondrocyte proliferation and synthesis of collagenous proteins. Also noted are increased proliferation of proteinases, growth factors, cytokines and other inflammatory mediators. These factors are thought to be an attempt by chondrocytes to regenerate ECM when stressed. Catabolic mediators include metalloproteinases and inflammatory cytokines, interleukin (IL)-1β, IL-17, IL-18, and TNFα. Anabolic mediators include transforming growth factor-beta (TGF-β), insulin growth factor-1 (IGF-1), fibroblast growth factors (FGF), and bone morphogenetic proteins (BMP). Recent genomic and proteomic profiling of early OA lesions show that they are inflammatory and have a cytokine milieu parallel to MS [15]. Chondrocytes are metabolically active and exhibit cellular activities related to fatty acid and cholesterol efflux, glucose transport, and mitochondrial and oxidative energy metabolism. These are the same metabolic pathways associated with MS, thus providing a potential pathophysiologic link between OA and MS.

Inflammation

Recent evidence suggests that inflammation plays an important role in OA. Macrophages play a central role in OA and are known to produce pro-inflammatory cytokines (IL-6, IL-8) that have been implicated in pathogenesis of OA. A similar cytokine profile (elevated IL-6, IL-8) is found in adipocytes in the setting of MS. Elevated levels of intra-articular IL-6 have been documented [16, 17]. IL-1 and TNFα are associated with OA and are known to modulate chondrocyte expression of proteases leading to ECM breakdown and cartilage loss. TNFα receptor polymorphisms have recently been associated with OA [18]. Several studies support the hypothesis that more active inflammatory responses are associated with more severe OA. One study demonstrated two distinct subgroups of OA patients based on gene expression profiles of peripheral blood leukocytes [19]. The group with elevated IL-1 levels ("IL-1β signature") had more pain, decreased function, and radiographic progression of OA [20]. In a post-traumatic OA mouse model, elevated joint levels of IL-1α and β and TNFα were associated with more severe OA [21]. Other pro-inflammatory factors including S100 proteins have been found in synovium of patients with OA and can stimulate the release of inflammatory cytokines including IL-6 and IL-8 [22].

Triglyceride and HDL Cholesterol and OA

Lipid abnormalities may play a role in OA pathogenesis. Total cholesterol and triglyceride levels have been found to be associated with new bone marrow lesions [23]. Genes regulating cholesterol efflux associated with HDL and triglyceride metabolism have reduced expression in human OA cartilage that is reversible with treatment affecting these same pathways [15]. Patients with knee OA have lower paraoxonase and arylesterase activities as well as low HDL levels suggestive of oxidative stress which has been implicated in not only atherosclerosis via lipid peroxidation but also on chondrocyte viability [24].

Hypertension and OA

Hypertension and OA are both common conditions and therefore an apparent association may be found just by co-existence of two common conditions. However, more recent data suggest otherwise. It is hypothesized that nitric oxide, endothelial function, and angiogenesis may provide a common pathway for the association. Namely, hypertension leads to endothelial damage and dysfunction that leads to both angiogenesis and/or reduced local blood flow to subchondral bone which in turn leads to OA [25].

Diabetes Mellitus and OA

Diabetes mellitus is hypothesized to be associated with OA pathogenesis through both glycolytic and oxidative pathways affecting chondrocytes. OA chondrocytes in the setting of high glucose concentrations downregulate glucose transporter-1 (GLUT-1) which leads to elevated reactive oxidative species (ROS) [26]. Elevated ROS are known to aggravate catabolic processes associated with OA. ROS leads to damage of mitochondrial DNA and impair mitochondrial repair function [27].

BMI, Adipokines, and OA

BMI is associated with OA both through mechanical loading on joints but also via metabolic pathways. A variety of adipokines are associated with obesity including pro-inflammatory adipokines: leptin, retinal binding protein-4, resistin, and anti-inflammatory adipokines: adiponectin, secreted frizzled –related protein-5, and vaspin. Among these adipokines, the most studied biomarker in relation to OA is leptin. Osteoblasts and chondrocytes both synthesize leptin which binds to receptors on articular cartilage. Synovial fluid levels of leptin correlate with BMI and OA

severity [28]. OA osteoblasts have elevated leptin production that is associated with subchondral sclerosis, a prominent feature of OA. Leptin is associated with catabolic functions in cartilage. It is known to induce the production of IL-1β, matrix metalloproteinase 9 (MMP-9), and MMP-13, all associated with cartilage degradation. It also induces the synthesis of IGF-1, TGF-β, and nitric oxide, IL-6 and IL-8, all associated with an enhanced inflammatory milieu [29, 30]. We recently analyzed the National Health and Nutrition Examination Survey (NHANES III) dataset and found a strong association between leptin and symptomatic hand OA in obese participants (OR = 6.1, 95 % CI 1.7–22.2).

Association of Adiposity Phenotypes and OA

Rather than focusing on MS itself, some investigators have evaluated adiposity as the primary risk factor for chronic diseases (diabetes, cardiovascular disease, OA) and then attempted to look at sub-phenotypes [31]. We evaluated the effect of any MS-like features (dyslipidemia, diabetes, or hypertension) on BMI in the Osteoarthritis Initiative at baseline. Compared to normal weight with no MS features those with obesity with and without MS were of similar ages, slightly more likely to be male, had more prevalent and severe (KL-3 or 4) knee OA and had greater knee pain and disability (Table 3.1). Within the obese category, those with MS had more prevalent knee OA but not more severe knee OA. The obese subjects with MS-like features had greater knee pain and disability. These findings are consistent with the hypothesis that obesity with metabolic derangements is associated with greater local painful phenomena (inflammation, venous outflow obstruction,

Table 3.1 Metabolic obesity and prevalent knee OA

	BMI < 25		BMI 25–29.9		BMI 30 or greater		*P*-value	*P* = value of trend
	No MS	One MS	No MS	One MS	No MS	One MS		
N	640	493	723	1109	475	1229		
Age	58.2	65.4	57.9	65.6	61.4	57.8	<0.001	0.17
Gender (% F)	70	68	54	49	61	58	<0.001	<0.001
BMI	22.6	22.9	27.1	27.6	33.2	33.8	<0.001	<0.001
KL-Grade								
0–1	75.5	67.6	61.9	54.7	51.9	41.6	<0.001	<0.001
2	17.7	19.4	24.4	25.7	31.0	33.9	<0.001	<0.001
3–4	6.7	12.9	12.9	13.7	19.6	17.1	<0.001	<0.001
WOMAC								
Pain	1.33	1.67	1.91	2.32	2.67	3.17	<0.001	<0.001
Disability	4.08	5.68	5.74	7.70	8.99	11.11	<0.001	<0.001

hypoxia) which lead to greater pain and disability even in the setting of increased joint loading from obesity.

Vascular Pathology in OA

Arterial cardiovascular disease is an important structural end product of the MS. A concordance of OA and arterial disease would suggest mechanisms common to OA and arterial inflammation and might suggest potential new therapeutic approaches.

Cardiovascular Comorbidities in OA

Epidemiological and observational evidence suggests associations among OA and systemic and skeletal vascular pathology and hypercoagulability [32]. Patients with OA of the hip exhibit a high prevalence of vascular comorbidities. In a cohort of 1000 patients undergoing hip replacement, 550 (55 %) had a cardiovascular, peripheral vascular, or respiratory comorbidity [1]. Of 660 cases of unilateral, atraumatic OA, 65 % had hypertension, 40 % had arteriosclerotic cardiovascular disease, and 10 % had arteriosclerotic peripheral vascular disease. Seventy-eight percent had elevated BMI and this was associated with the prevalence of comorbidities ($p<0.001$). Other studies as well have indicated associations among obesity, vascular disease, and OA [33–35]. One study reported that among 241 patients with OA, 75 % had clinically relevant cardiovascular symptoms [2].

Association of OA and Peripheral Vascular Disease

An association between OA and atheromatous vascular disease has been suggested [3]. A study of 5650 individuals found an association in women between OA of the knee and carotid wall thickness with an adjusted odds ratio of 1.7 ($p<0.05$) and a lesser, but significant, association between OA of the hand and carotid atheromatous plaque in women with an adjusted odds ratio of 1.4 ($p<0.001$) for distal interphalangeal joint, and 1.5 ($p<0.05$) for metacarpophalangeal joint, OA. No associations were demonstrated in men and other associations, e.g. hip OA, were not observed [36].

Of interest in peripheral vascular disease is intima-media wall thickness (IMT) as a measure of vascular damage, and flow patterns, expressed as volume (ml/min) or peak systolic velocity (cm/s). Our clinic studied 40 lower extremities in 20 patients with established OA of the knee with Doppler ultrasound for arterial blood flow volume and velocity (Fig. 3.1). Color Doppler sonography was performed bilaterally with a GE Logiq 9, 9 MHz transducer. Color Doppler imaging was used to

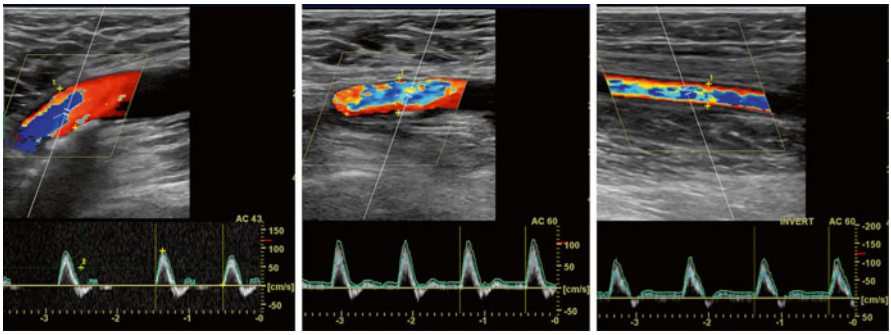

Fig. 3.1 Common femoral artery flow volume and IMT (*Left* = 614.7 ml/min; 0.99 mm *Center* = 418.3 ml/min; 0.70 mm. *Right* = Superficial femoral artery flow)

measure common femoral, superficial femoral, and popliteal artery flow volume (ml/min) and flow velocity (cm/s). Common femoral, superficial femoral, and popliteal IMT was measured with B-mode duplex scanning as an assessment of arterial damage. The IMT was defined by two parallel echogenic lines that corresponded to the lumen-intima and the media-adventitia interfaces. An increased IMT is a hallmark of arterial wall disease associated with atherosclerosis.

Reported studies of arterial *wall thickness* have been inconsistent. One study found no changes in femoral or popliteal wall thickness with OA [37]. Another study reported an association between generalized OA and popliteal artery wall thickness. This study, of 42 patients with symptomatic generalized OA, defined as two or more different sites (hand, spine, hip, knee), and 27 individuals without symptoms or radiographic OA, examined popliteal artery wall thickness by magnetic resonance imaging (MRI). Compared to a mean arterial wall thickness of 0.96 mm. in normal individuals, OA patients exhibited a mean wall thickness of 1.09 mm [38]. Our data is consistent with this study showing a mean (± SEM) popliteal arterial wall IMT of 1.8 ± 0.1 mm in patients with OA of the knee.

Observations of *arterial flow patterns* of the lower extremity have been reported in 39 female patients with OA of the knee with variable but suggestive results [37]. Notably, peak systolic velocity and flow volume were higher than normal in the external iliac and superficial femoral arteries but not in the common femoral arteries in patients with OA. Flow measured by velocity or volume was not different between OA and normal individuals in vessels distal to the femoral artery. Vessel diameter was smaller in OA compared to controls without OA in the popliteal, anterior tibial, and posterior tibial arteries. Data from our clinic has demonstrated significant increases in common femoral, superficial femoral, and popliteal artery flow volumes in patients with OA of the knee (Table 3.2). Although these data are emerging and confirmatory studies are needed, these initial studies suggest an association of structural vascular disease with OA.

Table 3.2 Blood flow

Blood flow (ml/min) in OA of the knee ($\bar{x}$ ±SEM)			
	CFA	SFA	Popliteal
OA	745±56	345±18	226±15
Normal [39]	284±21	152±10	72±5
P	<0.001	<0.001	<0.001

Hypercoagulation in OA

Hypercoagulation has been suspected in OA due to both thrombophilia and hypofibrinolysis. In patients with OA an increase in factor VIII, elevated D-dimer, euglobulin lysis times, and PAI-1 have been described in association with relative hyperlipidemia consisting of hypercholesterolemia and hypertriglyceridemia [40]. These observations are consistent with a pro-thrombotic state in OA. Elevated plasma lipids enhance platelet sensitivity to aggregating agents and this has been proposed as a significant pathway for increased PAI-1 activity in OA [40]. PAI-1 blocks the cleavage of plasminogen to plasmin and is the major regulator of fibrinolysis. Systemic elevations in PAI-1 observed in OA are associated with systemic hypofibrinolysis and contribute to hypercoagulability.

To examine the relationship of obesity to activation of the PAI-1 gene, genetically obese diabetic mice lacking the PAI-1 gene were used to test the hypothesis that elevated PAI-1 contributes to the hyperglycemia, hyperinsulinemia, and insulin resistance associated with the obese and diabetic phenotype [41]. Lack of PAI-1 reduced adiposity and improved hyperglycemia and hyperinsulinemia associated with obesity. Lack of PAI-1 also reduced TNFα expression. TNFα is a major inflammatory mediator in OA. Since TNFα can be produced by adipose tissue, these observations provide substantial linkages among obesity, hypofibrinolysis, and inflammation, and may be relevant to the association of MS and OA.

Inflammation and coagulation are intimately linked and activation of both coagulation and fibrinolytic pathways in arthritic joints are linked to articular inflammation [42]. Fibrinolysis is activated during joint inflammation as shown by a correlation of CRP, D-dimer levels, and plasminogen activators [42]. The inflammatory cytokine, IL-1, a key cytokine in the pathophysiology of OA, induces thrombin formation and increases PAI-1 [7]. Coagulation of whole blood is a stimulus for the production of IL-1 and this may be a mechanism by which thrombosis promotes inflammation [43]. Fibrin and fibrinogen degradation products have been shown to induce the expression of cytokines important in the pathogenesis of OA including IL-1 and TNFα [7, 44]. Inflammatory and coagulation proteins have deleterious effects on articular cartilage. Thrombin induces aggrecan release from both normal and OA cartilage [45]. Components of the fibrinolytic pathway, plasminogen, plasminogen activators, and plasmin have been found in increased concentration in OA

cartilage and are capable of activating MMPs and contributing to cartilage matrix breakdown [46]. Fibrin formation during inflammation is also catabolic to cartilage matrix.

Aside from direct effects of coagulation and inflammatory proteins on joint tissues, it has been speculated that changes in the physicochemical environment of subchondral bone may have direct regulatory effects on OA osteoblasts and that bone may emerge as a therapeutic target [25, 32]. Alterations in the circulation of OA subchondral bone consist of venous stasis and intraosseous hypertension and have been termed a "venous outlet syndrome" [47]. Decreased perfusion results in local hypoxia and reduced interstitial fluid flow. Osteoblasts are sensitive to their physicochemical environment and, in response to changes in pressure, fluid flow, and oxygen concentration, alter their expression of cytokines relevant to OA [48–50]. Notably, OA osteoblasts can degrade cartilage matrix and alter chondrocyte phenotype [51–53]. OA chondrocytes co-cultured with OA osteoblasts express less SOX9, type-2 collagen, and PTHrP, downregulate aggrecan, and upregulate MMP expression [54, 55]. In these ways, the effects of changes in arterial and venous circulation, coagulation proteins, inflammatory cytokines, and adipokines may be mediated by OA osteoblasts and play pathophysiologic roles in OA providing mechanistic linkages among obesity, hypercoagulability, and inflammatory components of the MS and OA.

We have studied hypercoagulation due to both thrombophilia and fibrinolysis in 40 patients with histologically proven OA of the hip compared to an age, gender, and BMI-matched cohort of 25 patients without OA. Proteins C and S, resistance to activated protein C, factor V_{Leiden}, lipoprotein A, antiphospholipid antibodies, lupus anticoagulant and LA (lupus anticoagulant) ratio were measured to assess thrombophilia; PAI-1 and tissue plasminogen activator were used to assess fibrinolysis. The presence of circulating antiphospholipid antibodies, anticardiolipins and lupus anticoagulant is associated with an increased incidence of venous and arterial thrombosis. These antibodies react against β-2 glycoproteins in cell membranes and activate clotting factors on platelet membranes. Mean values for LA ratio were 1.12 ± 0.02 in OA patients compared to 0.5 ± 0.01 in normal subjects ($p = 0.001$) (Fig. 3.2); the prevalence of abnormal lupus anticoagulant and LA ratio was 8/40 (20 %) in OA patients compared to 0/25 (0 %) in normal subjects ($p = 0.005$). The prevalence of anticardiolipins in normal subjects was 1/25 (4 %) while OA patients had a prevalence of 12/40 (30 %) ($p = 0.002$). Measures of risk and precision are displayed in Table 3.3. Impaired fibrinolysis was suggested primarily by elevated PAI-1. Mean levels of PAI-1 were 55.7 ± 6.8 in individuals with OA compared to 30.2 ± 3.6 in normal subjects ($p = 0.003$) (Fig. 3.2). The presence of elevated PAI-1 and LA ratio was highly specific, and had high positive predictive value, but was not sensitive, for OA. The prevalence of PAI-1 abnormalities was 21/40 (53 %) in individuals with OA compared to 7/25 (28 %) in normal subjects ($p = 0.005$). Together, these data indicate a greater prevalence of hypofibrinolytic and pro-thrombotic proteins in OA patients compared to normal subjects.

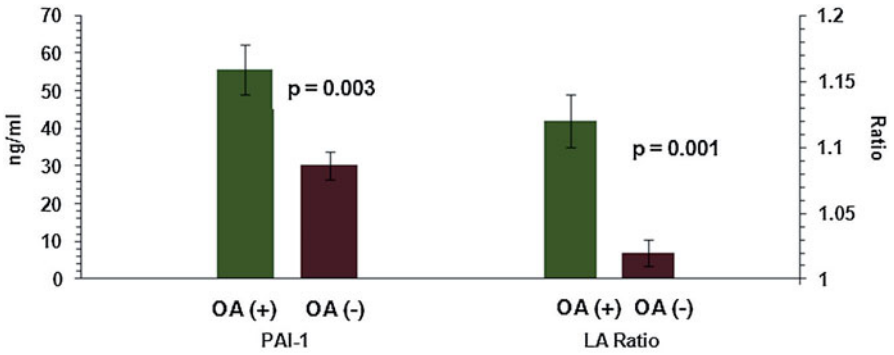

Fig. 3.2 Hyperfibrinolysis and thrombophilia in OA. Significant elevations in PAI-1 and LA ratio are seen in OA patients compared to non-arthritic control subjects (Mean ± SEM)

Table 3.3 Risk and precision of the association of PAI-1 and LA ratio with OA of the hip

	PAI-1	LA ratio
Relative risk	1.7	2.1
Odds ratio	10.3	38
Sensitivity	30 %	43 %
Specificity	96 %	100 %
PPV	92 %	100 %
NPV	46 %	52 %

Significance of Observations on Vascular Pathology and OA

These data suggest an association of arterial wall thickness and blood flow, which are markers of atherosclerosis, with OA of the knee. Markers of thrombophilia and hypofibrinolysis are elevated in OA. These observations raise questions of effects of common mechanisms of inflammatory and coagulation proteins in both OA and atherosclerosis. The observations are consistent with a growing body of evidence that OA may be linked to aspects of cardiovascular disease and the MS and may be related to atherosclerosis. Decreased venous outflow, venous stasis, relative hypoxia, angiogenesis, and inflammation have been observed in subchondral bone in OA. Hypoxia is a profound stimulus to vascular endothelial growth factor (VEGF) and VEGF-mediated angiogenesis and chondrocyte hypertrophy [56, 57]. Subchondral angiogenesis may be involved in breaching the calcified cartilage zone and contributing to cartilage degeneration [58]. While speculative, given the known responsiveness of osteoblasts to their physicochemical environment, the significance of circulatory changes in OA may be in alterations induced in the expression of cytokines that are related to cartilage breakdown and bone remodeling. These structural events may be mediated by proteins of the coagulation and inflammatory pathways, notably by IL-1 and TNFα, important in the pathophysiology of OA.

Conclusions

The association of OA with obesity, vascular disease, type-2 diabetes, and intraosseous vascular pathology suggests linkages between OA and MS [32]. Epidemiologic studies have collectively shown strong associations between components of MS and clinical OA. OA is a complex disease involving all tissues of the joint—bone, cartilage, synovium, capsule, and surrounding muscle—and it is not surprising that many potential mediators have been suggested contributing to pain and functional joint compromise. Prominent among them are inflammatory and coagulation proteins which themselves are linked by common biochemical pathways. A variety of adipokines are associated with obesity and OA including pro-inflammatory adipokines. Notably, leptin has a number of deleterious effects on bone and cartilage and has been associated with symptomatic OA. Another observation of interest is the hypercoagulability associated with OA. Cardiovascular disease is an important structural component of MS. A concordance of OA and arterial disease suggests mechanisms common to OA and arterial inflammation and might suggest potential new therapeutic approaches. This chapter has reviewed the emerging basic science, clinical and epidemiologic data regarding MS and its associated changes in inflammation, fibrinolysis and coagulation, cellular hypoxia, cytokine milieu, arterial and venous outflow as they affect OA and its symptoms. These lines of research need further exploration and confirmation but hold the promise of better defining future targets for therapy for this disabling disease process.

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Chapter 4
Biomechanical Considerations in Arthritis of the Hip

Agnes G. d'Entremont, Lawrence L. Buchan, and David R. Wilson

Introduction

Biomechanics plays a role in the etiology of hip arthritis and in its treatment. The objective of this chapter is to summarize our current understanding of hip biomechanics as it relates to arthritis.

Biomechanical Quantities and Their Importance

Biomechanics includes many quantities that are important in describing elements of hip function.

Kinematics describes movement of the joint. Range of motion is often used to summarize kinematics, and is important as an indicator of hip function, since the

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hip's substantial range of motion in all three anatomical planes is required for normal body movement. Reductions in range of motion are important because they may limit activity, and also because they may be signs of mechanical disruption at the joint itself which has further consequences on joint function, such as impingement of the femur on the acetabulum.

Resultant force on the hip and its line of action affects function as well. For example, there is a strong relationship between hip forces and muscle forces.

Stress describes how forces are distributed within a material, such as cartilage or bone. Contact stress describes how forces are distributed in a region of contact, such as between femoral and acetabular cartilage. Abnormal contact stress is widely believed to predispose a joint to osteoarthritis [1].

Joint fluid pressure is measured within the joint's synovial fluid, which is sealed in by the acetabular labrum. Loading the hip increases the pressure in this fluid, which plays a role in distributing load across the cartilage surface. Loss of pressure may reflect damage to the labral seal and disrupted patterns of contact stress.

Methods of Biomechanical Assessment

Biomechanics can be assessed using ex vivo experiments, in vivo measurements, and mathematical models. Each approach has strengths and limitations.

Biomechanics is studied ex vivo by instrumenting cadaver hips and then subjecting them to simulations of physiological movement and loading. The key advantage to this approach is that many mechanical quantities of interest—such as kinematics, resultant force, and contact stress—can be measured. A leading limitation of this approach is that substantial simplifications of the dynamic nature of activity are usually required (such as limited numbers of muscles, static postures, and limited ranges of motion).

Biomechanics is studied in vivo by making measurements in living participants. Motion analysis systems measure movement of the limb segments and external forces. Instrumented prostheses measure resultant force at the hip during activity. The key advantage of in vivo approaches is that measurements are made during real physiological activity. Two leading limitations of this approach are that many important mechanical quantities, such as contact stress on the cartilage surface, cannot be measured in vivo, and deformities and disorders cannot be simulated.

Mathematical models predict hip biomechanics from inputs such as joint geometry and mechanical properties of tissues. A key advantage of this approach is that a broad range of disorders and treatments can be simulated. The leading limitation of models is that many simplifications of joint properties must be made, and the impact of these simplifications on model predictions is often not known. Model predictions may therefore be poor reflections of hip biomechanics in vivo.

Biomechanics of Stabilizing Structures

The acetabular labrum is frequently torn. The biomechanics of the labrum and other stabilizing structures have been studied because of potential links between labral tears and osteoarthritis.

Range of Motion and Stability

Simulated circumferential and radial tears of the labrum did not affect the stability ratio (peak dislocation force/compressive force) in 22 cadaver hip specimens [2], but substantial labrectomy significantly decreased the stability ratio. Large circumferential tears of the labrum increased strain (reflecting increased stress) in the anterior labrum for combined anterior and compressive loads, while radial tears decreased strain in the anterior and anterior-superior labrum.

Sectioning the iliofemoral ligament increased external rotation and anterior translation in response to a standardized torque in 15 cadaver specimens [3], which led the authors to conclude that this structure plays a significant role in limiting external rotation and anterior translation of the femur.

Sectioning the labrum alone did not increase external rotation in response to a standardized torque [3] in 15 cadaver hips, but both external rotation and anterior translation were larger when both the labrum and the iliofemoral ligament were sectioned than when the iliofemoral ligament alone was sectioned, leading the authors to conclude that the labrum provides a secondary stabilizing role for external rotation and anterior translation. The impingement test (combined flexion, adduction and internal rotation) increased strain (reflecting increased stress) in the anterolateral labrum in 12 cadaver specimens [4], and other tested postures produced strain changes in other parts of the labrum. In a study of seven cadavers, five different loading maneuvers all produced strain in the anterosuperior part of the labrum. Maximum strains averaged 13.6 % in the axial direction and 8.4 % in the circumferential direction [5].

Pressure and Stress

In three loaded cadaver hips, resecting the labrum reduced the fluid pressure in the joint and speeded up cartilage compression, suggesting that the labral seal plays a key role in normal force distribution in the joint [6]. In an MRI study of six cadaver hips, labral repair caused a 2 % decrease in mean cartilage strain (reflecting contact stress) compared to a torn labrum, and labral resection caused a 6 % increase in maximum cartilage strain compared to labral repair [7]. These

findings suggest that the labral seal should be preserved whenever possible, and that its disruption may predispose the joint to osteoarthritis by increasing contact stress on the joint.

Biomechanical Effect of Problems in Acetabular Coverage

Developmental Dysplasia of the Hip

Developmental dysplasia of the hip (DDH) is a condition where the infant hip is dislocated and can be reduced, or can be provoked to dislocate, and has primarily acetabular anatomic abnormalities [8]. DDH is characterized by poor coverage of the acetabulum over the femoral head [9]. This condition is associated with early hip osteoarthritis.

Range of Motion

In an experimental study of hip range of motion, hips with unreduced developmental dysplasia (four hips) had slightly higher internal/external rotation ROM (combined with flexion/extension), and slightly lower abduction ROM, compared to a group of 325 normal children (Fig. 4.1) [10].

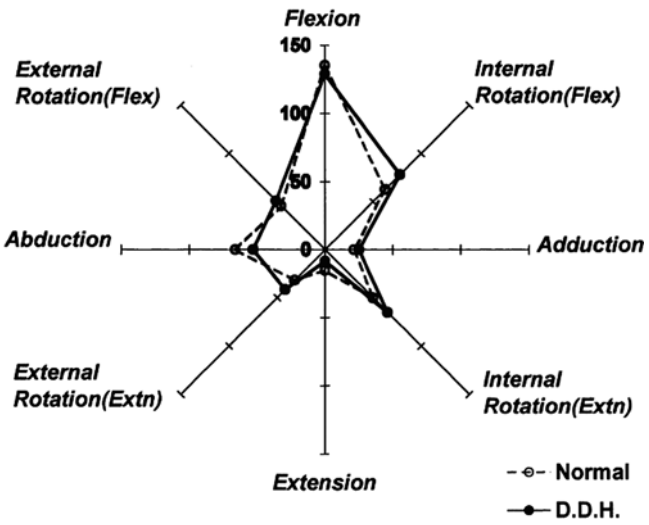

Fig. 4.1 Measured range of motion in normal children and children with DDH. [Reprinted from Rao KN, Joseph B. Value of Measurement of Hip Movements in Childhood Hip Disorders. J Pediatr Orthop [Internet]. 2001;21(4):495–501. With permission from Wolters Kluwer Health.]

Stress

Generally, the results from mathematical models show that higher hip contact stress is associated with more severe deformity and less positive outcomes. Increased deformity was associated with increased peak contact stress (Severin 1a and 1b: 2.3 MPa; Severin 2a and 2b: 2.4 MPa; Severin 3: 4.6 MPa) in a study using models whose geometry came from AP radiographs for 35 patients [11]. Peak stresses in both the femur and acetabulum increased with increasing deformity [12] in a study using a three-dimensional finite element analysis (FEA) of a CT-based normal hip joint model which was deformed to simulate three severities of DDH. Peak contact stress increased in hips with less acetabular coverage when the abductor muscle force became more vertical in models of dysplastic hips based on modifications to normal 2D models created from AP radiographs [13].

A study that used planar models from X-rays combined with duration of follow-up (mean 29 years) to calculate accumulated stress over time in 89 DDH hips identified a damage threshold of 10 MPa-years, finding that 80.9 % of all hips below the threshold had good outcomes based on Severin classifications, and 90.4 % of all hips above the threshold had poor outcomes [14]. Two non-uniform contact stress models based on longitudinal radiographic information from the same 89 DDH hips showed an association between higher loads and worse clinical outcomes, although the damage thresholds (based on clinical outcomes) were very different for the two models (2.0 MPa versus 4.5 MPa) [15].

Mathematical models have shown that various osteotomies used to treat DDH reduce peak stress or contact stress. Models based on radiographs showed that the Tonnis osteotomy for insufficient coverage and avascular necrosis of the femoral head reduced peak normalized contact stress by 55.9 % (peak stress/BW) in 75 patients [16]. A 2D model showed that triple osteotomy of the innominate bone decreased contact stress and increased contact area, although not to the level of normal controls [17]. A 3D model showed that the Bernese periacetabular osteotomy for residual dysplasia increased the normalized resultant hip force but reduced the peak contact stress normalized by BW from 5.2 to 3.0 kPa/N due to increased coverage [18]. Better long-term clinical outcomes were observed in hips with lower postoperative normalized peak stress [18]. The same 3D FEA model mentioned above was used to simulate a Bernese periacetabular osteotomy in each severity level of DDH. Peak stresses were found to decrease with osteotomy in both the femur and acetabulum, although none were reduced to the level of the normal model, and more severe deformity was associated with higher stress following osteotomy [12].

Force

Salter osteotomy reduced the measured resultant joint force on the hip from 2.7 BW (583 N) to 1.2 BW (266 N) in a plastic model of a patient's DDH joint created with rapid prototyping [19]. Mean gluteus maximus force was similarly reduced from 0.46 BW (100 N) to 0.24 BW (52 N).

General/Focal Acetabular Overcoverage

General acetabular overcoverage is characterized by a very deep acetabulum or circumferentially prominent acetabular rim [20]. Coxa profunda and protrusio acetabuli are defined by overlapping of the ilioischial line medial to the acetabular fossa or femoral head, respectively, on an AP radiograph. A center-edge (CE) angle below 25° is associated with dysplasia, while a CE angle above 39° describes overcoverage [20, 21].

The main biomechanical failure mechanism in general overcoverage (coxa profunda/protrusio acetabuli) is hypothesized to be dynamic pincer-type femoroacetabular impingement, which is associated with osteoarthritis. General acetabular overcoverage is often referred to as a pincer deformity. The mechanism of pincer impingement is thought to be characterized by linear contact of the femoral head-neck junction against the acetabular rim and labrum [22, 23]. Chondrolabral damage patterns related to pincer morphology are widely distributed around the acetabulum [24].

Focal acetabular overcoverage is characterized by a prominence of the acetabular rim in a specific location, and is often related to acetabular retroversion. In retroversion, the acetabular opening is oriented more posteriorly than normal [25]. Clinically, retroverted acetabula are commonly associated with posterior cartilage damage and anterior impingement-related chondrolabral pathology [25–27]. Retroversion is often indicated by the cross-over sign on a plain A-P radiograph, or can be determined using 3D CT [28].

As with general overcoverage, the main biomechanical mechanism of concern in retroverted hips is thought to be pincer impingement at the anterior rim. Therefore, retroversion is frequently combined with protrusio/profunda in the pincer impingement literature. It is important to note that some retroverted acetabula are associated with deficient posterior coverage [28, 29], and subsequently may have different static loading patterns compared to profunda/protrusio acetabula.

Range of Motion

In an in vivo study, 32 hips with cam or pincer pathoanatomy had a mean internal rotation ROM at 90° flexion of 4° ± 8° (range: −10° to 20°) compared to 28° ± 7° (range: 10–40°) in 40 control hips [30]. This study also quantified the neck-rim relationship on open-configuration MRI scans taken with hips in 90° of flexion using the β angle, defined by a line connecting the femoral head center to the head-neck junction, and a line connecting the femoral head center to the acetabular margin (Fig. 4.2). The mean β angle was only 5° ± 9° in the cam or pincer subjects compared to 30° ± 9° in the controls. This work supports the hypothesis that linear abutment of the head-neck junction against the acetabular rim (impingement) terminates motion.

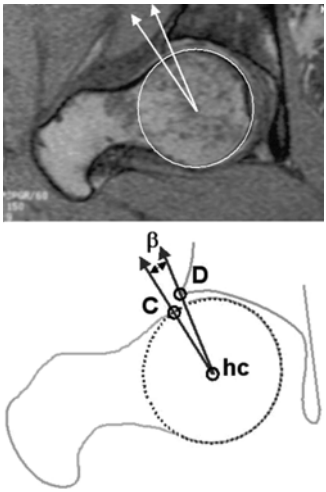

Fig. 4.2 (*Top*) Definition of the β angle on an MR image (*Bottom*) and on a diagram. [Reprinted from Wyss TF, Clark JM, Weishaupt D, Nötzli HP. Correlation between internal rotation and bony anatomy in the hip. Clin Orthop Relat Res [Internet]. 2007 Jul [cited 2013 Feb 5];460(460):152–8. With permission from Wolters Kluwer Health.]

Computer models confirm that most types of cam and/or pincer pathomorphology lead to reductions in flexion, internal rotation, abduction, and internal rotation at high flexion, although pincer and cam deformity have often been assessed together. Internal rotation at 90° flexion, a representation of the anterior impingement test, is commonly simulated with these models because it is thought to bring the anterior femoral head-neck junction close to the anterosuperior quadrant of the acetabular rim (often the most prominent part of the rim and a common site for chondrolabral pathology).

In a study using a mathematical model, 31 symptomatic hips with cam or pincer pathoanatomy (12 cam, 7 pincer, 12 mixed) had significantly decreased flexion, internal rotation at 90° of flexion, and abduction compared to a control group of 36 hips [31]. The same model was used to predict the location of impingement during internal rotation at high flexion in six hips with pincer deformities. The predicted impingement site for the pincer group was highly localized anterosuperiorly, whereas the actual site of chondral and labral damage observed in a separate group of 16 pincer hips spanned nearly the entire superior portion of the acetabulum and extended inferiorly [24].

Another model predicted that a group of 10 pure cam hips, 8 pure pincer hips, and 10 with combined cam/pincer pathoanatomy had limited flexion, internal rotation, abduction and internal rotation at 90° of flexion compared to 33 normal hips. The model predicted impingement on the anterosuperior quadrant of the acetabular rim for both control and FAI hips, with minimal difference in impingement zones between cam/pincer/combined hips [32].

Models of 50 hips undergoing arthroscopy for FAI showed that increased acetabular retroversion (simulated with increased anterior tilt) decreased internal rotation

ROM by 5.9° at 90° flexion, and by 8.5° at 90° flexion plus 15° adduction. Increased retroversion shifted the predicted impingement zone anteriorly. Increased acetabular anteversion (simulated with increased posterior tilt) increased internal rotation ROM by 5.1° at 90° flexion, and by 7.4° in FADIR [33].

Stress

Using idealized hip geometry in a finite element model, Chegini et al. evaluated the effects of varying α angles (40–80° range at 10° intervals) and center-edge (CE) angles (0–40° range at 10° intervals) on hip joint contact stress and acetabular cartilage stress during stand-to-sit and walking from heel-strike to toe-off [34]. Overcoverage reduced contact stress and chondral stress, while dysplasia greatly increased contact stress and chondral stress. Peak joint contact stress as well as chondral stress was inversely related to CE angle. Conversely, at deep flexion during stand-to-sit, a high α angle in combination with a high CE angle yielded the highest contact stress and acetabular chondral stress (Fig. 4.3). Cartilage stress distribution in the mixed cam-pincer hip during stand-to-sit was concentrated in the anterosuperior quadrant, where intraoperative cartilage damage is often observed (Fig. 4.4).

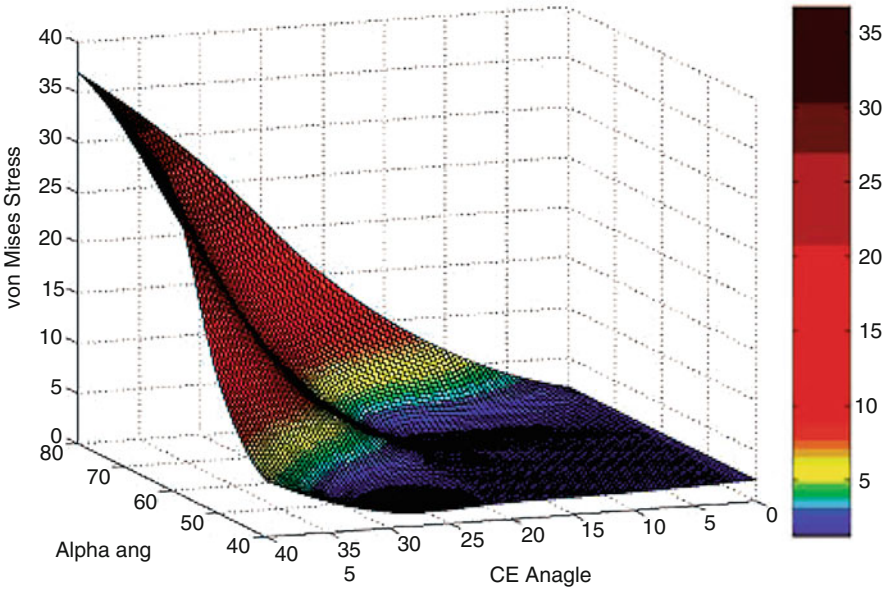

Fig. 4.3 Effect of CE angle and alpha angle on maximum von Mises stress in acetabular cartilage during stand-to-sit. [Reprinted from Chegini S, Beck M, Ferguson SJ. The effects of impingement and dysplasia on stress distributions in the hip joint during sitting and walking: a finite element analysis. J Orthop Res [Internet]. 2009 Feb [cited 2014 Jun 18];27(2):195–201. With permission from John Wiley & Sons, Inc.]

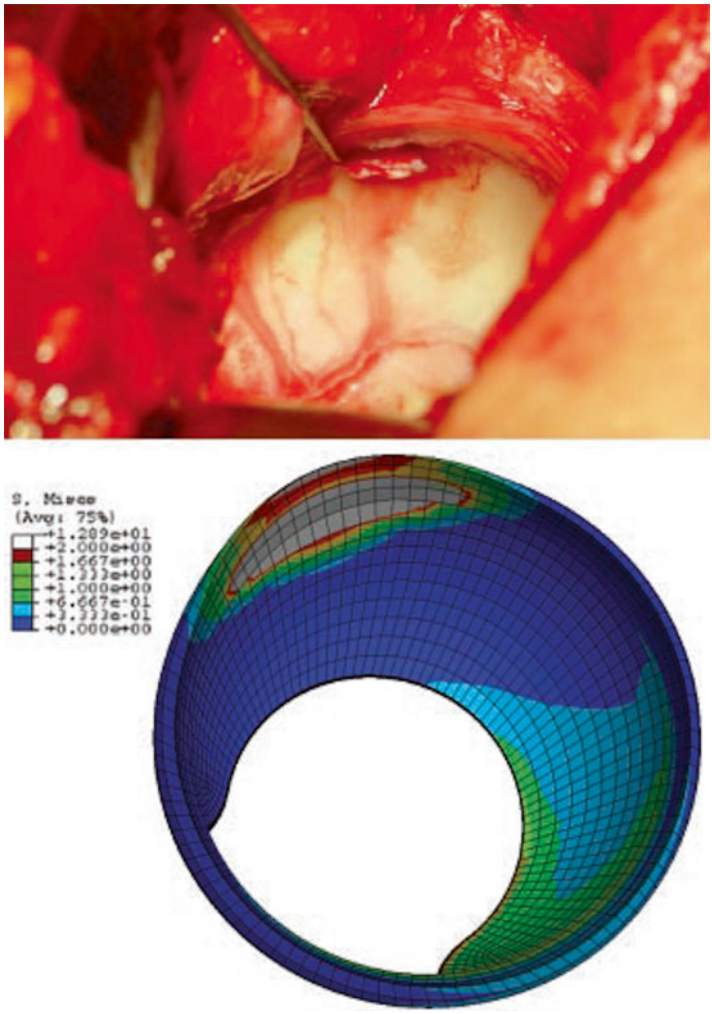

Fig. 4.4 (*Top*) Intraoperative image of cartilage damage in a cam-type hip. (*Bottom*) Cartilage stress distribution predicted by a model of a typical cam-type hip during stand-to-sit. [Reprinted from Chegini S, Beck M, Ferguson SJ. The effects of impingement and dysplasia on stress distributions in the hip joint during sitting and walking: a finite element analysis. J Orthop Res [Internet]. 2009 Feb [cited 2014 Jun 18];27(2):195–201. With permission from John Wiley & Sons, Inc.]

These results indicate that generally overcovered hips are likely not at risk for highly stressed posterior acetabular cartilage.

The applied forces and resulting peak stresses (3.3–16.5 MPa) from this model are within the same range reported by studies using CT-based patient-specific geometry for normal hips [35–38]. The contact stress magnitudes are consistent with experiments where miniature pressure transducers implanted

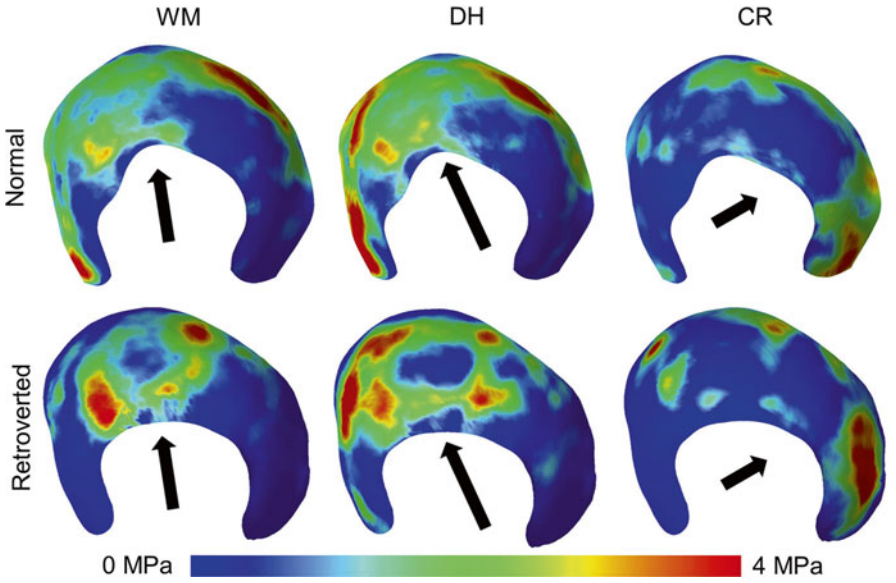

Fig. 4.5 Acetabular contact stress predictions for normal and retroverted hips for walking mid-stride (WM), descending stairs (DH) and chair rising (CR). The arrows indicate the approximate direction and relative magnitude of the load during each activity. [Reprinted from Henak CR, Carruth ED, Anderson a E, Harris MD, Ellis BJ, Peters CL, et al. Finite element predictions of cartilage contact mechanics in hips with retroverted acetabula. Osteoarthritis Cartilage [Internet]. Elsevier Ltd; 2013 Oct [cited 2014 Jun 17];21(10):1522–9. With permission from Elsevier.]

superficially into normal cadaver femoral head cartilage measured average peak contact stress in femoral cartilage to be 8.8 MPa for an applied vertical force load of 2700 N [39].

Subject-specific finite element models showed that contact stress was concentrated in the superomedial (SM) region in retroverted acetabula, while normal hips had more widely distributed contact stresses (Fig. 4.5). During walking and stair descent, normal hips had 2.6–7.6 times larger contact stresses in the posterolateral (PL) acetabulum. Conversely, retroverted hips had 1.2–1.6 times larger contact stresses in the superomedial acetabulum [37]. The authors suggest that these results refute the theory of high posterior stresses in retroverted acetabula due to decreased posterior coverage. A lack of concentrated loads on the posterior acetabulum suggests that retroverted hips with cartilage degradation on the posterior acetabulum may more likely be due to levering and "contre-coup" contact, rather than static posterior overload.

Posterior Overcoverage: Acetabular Anteversion

Acetabular anteversion is characterized by an acetabular opening that projects anteriorly. A prominent posterior wall may be associated with acetabular anteversion and might reduce the available bony range of extension and external rotation. Further,

the anterior wall might be deficient and lead to overload. However, we found no biomechanics studies that evaluated the effects of posterior overcoverage.

Biomechanical Effect of Problems in Femoral Neck Orientation

Femoral Anteversion and Coxa Valga

A valgus femur, or femur with coxa valga, is characterized by a caput-collum-diaphyseal (CCD) angle greater than 135° [40, 41]. Coxa valga is hypothesized to arise secondary to DDH and as such is associated with concentrated stresses on the acetabular roof. Femoral anteversion (or antetorsion) is characterized by a posteriorly oriented femoral neck, which is closer than normal to the posterior acetabulum and related acetabular structures. Recent work has focused on dynamic posterior impingement-related considerations in coxa valga and femoral anteversion.

Range of Motion

In an experimental study in children, hips with femoral anteversion had reduced external rotation in extension and abduction compared to normal subjects (Fig. 4.6) [10].

Mathematical models predicted reduced adduction, extension and external rotation range of motion in hips with both coxa valga and anteversion [42]. External rotation at 90° of flexion was also limited. These findings are consistent with experimental measurements of hip range of motion [10, 40]. The authors suggested that femurs with both coxa valga and anteversion are predisposed to a reduced range of external rotation and extension due to posterior extra-articular impingement. The findings suggest that hips with coxa valga and high femoral anteversion are at substantial risk for posterior impingement, and that treatment decisions involving coxa valga/anteversion should consider dynamic pathology in addition to static overload. Extra-articular structures like the anterior inferior iliac spine, ischial tuberosity, greater trochanter, and lesser trochanter caused terminal impingement much more frequently in the coxa valga/anteversion group than in the control group. The authors postulate that posterior impingement may induce a levering effect and eventually cause “contre-coup” chondrolabral lesions on the anterosuperior acetabulum—which would explain positive anterior impingement tests.

Femoral Retroversion and Coxa Vara

Coxa vara is characterized by a caput-collum-diaphyseal (neck-shaft) angle less than 125° [43, 44]. In coxa vara, the superior margin of the femoral neck is closer than normal to the anterosuperior acetabulum and therefore associated with loss of

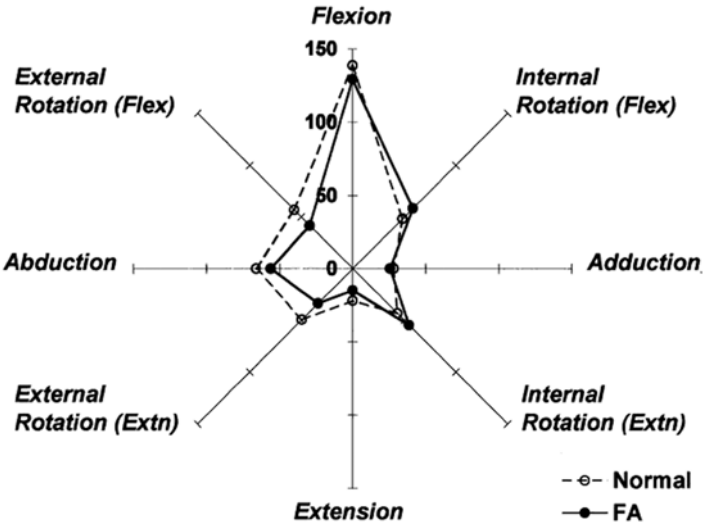

Fig. 4.6 Measured range of motion in hips with femoral anteversion (FA) and normal hips. [Reprinted from Rao KN, Joseph B. Value of Measurement of Hip Movements in Childhood Hip Disorders. J Pediatr Orthop [Internet]. 2001;21(4):495–501. With permission from Wolters Kluwer Health.]

hip ROM. Similarly, femoral retroversion (or retrotorsion) brings the anterior margin of the femoral neck closer to the anterosuperior acetabulum. Femoral version is defined in the axial or transverse plane by the angle between the femoral neck axis proximally and intercondylar line distally.

Range of Motion

Experimental measurements showed reduced abduction, internal rotation, and external rotation ROM in hips with infantile coxa vara compared to normals (Fig. 4.7) [10]. Hips with femoral retroversion had reduced internal rotation ROM and increased external rotation ROM compared to normals (Fig. 4.8) [10]. Hips with combined retroversion and coxa vara had substantially reduced abduction and internal rotation ROM and slightly increased external rotation than normal (Fig. 4.9) [10].

Although it is not clear that bony collisions terminate motion, this work demonstrates that abnormal morphology that brings the femoral neck closer to the acetabular rim in a specific plane is associated with limited ROM in that plane. In coxa vara, the femoral neck is brought closer to the superior acetabulum in the coronal plane, and likewise motion towards the superior acetabulum in the coronal plane—abduction—is limited. Similarly in retroversion, the femoral neck is brought closer to the anterior acetabulum, and likewise motion towards the anterior acetabulum in the axial plane—internal rotation—is limited. For this reason, it is hypothe-

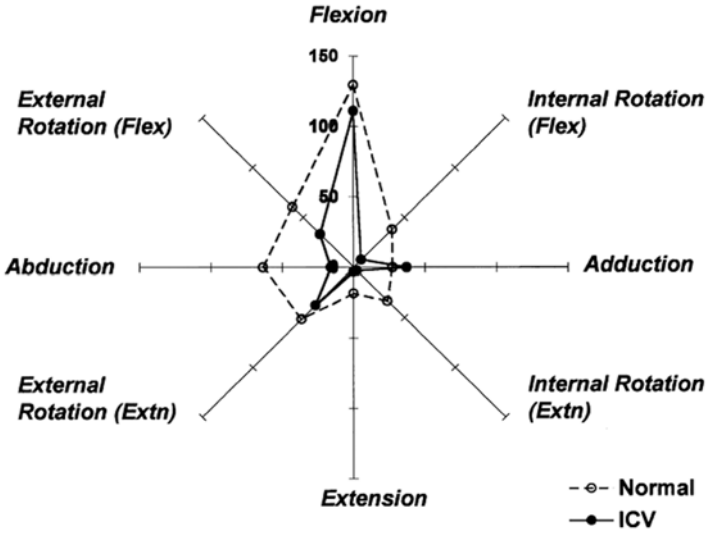

Fig. 4.7 Range of motion in normal hips and hips with infantile coxa vara (ICV). [Reprinted from Rao KN, Joseph B. Value of Measurement of Hip Movements in Childhood Hip Disorders. J Pediatr Orthop [Internet]. 2001;21(4):495–501. With permission from Wolters Kluwer Health.]

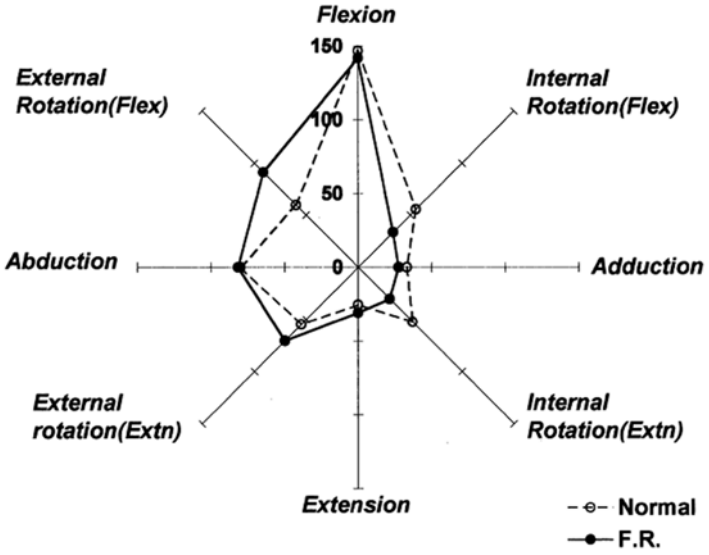

Fig. 4.8 Range of motion in normal hips and hips with femoral retroversion (FR). [Reprinted from Rao KN, Joseph B. Value of Measurement of Hip Movements in Childhood Hip Disorders. J Pediatr Orthop [Internet]. 2001;21(4):495–501. With permission from Wolters Kluwer Health.]

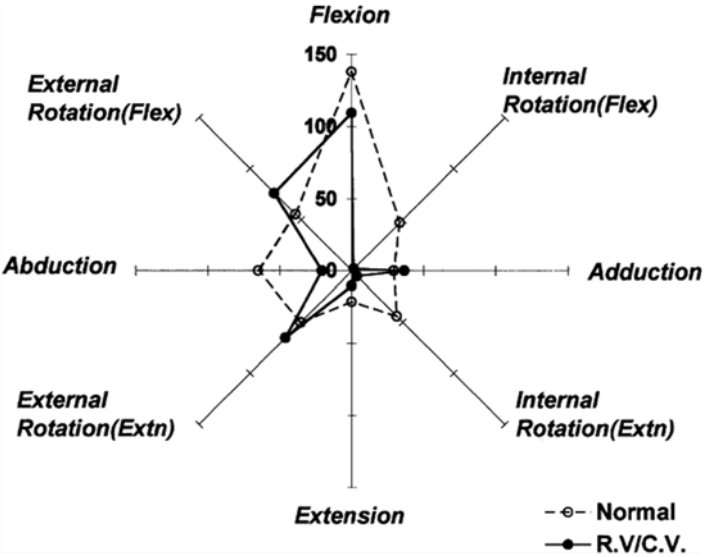

Fig. 4.9 Range of motion in normal hips and hips with coxa vara and femoral retroversion (R.V./C.V.). [Reprinted from Rao KN, Joseph B. Value of Measurement of Hip Movements in Childhood Hip Disorders. J Pediatr Orthop [Internet]. 2001;21(4):495–501. With permission from Wolters Kluwer Health.]

sized that coxa vara and femoral retroversion increase the likelihood of linear impact of the femoral neck against the acetabulum (i.e., pincer impingement) occurring during daily activity.

Biomechanical Effect of Problems at the Femoral Head-Neck Junction

SCFE

Slipped capital femoral epiphysis (SCFE) is a primarily adolescent disorder where the epiphysis slips in an inferior and posterior direction along the growth plate or physis, resulting in a femoral deformity believed to lead to acetabular impingement and cartilage damage [45].

Range of Motion

SCFE is expected to cause loss of ROM due to impingement of the deformed femoral head or neck on the acetabulum.

In a study using computer models from 31 SCFE patients and 15 contralateral controls [46], mild slips (as defined by Southwick angle) generally showed similar or slightly reduced ROM compared to controls (e.g., flexion: mild SCFE 89°, normal 99°), while severe slips had drastic reductions in ROM (e.g., flexion: severe SCFE 4°). For mild SCFE with a more prominent head-neck junction (type 2), ROM was further decreased (e.g., flexion: mild SCFE (type 2) 62°). Moderate SCFE cases were associated with larger decreases in ROM (e.g., flexion: moderate SCFE 14.2°), which were worsened by prominent head-neck junctions (e.g., flexion: moderate SCFE (type 3) 2°), while severe slips were not further affected by head-neck junction morphology.

Stress

Finite element models for both hips from two unilateral SCFE patients (one moderate, one severe) predicted that for a moderate slip, the peak contact stress was 17 % higher and maximum stress was 29 % higher than in the contralateral hip [45]. In the severe slip, peak contact stress was 49 % higher and maximum stress was 170 % higher. Simulated subcapital osteotomy through the proximal femoral epiphysis, base-of-neck osteotomy at the neck outside the capsule, and intertrochanteric osteotomy between the greater and lesser trochanter did not change contact stress or stress for the moderate slip, while the severe case saw reductions in maximum stress by about half (along with smaller reductions in contact stress), although this was still higher than the contralateral normal hips.

Cam Deformity

A cam deformity is typified by decreased concavity of the femoral head-neck junction. Cam deformities are widely thought to increase the risk of hip osteoarthritis. In 1965, Murray identified a “tilt deformity” of the femoral head and noted that radiographic tilt deformities were present in 79 out of 200 cases of hip OA [47]. In 1975, Stulberg et al. described the similar “pistol-grip deformity,” and in 1976 Solomon postulated that hip OA was secondary to such deformities [48]. In 2003, Ganz proposed that hips with tilt/pistol-grip deformities, resembling mechanical “cams,” mainly fail due to cam-type femoroacetabular impingement (Fig. 4.10) [22]. It was postulated that the cam deformity jams inside the acetabulum during forceful motion, particularly internal rotation at high flexion [22], leading to concentrated shear forces on intra-articular cartilage and acetabular labrum. The theory was largely driven by intraoperative findings from more than 600 surgical dislocations of the hip [22, 23], and evidence that patients with acetabular rim syndrome frequently have reduced concavity at the femoral head-neck junction [50, 51].

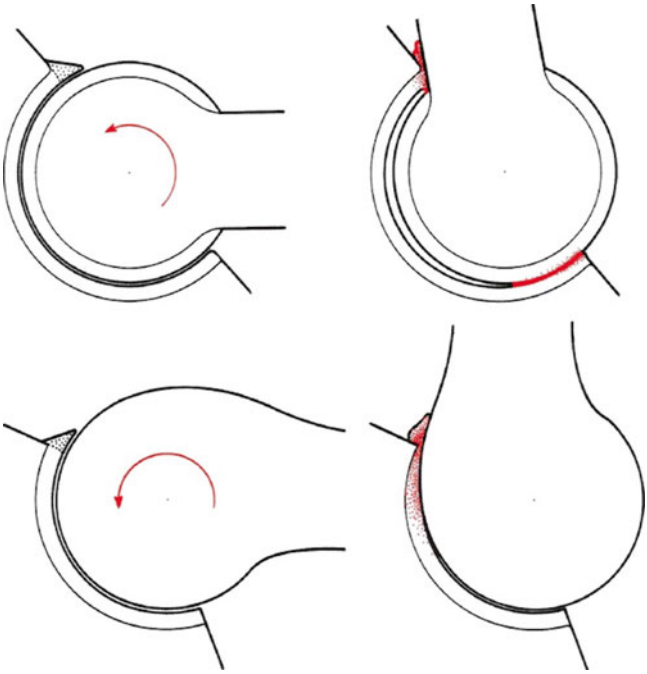

Fig. 4.10 Schematic diagrams of cam (*top*) and pincer (*bottom*) impingement. [Reprinted from Ganz R, Leunig M, Leunig-Ganz K, Harris WH. The etiology of osteoarthritis of the hip: an integrated mechanical concept. Clin Orthop Relat Res [Internet]. 2008 Feb [cited 2014 Jul 10]; 466(2):264–72. With permission from Springer Verlag.]

Biomechanics research of the cam-type pathoanatomy has focused on measuring three main factors that are related to the cam impingement pathomechanism: (1) reductions in hip ROM caused by bony impingement; (2) other kinematic changes that might be secondary to bony collision during cam impingement; and (3) the interaction between the cam deformity and acetabulum during motion (joint contact area, joint contact stresses, and cartilage/subchondral bone stresses).

Range of Motion

Patients with cam deformities typically present with restricted flexion, internal rotation, and abduction [52–55]. In theory, a reduced range of motion would mean a higher likelihood that cam impingement would occur in, and impede, daily activity (within the physiological range of motion). It is, however, not clear whether range of motion is dictated by bony morphology, soft-tissue constraint, or pain-related (compensatory) limits.

An experimental study of range of motion in three subgroups (symptomatic cam pathoanatomy, asymptomatic cam pathoanatomy, and controls, $n=24$ per group) showed that the symptomatic cam group had significantly reduced range of motion in all directions [56]. Notably, the asymptomatic cam group had significantly greater external rotation at neutral flexion and greater internal rotation at 90° flexion than the symptomatic group. There were no differences between symptomatic and asymptomatic groups for pure flexion and pure internal rotation. Models of 36 control hips and 12 cam, 7 pincer, and 12 mixed cam/pincer hips predicted no significant differences between cam, pincer, and combined pathoanatomies for flexion or internal rotation at 0° flexion [31].

Location of Impingement

Several approaches have been used to link predicted location of impingement with damage on the acetabulum.

In model simulations of internal rotation tests in high flexion (at intervals from 70° to 110° flexion, combined with −20° to 20° adduction), collisions consistently occurred on the anterosuperior portion of the acetabulum in ten symptomatic subjects with cam pathoanatomy, ten asymptomatic subjects with cam pathoanatomy, and ten healthy controls [57]. In control femurs, collisions were localized on the femoral neck anteriorly, while on the cam femurs, collisions were localized more superolaterally, where the cam deformity was located.

In a study combining in vivo measurement of joint movement with model predictions of impingement location, maximum flexion, maximum internal rotation at 90° flexion, and maximum abduction produced direct impingement between the cam deformity and the acetabulum. Furthermore, engagement began at positions much earlier than the terminal position. In flexion, engagement began at 80° although the motion range was 110°, and in internal rotation at 90° flexion, engagement began at 7.2° although the motion range was 19° [58].

In a similar study using in vivo motion tracking coupled with a model to predict impingement, the anterior impingement exam (flexion around 90°, adduction, and internal rotation) led to engagement of the inferomedial portion of the femoral head-neck junction with the anterosuperior portion of the acetabulum [59]. The engagement location was consistently on the anteroinferior portion of the femoral head/neck junction, as opposed to the anterosuperior portion where cam lesion size is often at its maximum. While the accuracy and repeatability of the model are well documented [60], the study was performed in only six control hips, one cam deformity hip, one hip with general acetabular overcoverage and one hip with femoral head asphericity plus acetabular overcoverage. Femoral head translation was seen close to the limit of motion during flexion-abduction-external rotation and anterior impingement exams. In particular the cam FAI patient had dramatic posteroinferior translation [59], which was evidence for the "levering" effect. Translation at this point has been theorized to increase loading on the posteroinferior acetabular

cartilage (opposite the contact or levering location) and has been termed the "contre-coup" effect. It was, however, not clear if any "contre-coup" joint contact occurred in the cam hip.

Pelvic Kinematics

In an ex vivo study of 12 cadaver hips, applied internal rotation torque beyond 12 N.m produced motion of the pubic symphysis in native hips that suggested contact between the femur and acetabulum (Fig. 4.11) [61]. The addition of simulated

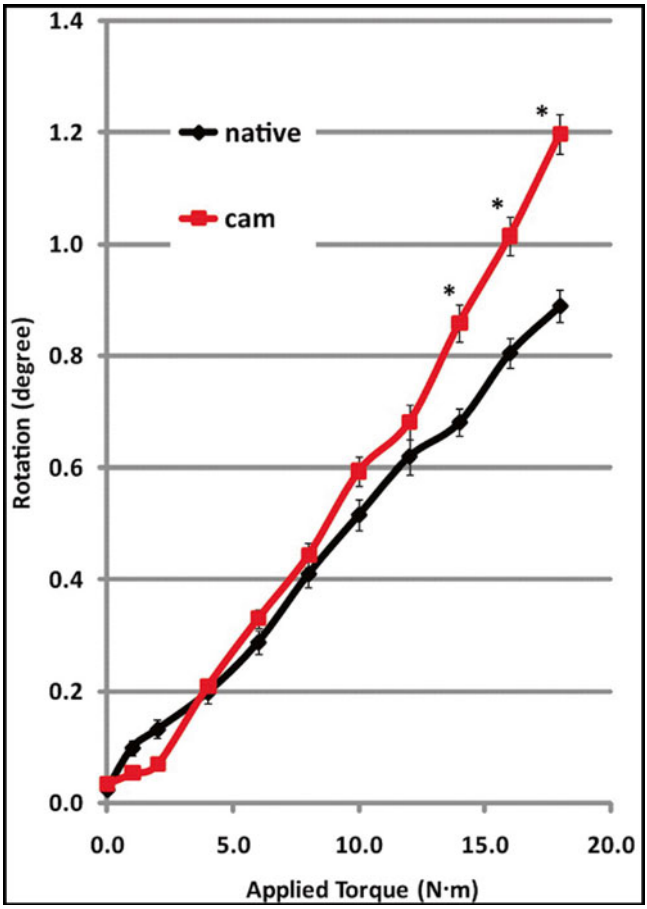

Fig. 4.11 Mean transverse plane rotation of the pubic symphysis as a function of applied internal rotation torque for native and simulated cam deformity in cadaver hips. [Reprinted from Birmingham PM, Kelly BT, Jacobs R, McGrady L, Wang M. The Effect of Dynamic Femoroacetabular Impingement on Pubic Symphysis Motion: A Cadaveric Study. Am J Sports Med [Internet]. 2012 May [cited 2014 Jun 17];40(5):1113–8. With permission from Sage Publications.]

cam deformities to each native hip changed the pattern of pubic symphysis motion, suggesting altered contact between femur and acetabulum.

In an in vivo study, a group of 15 patients with cam FAI had decreased sagittal pelvic inclination in a squatting activity compared to 11 controls ($14.7 \pm 8.4°$ for cams versus $24.2 \pm 6.8°$ for controls). This finding was independent of squat depth. Since pelvic inclination brings the anterosuperior portion of the acetabulum close to the femoral neck, this may explain the decrease in pelvic inclination for the cam FAI group. It is not clear whether the observed decrease in pelvic inclination was compensatory or driven by bony impingement. Interestingly, there were no differences in hip joint angles at maximal squat depth [62].

Joint Fluid Pressure

Joint fluid sealing ability was reduced in four cam-type hips with chondrolabral damage compared to six normal controls during pivoting activities but not in stooping or gait [63].

Stress

A finite element model based on idealized geometry predicted that simulated cam deformity size (α angle) had no effect on peak contact stress or acetabular cartilage stress during walking [34]. However, at deep flexion during stand-to-sit, larger cam deformities led to higher joint contact stresses given normal acetabular geometry (at $\alpha = 40°$, peak contact stress was 3.66 MPa versus 8.84 MPa at $\alpha = 80°$). The highest peak joint contact stress, 16.51 MPa, was observed at the highest α angle in combination with a high CE angle (mixed-type impingement morphology). Acetabular cartilage stress was also greatest with the highest α angle and highest CE angle.

Subject-specific finite element models of two hips from patients with large cam deformities ($\alpha = 83°$ for both) and related symptoms, and two hips from matched normals ($\alpha = 42°$, $45°$) were combined with subject specific squat kinematics that had been gathered in a separate study [62] to evaluate locations and magnitudes of stress in acetabular cartilage and underlying subchondral bone in functional positions (standing and maximum squat) [38]. Cartilage stresses were higher in the cam patients than in the controls. The biggest difference between cam and control hips was found in underlying bone during squatting: in cam deformity hips, peak maximum bone shear stress was 13.4 and 16.9 MPa in the cam hips versus 4.4 and 4.5 MPa in the control hips.

A patient-specific finite element model was combined with subject specific ROM of one pathological pure-cam FAI hip ($\alpha = 98°$) and one control ($\alpha = 48°$) to predict contact stresses for three positional tests: 90° flexion, 24° internal rotation, and combined internal rotation at 90° flexion [64]. Cam deformity raised peak contact stress substantially relative to the control hip: peak contact stress was 6.60 MPa

(flexion) and 6.04 MPa (internal rotation) compared to 9.65 MPa (flexion) and 11.68 MPa (rotation) in the cam hip.

Subchondral Bone Density

In an in vivo quantitative computed tomography study, symptomatic and asymptomatic cam-deformity groups ($n = 12$ for all groups) had greater bone density in the anterosuperior acetabular region than controls by 14–35 % and 15–34 %, respectively [65]. Bone mineral density had a mild positive correlation with alpha angle. The increase in bone density may reflect repeated engagement between the deformed femur and the acetabulum.

Biomechanical Effect of Poor Congruency

Perthes' Disease

Legg-Calvé-Perthes disease (Perthes' or LCPD) is a childhood disorder where a loss of blood flow to the femoral head leads to necrosis and frequently results in residual deformity upon healing. The effect of joint deformity in the healed stage of Perthes' hips on joint contact stress is of particular concern because of the higher risk of early hip osteoarthritis in Perthes' patients.

Range of Motion

Perthes' hips had reduced abduction and all combinations of internal/external rotation with flexion or extension compared to normal hips (Fig. 4.12) [10]. The reduction of internal rotation was more marked than that of external rotation. Flexion, extension, and adduction were similar to results from normal children.

Joint preserving surgery increased ROM in all directions except flexion (average loss of 1° ROM) in 50 hips in 50 Perthes' patients at a mean of 8.2 years of follow-up, although changes were small (smallest: +2.3° mean adduction, largest: +7° mean external rotation) [66].

To help determine the cause of loss of ROM in Perthes', 27 patients, 6–10 years old (average 7.9 years) with early Perthes' disease who failed non-operative management and had normal ROM in the contralateral hip were examined for ROM both pre-operatively and under anesthesia [67]. Twenty-one of twenty-seven patients (77.7 %) had ROM of the Perthes' hip within 5° of the contralateral when examined under anesthesia and the remaining six patients had reduced abduction (<50°). The author speculated that pain and muscle spasm, rather than deformity and impingement, were the cause of loss of ROM in this population.

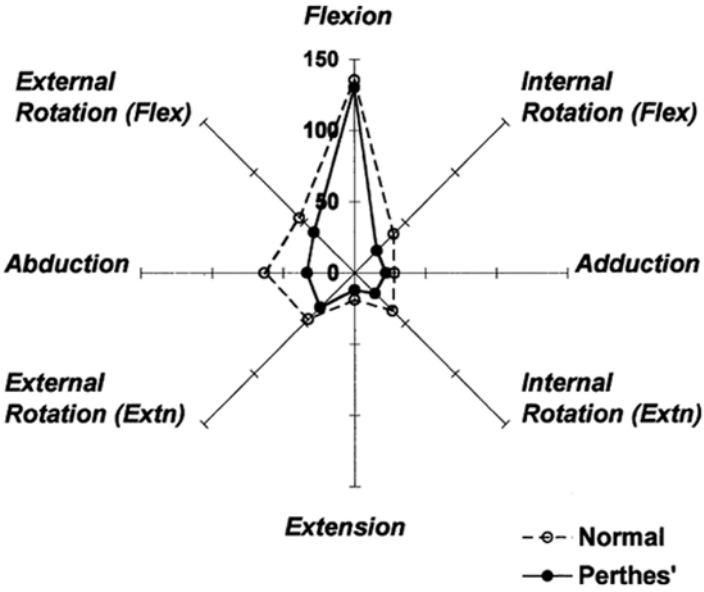

Fig. 4.12 Range of motion in normal hips and hips with Perthes' disease. [Reprinted from Rao KN, Joseph B. Value of Measurement of Hip Movements in Childhood Hip Disorders. J Pediatr Orthop [Internet]. 2001;21(4):495–501. With permission from Wolters Kluwer Health.]

In a different approach to understanding loss of ROM in Perthes' disease, geometric models of 13 hips with Perthes' (41 years old, 22–69, Stulberg grades III–V) were compared to 27 normal hips (54 years old, 31–74). Hips with Perthes' disease had a reduced ROM in all movements (e.g., flexion: Perthes' 103 ± 40° (26–144), normal 125 ± 13° (103–146)). The location of impingement was also different, with a majority of Perthes' hips in an anterior impingement test simulation having femoral intra-articular (79 %) and extra-articular (86 %) impingement, compared to normal hips (15 % and 15 %, respectively). The primary limitation of this approach was that soft tissue, including cartilage and labrum, were not simulated, which would likely limit ROM prior to bony impingement in some cases.

Stress

Models of 135 patients predicted that there was no difference in peak joint contact stress (normalized by body weight) between Perthes' and contralateral hips (2940 ± 885 versus 2946 ± 793 m^{-2}, respectively). There was a difference in the normalized values of contact stress gradient index (defined as the gradient magnitude at the lateral acetabular rim) between Perthes' and contralateral hips (4334 ± 51,011 versus −37,959 ± 35,848 m^{-3}, respectively), where the difference in sign is a result of the peak contact stress for a normal contralateral hip lying medial to the lateral

acetabular rim (resulting in a negative gradient as defined in this study—contact stress increases medially, and then decreases after the peak), and the peak contact stress for a Perthes' hip being at the lateral acetabular rim (resulting in a positive gradient as defined in this study—contact stress decreases medially). Models were based on simplified representations of the hip geometry based on 2D radiographs.

Joint Fluid Pressure

Joint fluid pressure, measured in various joint positions (several with traction) under sedation using an arterial pressure transducer in 94 hips (81 children) was significantly lower in Perthes' hips than in other conditions (mean of three positions: Perthes' 2.8 kPa ($n=9$), transient synovitis 9.8 kPa ($n=74$), septic arthritis 10.1 kPa ($n=4$), reactive arthritis 16.0 kPa ($n=2$), arthritis with urticaria 20.3 kPa ($n=3$)) [68].

Cartilage and Bone Material Properties

In a piglet model of Perthes' disease, Perthes' hips had lower bone stiffness (80 % lower) and yield strength (50 % lower) compared to the contralateral hip at 8 weeks, as well as a 31 % increase in bone collagen and a 25 % decrease in bone mineral content [69]. Perthes' hips also had lower cartilage stiffness (54 % lower) and yield strength (34 % lower) compared to contralateral hips at 8 weeks, although no differences were found in overall glycosaminoglycan concentration [69].

Coxa Magna

Coxa magna, defined as overgrowth of the femoral head and neck, can be a sequela of Perthes' disease, transient synovitis, congenital hip dislocation, septic arthritis, osteomyelitis, juvenile rheumatoid arthritis, and trauma [70]. Coxa magna is frequently assessed by comparing the affected and contralateral sides using such criteria as an increase in femoral diameter of greater than 10 % [70] or a femoral head ratio of less than 0.9 (unaffected head diameter/affected head diameter) [71]. The thickening of the femoral neck means that this condition may also be categorized as resulting in poor clearance [72]. Although these findings strongly suggest that coxa magna modifies joint biomechanics, no studies that quantify this effect are available in the literature.

Conclusions

It is surprising how little is known about hip biomechanics, given the prevalence of hip arthritis, the importance of biomechanics to many types of arthritis, and how much more is known about the biomechanics of other joints. The limited number

of experimental studies, both in vivo and ex vivo, is of particular concern. Model predictions must be treated with caution. While models make simulating diseases, deformities and surgical procedures possible, few biomechanical models have ever been shown to make reliable predictions of real measurements.

Overall it is clear that many hip conditions reduce joint range of motion. The evidence does not appear clear whether these reductions in range of motion are due to bony impingement or soft tissue changes. Models predict that hip disorders change contact pressure as would be predicted intuitively, and that surgical procedures like osteotomies have the desired effect on contact pressure. However there is very limited experimental evidence to back up these predictions or quantify them reliably.

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Chapter 5
Gait Pathomechanics in Hip Disease

Kharma C. Foucher

Overview

Mobility is an important aspect of our daily lives that is often taken for granted. Everyone, from those of us who are sedentary and those of us who are elite athletes, must be able to walk, climb stairs, and sit at some point in our daily routines. For some of us, kneeling and squatting are also important. Ideally, we can do all of things without thinking about it. Hip disease, however, can prevent this "thoughtless" mobility. A research participant in our laboratory remarked that she knew it was time to seek care for her hip because she noticed that she was thinking about her hip all the time; in her words "a 30 year old should not be thinking about her hip!" Arguably, 50 year olds and 90 year olds should not be thinking about their hips either. Neither the young ballet dancer with symptoms of femoroacetabular impingement (FAI) nor the grandmother who wants to stay active after hip arthroplasty should have their mobility compromised or be annoyed by thoughts about their hips.

The way that pathology affects mobility is central to the patient experience of disease. It is therefore critical for surgeons and care providers to understand how important mobility is to the individual patient experience. Take, for example, total hip arthroplasty (THA), which can be considered the end of the spectrum of degenerative hip disease. Most of criteria for surgical success are implant-oriented, e.g. quality of fixation, signs of loosening, revision rates [1–3]. However, as the use of patient-oriented or patient-reported outcome measures (PROMs) increases, and the concepts of "value" and appropriateness for surgery are expanding [4, 5], it is

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increasingly important for surgeons to consider how much THA improves patient well-being and quality of life as well. New research from large patient cohorts in the US and abroad is showing that up to 50 % of patients have some self-reported functional limitations 2–5 years after THA [6–8]. Severe limitations or a failure to have a meaningful clinical response based on change in PROMs may affect 4–15 % of unilateral THA patients in these studies. This is a problem. Recent studies also show that the most important desires or expectations that people undergoing THA report involve regaining the ability to be physically active [9–11]. In fact, participation in valued activities may be even more important to people than pain relief itself is per se [11]. This bears repeating. People seeking THA want to be able to move, work, and play even more than they want their hip to stop hurting. Considering that over 300,000 THA procedures are performed each year, and the prevalence of THA is ever-increasing [12, 13], the fact that tens of thousands of patients may be having inadequate functional recovery after THA should raise alarms for practitioners working in a value-driven environment. Understanding motion and how disease or trauma affects motion is an important part of providing good care.

Understanding how gait mechanics change with common hip pathologies is important because doing so can give insight into how to diagnose and treat, and how to assess a treatment's effectiveness. The goal of this chapter will be to explain how, and possibly why, hip pathology affects gait mechanics. The chapter will be organized around two (related) ways to think about gait pathomechanics:

1. Gait pathology as disruption of the normal relationship between structure and function.
2. Gait pathology as a behavioral response to disease.

After a brief discussion of terminology, these concepts will be presented with examples taken from morphological disorders (hip dysplasia, FAI), hip osteoarthritis (OA), and THA. The bulk of the chapter will be spent considering the structure–function framework, followed by a brief discussion of behavioral aspects of gait mechanics.

Terminology

This section will define basic terminology needed to describe key events of walking. At the same time, we will discuss the events that characterize normal gait and hint at gait alterations that can occur during hip pathology. At this time, it should be noted that for the most part the terms "gait" and "walking" will be used interchangeably in this chapter. However, hip pathology can affect other activities like stair climbing, sit-to-stand, running, etc., and the terms and methods discussed in this chapter can be and have been applied to other activities.

Gait Cycle and Gait Variables

Walking is a cyclic activity that can be demarcated by several key events. Hip pathology can change the timing of any these events, with reverberations throughout the cycle. The most basic way to divide the gait cycle is into two main phases—stance and swing. The stance phase of gait, intuitively, refers to the time when the foot is on the ground. It typically lasts approximately 60 % of the gait cycle. The swing phase of gait, again intuitively, refers to the time when the foot is off the ground. It typically lasts approximately 40 % of the gait cycle. Stance and swing can further be subdivided. Typically this is done based on the actions of a *lead limb*, compared to a *trailing limb* (Fig. 5.1). Alternatively, the stance phase can be considered in terms of periods of double support or *double limb stance*, when both feet are on the ground during loading response and preswing, and a period of *single limb stance* when only one foot is on the ground during midstance and terminal stance. This concept is useful when attempting to understand the effects of hip pathology because, as we will discuss later, hip musculature plays a key role in frontal plane

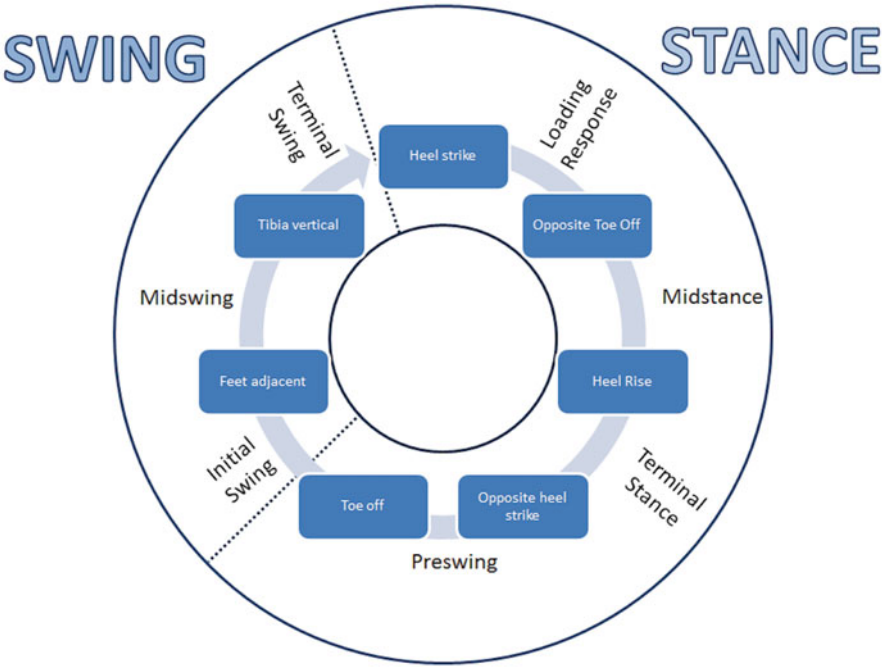

Fig. 5.1 Terminology defining the phases and subphases of the gait cycle. The key events that delineate each phase are shown. Stance can also be considered as two periods of double limb support—loading response and preswing, and a period of single limb support—midstance and terminal stance

control of the upper body, and the ability to smoothly accomplish weight transfer from one limb to the other.

There are several types of variables that can be measured during gait analysis. We'll discuss them here in order of increasing complexity with respect to equipment and computations required.

Spatiotemporal Gait Variables

Spatiotemporal gait variables describe the timing of the events of gait. Walking speed is perhaps the simplest and most intuitive gait variable. It is also the easiest to measure, requiring no specialized equipment, and the one with perhaps the broadest relevance. Walking speed has been proposed as a "6th vital sign" because of its relevance to so many aspects of health and the ease and reliability of its measurement [14, 15]. *Speed* is simply distance traveled per unit of time. (Some authors prefer to use the term velocity, which refers to speed combined with an indication of direction.) To increase (or decrease) your walking speed, you can either take more (or fewer) steps, take longer (or shorter) strides, or both. In other words you can alter your *cadence*—steps per unit time, *stride length*—distance per stride, or both. The relationship between speed, cadence, and stride length can be described by the equation: speed = cadence x stride length. Be aware that some authors may refer to *step length* rather than stride length. A *step* is demarcated by heel strike of one foot to heel strike of the other foot; a *stride* is demarcated by heel strike of one foot to heel strike of the *same* foot. A stride is therefore composed of two consecutive steps.

Kinematic Gait Variables

Kinematics refers to joint angles and motions. Motions of the hip can be described in sagittal, frontal, and transverse planes. In the sagittal plane, the hip typically passes through an arc of 30–40°. It is maximally flexed—around 15–20°—at heel strike. The hip typically passes through a smooth arc of extension, and reaches up to 20° of extension by toe off. Next, during the swing phase, the hip flexes to about 15–20° and the cycle repeats. In the frontal plane, the hip passes through a small arc of approximately 15°. The hip is typically neutral at heel strike, then adducts to approximately 10° during loading response. The hip then gradually abducts reaching approximately 5° of abduction during the swing phase. Motions in the transverse plane are very small. The hip is typically neutral at heel strike. During stance, a small amount of internal and external rotation of the femur with respect to the pelvis may occur, but the total range of motion is typically less than 10°.

Although it may seem obvious, at this point it is important to note that the hip and pelvis function together. It is both conceptually and methodologically difficult to isolate the hip and pelvis. This is particularly true when describing the frontal and transverse plane motion of the hip. For example, much of the internal rotation of the thigh on the leading limb during stance is perhaps more accurately thought of as

transverse plane rotation of the pelvis as the trailing limb enters the swing phase of its gait cycle. Even in the sagittal plane, the small amount of pelvic tilt that occurs during walking can be difficult to distinguish from hip flexion. There are two methodological challenges in separating pelvis motion from hip motion. First, some commonly used marker sets use the anterior superior iliac spine to define the proximal end of the thigh segment, because this pelvic landmark can be easily palpated. This means that the measurements of thigh motion being taken are quite literally a measurement of coupled thigh and pelvic motion. Secondly, whatever the marker set, soft tissue movement can introduce measurement error that is larger around the hip. The reader is also cautioned that hip angles are occasionally reported as the position of the thigh relative to the vertical, instead of relative to the pelvis. Range of motion should be comparable in either case, but the absolute angles would differ.

Kinetic Gait Variables

Kinetic variables can refer to power, work, and external moments. The discussion here will be limited to external moments. Other sources can provide more information on other kinetic variables. (A classic text by Jacquelin Perry, MD—recently updated with Judith Burnfeld, PhD, PT is an excellent supplemental source for all of the basic gait terminology discussed here [16]).

Why measure external moments? The goal of quantitative gait analysis is to learn information about how muscles may be functioning to accomplish the task at hand. As yet, there is no way to measure muscle forces in vivo. Electromyography (EMG) can be used to detect the electrical activity of the muscles, which can then be used to infer the on-off timing of muscle firing and the relative intensity of the contractions. The actual amount of force being produced *internally* by the muscles cannot be measured or approximated, even with EMG. Forces *external* to the body, however, can be easily measured. We can measure the forces between the foot and the ground, the ground reaction force during walking, and calculate the external moments and forces that act at each joint using *inverse dynamics.* Based on Newton's second law—the principle that for every action there is an equal and opposite reaction—we can infer the functional activity of agonist muscle groups in each plane during walking.

External moments arise by the action of the ground reaction force acting at a certain distance from the joint (hip) center. This distance is the *lever arm* or *moment arm*. The torque created by this force is called an external moment. A schematic depicting measurement and interpretation of the hip moments in the sagittal plane at three instances during stance is shown in Fig. 5.2. At heel strike and during loading response, the GRF is passing anterior to the hip center and the moment arm is quite large. We would measure an external moment that tends to flex the hip. We know that there must be an equal and opposite moment that tends to extend the hip. The hip muscles are primarily responsible for creating this internal moment. Thus we can infer that there must be net activity of the hip extensors. During midstance, the GRF is large but it passes very near to the hip center. The moment arm is

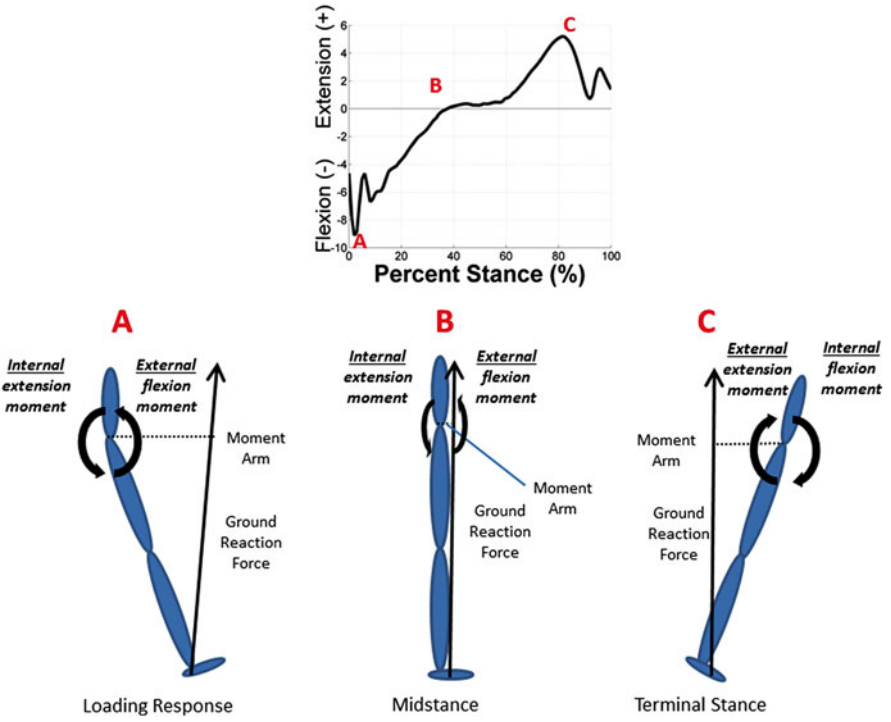

Fig. 5.2 Cartoon depiction of the moments about the hip in the sagittal plane. During loading response (**a**), the ground reaction force (*black arrows*) passes in front of the hip center. This *external* force will cause a moment tending to flex the hip. It must be balanced by an equal and opposite internal moment. Similar reasoning can be applied during midstance (**b**) and terminal stance (**c**) to interpret the pattern of external and internal moments. The magnitude of the ground reaction force and the size of the moment arm determine the size of the external moment measured

therefore very small and the corresponding external flexion moment is near zero. Finally, during terminal stance and preswing, the GRF passes posterior to the hip center and the moment arm is large again. An external extension moment would be measured; this moment must be balanced by the hip flexors.

Similar reasoning can be used to understand the pattern of moments seen in the frontal and transverse planes. In the frontal plane, the GRF passes medial to the hip center during most of stance. This means that there is an external adduction moment for most of stance that must be balanced by the hip abductors. Sometimes, during loading response or preswing, the GRF passes lateral to the hip center and an external abduction moment is measured. Finally in the transverse plane, an internal rotation moment, which must be balanced by the muscles that externally rotate the hip, is typically seen in the first half of stance. An external rotation moment, which must be balanced by muscles that internally rotate the hip, is typically seen in the second half of stance.

There are some additional caveats about interpreting external moments. Note that measuring an external flexion moment, for example, and using this information

to infer net hip extensor activity does NOT mean that the hip flexors are not active. In fact, one of the main limitations of gait analysis is that these measures tell nothing about antagonistic muscle activity. Electromyography can be a useful adjunct to measuring external moments, to give additional information about muscle firing patterns. Given that the rationale, stated above, for conducting quantitative gait analysis was to understand the forces within the muscles, it should also be noted that muscle forces per se cannot directly be measured using gait analysis. The external moments measured can be used with or without electromyographic information as input into computer models to calculate potential muscle and joint forces [17, 18].

Next, it is often only the peak external moments about the hip that are reported and analyzed in research studies. While this common approach neglects some potentially useful information, it does provide a useful snapshot of dynamic muscle function in each plane and is used in research routinely to study hip pathology. Finally, readers should be aware that while it is *external* moments that are measured during gait analysis, some authors prefer to report them as their corresponding *internal* moments. This may or may not be explicitly stated. To determine which convention the author is using, look for clues such as indications about the timing of the peak moments. For example, if an author refers to a peak extensor moment at heel strike, the reader should be alert that internal moments are being reported. This distinction is critical for accurate interpretation of data presented.

Newcomers to the gait analysis literature should be cautioned against conflating moments and motion. When interpreting external moments, one must think about the position of the GRF relative to the position of the hip center. While these relative positions are certainly related to the action of the hip at that time, the motion and moments are not the same. For example, when the peak flexion moment is measured, the action that the hip is undergoing is *extension.* Likewise, an external adduction moment can be measured both while the hip is ADducting, as during midstance, and while the hip is ABducting, as during terminal stance. Also note a related methodological point—one does not need to be able to measure motion in a given plane in order to measure external moments in that plane. For example, although transverse plane *motion* cannot be accurately measured with some common marker sets, the coordinates of the proximal and distal ends of each limb segment and the joint centers can be accurately localized in 3D space. Thus all the necessary information for calculating transverse plane *moments* is available. A knowledge of relative joint motion could be helpful to enhance the overall interpretation of the findings, but is not necessary for accurate calculation of external moments.

Summary of This Section

At this point we have introduced the most common variables used to describe gait mechanics in health and disease. Spatiotemporal (speed, stride, cadence), kinematics (motions), and kinetics (moments). Normal hip kinematics and kinetics have been outlined briefly. In the next two sections we will discuss how gait mechanics change with pathology, gait *patho*mechanics.

Gait Pathomechanics as Disruption of Structure–Function Relationship

Overview of This Section

Structure and function are intimately related. Structural changes in the hip joint, due to pathology, change hip function. These changes can be reflected as changes in one or more of the gait variables discussed above. To explore this concept, we will consider how hip joint structure influences function throughout the spectrum of hip degenerative disorders. We will first consider two disorders of hip morphology, dysplasia and FAI. This will be followed by hip osteoarthritis (OA) and THA. In each case, the common gait anomalies seen before and, where applicable, after surgical reconstruction will be described. Next the connection between abnormal structure and gait function will be discussed.

Pathological Disorders of Hip Morphology (Hip Dysplasia and FAI)

Hip dysplasia and FAI are considered to be disorders of hip morphology that are believed to be precursors to hip OA [19]. Their pathophysiology is covered in detail elsewhere in this volume, but most simply, in either case the relative coverage of the femoral head by the acetabulum is either less (dysplasia) or more (FAI) that what is considered normal. This structural abnormality has three interrelated biomechanical consequences. First, the way that the joint surfaces move against each other—the *arthrokinematics*—will be abnormal. This is a problem because it puts parts of the joint in contact that aren't designed to be in contact, and changes the pattern of stress distribution at the joint [20, 21]. When areas of cartilage encounter stresses to which they are not adapted, damage can occur; this is a proposed mechanism for OA initiation [22, 23]. Secondly, changing the shape of the femoral head or acetabulum can change the location of the hip center. This will in turn alter the moment arms for the muscles that cross the hip. This could have consequences for the ability of the muscles to balance the loads required by normal gait—adaptations may arise that are reflected in the external moments measured. Finally, these disorders may physically reduce the available range of joint motion at the hip. This will also lead to gait adaptations that will be manifested in the gait variables measured.

There are surprisingly few quantitative gait analysis studies in the literature on hip dysplasia and FAI. In the case of hip dysplasia, this may be because our awareness of this disorder emerged well before the advent of clinical gait analysis, and because it is typically diagnosed and treated in pre-ambulatory children. FAI, on the other hand, is a recently recognized and still controversial disease entity. There are

only a few studies on gait analysis in people with FAI because the knowledge is still emerging. This is currently a very active research area, however, and new studies appear in the literature regularly.

Gait Alterations in Hip Dysplasia

A review of the literature identified four fairly recent studies that report some of the spatiotemporal, kinematic, or kinetic gait variables discussed above in patients with hip dysplasia (Table 5.1) [24–27]. Unfortunately the literature is relatively sparse and the study populations are very different so it is difficult to identify common trends. Compared to control subjects, subjects with hip dysplasia may have less hip extension during walking [25, 27]. This restriction may be compensated for with increased pelvic excursion [25]. Reduced peak hip extension moments have also been seen [25, 27]. This indicates reduced net activity of the hip flexors in terminal stance or preswing. Two studies that evaluated subjects before and after a surgical intervention found that surgery did not significantly alter spatiotemporal or

Table 5.1 Summary of recent gait analysis studies involving subjects with hip dysplasia

Source	Study population	Select gait variables (of those discussed in this chapter)	Significant findings
Pedersen et al. [24]	9 adult women, 18 months pre/post periacetabular osteotomy	• Max hip extension • Peak flexion moment • Peak extension moment	Pre-to-post: • No change in hip extension • Peak flexion moment decreased
Omeroglu et al. [25]	10 children with previously treated DDH undergoing soft tissue release 20 healthy children	• Speed • Step length • Pelvic and hip kinematics Sagittal and frontal plane hip moments	Vs. control: • Increased frontal and sagittal plane pelvic excursion • Slightly reduced peak extension moment • Delayed transition from flexion moment to extension moment during midstance
Sucato et al. [26]	21 adolescents and young adults evaluated before and after Ganz periacetabular osteotomy	• Speed Hip Abductor Impulse (time integral of hip adduction moment)	Vs. control: • Slower speed both before and after surgery Pre-to-post: No differences by 1 year
Jacobsen et al. [27]	32 adults with untreated hip dysplasia 32 control subjects	• Sagittal plane hip kinematics • Sagittal plane hip moments	Vs. control: • Less hip extension • Lower peak extension moment

kinematic measures taken [24, 26]. One study did find that the peak flexion moment, which peak during loading response and indicates net activity of hip extensors, decreased after surgery [24].

A methodological aside: Two studies [24, 26] employed an interesting technique of analyzing gait variables that was not discussed above. In both studies, the angular impulse—the time integral of the moment—was calculated. This technique takes advantage of more of the available information. In knee OA, the angular impulse of the adduction moment has been shown to be a more sensitive marker of disease than the peak adduction moment [28]. The significance of the angular impulses of moments at the hip has not been fully established but this use of this new variable is an interesting emerging trend. Similarly, two studies analyzed the temporal properties of the sagittal plane moments. Omeroglu et al. noted that the transition between having an external flexion moment and an external extension moment, which usually occurs in the middle of the stance phase of gait (see center of Fig. 5.2) was delayed in subjects with hip dysplasia [25]. We have noticed this trend in subjects with hip OA (unpublished additional finding from a previously published study [29]). Again, the significance of this is as yet unknown, but it may indicate a subtle deficit in postural control during single limb stance. Finally, the paper by Pedersen et al. offers a good example of the need to ascertain whether or not the terminology being used matches the terminology with which one is familiar. When describing the sagittal plane moments that were analyzed, Pedersen refers to "maximal extensor dominance in the first half of the stance phase (H1) and maximal flexor dominance in the second half of the stance phase (H2)." [24] The reference to the timing of these peaks tells us that the authors are referring to what we have called, respectively, the peak external flexion moment—balanced by net hip extensor activity, and the peak external extension moment—balanced by net hip flexor activity.

Gait Alterations in FAI

Gait alterations associated with FAI both before and after surgical intervention have been nicely summarized in two very recent review articles [30, 31]. Only five studies, so far, have reported results of walking gait analysis studies (Table 5.2) [32–36]. Across these studies, limitations in range of motion in all planes have been found in people with FAI compared to self-reported healthy subjects or, where available, subjects with verified radiographically normal hips. Hip kinetics have been less frequently reported, and findings have been less consistent so far. While Hunt and Brisson have found reduced hip moments either before [35] or after [36] surgery for FAI, others have not. It should be noted that so far, gait studies of FAI subjects have had small sample sizes (typically fewer than 20 subjects) and have not been heterogeneous with respect to type of FAI (cam vs. pincer vs. mixed) or surgical approach and management. Thus it is so far difficult to draw detailed conclusions about the effect of FAI on gait.

Table 5.2 Summary of recent gait analysis studies involving subjects with femoroacetabular impingement

Source	Study population	Select gait variables (of those discussed in this chapter)	Significant findings
Kennedy et al. [32]	17 subjects with cam FAI 14 controls	• Speed and step length • 3D pelvis and hip kinematics • 3D hip moments	Vs. control: • Reduced sagittal and frontal plane hip and pelvis range of motion (ROM)
Rylander et al. [33]	11 subjects tested before and 1 year after arthroscopic reconstruction	• Speed • Sagittal and frontal plane hip kinematics and kinetics	Pre to post changes: • ROM increased Max flexion increased
Hunt et al. [35]	30 subjects with FAI 30 control subjects	• Speed, step length, cadence • 3D hip kinematics 3D hip kinetics	Vs. control: • Slower speed, cadence • Lower ROM all planes • Lower peak flexion, external rotation moments
Brisson et al. [36]	10 subjects with cam FAI tested before and after open hip reconstruction 13 control subjects	• Speed, stride length, cadence • 3D pelvis and hip kinematics 3D hip kinetics	Vs. control: • Reduced sagittal and frontal plane hip ROM • Reduced peak adduction, internal rotation moments after surgery
Rylander et al. [34]	17 patients with FAI tested before and after arthroscopic surgery 17 healthy controls	• 3D pelvis and hip kinematics	Vs. control • ROM reduced in all planes before surgery • Sagittal and transverse plane ROM improved to within normal

An additional methodological note: Some studies have observed a reversal of sagittal plane hip motion during walking (Fig. 5.3) [33–35]. We have also identified this kinematic pattern in patients with mild to severe hip OA [29], and others have seen it in endstage hip OA [37]. Brisson and Kennedy specifically noted that they did not observe this motion pattern [32, 36], but this could be because their studies were restricted to cam-type FAI, or because of slightly different gait methodologies. (See Michaud 2014 for a discussion of different methods of identifying relative joint motions [38].)

Gait Alterations in Hip Dysplasia or FAI as Alterations of the Structure–Function Relationship

Today, both hip dysplasia and FAI can best be understood as heterogeneous families of hip morphologic abnormalities. It is clear that altering the shape of the femoral head and its articulation with the pelvis results in some gait changes. The fact that

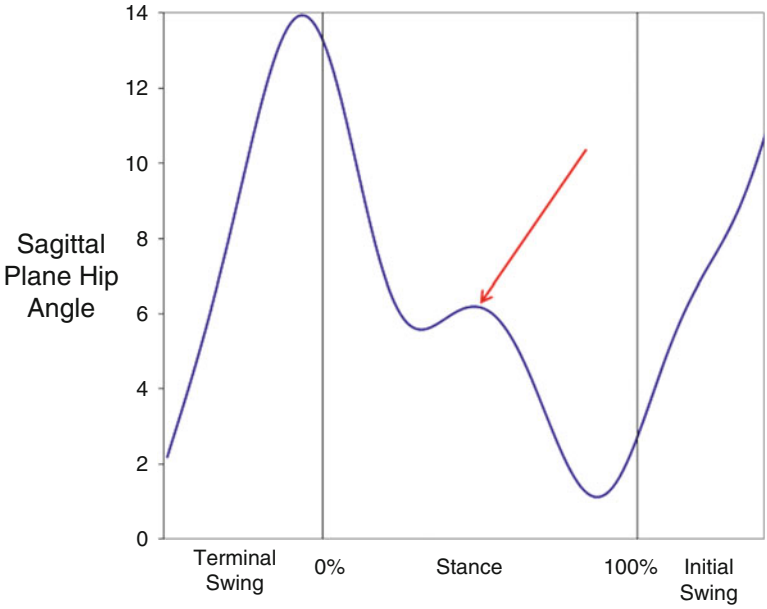

Fig. 5.3 Sagittal plane hip angle in degrees for a subject with severe hip osteoarthritis. *Arrow* indicates a reversal of hip motion in midstance. This kinematic pattern has been observed in patients with femoroacetabular impingement [33] and hip osteoarthritis [29]

restoring normal morphology only partially normalizes gait (with even more residual abnormalities observed during more demanding activities like squatting and stair climbing [34, 39]), however, demonstrates that abnormal bony morphology is not solely responsible for gait changes. Weakness of the gluteus medius and other muscles, as well as alterations in the anatomy of the hip abductors has been observed in both hip dysplasia and FAI [40, 41]. These and other structural changes in the soft-tissue could certainly contribute to the gait alterations seen before surgery in both disorders. Liu in particular notes that the surgeon must be mindful of muscular abnormalities when planning treatment and postoperative physical therapy so that a fuller recovery can be achieved.

Gait Alterations in Mild to Moderate Hip OA

Most studies of gait in hip OA have focused on patients with endstage disease. A few articles—most notably a 2012 study by Eitzen et al.—have either focused specifically on subjects with mild to moderate disease [42] or included subjects with less severe disease [29]. In addition, a recent review article summarized spatiotemporal characteristics of gait in hip OA [43].

Almost universally, people with mild to moderate hip OA walk with reduced speeds [29, 42, 43], Constantinou's review suggests that this speed deficit is attributable to reduced stride lengths [43]. However, even after statistically accounting for the effect of walking speed, kinematic and kinetic differences are found in people with OA compared to healthy controls [29, 42]. Eitzen reported that the hip range of motion in the sagittal plane is reduced in subjects with mild to moderate hip OA compared to controls, most notably in extension (Fig. 5.4) [42]. We have also observed reduced hip range of motion in the sagittal plane in subjects with mild to severe hip OA [29]. Furthermore, we have also reported an increased prevalence of the hip motion discontinuity gait pattern discussed above (Fig. 5.3) [29]. This sagittal plane motion pattern was associated with presence of hip OA, having more radiographically severe OA, and having more severe gait abnormalities overall.

Kinetic gait abnormalities have also been reported. Eitzen demonstrated that the sagittal plane hip moments are reduced compared to control subjects, with the greatest deficits again seen in the second half of stance (Fig. 5.4) [42]. In Eitzen's figure we can also appreciate the delay in the timing of the sagittal plane hip moment's switch from an external flexion moment to an external extension moment, similar to

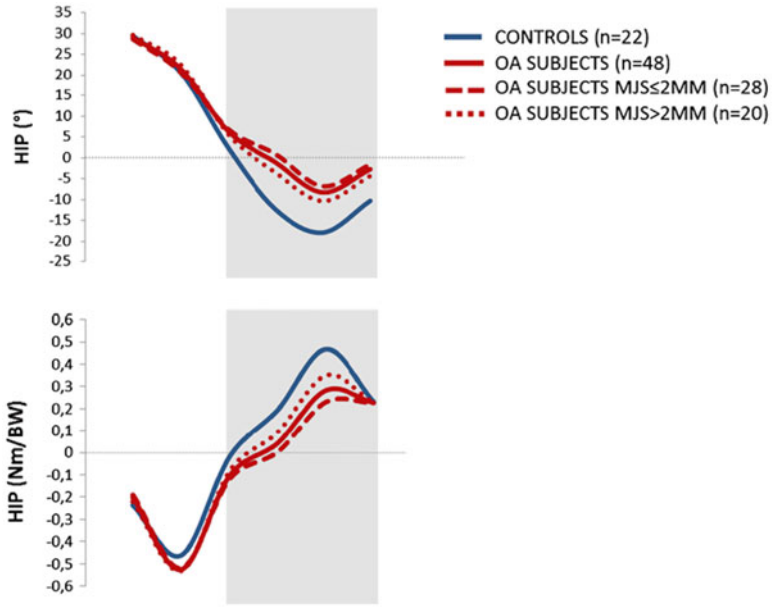

Fig. 5.4 This figure shows sagittal plane hip motion (*top*) and moments (*bottom*) for subjects with and without mild to moderate symptomatic hip OA. Subjects were subdivided based on radiographic OA severity based on Minimum Joint Space (MJS). Deficits in hip extension angles and the peak extension moments are seen in late stance. [Modified from Eitzen I, Fernandes L, Nordsletten L, et al. Sagittal plane gait characteristics in hip osteoarthritis patients with mild to moderate symptoms compared to healthy controls: a cross-sectional study. BMC Musculoskeletal Disorders 2012; 13: 258. With permission from BioMed Central, Ltd.]

the shift seen in subjects with hip dysplasia reported by Omeroglu et al. [25], as discussed above. We have also reported abnormalities in the other planes. With the exception of the peak hip abduction moment, all peak external moments were reduced in subjects with hip OA compared to control groups [29].

Gait Alterations in Mild to Moderate Hip OA as Alterations of the Structure–Function Relationship

As was hinted at in the discussion of hip dysplasia and FAI, there is a rapidly emerging body of evidence suggesting that femoral head shape is an important contributor to hip OA etiopathogenesis [44–47]. Modeling studies reveal that cartilage stresses are sensitive to the shape of the femoral head [21]. It would not be a stretch to consider that gait differences associated with early OA may be associated with subtle alterations of hip articular structure. There is evidence of a relationship between radiographic hip OA severity, as determined by the modified Kellgren–Lawrence (KL) grading system [48], and peak external moments during gait (Fig. 5.5). KL grading is arguably a relatively crude metric of hip structure, as it is based on a visual inspection of the joint space, and does not account for the morphologic changes that have recently been associated with OA. Nevertheless, an overall unloading pattern can be seen as hip OA severity increases. We have also demonstrated that having the sagittal plane motion discontinuity described above is associated with having reduced sagittal plane range of motion and peak flexion, extension, and internal rotation moments. As discussed above, several authors have speculated that there

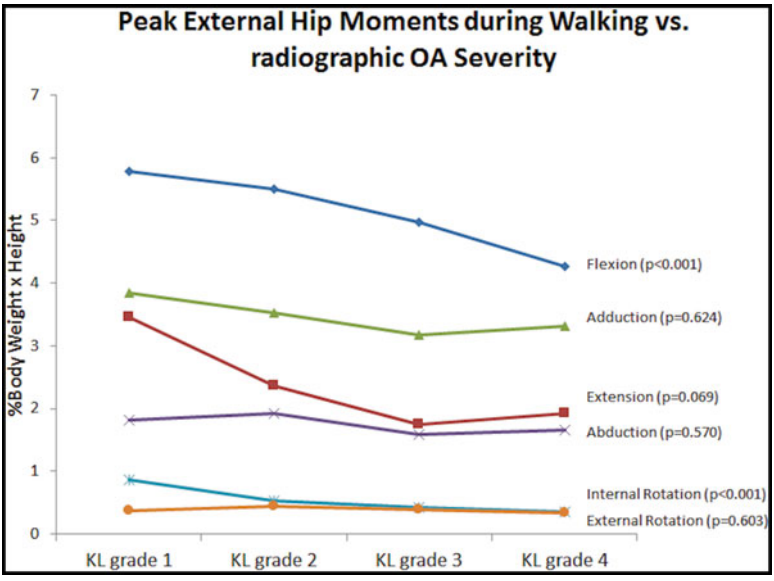

Fig. 5.5 The peak external moments during walking plotted against radiographic hip OA severity. In general an unloading pattern is seen. Correlations were statistically significant for the peak flexion and internal rotation moments

is an association between this sagittal plane motion discontinuity and abnormal hip morphology. Together these findings provide at least circumstantial evidence for a link between abnormal hip structure and abnormal gait function in hip OA.

Gait Alterations, Structure, and Function Links, Before and After THA

Gait in Endstage Hip OA

Endstage hip OA, which is the indication for more than 80 % of all THAs [49], is associated with markedly abnormal gait. Most of the gait anomalies seen in endstage OA can be viewed as more severe forms of the adaptations discussed above. Slower gait speeds, reduced stride lengths, reduced range of motion, and markedly reduced peak external moments have all been reported. Figure 5.5 illustrates how subjects with moderate to severe hip OA (KL Grade 3 and 4) have markedly reduced external moments compared to their counterparts with less severe disease. Sagittal plane gait mechanics have been discussed in detail above; reductions in hip range of motion, peak flexion and peak extension moments are even more dramatic in endstage hip OA. Arguably the most vulnerable muscle group in hip OA and THA, however, is the hip abductors. The frontal and transverse plane gait moments reflect the role of these muscles so they are important to consider in a bit more detail. The peak hip adduction moment in endstage hip OA is markedly reduced compared to healthy subjects [50, 51]. As we have previously discussed, an external adduction moment must be balanced by an internal hip abduction moment. The hip abductors (i.e., gluteus medius and gluteus minimus) are primarily responsible for this balance, so this gait deficit is usually interpreted as a sign of dynamic abductor dysfunction. During walking, the hip abductors are also well positioned to balance transverse plane loads [52, 53]. Thus the reduced internal rotation and external rotation moments that are also seen before surgery [50, 51] may reflect abnormal function of these muscles as well.

Structure Function Link in Endstage OA

Spatiotemporal and sagittal plane gait deficits in endstage OA may be associated with the sagittal plane motion restrictions associated with endstage OA and apparent on clinical exam. Loss of passive hip extension and hip flexion contractures are common in people with severe hip OA. Loss of passive extension is associated with restricted dynamic range of motion in the sagittal plane in people with hip OA as well as healthy elderly [37, 54, 55]. Hip extension is needed in the second half of stance to achieve "normal" gait patterns. Restricted hip extension will necessarily reduce stride length, which will in turn reduce speed. (Recall that speed = stride length × cadence). Flexion contractures can also influence the sagittal plane moments by affecting the position of the ground reaction force with respect to the hip center. If a patient has a flexed hip for most or all of stance, as

in the example shown in Fig. 5.3, even in late stance she may not be able to move the ground reaction force posterior to the hip center. This means it will not be possible to produce the large hip extension moment typically seen in late stance (refer back to Fig. 5.2c).

The frontal and transverse plane gait abnormalities could be partly explained by structural changes that happen within the abductor muscles. Hip OA is associated with atrophy and fatty infiltration of the hip abductors, as well as weakness [56–58]. While strength and external moments are not always directly correlated [59], these structural changes can still affect external moments. Maintaining a level pelvis during single limb stance is conventionally thought of as the primary role of the abductors during gait. If the abductors cannot function normally to achieve this, the body must compensate. This compensation is commonly done with exaggerated trunk lean. Even a small amount of lateral trunk lean moves the ground reaction force closer to the hip center in the frontal plane. This action thus reduces the effective moment arm and reduces the external adduction moment and thus the demand on the hip abductors. To understand the transverse plane moment deficits, consider both about a permanently flexed hip and weakened abductors. With persistent hip flexion, the anterior fibers of the gluteus medius and minimus, which contribute most to internal rotation, are being shortened and the posterior fibers, which contribute most to external rotation are being stretched. Neither position will result in an optimal fiber length for contraction, and the transverse plane moment generating capacity of the abductors will be diminished.

Gait After THA

Along with dramatic improvements in pain and quality of life, THA improves most aspects of gait. In one study by our group in which subjects who underwent primary unilateral THA with one of two minimally invasive surgical approaches, after a decline in ROM and external moments 3 week after surgery, there was a dramatic improvement in most gait measures, with gait stabilizing by 6 months after surgery (Fig. 5.6) [51]. There are, however, significant gait abnormalities after surgery [60], that may in part reflect a persistence of abnormal preoperative gait patterns [50]. A review and meta-analysis by Ewen et al. summarizes several studies in which the gait of patients after THA has been compared to that of healthy controls and identifies several consistent deficits [60]. These are walking speed, stride length, sagittal plane hip range of motion and the peak adduction moment. The most dramatic gait abnormality is again the significant reduction seen in the hip adduction moment compared to healthy subjects. Not only is it well below normal both before and after surgery, from Fig. 5.6 we can appreciate that not much improvement takes place on average.

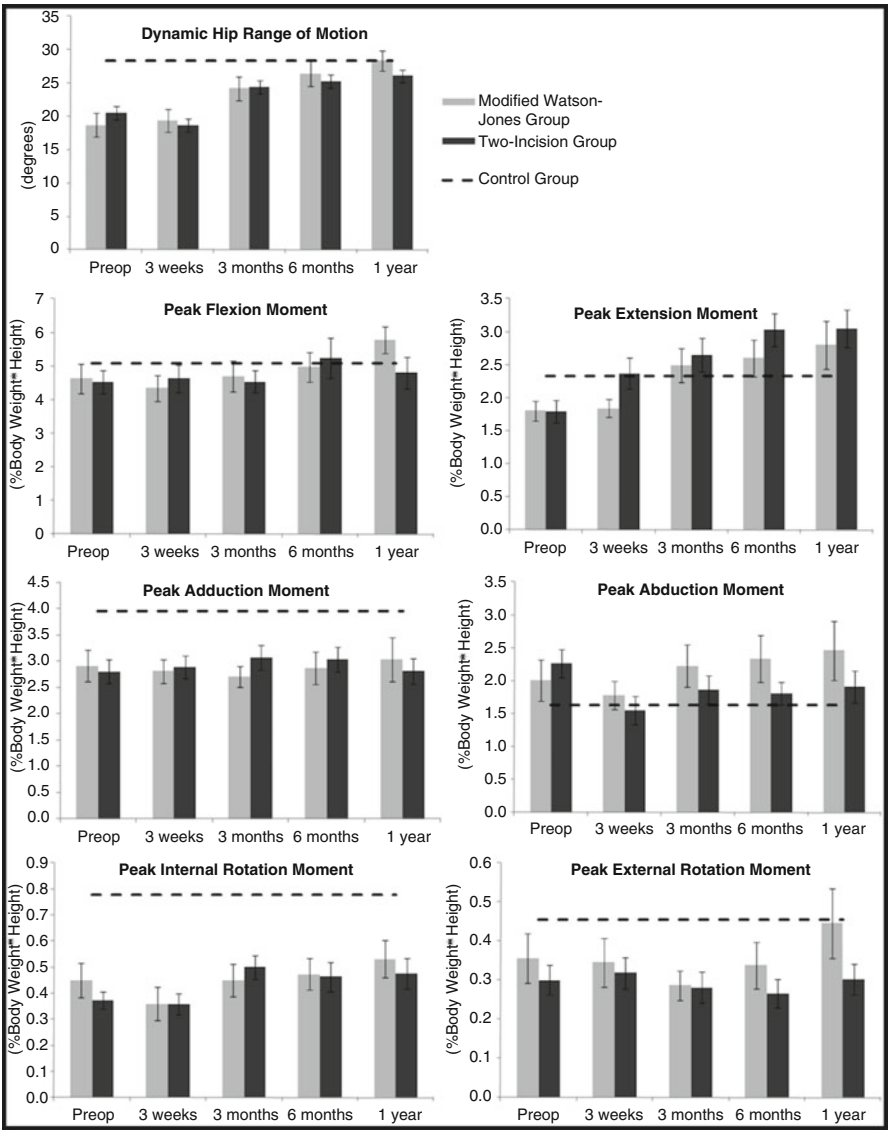

Fig. 5.6 Peak external moments before and during the first year after primary unilateral total hip arthroplasty conducted with two minimally invasive approaches. There were no differences in rate of recovery between the two approach groups. *Horizontal lines* show mean values for a group of age-matched control subjects. [Reprinted from Foucher KC, Wimmer MA, Moisio KC, et al. Time course and extent of functional recovery during the first postoperative year after minimally invasive total hip arthroplasty with two different surgical approaches—a randomized controlled trial. Journal of Biomechanics 2011; 44(3): 372–378. With permission from Elsevier]

Postoperative THA Gait as Alteration of the Structure–Function Relationship

While some gait abnormalities after THA may be attributable to the same factors that contribute to abnormal preoperative gait, postoperative joint geometry may also play a role. Neck length, femoral offset, cup inclination angle, and other aspects of hip joint geometry can all be directly or indirectly manipulated by the surgery. Although the relationships between joint geometry and implant longevity have been investigated, there have been few in vivo studies on the relationships between joint geometry and gait. We can consider these relationships indirectly, however, but reviewing what is known about the influence of hip joint geometry on muscle strength or function and on hip joint forces.

The joint geometry measures linked to adverse events, including poorer clinical outcomes, include shorter femoral neck, reduced femoral offset, or a more superior or lateral position of the hip center [61–67]. In theory, these positions may all reduce the moment generating capacity of the hip abductors [62, 68–70]. The result will be either that the muscles must produce more force to generate the same moment or that there must be a compensation to reduce the demand on these muscles [71].

These theoretical findings seem to hold true in recent and older studies. Reduced femoral offset relative to the healthy contralateral hip is associated with a reduced hip range of motion in the frontal plane [72, 73]. Lower offset is also associated with reduced abductor muscle strength [72, 74–76], and greater abductor muscle activation [76]. Higher hip centers are also linked to reduced abductor strength [77–80]. These findings suggest that indeed more force is needed from the muscles to accomplish the task at hand when joint geometry is different from what is optimal.

What does this mean in practice? Careful preoperative planning and templating is done to optimize joint geometry. However there has arisen recent concern in the literature that templating based on X-rays may underestimate femoral offset, particularly when hip or pelvic rotation is present [78–80]. Reduced offset can adversely impact hip abductor function—which is already compromised due to the effects of the underlying disease. Clinicians should be watchful for subtle deficits in abductor function. While joint geometry cannot be changed after surgery, rehabilitation interventions can help patients regain lost strength needed to overcome the residual disease effects or the effects of slightly suboptimal implant positioning.

Summary of This Section

This section described how gait pathomechanics can be viewed as a disruption of the normal structure–function relationship of the hip joint and its surrounding structures. This is true throughout the spectrum of hip degenerative diseases from prearthritic conditions through recovery from THA. Considering this spectrum, it is noteworthy that dynamic hip extension, which is intimately linked to hip joint

structure, may be one of the first manifestations of functional impairment and one of the last to recover. The evolution of abductor muscle impairment in hip OA and its persistence after THA also raises interesting questions about the relationship between intramuscular structure and gait function, joint geometry, body position and gait function, and the role of implant positioning. Future work in developing patient-specific biomechanical models in hip OA and prearthritic conditions will lead to new advances in the coming years that promote optimal functional recovery.

Gait Pathomechanics as Behavioral Response to Disease

Overview

Although structure and function are intimately connected, the patient's experience of hip pathology revolves around the connection between pain and function. Pain, or more accurately, the inability to adequately modify activities to reduce pain, sends patients to a clinician. So it is also useful to consider pathomechanics in terms of people's conscious or unconscious strategies to alleviate pain. To do this, we will briefly revisit some of the gait adaptations seen in hip OA and THA.

Slowing Down and Other Spatiotemporal Gait Adjustments

Walking speed has been proposed as a sixth vital sign [14, 15]. It can be easily measured clinically with little to no specialized equipment. Walking speed is associated with fall risk [81], incident disability, cognitive decline, and even mortality [15, 82, 83]. Thus, although all of the disorders discussed above have reduced walking speed as one of their main signs, the fact that walking speed does not return to normal after THA is particularly concerning.

In one study we measured self-selected normal walking speeds for subjects who had undergone primary unilateral THA, and a group of health controls, a gait analysis lab, then assessed habitual speed with ankle-worn activity monitors for 24 h in subjects' home environments [84]. We found that both subject groups walked faster in the gait lab than they did in external settings. This was perhaps due to a desire to perform well for observers. However the gap between lab-based speed and habitual speed was larger in the control group. Our interpretation was that people who had THAs might have wished to walk faster, but may have been unable to do so because of the residual gait abnormalities discussed above. This "speed-gap" may have important implications for subjects' overall health and well-being. Evidence of a functional speed-gap also comes from Mauffiuletti et al., who showed that gait characteristics were comparable between subjects after THA and controls when walking at a self-selected normal speed, but that differences emerged when subjects walked a fast speeds [85].

In another recent study of 163 subjects tested before and after primary unilateral THA [86], we examined the relationships among walking speed, kinematic and kinetic gait variables, and Harris hip scores (HHS) before and after THA. Notably, there were no statistically significant relationships between pain and walking speed either before or after THA, or between change in pain and change in walking speed ($R = 0.120$, $p = 0.154$). This suggests that slower walking speeds are not actually a response to pain, but may be more strongly associated with other aspects of abnormal hip biomechanics. Indeed, speed was significantly correlated with all of the other kinematic and kinetic gait variables measured about the hip ($R = 0.178$–0.614, $p < 0.001$ to $p = 0.018$). In a way, this is good news because it means that speed deficits could be amenable to rehabilitation or other interventions.

Gait Kinematics and Kinetics

Gait kinematics and kinetics are not volitionally adjusted in response to pain and other behaviorally experienced aspects of hip disease. Lab-measured hip gait kinematics and kinetics, however, directly influenced by walking speed [87], and related to self-reported pain and other aspects of clinical function. In patients with hip dysplasia, Jacobsen et al. found that self-reported pain and sports/recreation function scores were significantly correlated with the peak hip extension angle and the peak external extension moment [27]. We have had similar findings at the other end of the disease spectrum.

In our study of THA subjects discussed above [86], we identified several associations between pain or self-reported function and gait kinematic and kinetic variables. More preoperative pain was associated with lower peak extension moments and more having a greater postoperative improvement in pain was associated with greater increases in dynamic sagittal plane range of motion and the peak external rotation moment. In contrast to pain, both preoperative and postoperative hip function scores were strongly associated with walking speeds. After statistically controlling for these relationships, we found that improvement in self-reported gait function was associated with improvement in the hip range of motion, peak adduction moment, and peak external rotation moment. Note that these are the same gait variables in which recovery has been found to be lacking [50, 51, 60].

Summary of This Section

Briefly, this section should have convinced you that, while structure and function are intimately related, function is also influenced by the patient's symptoms and experience of disease. It is not truly possible to separate these two concepts. Clinicians are asked to treat pain by restoring structure, with the sometimes indirect goal of restoring function. The assumption that restoring structure will restore

function is not always accurate. So far the consensus in both the surgical treatment of hip dysplasia and FAI is that even when structure is normalized, functional deficits can persist. The problem of incomplete functional recovery after THA is also gaining recognition. With a more thorough understanding of the connections among gait mechanics, structure, function, and symptoms, clinicians of the future will have the opportunity to further improve recognition and treatment of hip pathology.

Final Summary and Recommendations for Use of Clinical Gait Analysis with Hip Pathology

This chapter has presented variables that describe the spatiotemporal characteristics of walking, hip motions, and, indirectly, hip muscle activity and function. By way of a summary, this final section will touch on some ways that clinicians may choose to apply these concepts, and briefly mention some methods for doing so.

Most of this chapter has dealt with quantitative gait analysis as conducted in a fully equipped gait analysis laboratory. However, one of the most important gait measures can be assessed in the clinic with only a stopwatch. The 10 or 4 m walk tests can be used to assess speed in a clinical setting [15]. Walking speed is reduced in all of the hip conditions described here and does not return to normal after THA. Walking speed may also be directly linked to the hip structural changes associated with hip pathology. We have argued that limitations in hip extension, which again is seen in each of the conditions discussed, can lead to reduced walking speeds via reduced stride length. Walking speed is associated with self-reported function in people after THA, and as such is a good objective reflection of the patient's experience of disease that has good clinimetric properties compared to PROMs. Finally, in older adults, walking speed is linked to incident disability, other mobility restrictions, and a host of other general health problems. It is important to know whether or not hip pathology is the source of reduced walking speed in your older patients. An assessment of walking speed is an excellent complement to other clinical tests that adds little time and no cost to the clinical encounter.

Walking speed, along with ever more complicated gait measures, can now be measured outside of the traditional lab setting as well. Instrumented mats and walkways can be used to measure spatiotemporal gait characteristics. Body worn sensors and activity monitors are also rapidly evolving [88]. These technologies, often based on accelerometers, can be used to quantify speed and other spatiotemporal gait variables as we have discussed [84]. Activity levels can also be quantified using these devices [51, 89, 90]. Some technologies can also be used to actually obtain joint angles as well [88]. An important feature of these types of devices is that feedback can be given to the wearer in real time.

Detailed kinematic and kinetic analysis can be performed most accurately in a gait laboratory. A basic gait lab will have at least four cameras (eight to ten are most common now), at least one multi-directional forceplate embedded in a walkway at least

8–10 m long. Reflective markers are placed in defined locations on the lower extremities or the entire body. At least two markers are necessary to define the proximal and distal ends of each segment; a third marker is necessary if rotations will be measured. The cameras typically emit pulses of infrared light and record the reflection of the light from the markers. Before testing, the system is calibrated so that the 3D coordinates of each point in the volume space is known. Then as long as at least two cameras can "see" a marker, its 3D position can be determined. From marker locations, ground reaction forces, measured by the force plates, and joint centers either determined by marker positions or by other methods, *inverse dynamics* can be used to calculated external moments about the hip and other joints. There are many vendors that produce and distribute camera systems, forceplates, and analysis software.

Today it would be unusual to find an academic medical center or major research hospital without at least one gait analysis lab. Labs are typically housed within orthopedic surgery, physical therapy, kinesiology, or bioengineering departments. Many institutions may have more than one. There is strong support for the efficacy of clinical gait analysis [91]; however, its use is still currently primarily in children. Gait analysis has been investigated as a potential outcome tool for FAI [30, 34] and hip OA [92, 93]. In addition, Bhave et al. published a case series in which gait analysis and complementary assessments were used to customize rehabilitation intervention for THA patients who failed "conventional" therapy [94]. The potential is there. With additional work in this area, there is great potential for gait analysis to be a useful, and reimbursable, clinical tool for many type of hip pathology in various patient populations. Clinicians should consider ordering gait analysis studies where available and reimbursable.

There are several important concepts that were beyond the scope of this chapter but are relevant to this material. First, activities other than walking were not considered here. More intense activities such as squatting, stair climbing, and running may be needed to fully assess the capabilities and limitations of younger patients with the prearthritic conditions [27, 34, 39]. Second, we have neglected the effects of hip pathology on joints other than the affected hip. For example, Eitzen et al. nicely describe the sagittal plane kinematics and kinetic changes at the knee and ankle associated with mild to moderate hip OA [42]. Shakoor et al. have established that the pattern of joint-to-joint progression of OA is "nonrandom" and can be linked to the abnormal hip joint loading patterns [95, 96]. We have also investigated the longitudinal effects of THA on the contralateral hip and knee [97, 98]. Finally, numerical modeling was only hinted at here. Musculoskeletal models, including finite element analysis, discrete element analysis, and simulations, have great potential to be invaluable clinical tools in the future [21, 99]. Predicting and personalizing interventions will no doubt be essential in the years to come.

After reading this chapter, you should be convinced of the importance of understanding gait, and have gained a foundation for how to approach gait pathomechanics associated with hip disease. When approaching the patient with hip pain or known hip disease, gait should always be assessed at least observationally. Whether gait analysis is conducted just using visual observation, or in a gait lab, watch for

events at key points in the gait cycle. For example, the transitions from double limb stance to single limb stance, and the midpoint of the stance phase of gait have been shown to be important in multiple pathological conditions. Try to make connections between walking and other activities that may be meaningful to the patient. When available, consider utilizing quantitative gait analysis, and documenting how it guides your clinical practice. Understand the importance of gait function in your patients' daily lives—doing so is essential to providing good patient care.

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Chapter 6
Femoroacetabular Impingement

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Pathology of Femoroacetabular Impingement

Femoroacetabular impingement (FAI) results from abnormal contact between the acetabulum and the femur. Femoral-sided impingement, also known as *cam impingement*, damages the labrum and intra-articular cartilage as the aspherical femoral head reaches terminal range of motion. *Pincer impingement* occurs due to acetabular over coverage, which may be focal or global, and damages the labrum as the excess rim impacts against the femoral neck. Both cam and pincer impingement limit hip range of motion and cause repetitive edge loading. This results in progressive labral injury, chondral injury, and hip degeneration that is irreversible [1].

The etiology of FAI is multifactorial, with both genetic and acquired components. One explanation for the variations in hip morphology stems from the adaptive changes that occurred as humans evolved into a bipedal species. The ape ancestral lines demonstrated *coxa rotunda*, or round, spherical hips to facilitate the ability to climb. This type of hip is rarely seen in mammalian runners and jumpers that require a sturdy, stable hip with a thick neck, or *coxa recta*. The human hip exhibits the evolution from climbers to upright runners, with morphologic components of both

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coxa recta and *coxa rotunda* that may contribute to FAI [2]. Impingement appears to be a heritable trait, as evidenced by the fact that siblings of patients with FAI have a relative risk of 2.8 that they will also have the cam deformity [3]. FAI also has been shown to result from acquired deformities, such as in the case of slipped capital femoral epiphysis resulting in a cam deformity [4]. Increased athletic loads in skeletally immature ice hockey players have a greater prevalence of α angles associated with cam FAI than do skier-matched controls [5].

The abnormal bony morphology that characterizes FAI creates pathologic changes to the hip joint over time. Studies have shown that 90 % of all patients with labral and chondral damage have underlying bony abnormalities [6, 7]. Hip pathomorphology predictably leads to abnormal loading of the hip joint, which causes progressive joint deterioration [8–10]. The two most common mechanisms for abnormal joint loading are FAI and dysplasia [11–13]. Abnormal hip loads result from static and dynamic mechanisms, and it is essential for the clinician to understand the roles of these mechanisms as this will direct treatment strategies. The etiology of overload may be multifactorial: FAI may occur in the setting of dysplasia or acetabular overcoverage. Some patients have mild dysplasia and impingement, which can prove to be a difficult clinical dilemma in identifying whether their symptoms are from dynamic impingement or static overload.

Static Overload

Static overload occurs due to abnormal stress and asymmetrical loading between the femoral head and the acetabulum in the axially loaded position. This results in an incongruent joint with abnormal loading of the acetabular and femoral cartilage, with or without instability. Hip pain related to static overload does not require motion across the hip in order to be painful. The most common type of static overload is dysplasia with lateral or anterior undercoverage of the femoral head. It can also result from excessive femoral antetorsion or a proximal femoral valgus deformity. The key clinical component when evaluating patients with dysplasia is to identify whether the patients are experiencing pain from static overload, which may be best treated with osteotomies that modify the amount of acetabular coverage and/or the position of joint loading. Arthroscopy, which addresses pathology from dynamic components, is unlikely to be helpful for pathologies that are the result of static mechanisms. However, some patients with hip dysplasia also have components of dynamic impingement, which is modifiable with arthroscopic surgery.

Impingement

Impingement occurs with dynamic movements across the hip joint, and therefore involves both fixed anatomical structures (the bones and joint) and soft tissues such as muscles (nerves, tendons, ligaments, and blood vessels). Dynamic intra-articular

impingement occurs with cam impingement, pincer impingement, or a combination of both. Pain develops secondary to repeated functional movement patterns that exceed the anatomic and physiologic capacity of the joint [8]. As joint pathology develops, patients will frequently develop compensatory muscular dysfunction involving the adductor longus, proximal hamstrings, hip abductors, and hip flexors [9, 11, 13]. Muscle atrophy or weakness and motor control deficiencies should be addressed in physical therapy prior to possible surgical intervention. Even in patients with recalcitrant symptoms, it is important to address the muscle weakness postoperatively within pain-free limits in order to maximize their outcome.

Cam impingement is defined by a loss of femoral head–neck offset and an aspherical femoral head. The insufficient offset typically occurs at the 1–2 o'clock position of the femoral head (12 o'clock being the most superior aspect of the femoral head in a standing position). Cam impingement is the most common morphology found in young athletic males [14]. Pathologic changes are caused by repetitive entry of the aspherical portion of the femoral head into the hip joint during flexion and internal rotation. This results in a shear injury to the transition zone of the labrum and the adjacent acetabular articular cartilage [15, 16]. The clinical pathology from cam impingement is a detachment of the transition zone cartilage rather than an intrasubstance labral injury [6, 17]. The size of the cam correlates with the degree and location of cartilage injury [18]. Patients who present with a longer duration of symptoms typically have a higher severity of cartilage injury [17–19]. Transition zone tears that occur in cam deformities may have a better prognosis than intrasubstance labral tears because the transition zone preserves the vascular supply from the capsule [20].

The second common category of dynamic impingement is pincer or rim impingement, and results in compressive injury to the labrum. Rim impingement can result from acetabular retroversion or overcoverage. Acetabular retroversion can be seen on plain radiographs as a cross-over sign. However, the cross-over sign on plain radiographs can be manipulated by orientation of the acetabulum, so retroversion is best categorized on cross-sectional imaging [21–23]. Focal overcoverage at the anterior superior acetabulum can appear as a cross-over sign on plain radiographs even though the patient has normal acetabular version as seen on a CT scan. Focal resection of the overcovered area is most appropriate in this clinical scenario as opposed to an osteotomy to correct version. Both focal retroversion [12] and global overcoverage are more common in females [13, 24, 25]. Another mechanism for rim impingement occurs with retrotorsion of the proximal femur. Patients with retrotorsion have reduced functional internal rotation and increased external rotation [8, 26, 27]. Compressive injuries to the labrum cause an intrasubstance injury, which frequently results in heterotopic bone formation, making it less amenable to repair [21]. Rim impingement results in more limited chondral damage as compared to cam injury mechanisms [8]. With rim impingement, occasionally the femoral head will lever out of the joint from supraphysiologic motion against a relative point of rim overcoverage, resulting in a contrecoup chondral injury [12, 28]. Patients that fall on a flexed and adducted hip with a posteriorly directed force can experience hip instability. Hip subluxation or dislocation can result due to abnormal contact between the anterior

femoral head against the acetabulum [28, 29]. Posterior hip instability, ranging from frank dislocation to subtle instability, has been documented in the setting of femoroacetabular instability due to posterior levering of the femoral head from decreased internal rotation [30]. While rim impingement can occur in isolation, the most common presentation is a mixed form of cam and rim impingement [6, 12].

Extra-Articular Impingement

In addition to intra-articular impingement, trochanteric-pelvic, ischio-femoral, and subspine extra-articular impingement may occur. Trochanteric-pelvic impingement occurs when the greater trochanter abuts up to the pelvis during abduction and extension, and is typically caused by Perthes disease and the resultant short varus femoral neck [22, 31]. Ischio-femoral impingement is a result of abnormal contact between the ischium and the lesser trochanter. Clinical examination may identify this with posterior hip and buttock pain that are incited and exacerbated by extension, adduction, and external rotation of the hip [23, 24] Subspine impingement results in contact between the anterior inferior iliac spine and the inferior femoral neck in hyperflexion. Apophyseal avulsion injuries in adolescents can lead to an elongated anterior inferior iliac spine, and a narrowed subspine space. Extra-articular impingement can result in localized pain to the site of impingement, but it also could present atypically if nervous or vascular structures are caught in the sites of impingement.

Clinical Evaluation of Femoroacetabular Impingement

History of Present Illness

The clinical evaluation and workup for patients with FAI can be challenging due to the various types of impingement and overlapping pathologies. A layered approach to diagnosis often will provide a comprehensive diagnosis [32]. The layers from deep to superficial are comprised of the osteochondral layer, capsule-ligamentous layer, muscular layer, and the neural layer. The diagnosis should take into account the effects of the underlying bony morphology upon these tissues. The history should guide the clinical examination, and should, in turn, direct the imaging studies conducted.

The patient's history is the cornerstone of appropriate decision making in the setting of hip pain and FAI. Many patients with FAI by radiographic criteria alone are asymptomatic [33–37]. It is therefore essential to identify whether the patient's symptoms are a result of FAI or a different etiology. Pain from FAI typically occurs with specific activities that create anatomical impingement. Internal impingement caused by a mixed cam and pincer mechanism frequently results in groin pain that is exacerbated by activities that place the hip into a position of impingement: flexion, adduction, and internal rotation (FADIR). Patients typically report difficulty

sitting for long periods of time or pain with activities that require recurrent or constant hip flexion such as maintaining an athletic stance. Patients with a longer duration of symptoms will likely have more severe cartilage injury and may have a worse prognosis than patients with a shorter duration of symptoms. Traumatic injuries such as a fall onto a flexed knee with a flexed hip above it may signal a potential subluxation event. Snapping, popping, clicking, or catching may be the result of labral pathology, synovitis, loose bodies, a hypertrophic ligamentum teres, iliopsoas snapping over the anterior capsule-labral complex, or IT band snapping over the greater trochanter. The location of the pain also helps establish the diagnosis. Hip pain from mixed cam and pincer FAI frequently localizes to the groin, directly anterior to the hip joint. The senior author has noted a possible correlation between patients with posterior buttock pain that have synovitis of the ligamentum teres, with resolution of symptoms after ligamentum teres debridement. Pain frequency and temporal pattern are also important components of the history, since pain from FAI is less likely a constant phenomenon, and more likely to have a mechanical etiology. Constant pain may be unrelated, or it may reflect more severe joint damage. It is also important to understand the patient's current activity levels and desired activity levels. The patient's athletic participation should be assessed as well as the level at which they participate. The patient should be questioned about potential modifications that they have had to make to their normal performance. If surgical treatment is indeed the plan, expectations for return to sport should be assessed and counseled. Each of these questions will help the clinician better understand the patient's problem and goals for treatment.

Effectiveness of prior treatments should be described during the initial assessment. Common modalities for hip pain include physical therapy, active release therapy, non-steroidal anti-inflammatory medications (NSAIDs), and steroid injections into the hip. The efficacy of the treatments can help the clinician understand the patient's specific pathology and direct further treatment. It is also important to understand the types of treatment that occurred in physical therapy, passive therapy consisting solely of modalities is much less effective than a combination of deep tissue work and specific core and gluteal strengthening exercises. Also, the patient's specific response to an intra-articular hip injection should be investigated, as often times the relief will be fleeting and therefore deemed to be unsuccessful by the patient. This could suggest that the local anesthetic identified the problem as being intra-articular, even though the steroid was not efficacious.

Physical Examination

The information revealed through the patient's history will guide the physical examination. The physical examination is used to narrow a differential diagnosis and direct imaging studies and treatment. The essential components of the clinical examination include gait assessment, hip range of motion, provocative pain testing, assessment of tenderness to palpation of the periarticular hip regions, and a neurovascular examination.

The functional assessment for hip patients is typically accomplished by watching the patient ambulate, but for FAI the highest yield may begin by observing the patient's posturing upon entry into the room. Patients with FAI may sit with the affected hip slightly more extended, or they may lean back in the chair rather than sitting upright because the flexed femur is impinging on the anterior acetabulum. Patients may use their hands to lift themselves up out of a chair rather than leaning forward. An externally rotated affected lower extremity may be noted during gait, but one must also screen for torsion abnormalities, as patients with femoral retroversion may present the same way. The gait assessment incorporates components of a neurological examination, as functional strength may be evaluated during such tasks as sit to stand and ambulation; one may further examine the patient's distal motor function with toe-walking and heel walking.

Range of motion is assessed with the pelvis stabilized in order to avoid missing contractures by compensatory pelvis mobility and misinterpreting extraneous motion as hip motion. Motion can be retested in a seated, supine, or prone position to verify contractures. Hip extension should be tested with the patient supine and the contralateral hip flexed to the chest. This isolates the pelvis, and if the patient cannot rest the ipsilateral hip and knee flat on the table, it suggests there is a flexion contracture of the hip. Normal hip rotation range of motion should include 30° of internal and 45° of external rotation; any asymmetry should be noted. Those with FAI typically present with decreased internal rotation without the same gain in external rotation (e.g., 45° of external rotation and 10° of internal rotation). FAI patients typically have reduced hip flexion and hip internal rotation at 80–90° of hip flexion. Range of motion is one of the most important portions of the examination for FAI, as it may elucidate the underlying bony structure.

A key component of the range of motion is the dynamic assessment of motion with attention paid to the resulting pain location and intensity. Patients with FAI typically have anterior pain with FADIR. Pain in the groin with straight flexion may suggest subspine impingement. Pain in the buttocks with hip extension and external rotation could be a result of trochanteric pelvic impingement. Pain in the medial groin or genital area with adduction and external rotation could suggest ischiofemoral impingement.

Imaging Evaluation

Imaging evaluations should be obtained to confirm the diagnosis, using the clinical history and examination as a guide. Radiographs that are commonly used as the first line of evaluation include the Dunn view at 45° or 90° of hip flexion, the AP pelvis, and the false profile view. The Dunn view is preferable to the frog leg lateral view because it allows a profile evaluation of the location of most femoral neck cam deformities [38]. The alpha angle is also calculated from the Dunn view to estimate the severity of the cam deformity. The AP pelvis examination is helpful to evaluate for retroversion of the acetabulum by the presence or absence of a crossover sign, the amount of acetabular coverage of the femoral head, and any evidence of arthritis. The false profile view is

helpful to evaluate anterior coverage of the femoral head in the setting of dysplasia as well as to evaluate the anterior inferior iliac spine region for subspine impingement.

Magnetic resonance imaging (MRI) is the next most common step to evaluate FAI. It provides an accurate evaluation of the hip cartilage, ligamentum teres, labrum, capsule, and surrounding muscles and nerves. Recent advancements in cartilage imaging through special sequences, including dGEMRIC, T1 rho, and T-2 mapping, have significantly improved our ability to evaluate delamination, focal cartilage loss on the acetabulum or the femur, and chondromalacia [39, 40].

Computed tomography scan (CT scan) is the gold standard for the evaluation of anatomical bone deformity. 3D reconstructions provide a detailed analysis of the proximal femoral and acetabular anatomy. In addition, dynamic modeling software is now available that allows for the evaluation of impingement patterns [41]. CT scans can clarify whether deformities are better treated with open versus arthroscopic procedures, as they readily identify patients with severe dysplasia, acetabular version, or femoral torsion abnormalities. CT scans with 3D reconstructions give the surgeon a template upon which precise surgical planning may occur, directing the exact areas for femoral and acetabular decompression.

FAI Management

Non-operative Treatments

The first line of treatment for patients diagnosed with FAI is non-operative management. Activities that exacerbate the patient's symptoms should be modified to alleviate pain. NSAIDs taken on a consistent basis may assist with pain and inflammation secondary to impingement. Physical therapy should be directed to address muscular weakness, motor patterning, posture, and soft tissue restrictions. If the patient has an increased pelvic tilt, physical therapy may be beneficial in restoring lumbopelvic control and aiding the patient in establishing greater arc of pain-free motion. No data currently demonstrates the efficacy of these interventions for symptomatic hips, and further research is needed in this area.

Corticosteroid injections with local anesthetic may be a useful modality to localize pain and treat inflammation. Patients that have significant pain relief following a local anesthetic injection have a 90 % likelihood of an intra-articular abnormality [42]. While it is expected that symptoms from intra-articular impingement will resolve with an injection, symptoms from extra-articular impingement should not be affected [43]. Lower volume anesthetic injections (<5 mL) are less likely to cause discomfort from capsule over-distension, which may result in a persistent pain from the injection even though the patient's underlying symptoms are completely masked. If the injection is diagnostic, it is important that a clinical examination is performed prior to the injection, and again shortly after it is completed. This allows the patient and the surgeon to compare how effective the injection was in alleviating impingement symptoms. It is unknown whether corticosteroid injections provide any benefits or detriment to the hip joint in the treatment of FAI.

Surgical Treatment for FAI

Indications

Many studies have demonstrated that open and arthroscopic surgical approaches can be effective for the correction of mechanical abnormalities due to symptomatic FAI [11, 44–51]. The operative intervention that the surgeon is most comfortable with should be used to correct the pathoanatomy identified during the workup. In the setting of FAI, the surgeon should be able to perform an acetabuloplasty, a femoral head osteoplasty, chondroplasty, and labral debridement or refixation. There are unique challenges to both open and arthroscopic techniques to treat these pathologies. Some pathologies are better suited for open procedures, such as FAI with underlying femoral torsion or acetabular version abnormalities.

The indication for surgery in patients that have a diagnosis of FAI is recalcitrant pain despite conservative modalities. Ideally, the patient exhibits clear evidence of a treatable structural pathoanatomy that correlates with soft tissue injury patterns and pain on clinical examination. The ideal candidate should present with no evidence of articular cartilage wear.

Surgical contraindications include cartilage loss and asymptomatic patients with incidentally found labrum tears or FAI. Cartilage loss is evaluated on both plain radiographs and MRI, and correlates with a poor prognosis for FAI surgery. Factors that may be indicative of a poor outcome include loss of >50 % of the cartilage thickness in a weight bearing zone, less than 2 mm of joint space in the weight bearing zone, or the presence of full thickness cartilage loss with exposed subchondral bone [47]. Many patients may be diagnosed with FAI or a labral tear incidentally in the process of a workup for a different pathology. Asymptomatic patients with FAI or a labral tear should not undergo surgery based upon the current best available evidence [33–37, 52].

Complications of Surgery

For patients who undergo surgical intervention for FAI, numerous complications should be considered and discussed with the patient prior to the procedure. The most likely complication is continued pain from insufficient bone resection and persistent postoperative impingement [53]. Inadequate resections are related to surgeon inexperience and inaccurate portal placement, and is the most commonly cited cause for failure in the literature [53, 54]. Many other intraoperative complications such as iatrogenic cartilage injuries, labral injury due to traumatic access into the central compartment, or instrument breakage, are likely underreported. Transient or permanent nerve palsies can also result from prolonged traction times and inexperience [54]. Injuries to the sciatic, femoral, lateral femoral cutaneous, and the pudendal nerves occur at a rate of 10 % of the cases performed [55, 56]. Placement of the

perineal post for traction results in the potential for pressure necrosis of the skin in the perineum secondary to prolonged traction times. Abdominal compartment syndrome has been reported in the literature as a result of fluid extravasation from the hip into the abdomen [57, 58]. Avascular necrosis is a complication which likely results from disruption of the blood supply to the femoral head from traction or surgical techniques [59]. Instability and dislocations have been reported to occur after capsulotomy in patients undergoing hip arthroscopy. Patients with dysplasia are at a higher risk for postoperative instability [27]. Heterotopic ossification occurs in as many as 8 % if cases of FAI surgery [60]. Heterotopic ossification likely arises secondary to increased bone debris from the osteoplasty as well as increased bleeding associated with capsular incisions. It can be reduced to <1 % of patients with NSAID prophylaxis with Indomethacin 75 mg daily for 4 days followed by Naprosyn 500 mg twice daily for 4 weeks [60]. Most cases of heterotopic ossification are asymptomatic; however, there are rare cases of symptomatic Brooker III or IV heterotopic ossification after hip arthroscopy. Heterotopic ossification restricts motion and causes pain that may require revision surgery. The incidence of deep venous thrombosis is reported to be as high as 3.7 %, but the senior author's experience is that the rate is substantially lower [53, 61]. Femoral neck fracture is another rare complication that can occur from over-resection of the cam deformity [62].

Goals of Surgery

Arthroscopic surgery for FAI is the treatment of choice by the senior author. The surgery is divided into eight separate steps in order to systematically approach each component of pathoanatomy. The steps are: (1) patient positioning, (2) portal access, (3) joint visualization, (4) rim preparation, (5) labral refixation, (6) establishing access to the peripheral compartment, (7) femoroplasty, and (8) capsule closure. The procedure is divided into these steps in order to delineate clear goals with each step that will maximize patient safety and good outcomes.

(1) Positioning
The first step of surgery is patient positioning. The goal is to position the patient so that safe, reliable access can be obtained for the procedure while minimizing risk to the patient. Consistency in positioning techniques with the surgeon and the ancillary staff will minimize errors. Hip arthroscopy can be accomplished in both the supine and lateral positions. The ipsilateral arm should be positioned securely with padding so that it remains outside of the operative field throughout the procedure. A large, padded perineal post is used to decrease the risk of pressure necrosis or pudendal nerve palsy during traction. The feet should be securely attached with appropriate padding so that traction can be maintained throughout the procedure. A small amount of counter-traction should be applied to the contralateral hip during setup to provide a fulcrum through which the hip post can maintain traction.

Traction is initially applied by placing longitudinal manual traction to the ipsilateral hip while it is positioned in about 30° of abduction. The hip is then adducted to a neutral position while visualizing the amount of distraction with fluoroscopy. Approximately 8–10 mm of joint space widening confirms adequate distraction. It also is helpful for the surgeon to be attentive to the suction seal on the hip and the ease with which the hip is dislocated. Hips that easily dislocate with minimal traction may be less stable, which may indicate how robust a capsule repair is required to prevent postoperative instability. If the traction seal is not broken with distraction, then a spinal needle can be carefully placed into the joint at the beginning of the procedure. Internal or external rotation of the hip may also facilitate hip joint access for patients that have proximal femoral torsion deformities (attempt to mitigate the deformity by rotating the foot in the opposite direction of the deformity). It typically requires about 50 pounds of force to ensure adequate distraction during the procedure. Traction time should be minimized to reduce the risk of pressure necrosis or neurologic traction injury.

(2) Portal Access

The second step in hip arthroscopy is to gain access to the joint through portal placement. Byrd described three portals to access the hip joint: the anterolateral peritrochanteric portal, the posterolateral peritrochanteric portal, and the anterior portal [63, 64]. Since then, many different portals have been described, but the two most commonly used portals are the anterolateral peritrochanteric portal and an anterior portal. Additional portals include the distal anterolateral accessory portal, the posterolateral peritrochanteric portal, the proximal anterolateral accessory portal, and various distal entry points that optimize suture anchor placement [65].

The first portal established is the anterolateral peritrochanteric portal. A spinal needle is placed approximately 1–2 cm superior and 1–2 cm anterior to the anterosuperior edge of the greater trochanter. While the hip is in traction, a palpable band (the iliotibial band under tension with the attachment of the gluteus maximus) can be felt just superior to and along the anterior edge of the greater trochanter. The portal should be placed just posterior to this band. A spinal needle is then advanced parallel to the floor into the hip joint. Ideally, the spinal needle plane on AP fluoroscopy is parallel to the sourcil of the acetabulum, and positioned as closely to the femoral head as possible without hitting the articular cartilage. This placement decreases the likelihood of passing the needle and subsequent cannula through the labrum. As the suction seal is released by way of an air arthrogram, there may be an increase in the amount of distraction. If the spinal needle maintains proximity to the femoral head with increased distraction, then it is less likely that the labrum was penetrated. Lastly, the joint should be insufflated with about 20 mL of saline, which should then produce a fluid flashback to confirm intra-articular placement without labral or soft tissue blockage. After this is verified, a guide wire is then placed through the spinal needle until it rests in the central fossa of the acetabulum. A small diameter cannula (4.5–5.0 mm) is then advanced into the joint over the guidewire. A 70° arthroscope is

then advanced into the joint through the cannula. The scope is aimed in the anterior direction in order to visualize the junction between the femoral head and the anterior acetabulum and labrum. The fluid pump is left off until an outflow is established.

An anterior portal is established with at least 6 cm of space between the portal sites in order to have maximum working utility between the two portals, as portals nearer together can make intra-articular work difficult. The anterior portal is at the greatest risk for causing neurovascular injury due to its close proximity to the lateral femoral cutaneous nerve [65]. The anterior portal is placed just inferior to a line extended laterally over the pubic symphysis, and just lateral to a line drawn inferiorly from the anterior superior iliac spine. The spinal needle is directed 45° cephalad and 30° medial into the joint. Direct visualization of the anterior triangle with the arthroscope can assist in providing careful entry into the joint without injury to the femoral head. It is also recommended that the surgeon place the needle closer to the acetabulum, as it is better to walk the spinal needle inferiorly along the anterior inferior iliac spine towards the acetabulum rather than causing repetitive injury to the femoral head cartilage if the needle is walked superiorly along the femoral head until it is identified by arthroscopy. Lastly, it is helpful in this step to use a hemostat to bluntly probe the anterior triangle joint capsule in order to confirm the trajectory for the spinal needle prior to placing it through the capsule. Once the second spinal needle is placed, the fluid can be turned on to flush the joint and improve visualization. A guide wire is then placed through the spinal needle and the second trochar can be advanced into the joint atraumatically over the guide wire. As the trochar is advanced over the guide wire, the wire is withdrawn until it protrudes no more than a centimeter through the capsule to ensure that it is not forced into the joint and inadvertently broken. Once these two portals have been established, the surgeon can move onto the next step to improve access to the joint by performing the capsulotomy as described below. Additional portals may be placed after the capsulotomy is performed, depending on the preference of the surgeon and the need for access to specific anatomical pathologies.

The most common additional portals include the distal anterolateral accessory portal and the posterolateral peritrochanteric portal. The distal anterolateral portal is placed in line with the lateral portal and approximately 5–6 cm distal to it. This portal can be used for percutaneous placement of anchors during labral repair in order to decrease the risk of intra-articular breech of the anchor, which can occur with more proximal starting point trajectories. It also allows the anchor to be placed closer to the acetabular rim. The distal portal also can be used during the T capsulotomy, femoroplasty in the peripheral compartment, and capsular closure. The posterolateral peritrochanteric portal is placed just posterior and proximal to the posterolateral tip of the trochanter. Caution should be used when placing this portal due to its close proximity to the sciatic nerve. This portal is more commonly used in the lateral position.

(3) Joint Visualization and Capsulotomy
The interportal capsulotomy is performed after the first two portals are established. The capsulotomy should be planned to completely expose the rim and labrum pathology. The capsulotomy should be planned several millimeters away from its attachment of the capsule on the acetabulum so that there is a rim of tissue on the acetabulum that may be used for repair of the capsulotomy after the procedure. Since the capsule is thick and can be difficult to cut, it is helpful to use a sturdy and sharp arthroscopic knife, which allows the surgeon to have more control.

While some surgeons only utilize the interportal capsule cut to perform arthroscopy, visualization for the femoral osteochondroplasty can be improved substantially by performing a T-capsulotomy. This is completed after the traction is released, most frequently after all work in the central compartment (rim resection, labral refixation, etc.) is completed. The T-capsulotomy is performed by cutting along the capsule overlying the femoral neck from the interportal capsulotomy to the distal attachment of the capsule as needed for visualization.

(4) Rim Preparation/Resection
After the interportal capsulotomy is completed, a dissection is performed between the labrum and the capsule, along the length of the labral injury. The dissection is performed with low frequency radio-ablation devices and a small motorized shaver. The rim of the acetabulum is exposed by dissecting subperiosteally towards the capsule and the labrum. This usually does not completely detach the labrum, but provides exposure to recess the rim of the acetabulum in cases of rim impingement. This also allows for decompression of any areas of impingement in the subspine region [31]. If the subspine area is decompressed and/or the rim is recessed, it is imperative that the decompression is extended to the transition zone cartilage. This ensures an adequate decompression. Overresection of the acetabular rim can also result in poor outcomes [66]. Fluoroscopy is an additional tool that can be used as an adjunct to arthroscopy to ensure the appropriateness of rim and subspine resection [67].

(5) Labral Refixation or Debridement
After the rim resection is performed, the labrum will likely be destabilized. The detached or destabilized labrum should be secured to the acetabular rim with suture anchors. Suture anchors are placed through the most distal portal in order to achieve an entry trajectory into the acetabular rim that is parallel to the joint surface in order to avoid joint penetration. As anchors are placed along the anterior and medial aspect of the acetabulum, it is possible for the anchor to protrude through the pelvis and into the iliospoas tendon, causing persistent pain following surgery. This can be prevented by passing a guide wire through the drilled tunnel prior to anchor placement. If the wire hits a bony endpoint, then the anchor is completely inside the bone. If the wire passes bi-cortically, then the tunnel should be redrilled to ensure that the anchor is not prominent. In addition to this, if the anchor trajectory converges on the acetabulum, it is possible for the anchor to pass through the acetabular cartilage. Direct visualization

of the acetabular joint surface during drilling will help the surgeon verify that the anchor is placed outside of the joint.

Once the anchors are placed, the suture is passed through the labrum. If the labrum is robust, then a vertical mattress suture pattern will re-establish an intact labrum appearance most anatomically. This ensures that the labrum isn't deformed, it keeps the knot away from the joint surface, and it minimizes suture contact with the femoral head. If the labrum is friable or attenuated, passing a vertical mattress suture could possibly destroy what good tissue remains. In this scenario, simple sutures should be placed around the labrum with the knots tied next to the anchors, as far from the articular surface as possible. Suture anchors and sutures are placed around the labrum until the labral seal effect has been re-established [68–70]. Labral eversion should be avoided in order to maximize the suction seal.

(6) Access the Peripheral Compartment
After rim resection and labral refixation, the traction is released and the limb is brought into 30–45° of hip flexion. The most common cause of hip arthroscopy failure is inadequate resection, and it is therefore imperative to have visualization that adequately allows inspection of the femoral neck in order to evaluate the adequacy of the resection. If the interportal capsulotomy does not allow for adequate visualization, a "T" capsulotomy should be performed. The T-capsulotomy is performed over the center of the cam lesion, generally at approximately the 1:30 position. During arthroscopy, this position can be identified by placing the arthroscope into the anterior portal and placing a switching stick in the distal anterolateral portal. The switching stick is advanced along the hip capsule through the intermuscular interval between the capsular insertion of the gluteus minimus on the lateral limb of the iliofemoral ligament, and the capsular insertion of the iliocapsularis on the medial limb of the iliofemoral ligament. Once this plane is identified, a cannula is advanced into the space and a radiofrequency ablation probe is used to demarcate the interval. A beaver blade is then used to incise the capsule along the neck of the femur toward the intertrochanteric groove. This leaves sharp edges on the capsule that can be repaired after the femoroplasty. Once the T-capsulotomy is performed, there should be excellent visualization of the femoral neck from the inferior vincula to the superior and posterior retinacular vessels. With a 70° arthroscope, visualization can be achieved circumferentially around the hip. A switching stick can be used to mobilize edges of the capsulotomy for improved visualization during the femoroplasty.

(7) Femoroplasty
The goal of the femoral osteochondroplasty is to achieve impingement-free range of motion throughout a dynamic examination by restoring the normal head–neck sphericity and adequate offset. Under-resection can result in persistent symptoms postoperatively, and resection of greater than 30 % of the head–neck junction can weaken the load-bearing capacity of the femoral neck and result in a fracture [71]. For this reason, it is important to repeatedly inspect the femoral osteoplasty with fluoroscopy as the procedure is performed. It is also helpful to change arthroscopic views frequently to give different perspectives

on the adequacy of resection. The osteoplasty is preceded by marking the periphery of the cam lesion with a radiofrequency ablation probe, and then a shaver is used to remove the periosteum over the cam. A 5.5 mm burr may then be used for bony resection. Caution must be taken when using fluoroscopy in order to prevent over-resection, as it only shows the resection in terms of a tangent line along the edge of the femoral neck. If the osteoplasty is being performed anterior or posterior to this tangent line, then it will appear on fluoroscopy as if no resection has been performed, even if a substantial portion of the femoral neck were resected. One way to verify that the fluoroscopy is evaluating the same plane in which the burr is working is to place the burr on the bone and then rotate the fluoroscopy unit until the radiographic image shows that the burr is on the very edge of the femoral neck, with no overlap between the cortex and the head of the burr. Sequential removal of the cam deformity occurs in the superior, superolateral, anterior, anterolateral, and inferior portions of the cam lesion. Care should be taken to identify the posterior retinacular vessels by their shape and pulsation, and preserve them during the posterolateral portion of the resection. The resection can proceed posterior to these vessels so long as the instruments remain proximal to the point where the vessels enter the femoral head/neck. If the cam lesion extends superior and lateral, it is helpful to extend and internally rotate the hip to improve access for the femoral osteoplasty. Similarly, if the cam lesion extends medially and inferiorly, it is helpful to increase hip flexion and internal rotation for improved access for the femoral osteoplasty. The vast majority of cam deformities can be adequately decompressed without traction; however, traction may be considered for some severe deformity scenarios. At the completion of the osteoplasty, bony debris should be removed from the peripheral compartment and a dynamic examination should be performed to verify improved and impingement-free motion.

(8) Capsular Closure

While there may be indications for a release of the capsule in some individuals, basic surgical principles indicate that normal anatomy should be restored at the completion of the surgical procedure [72]. Hip instability may occur if the capsule is not adequately repaired [27]. It is helpful after the femoral osteoplasty to use a radiofrequency ablation device to further clear off the edges of the capsule and develop a small extra-capsular working space for capsular repair. We repair the T portion of the capsulotomy first with 3–4 side-to-side, simple interrupted sutures. This may be accomplished by using a penetrating suture passer and retriever to pass sutures through each limb of the capsulotomy. Once the T portion of the capsulotomy is completed, the interportal capsulotomy is then closed. If adequate capsule was preserved on the acetabular rim, then the capsule can be repaired to itself. Not uncommonly, the capsule on the rim of the acetabulum has to be taken down to perform the rim resection or subspine decompression. In this scenario, the capsule is repaired to the indirect head of the rectus femoris. It is helpful if the suture is passed first through the femoral or distal limb of the capsule, and then an arthroscopic grasper can be used to place the free end of the suture into the recess between the labrum and the

acetabulum capsule. A penetrating suture retriever can then be placed through the acetabular capsule (or indirect head of the rectus femoris) and grasp the free suture limb that is then pulled back through the capsule on the acetabulum to complete the simple interrupted suture pattern. Arthroscopic knots are used to tie all sutures. The interportal capsulotomy usually requires 2–4 simple interrupted sutures. The authors place sutures until the head and neck are completely blocked from view with the arthroscope.

Postoperative Rehabilitation

The physical rehabilitation after hip arthroscopy for FAI will vary depending on the patient's pathology and the specific procedures performed. The authors routinely restrict patients to foot-flat weight bearing for a range of 10 days to 4 weeks, depending on the magnitude of the cam resection for FAI and concomitant procedures. Patients utilize a continuous passive motion (CPM) machine and instructions for 2–4 h daily use, or a stationary bike without resistance. The CPM may reduce adhesions between the capsule and the labrum, increase joint lubrication, and prevent contractures from developing. As the weight-bearing restrictions are lifted, there is a gradual progression and weaning from the crutches. Patients will often demonstrate decreased gluteus medius endurance and decreased extension range of motion, which will impede normal gait. The first 6 weeks of the rehabilitation process are focused on increasing range of motion within the pain-free range and returning to normal activities of daily living. The second 6 weeks build upon the gains from the first phase and transition to more functional strengthening of the core and hip (namely the gluteus medius and maximus) musculature. This is in preparation for the third phase during which the patient may begin to progress to light jogging and plyometrics. The patient must demonstrate adequate lumbopelvic stability and muscular endurance in order to progress to this phase. The progression is based not only upon soft tissue healing time frames, but also the achievement of functional milestones. Full return to sports can generally be achieved within 6 months. Patients may continue to experience improvements up to 1 year postoperatively [73, 74]. It is important for patients to maintain a core and gluteal strengthening program as long as they are active.

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Chapter 7
Osteonecrosis

David R. Steinberg and Marvin E. Steinberg

Introduction

Osteonecrosis, also known as avascular necrosis, aseptic necrosis, and idiopathic necrosis of the femoral head, is not a specific disease entity but is rather a condition in which a localized area of bone becomes necrotic primarily due to an impairment of its blood supply. This may result from a number of etiologic factors acting alone or in concert. It was first described in 1738 by Alexander Munro [1], and since then has been the subject of a number of reports which have appeared with increasing frequency. This chapter will not attempt to provide a comprehensive review of osteonecrosis (ON), but will focus on our current understanding of the etiology and pathophysiology as it directly affects our ability to diagnose and treat this condition. We will be concerned primarily with non-traumatic ON in the adult hip since this is the anatomic region most often affected and most studied.

Clinical Features

The clinical picture of ON is nonspecific. The exact prevalence is unknown but it is estimated that over 30,000 new cases are diagnosed annually in the United States alone, and that approximately 10 % of all primary total hip replacements are performed for ON. The incidence is considerably higher in other parts of the world,

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especially in Asia. This condition affects primarily younger adults in their 30s and 40s. For weeks, and perhaps even months, after the initial vascular insult the affected area may remain asymptomatic. When symptoms develop, they do so gradually. The femoral head is the region most involved, followed by the humeral head, the knee, and less frequently the small bones of the wrist and foot. When one hip is affected, the other will be involved over 60 % of the time, and in 15 % of cases other regions of the body will also be involved. Symptoms do not develop simultaneously in all affected regions. In approximately 80 % of clinically diagnosed cases of hip involvement, the condition will progress without specific treatment, and will usually result in flattening of the femoral head and eventually degenerative changes in the joint. Pain and disability increase gradually, often becoming severe, and may be associated with a limp and decreased range of motion. However, small areas of necrosis, especially if not close to a weight bearing articular surface, may remain asymptomatic and heal spontaneously. Known etiologic factors can be identified in approximately 80 % of cases if searched for carefully and are important in leading to the diagnosis. This is usually confirmed by a characteristic radiograph appearance. If radiographs fail to confirm the diagnosis or if they show involvement of only one region, it is essential that other suspected areas, especially the opposite hip, be examined with MRI. This is a very sensitive and specific test for ON. If an area appears normal on MRI, the chance that ON will appear later is less than 10 % [2].

Other conditions which may resemble ON, such as transient osteoporosis of the hip (TOH) or bone marrow edema syndrome (BMES), cystic lesions within the femoral head, subchondral insufficiency fractures, and rapidly progressive osteoarthritis, must be ruled out. Other imaging studies, such as computerized tomography (CT), are of limited value. Positron emission tomography (PET) might eventually allow us to identify areas of ON even before MRI, but at present these techniques are not routinely employed. Laboratory tests are generally within normal limits, but may help to diagnose certain associated conditions such as Sickle Cell disease, hyperlipidemias, and certain coagulopathies. In selected instances genetic testing might indicate patients at risk for developing ON.

Early diagnosis, before femoral head collapse, is essential as it will allow early treatment with better results.

Etiology

The most common cause of osteonecrosis is trauma, such as a dislocation or displaced fracture of the femoral neck. In these cases the etiologic factor is mechanical injury to or compression of the vessels which supply the femoral head. In nontraumatic ON of the femoral head, a number of etiologic factors have been identified. The relative frequency with which they are encountered varies considerably and depends upon the demographics of the population from which the patients are drawn. In most series excessive alcohol consumption and prolonged corticosteroid

administration are by far the leading causes. The mechanisms involved are not entirely clear, but it is presumed that they involve alterations in blood coagulability and circulating lipids. This in turn results in intravascular thrombosis and/or embolization by red blood cells or lipid droplets [3]. In patients with hemoglobinopathies, such as Sickle Cell disease, emboli composed of clumps of abnormal red blood cells are formed, and in "Caisson disease" or dysbaric osteonecrosis, intravascular and perivascular nitrogen bubbles are responsible for interfering with the circulation. A number of other factors have been identified in patients with ON including local vascular abnormalities, gout, smoking, liver disease, systemic lupus erythematosus (SLE), and myeloproliferative disorders but etiologic associations are difficult to establish. Early in the investigation of this condition, an increase in the intraosseous pressure of the involved femoral head was noted and was considered to be a primary cause of osteonecrosis. However, later studies found increased pressure to be present in a number of other conditions unrelated to osteonecrosis and most investigators now consider this to be the result, rather than the cause, of ON.

In the 1990s Glueck et al. found that up to 70 % of their patients with osteonecrosis had certain subtle coagulopathies, specifically thrombophilia or hypofibrinolysis. They later found these conditions to be caused by specific gene mutations and a familial incidence was noted [4]. For quite some time it has been recognized that there is a high prevalence of ON in populations in China, Japan, Korea, and Taiwan. Recent studies have identified certain genetic abnormalities in these patients which could affect coagulation mechanisms. These include vascular endothelial growth factor (VEGF) polymorphism [5], and endothelial nitric oxide synthase (eNOS) [6] which could affect angiogenesis. Other recent findings include increased levels of plasma cryofibrinogen which could induce thromboembolic events, and modulation of P-glycoprotein activity, known to play a role in steroid hormone metabolism [7]. The role of marrow adipocytes has received further attention. An increase in their size or number could cause vascular impairment through mechanical pressure on local vessels similar to the presumptive mechanism in Gaucher's disease. In addition to factors which can have a direct effect on bone circulation, there are others whose action directly affects cell viability. Recently adipocytes have been found to release substances that can alter the function of osteocytes, as can circulating corticosteroids. Various cytotoxic agents and chemical substances, as well as radiation, can also directly affect cell viability.

Our understanding of the etiology of ON would appear to be getting more complex as new agents and factors are being identified. In certain situations a single factor alone can cause ON, whereas under most circumstances several factors may act in concert, hence the "multifactorial" basis for ON [8]. It should be emphasized that, although a number of systemic factors may play a role in the development of ON, the local vascular anatomy of the affected region is most important in explaining why it is these regions with limited collateral circulation and not the skeleton at random which develop ON. Despite a careful search for possible etiologic factors, in most series none can be clearly identified in 15–20 % of cases. These are often categorized as "idiopathic."

Pathophysiology

Although several systemic factors have been implicated in the development of ON, in the majority of cases it is the local factors which are most important. Hence osteonecrosis develops in certain specific anatomical regions where the circulation is limited with few collaterals. Impairment of the blood supply in these regions may result in local death of marrow elements and osteocytes. Anatomic and histologic studies of the proximal femur have identified the normal vascular anatomy of the region and have shown the pathologic changes in cases of ON. These are shown schematically in Fig. 7.1. The primary blood supply to the femoral head originates from the deep branch of the medial femoral circumflex artery (MFCA) which gives rise to the superior and inferior retinacular vessels. These, in turn, branch into the superior and inferior metaphyseal and the lateral epiphyseal vessels. The obturator artery supplies the artery of the ligamentum teres which ends as the medial epiphyseal artery. The most important vessels are the superior retinacular and lateral epiphyseal vessels which supply the anterior–superior aspect of the femoral head, the main weight bearing region and the area primarily affected by osteonecrosis. The other regional vessels are considerably less important and local anastomoses are limited [9–14].

Histologic and angiographic studies of femoral heads with osteonecrosis have identified consistent involvement of the superior retinacular and lateral epiphyseal vessels. Some attempt at vascular repair can be seen with ingrowth of new vessels from the stumps of occluded vessels and from other vessels in the region. However,

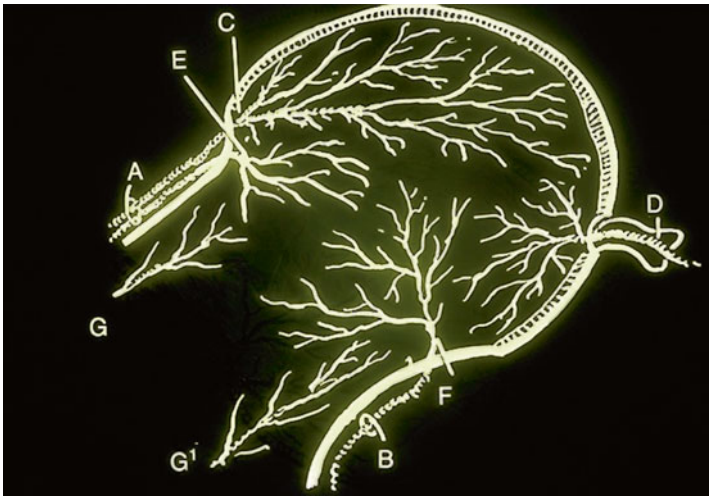

Fig. 7.1 Schematic drawing of the blood supply to the femoral head. (*A*) Superior retinacular vessels. (*B*) Inferior retinacular vessels. (*C*) Lateral epiphyseal artery. (*D*) Medial epiphyseal artery. (*E*) Superior metaphyseal artery. (*F*) Inferior metaphyseal artery. (*G*) Intramedullary vessels

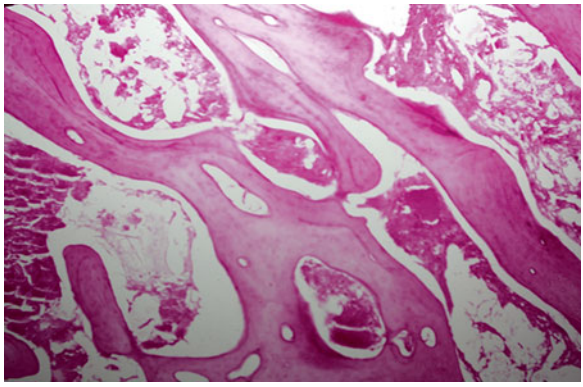

Fig. 7.2 Dead bone and marrow elements from the center of the necrotic lesion

this process is usually limited and is often blocked by the presence of necrotic material and collapsed bone (personal observation, MES).

Within hours of the vascular insult, death of marrow elements can be seen. Death of bone also takes place, but cannot be identified histologically until several days later when disappearance of osteocytes from their lacunae is noted (Fig. 7.2). Osteoclasts and phagocytic cells infiltrate the margins of the necrotic region and begin to remove dead tissue. This process is accompanied by the release of lysosomal enzymes. This is followed by the arrival of osteoblasts which attempt to repair the damage by laying down new bone directly upon the surface of dead trabeculae (Fig. 7.3). This composite of living and dead bone results in markedly thickened trabeculae which appear as radiodense or "sclerotic" regions at the margins of the infarct (Fig. 7.4). Adjacent areas from which dead bone has been removed become filled with fibrous tissue and amorphous debris, appearing as radiolucent or "cystic" areas.

(We use the University of Pennsylvania Classification of Osteonecrosis—Table 7.1). Within the first 2–3 weeks after the vascular insult, X rays appear normal but changes can usually be detected on MRI (Stage I) (Fig. 7.5a, b). However, they do not appear on routine radiographs until several weeks to months later (Stage II) (Fig. 7.6). The processes of osteolysis and bone resorption and bone repair continue, during which the affected area steadily loses mechanical strength. Because the superior retinacular and lateral epiphyseal vessels, which supply the antero-superior aspect of the femoral head, are primarily involved, and since this is also the area of maximal weight bearing, collapse of subchondral trabeculae gradually develops in this region. This often takes place before the articular surface itself is affected and may appear as a radiolucent "crescent sign" (Stage III). This stage is not always seen as collapse of the articular surface with the subchondral bone may occur more or less simultaneously. If the necrotic region is small and not close to an area of major weight bearing, the situation may stabilize and the repair process may provide it with sufficient strength so that it does not collapse. It may persist as an area of radiodensity, although occasionally it is resorbed and disappears from radiographs.

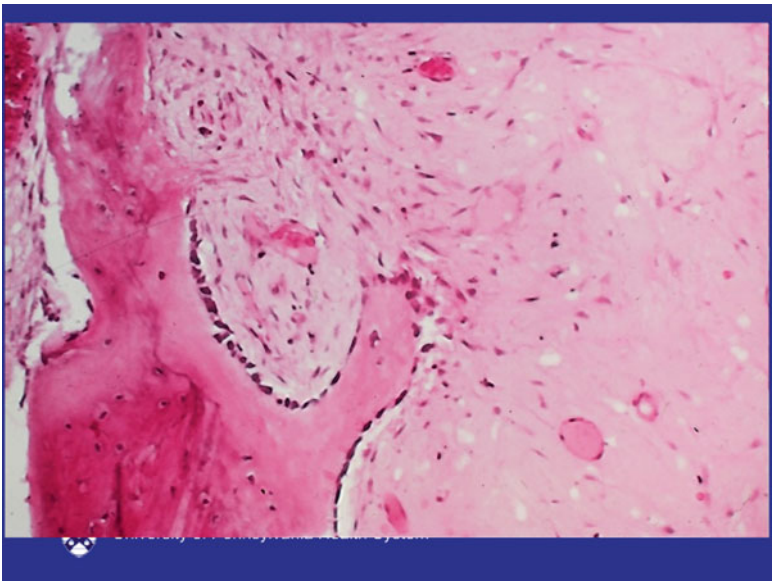

Fig. 7.3 Osteoblasts forming new bone directly on old, dead trabeculae

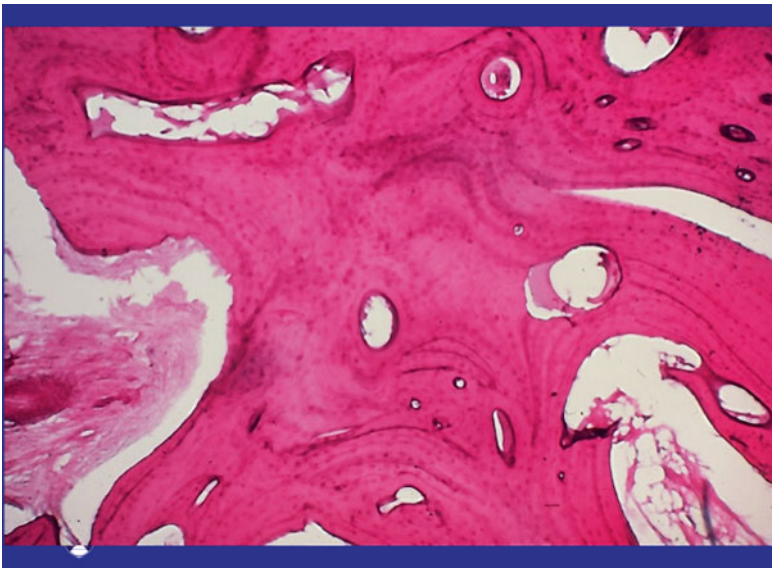

Fig. 7.4 Markedly thickened trabeculae at the margins of the necrotic region are composed of both living and dead bone

Table 7.1 University of Pennsylvania classification of osteonecrosis

Stage	Criteria	
0	Normal or nondiagnostic radiograph, bone scan, and MRI	
I	Normal radiograph; abnormal bone scan and/or MRI	
	A: Mild	(<15 % of head affected)
	B: Moderate	(15–30 %)
	C: Severe	(>30 %)
II	Lucent and sclerotic changes in femoral head	
	A: Mild	(<15 %)
	B: Moderate	(15–30 %)
	C: Severe	(>30 %)
III	Subchondral collapse (crescent sign) without flattening	
	A: Mild	(<15 % of articular surface)
	B: Moderate	(15–30 %)
	C: Severe	(>30 %)
IV	Flattening of femoral head	
	A: Mild	(<15 % of surface and <2 mm depression)
	B: Moderate	(15–30 % of surface or 2–4 mm depression)
	C: Severe	(>30 % of surface or >4 mm depression)
V	Joint narrowing and/or acetabular changes	
	A: Mild	Average of femoral head involvement as determined in Stage IV, and estimated acetabular involvement
	B: Moderate	
	C: Severe	
VI	Advanced degenerative changes	

This corresponds with the clinical observation that very small lesions, especially those located medially, have a good prognosis. However, less than 5 % of lesions meet these criteria [15, 16]. It has also been observed that the prognosis for sclerotic lesions is better than for lesions which appear cystic. This is most likely due to the fact that sufficient new bone has been formed to provide mechanical strength to the region and hence decrease the incidence of collapse [17].

With progressive collapse of subchondral trabeculae, the unsupported articular surface eventually begins to flatten. This represents an irreversible stage in the pathogenesis, Stage IV (Fig. 7.7). The articular cartilage is attached to the subchondral plate and remains viable, since it is nourished by diffusion from the synovial fluid and not by the vascular supply to the femoral head itself. However, the attached bone plate becomes necrotic (Figs. 7.8 and 7.9).

Radiographs of the hip continue to show a normal appearing acetabulum for quite some time after femoral head collapse. This can be misleading as histological changes in the articular cartilage are already taking place. In a study of 41 hips with ON which underwent total hip replacement despite a radiographic diagnosis of a "normal acetabulum," 40 hips showed gross changes in the acetabular cartilage, and

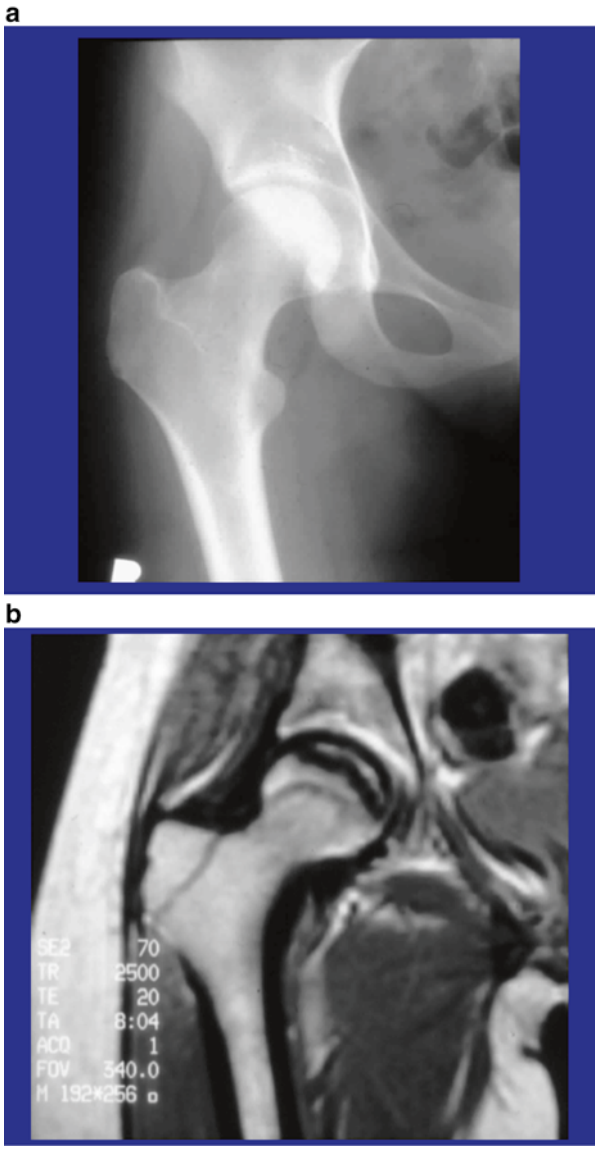

Fig. 7.5 Images of a young male with Stage I steroid-induced osteonecrosis of right hip. (**a**) Plain radiograph appears "normal." (**b**) T1 Weighted MRI shows characteristic changes of ON

all 41 showed histologic degeneration [18]. It is important to keep this in mind when considering a hemi-arthroplasty involving only the femoral head with the assumption that the acetabulum is "normal."

Progressive degenerative changes take place in the acetabulum secondary to the abnormal mechanical stresses imposed by the collapsed femoral head. Initially they involve only the articular cartilage as indicated by radiographic narrowing of the joint line. Later the underlying bone becomes affected and radiolucent and sclerotic

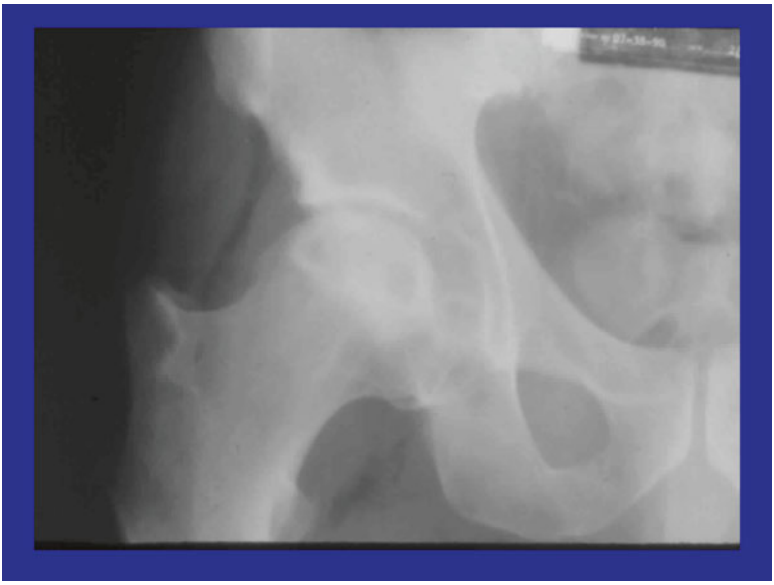

Fig. 7.6 Sclerosis and lucency within the femoral head are characteristic of Stage II ON

regions appear in the roof of the acetabulum, often accompanied by marginal osteophyte formation. This represents Stage V radiographically. In a small number of cases this process continues until the joint is almost completely obliterated, which represents Stage VI [19].

Classification and Staging

The pathophysiologic sequence of events outlined usually follows a relatively predictable course. As a result, it is possible to describe the status of the osteonecrotic hip by means of a system of classification and staging.

The first classification system for ON was described in the early 1960s by Arlet and Ficat [20] and included three specific stages. A fourth stage was added in the 1970s and this is the version most widely used today, although in 1985 six stages were described [21, 22]. MRI was not originally included as it was not available at the time, and there was no attempt to indicate the size of the infarct nor the extent of joint involvement. Other classifications followed including those described by Marcus et al. [23], Sugioka [24], and the Japanese Investigation Committee for Avascular Necrosis [15].

The University of Pennsylvania Classification was developed in the early 1980s and identified seven clearly defined radiographic stages. It was the first to employ

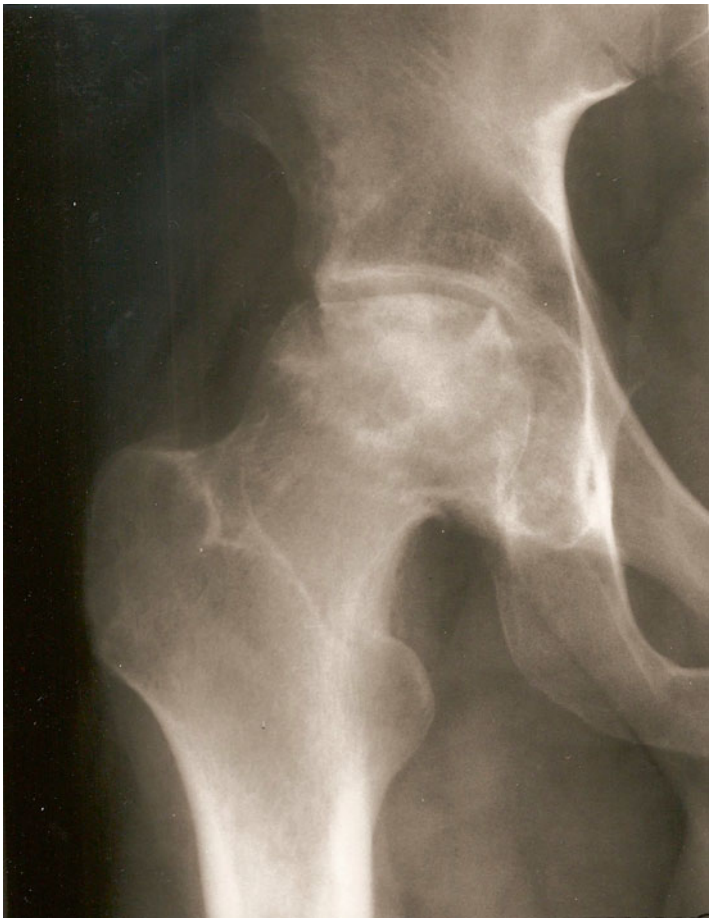

Fig. 7.7 Marked collapse and flattening of the femoral head without radiographic evidence of acetabular abnormality represents Stage IV ON

MRI as a specific modality for determining the stage, and was the first to include direct measurement of lesion size and the extent of joint involvement [19, 25, 26] (Table 7.1). In 1991 this classification was endorsed by the Association Research Circulation Osseous (ARCO), although modifications were made in 1992 and 1993 [27–29]. In 1992 it was also endorsed by the Committee on the Hip of the American Academy of Orthopedic Surgeons.

Recognizing the importance of the size of the infarct, a number of methods for measuring lesion size have been described during the past several years. However, most have relied on simple angular measurements made on plain radiographs or MRI, which are approximations rather than accurate measurements. In addition,

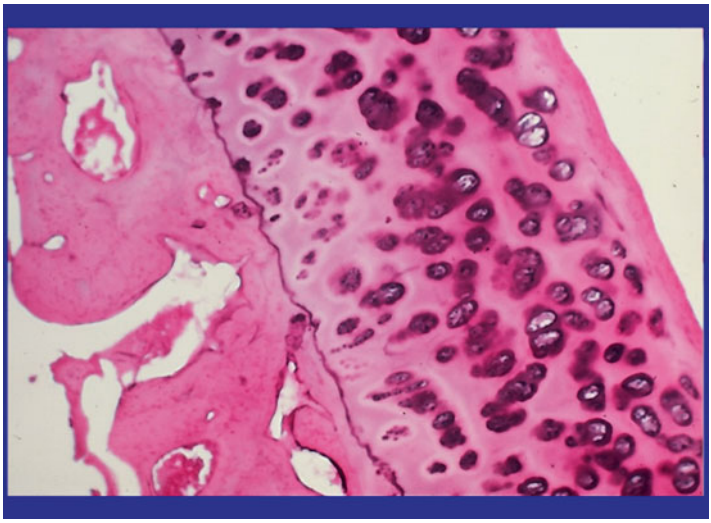

Fig. 7.8 Photomicrograph of a section of articular cartilage attached to its subchondral bony plate from a Stage IV hip. The cartilage remains viable whereas the bone is dead, as indicated by the empty osteocyte lacunae

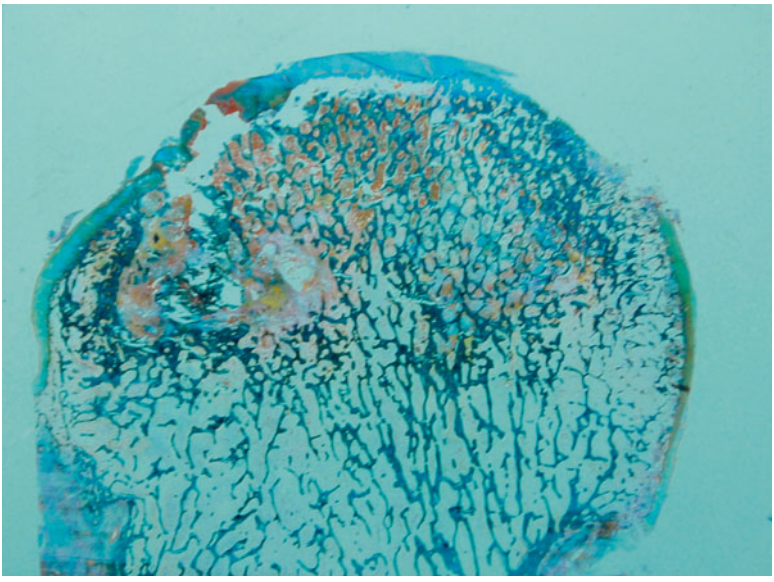

Fig. 7.9 Low power photomicrograph of a section through the femoral head shows a large lesion with elements of necrosis and attempted repair

these measurements have been used primarily to supplement non-quantitative classifications rather than as an integral part of one system [30–32].

MRI is currently the best modality for early diagnosis of ON, before changes appear on plain radiographs [33, 34]. This is important as the best results are obtained by early treatment, which in turn requires early diagnosis. The prognosis and treatment of hips with ON is also directly related to the size of the necrotic lesion and the extent of joint involvement. Accordingly, the clinical importance of using a comprehensive classification that indicates the extent of necrosis in addition to the stage is well recognized [19, 35–37]. This helps establish a prognosis, follow improvement or progression, compare different treatment options, and determine the best method of management for patients with different stages of ON. The uniform use of such a classification will help clarify the current confusion regarding both the natural history and the treatment of ON, and improve our management of patients with this perplexing disorder. A recent review of the literature shows a steady trend in this direction [36, 38].

At the present time, there are ongoing efforts to reach a consensus regarding the uniform use of a single effective classification. With advances in imaging techniques, it is now considerably easier than it was initially to measure accurately the size of the necrotic segment and the extent of joint involvement.

Management

Despite the increasing interest in osteonecrosis and the advances in understanding its etiology and pathophysiology, we still do not have an entirely satisfactory treatment. This is of particular concern because it affects most often younger adults, involves major weight bearing joints, and is usually progressive without appropriate treatment.

Prevention

A number of risk factors have been identified and these should be eliminated to the extent possible. These include alcohol ingestion, smoking, exposure to hyperbaric conditions, and corticosteroid administration. The postoperative management of organ transplantations has changed over the years, modifying the role of steroids, and accordingly the incidence of ON has diminished. When guidelines for divers and others working under hyperbaric conditions are followed, the incidence of ON decreases. During the past few years a number of genetic abnormalities have been identified which predispose patients to ON. In this group at risk, particular efforts should be exerted to minimize exposure to factors which could lead to the development of ON. Patients with hyperlipidemias might benefit from measures to control circulating lipid levels. In patients with certain coagulation abnormalities, some authorities have suggested long-term anticoagulation [4]. However, this approach

has not been generally accepted since there is little evidence that this treatment is effective in preventing ON and the dangers of routine anticoagulation most likely outweigh the theoretical benefits.

Non-operative Management

A primary goal is to diagnose ON as early as possible, before collapse of the femoral head begins. This enables us to initiate measures designed to retard or prevent progression. A number of non-operative measures have been described. Patients are often placed on limited or non-weight bearing when the hip or lower extremity is affected. Although this may help to decrease pain, there is no evidence that it will retard progression and prevent eventual joint collapse. Various physical modalities have been advocated, including ultrasound and different types of electrical stimulation. At present they are used infrequently, and further evaluation and development may be indicated [39, 40]. There was also earlier enthusiasm about the role of hyperbaric oxygen, however there is little evidence that it is effective and it is rarely used [41]. Bisphosphonates have been given to slow the progress of bone resorption and thereby delay or prevent collapse. This approach is theoretically attractive and a limited number of studies have shown early promise. However, other investigators have failed to demonstrate a positive effect in patients followed over 2 years [42] (ref). Other agents, such as vasodilators and fulleral, a powerful antioxidant, have been suggested but their effectiveness has not yet been established.

Treatment Before Femoral Head Collapse

When osteonecrosis is diagnosed before femoral head collapse has taken place, a number of surgical procedures have been employed to delay or halt progression and promote healing. Technically, they vary considerably from one another, but essentially all are based upon physiologic principles, which address one or more aspects of the pathology involved. The results and complications reported have varied widely from one series to another. This section gives only a very brief overview of some of these procedures, and the reader is urged to look elsewhere if more information is required. Some surgeons have been reluctant to treat asymptomatic lesions, especially when complicated techniques are being considered. However, prior to trabecular collapse there is little correlation between the degree of pain per se and the outcome, and the majority of asymptomatic lesions do eventually become painful. Therefore, treatment designed to preserve the femoral head should not be withheld or delayed solely because the osteonecrotic lesion is asymptomatic or minimally painful [2, 43–45].

Core Decompression

One of the earliest and most often used methods of treating ON of the femoral head is "core decompression" [46, 47]. During the 1960s Arlet and Ficat, as part of their study of ON, removed diagnostic cores of bone from the femoral head and neck [20]. Patients noted prompt relief of pain following this procedure, which was felt to be due to relieving the high intraosseous pressure found to be present. This procedure became known as "core decompression" and was widely used to treat early cases of ON. Subsequently it has undergone several modifications including the use of several small perforations into the lesion rather than a single large core track. It has also been supplemented with electrical stimulation [40, 48] and by the addition of bone grafts and various agents to stimulate vascular ingrowth and bone formation, such as VEGF, bone morphogenetic protein (BMP), demineralized bone matrix (DBM), and mesenchymal stem cells, which will be discussed later.

The results reported following conventional core decompression have varied widely, but a review of the literature found a very low incidence of complications and a satisfactory result in 65–70 % of patients treated early [49–51]. Core decompression is now the most widely used joint preserving procedure in the United States. It can act through several mechanisms including decreasing elevated intraosseous pressure, removing areas of necrotic bone, stimulating the ingrowth of new vessels, and possibly as a channel for the introduction of materials that can stimulate vascular and bone growth. It is a relatively simple procedure with a very low rate of complications, when performed properly. Results with smaller lesions are better than with larger lesions, and it has been suggested that lesions which occupy less than 15 % of the femoral head, especially if located medially in a region of minimal weight bearing, may heal spontaneously and do not necessarily require treatment. In the cases that fail core decompression, later conversion to hip arthroplasty is not compromised.

Osteotomy

Various types of intertrochanteric osteotomies have been used. The rationale for these procedures is the ability to shift the necrotic segment out of the major weight bearing region of the femoral head, and replace it with normal cartilage and bone. Only a limited amount of displacement is possible with varus/valgus or flexion/extension osteotomies [52], but considerably more displacement can be obtained by anterior or posterior transtrochanteric rotational osteotomies. These have been described by Sugioka [24] and Atsumi et al. [53]. These procedures have also been used after a certain amount of femoral head collapse has occurred and seem effective, so long as it is possible to shift a relatively normal segment of joint surface into

the weight bearing region. It is necessary to study X-rays carefully prior to determining whether the procedure is indicated, and if so, the type and extent of the osteotomy. Satisfactory results have been attained at selected centers familiar with these procedures, but they are technically difficult and have not attained widespread popularity.

Bone Grafting

A number of bone grafting procedures have been described using cancellous and cortical bone, bone substitutes, and vascularized grafts. Grafts can be inserted into the necrotic region through a channel made in the lateral femoral cortex, through the femoral neck, and directly through a trap door in the articular surface of the head [54–56].

Phemister [57] and later Bonfiglio and Bardenstein [58] created a channel extending from the lateral femoral cortex into the necrotic region of the head. Dead bone was removed and a cortical graft, usually composed of a nonvascularized fibula, was inserted. More recently, vascularized fibular grafts have been used. Rosenwasser et al. [59] made a window in the anterior femoral neck through which they removed most of the necrotic material and filled the cavity with autogenous bone from the ilium. In a small series they found intermediate term results to be quite satisfactory. In order to restore the circulation to the necrotic region more quickly, a number of techniques have been employed which insert a segment of bone with its attached muscle-pedicle directly into the region [12, 54, 55]. Satisfactory short and intermediate term results have been observed in a small number of studies, but long-term success with most of these techniques has not been confirmed and they are now used infrequently.

Free Vascularized Fibular Grafts

The use of free vascularized fibular grafting (FVFG) deserves particular attention. Since its introduction in 1979, it has been performed at a limited number of specialized centers in the United States, Asia, and Europe [60–64]. Similar to a conventional core decompression, a large channel is prepared extending from the lateral femoral cortex into the head, ending close to the articular surface. After debriding the necrotic material and inserting cancellous bone, a segment of the patient's ipsilateral fibula together with arteries and veins is placed within this channel. A micro-vascular anastomosis to local vessels is then performed. In addition to providing decompression and removal of necrotic material, the revascularized fibula brings an immediate vascular supply to the region and provides support

to the articular surface to retard or prevent collapse. The procedure is technically demanding and requires the participation of a well-trained micro-vascular surgeon. It is performed ideally by two teams operating simultaneously and has a steep learning curve. The complication rate is not insignificant and later conversion to total hip replacement may be difficult. However, gratifying results have been reported from those centers experienced with FVFG. The 2-year survival rate has been reported as high as 60–98 %, and the survival for hips operated upon before collapse is between 78 and 100 % [64] (ref). Results with small lesions are better than with large lesions, and patients treated prior to collapse have better results than those treated after a limited amount of collapse. Relatively few patients with Stage I lesions have undergone FVFG. The procedure remains controversial and many feel that the disadvantages outweigh the possibility of obtaining results that are better than with simpler procedures, such as core decompression. If it is to be performed, it should be done primarily at selected centers. The specific indications and contraindications have not yet been established, and further studies are required to determine them.

Mesenchymal Stem Cell Introduction

The use of mesenchymal stem cells derived from autologous bone marrow to treat osteonecrosis was pioneered by Hernigou in 1989 [65]. Various modifications of the original technique have been described. Over 2000 patients have been treated during the past 20 years and the results reported by Hernigou, Gangji, and others were superior to those achieved by core decompression alone. This is perhaps the most promising of the newer techniques for the early treatment of ON. In addition to the biological effects of core decompression alone, this technique adds the active role played by these mesenchymal stem cells in promoting bone and vascular regeneration. It has been utilized to date at relatively few centers, but if the results obtained by additional investigators continue to be promising, it may enjoy much wider use in the future [65–67].

Treatment After Femoral Head Collapse

Most of the techniques described above for treating hips before femoral head collapse can also be used after a limited amount of collapse has occurred. Results in general are not as good as when they are employed earlier, prior to collapse, but most series have recorded better outcomes than for hips managed non-operatively. The indications and contraindications should be considered carefully.

Subchondral Collapse: Stage III

A small number of patients will be seen with the presence of a crescent sign, indicating collapse of subchondral bone, but without gross flattening of the articular surface. For simplicity some classifications have grouped these together with hips in which flattening of the femoral head has already taken place. In view of the known pathophysiology of ON, it would seem possible that so long as the articular surface remains anatomically round, healing of the underlying cancellous bone, either spontaneously or assisted by grafts or other surgical techniques, could result in a relatively anatomical joint. There are few reports regarding treatment of hips at this stage. However, they indicate that the outcome following various methods of management was better than for hips in Stage IV where femoral head flattening was present [65–68]. This underscores the value of using a classification system which clearly identifies this stage as separate from hips with gross collapse. In Stage III we would therefore favor treatment methods designed to preserve the joint.

Collapse of the Articular Surface: Stages IV–VI

Once irreversible collapse of the articular surface has taken place, attempts to preserve the femoral head will be less successful. However, where the amount of collapse is small and is not accompanied by significant pain, disability, or radiographic involvement of the acetabulum, it is often reasonable to consider one of the joint preserving procedures described earlier. Although the results in general are not as good as when these are performed earlier, it is often possible to retard progression, relieve discomfort, and buy time before hip arthroplasty is required. For example, FVFG has been advocated by some in cases of early collapse. Those experienced with rotational osteotomies have obtained satisfactory results even after femoral head collapse, as long as it was possible to rotate the collapsed area out of the region of major weight bearing.

However, if the pathology has progressed beyond the point of early collapse, joint preserving procedures may no longer be indicated. Previously, hips in Stage IV without radiographic evidence of acetabular involvement were considered candidates for femoral endoprosthetic replacement or hemi surface replacement arthroplasty (SRA) by some surgeons. Although early results were usually satisfactory, these procedures did not do well with longer follow-up. Even a normal acetabulum cannot for long withstand the presence of a metallic prosthesis, and subsequent studies showed that by the time arthroplasty was indicated clinically, the acetabular cartilage had already undergone degenerative changes [18]. Hemi-arthroplasty is therefore seldom used today.

When the pathologic changes have progressed to the point where unequivocal acetabular degeneration is present, Stages V through VI, hemi-arthroplasty is rarely considered and some type of total hip replacement is the procedure of choice when

clinically indicated. When THR was initially introduced there was serious concern about performing this procedure in the young, active patient with ON because of the high incidence of failure and the short survivorship as compared to the older patient with degenerative joint disease (DJD) [69, 70]. However, since that time there have been considerable improvements in surgical techniques and design and manufacture of THR prostheses. The outcomes and survivorships reported in more recent studies approach those of older patients with other conditions. Although it is still preferable to preserve the normal hip where possible, there is no longer the urgency to do so at all costs and perhaps embark on a complicated procedure with a questionable chance of success. Where clinically indicated, standard THR for the patient with advanced stages of ON is now usually the preferred procedure. Results are generally excellent, complications are limited, and mean survivorship of 25 or more years may be anticipated [46, 47, 71–73].

An alternative to conventional THR is SRA. The rationale for this procedure is that it is less invasive and more physiologic than THR since only the diseased portion of the femoral head is sacrificed and the normal neck and shaft are not violated. In the 1970s the reluctance to perform standard THR on younger patients with ON led to interest in SRA. However, an increasing incidence of failure with these early designs led to their virtual abandonment by 1982 [74]. However, it was felt by some that the problem was due to failure of the acetabular component which required a thin shell of polyethylene cemented into place with a thin layer of methacrylate to accommodate the large femoral head. This led to a basic change in component design which now employs a biologic ingrowth metal rather than a plastic acetabular component, articulating with the metal femoral cap. The early and intermediate results with these components were quite good and many felt that the basic problem had been solved. These metal-on-metal SRAs gained a significant degree of popularity and were preferred by many for the young, active, male patient with ON and other conditions [75, 76].

Unfortunately, a different set of problems began to develop which were related specifically to the metal on metal articulations of both SRAs and standard THRs. By 2008 there were reports of local soft tissue reactions and pseudo-tumor formation around some of these components, which caused pain, component loosening, and revision surgery [77, 78]. There was also increasing concern regarding possible long-term systemic effects of metallic ions. As a result, there has been a dramatic shift away from these components, although a limited number of surgeons continue to use SRA for selected patients, such as the young active male with ON.

Future Goals

Although we have made reasonable progress in understanding and treating osteonecrosis during the past several years, there is considerably more to be accomplished. We must continue to learn more about the etiology, pathogenesis, and treatment of ON. This will be aided by the development of an effective experimental model, which is currently not available.

It is important that orthopedists and radiologists continue to increase their awareness regarding the need for earlier diagnosis and evaluation of the patient with ON using modern, comprehensive methods of staging and classification which indicate both the stage and the extent of involvement. This in turn will lead to a more accurate evaluation and comparison of the various methods of treatment, and will enable us to improve our management of patients with osteonecrosis.

A number of joint preserving procedures have been described, some of which have been mentioned here. In most instances, the authors who have devised and used these techniques have reported good results. However, many of these reports have involved small numbers of patients, short follow-up and use by a limited number of investigators. It is important to have the more promising techniques evaluated independently by others using well-designed studies. This will provide objective and accurate information regarding the effectiveness of these techniques which in turn should lead to increased use of those found to give the best results. In addition, a number of newer approaches to the treatment of ON have been suggested during the past few years. These include the use of mesenchymal stem cells, bisphosphonates, and various bone and vascular growth enhancing factors. Genetic studies have already yielded important information which could improve treatment and possibly lead to gene therapy in selected cases. We will await with interest the further development and evaluation of these techniques to determine their potential clinical role.

And finally, significant improvements in arthroplasty have taken place since its introduction. Total hip replacement now plays an important role in the treatment of patients with advanced stages of ON, and is the most frequently employed procedure once it is determined that joint preserving surgery is no longer indicated. Improvements in surgical technique, and in the design and manufacture of components will continue and will lead to increasing survivorship of these prostheses. Although we will still seek to prevent the development of ON and to preserve rather than replace the normal joint whenever possible, these advances will provide a practical solution to the management of the young active patient with ON in whom progression and severe joint damage cannot be prevented.

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Chapter 8
Osteoporosis and Hip Fractures

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Epidemiology and Consequences of Hip Fracture

With the median age of the United States growing increasingly older, osteoporosis is rapidly becoming a major public health concern. One of the most devastating complications from osteoporosis is a fragility fracture, which negatively impacts both healthcare expenditure and patient outcomes. Hip fractures are particularly worrisome, as they account for over 70 % of total fragility fracture treatment costs despite constituting less than 15 % of these fractures [1]. The disproportionate contribution is due to comprehensive management that includes emergency care, inpatient hospitalization, and physical rehabilitation. Despite these interventions, 1-year mortality is approximately 25 %, and up to 70 % of patients will suffer permanent residual functional impairments or physical limitations [2, 3]. These patients are also at greater risk of subsequent fracture and must be carefully followed [2]. Therefore, treating and preventing osteoporotic hip fractures are critical to reduce costs, morbidity, and mortality. In this chapter, we will discuss osteoporosis management, fragility fracture risk factors, and interventions to treat and prevent these fractures.

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Definition of Bone Strength, Fragility Fractures, and Consequences of These Fractures

Osteoporosis is a condition of decreased bone strength that is characterized by a reduction in bone mass with a decrease in density and enlargement of bone spaces, producing porosity and brittleness [4]. It affects people of all races, both male and female, though post-menopausal Caucasian and Asian women are most commonly seen with this condition [5]. The decreased strength of the bone is not only related to the decreased mass, but also to the quality of the bone. This latter aspect is more challenging to define, but includes such factors as microanatomy and integrity, mineralization (which is affected by calcium and vitamin D intake), and microdamage at the cortical and trabecular level. There is no good test to evaluate bone quality, other than assessing calcium and vitamin D status for mineral health. In spite of deficient laboratory tests, the presence of fragility fractures is sufficient to imply altered bone mass and/or quality.

Fragility fractures, which were originally defined as low energy falls from standing height or less, are almost all associated with an increased mortality rate. An individual who sustains a vertebral fracture has roughly a fivefold increased risk of sustaining a second vertebral fracture [6], and a twofold increase in the chance of sustaining a hip fracture over the general population [7]. Many elderly individuals with osteoporosis can sustain osteoporotic spine fractures even when there is a small amount of energy imparted. If the individual sustains a fracture that would not normally occur at that energy level in a young adult, suspicion should be raised for both bone quality and quantity.

Workup of a Fragility Fracture Patient, Including DXA, FRAX, and Laboratory Studies

Evaluation of a person with suspected osteoporosis should include both determination of bone mass and a series of laboratory studies. Osteoporosis was originally determined by seeing a decreased density on dual energy X-ray (DXA) scan. DXA typically assesses the spine and hip, and occasionally the wrist. Its accuracy decreases as the body part scanned moves further away from the periphery. The World Health Organization defined criteria for the diagnosis of both osteopenia and osteoporosis. When comparing to the young adult mean (T-score), a bone density less than one standard deviation but better than 2.5 standard deviations below the mean is considered low bone density, or osteopenia. A bone density greater than −2.5 standard deviations would be considered osteoporosis. These definitions have been challenged in recent years and are now collectively referred to as low bone mass or decreased bone mass. A person with a T-score of −1.5 without secondary risk factors has minimal risk of fracture, whereas a person with a T-score of −2.5 has a much higher risk of

fracture. This is especially true when coupled with secondary causes of low bone mass or bone quality such as chronic steroid use or diabetes, or prior history of low energy fracture. The DXA is a measure of bone density and still remains the gold standard for diagnosis. Other methods to determine bone mass and gain more insight into quality include quantitative computed tomography (qCT) and ultrasound.

Review of the literature and data reports reveal some issues that still need to be addressed. Most notably, in patients who have not achieved peak bone mass (those under age 35) may have lower T-scores than the mature adult standard. Therefore, the bone density has to be corrected for age, and this is referred to as the Z-score. The Z-score is particularly useful when treating patients under age 25, and can also be used to compare an individual to their age-matched peers [8]. A Z-score of −1.5 or worse may indicate a secondary disease process that may be contributing to bone loss [8]. Up to 65 % of men and 35 % of women will have secondary diseases contributing to loss of bone. Common associated causes are alcohol use, smoking, steroid use, renal disease, and autoimmune disorders. However, based on the fracture population in the Metabolic Bone Disease Registry at Hospital for Special Surgery in NYC, the incidence of a secondary disease process is much higher, approaching 95 % in men and 65 % in women who suffer fragility fractures. In addition, the majority of hip fractures occur in individuals who are considered osteopenic, rather than osteoporotic. This is due in part to the fact that the pool of patients with osteopenia is significantly larger than the osteoporotic pool. One question that persists is why some people with a given bone density get fractures, while others with the same bone density do not. It has been shown that when just looking at age and bone density, an 80 year old with a bone density of −3.0 has an 18 % chance of suffering a hip fracture within 10 years, while a 50 year old with the same bone density has only a 2.5 % chance [9]. Whether it is poorer health or more falls, the reason for the increase with age is not clearly defined.

A method for integrating other risk factors to calculate fracture risk, called the Fracture Risk Assessment Tool (FRAX index), was developed by Kanis et al. The FRAX takes into consideration factors such as height and weight, or implied body mass index (BMI), history of prior fracture, past and current smoking status, exposure to steroids, presence of autoimmune disease (particularly rheumatoid arthritis), alcohol consumption, parental history of hip fractures, and known secondary causes of osteoporosis [10]. Combining this information along with age and gender can help determine proper treatment methods. Individuals with hip fracture risk over 10 years of 3 % or greater or long bone fracture risk of 20 % or greater would benefit from being placed on anti-osteoporotic medication [10]. The FRAX can also be used without a DXA, but is less accurate. DXA is warranted in individuals who are found to have a 10 % risk of long bone fracture or 1.5 % risk of hip fracture [10].

Once concern for metabolic bone disease has been established, a metabolic workup should be initiated. If surgical intervention is warranted, laboratory data should be collected before surgery, since fluid loading may compromise the interpretation of the tests. Critical elements to be evaluated should include a complete

blood count to rule out anemia and alert individuals to possible other entities such as multiple myeloma. A general screening laboratory panel including albumin, calcium, renal and liver function tests should also be included. A 25-OH vitamin D should also be performed for vitamin D status. There has been some conflict with regard to what is considered a normal calcium and vitamin D. To determine appropriate calcium levels for a given individual, it should be corrected for serum albumin levels. Among active people, especially those who exercise regularly, a vitamin D level of approximately 45 ng/mL has been suggested to lead to better motor function, lower fall rate, and faster reaction. Therefore, a vitamin D over 30 ng/mL would be acceptable, however when trying to maximize physical function, a vitamin D closer to 45 ng/mL would be ideal. If there is a history of thyroid disease, a T3, T4, and thyroid stimulating hormone (TSH) should also be performed. Ideally, bone markers should be tested, particularly if the patient reports a history of prior bisphosphonate use. Serum C-terminal telopeptide (CTX) or the second morning urine N-terminal telopeptide (NTX) is often used to assess active bone resorption. Among bone formation markers, procollagen type 1 N propeptide (P1NP) can be used to measure type 1 collagen synthesis. Bone specific alkaline phosphatase can also be used to reflect the biosynthetic activity of bone forming osteoblasts serving as a reliable indicator of bone metabolism. Other tests should be considered on a case-by-case basis, depending on index of suspicion. These may include urine and blood immunoelectrophoresis to rule out multiple myeloma, testosterone levels in thin debilitated men, steroid levels including cortisol to rule out subclinical Cushing's disease, and a Hemoglobin A1C for patients with a history of diabetes. In addition, an intact parathyroid hormone (PTH) should also be ordered. If the calcium is low for that particular individual, the PTH level will be elevated over the usual normal value of 50 pg/mL. If the individual has excess calcium, the PTH will be suppressed, with levels below 20 pg/mL. The ideal calcium level will be associated with an intact PTH level between 20 and 50 pg/mL, preferably in the 30s [11]. PTH will also rise with low vitamin D (25(OH) vitamin D >30 mg/mL) so that vitamin needs simultaneous correction.

Osteoporotic Fractures of the Hip and Pelvis

The major consequence of osteoporosis as related to the pelvis and hip joint is clearly the fragility fracture. Classified according to their anatomic location, these fractures most commonly affect the neck and intertrochanteric regions of the proximal femur and the pelvis [12]. Regardless of the area that they affect, fragility fractures have in common their occurrence in patients with diminished bone mass due to low energy trauma and result in similar radiographic configurations but vastly different clinical pictures from their high-energy counterparts in healthy young adults.

Hip (Proximal Femur)

The colloquial term "hip fracture" denotes fractures in the proximal end of the femur, including the head, neck, intertrochanteric and subtrochanteric areas. They are generally divided into intracapsular (femoral head and neck) and extracapsular (basal neck, intertrochanteric and subtrochanteric) fractures. Most common configurations in osteoporotic individuals are the fractures of the femoral neck and those of the intertrochanteric region, accounting for nearly 90 % of all osteoporotic hip fractures [13, 14], and will therefore be referred to as representatives of their respective group.

66 million hip fractures occurred in the world in 1990, a number that is expected to rise to 6.26 million in 2050 [15]. Twelve to thirty-five percent of patients who have had a hip fracture will not survive 1 year [12, 13, 16–20] and a larger number of them will not regain their pre-fracture level of activity [18, 21, 22]. Nine out of ten hip fractures will occur in patients over the age of 65, and 3 out of 4 of these patients will be women.

While it is theoretically possible that an osteoporotic individual may suffer a subtrochanteric femur fracture, less than 10 % of primary low-energy femoral fractures will have this configuration and therefore will not be discussed in detail. More likely in the subtrochanteric region of the osteoporotic population is the atypical fracture, which has been reported to be a consequence of long-term bisphosphonate use [23, 24].

Femoral Neck Fractures

Femoral neck fractures are intracapsular fractures, and due to their constant exposure to synovial fluid are generally thought to have a higher risk of nonunion. Stability of the fracture is determined by the angulation of the fracture line as compared to the perpendicular; the popular Pauwels' classification is based on this feature [25]. As fracture line verticality increases, so do the shear forces acting upon the fracture, increasing its instability. Another classification by Garden et al. depends on the displacement of fracture fragments [26]. Displacement is one of the major determinants of prognosis. As fracture displacement increases, complications such as nonunion and avascular necrosis become more common [26–28].

The gold standard treatment for femoral neck fracture is surgical intervention, though the specific technique will vary according to patient, fracture morphology and surgeon preference. Conservative treatment with bed rest may be considered in patients with prohibitive comorbidities; however, the certainty of complications associated with prolonged bed rest generally easily overcomes the risks associated with surgical treatment.

Surgical options for femoral neck fractures range from the less invasive percutaneously placed three cannulated screws to total hip arthroplasty. In general, the

younger the patient's age and the higher their functional level, the greater the attempt to preserve bone stock by obtaining anatomic reduction and stable fixation. Time of presentation also plays a role in treatment selection, with delayed fixation resulting in poorer outcomes [29].

Closed or open reduction and cannulated screw fixation is one of the mainstays of femoral neck fracture treatment. Many biomechanical studies have been performed regarding the configuration of these screws, and it is now accepted that the best configuration is the three screws in an inverted triangle configuration [30–32]. Current concern is greatest regarding the ability of fixation constructs to prevent shortening of the femoral neck [33–35]. Results of fixation with cannulated screws have been disappointing in this matter, leading to the search for alternative fixation constructs, such as length-stable screw constructs, dynamic hip screws (DHSs) with antirotation screws and fibular allografts [36–40]. Following fixation, patients will need to remain non-weight or partial-weight bearing on the affected extremity, a difficult feat for frail and infirm patients. Results of reduction and fixation remain suboptimal, with rates of loss of reduction, avascular necrosis, nonunion and subsequent need for reoperation reported to occur in up to 39 % of patients [18, 27, 41].

The second treatment option for femoral neck fractures is arthroplasty, either hemiarthroplasty or total hip replacement (THR) [42]. Advantages and disadvantages to both options exist [27, 43]. Hemiarthroplasty is a quick, technically less challenging method that is associated with less intraoperative burden (operative time, estimated blood loss, etc.) that, when combined with cemented fixation, allows the patient to weight-bear as tolerated immediately after the operation. Its main drawback is erosion of the unreplaced acetabular cartilage, but revision rates for this reason are low [27, 42]. Bipolar hemiarthroplasty prostheses have been designed to decrease cartilage wear, but studies have shown that the bipolar articulation is essentially quiescent and may lack motion in vivo [44–48]. Unipolar hemiarthroplasty is the more cost-effective option.

Hip replacement attempts to address these disadvantages [49]; however, results in this patient group remain inferior to the primary THR group, most significantly due to higher dislocation rate [42, 50]. Total hip arthroplasty should also be primarily considered in patients with pre-existing arthritic disease of the hip. Constrained cups in this patient population are generally contraindicated, again due to poor bone stock, which may cause increased wear and premature failure with the increased biomechanical strain placed on constrained cups [51]. Research concerning the newly designed tripolar cups appears promising and may obviate the problem of increased dislocation in the future [52].

Another unsettled issue is the utilization of cement. Bone ingrowth prostheses require good bone stock, which elderly patients generally lack. Cement provides instant stability and the opportunity to weight-bear as tolerated immediately following surgery. However, it has the drawback of causing fat emboli to enter the bloodstream during pressurization, resulting in higher early mortality as opposed to non-cemented prostheses [53]. Several reports, including those from the Australian arthroplasty registry, have shown increasingly better results in hemiarthroplasty for femoral neck fractures in the osteoporotic population when cement was employed [54–56].

Many treatment algorithms for femoral neck fractures have been proposed, but none have received widespread popularity. The general tendency is toward fixation in non-displaced fractures, reduction and fixation in younger (<70 years) patients presenting early, and hip replacement for displaced fractures. Patients' medical fitness and pre-fracture activity level remain the chief determinants of the selection of surgical options, and should therefore include the reason for the fall that led to the fracture. For instance, if the well-functioning patient fell due to suffering a stroke, this stroke may cause further debilitation and change the patient's functional status regardless of the fracture. This must be taken into consideration when treatment decisions are made. Due to high nonunion rates, especially if fixation is the treatment of choice, additional adjuvants for healing such as teriparatide and basic metabolic protein (BMP) may be considered [38, 39, 57].

Intertrochanteric Fractures

Inter trochanteric fractures are proximal femoral fractures that occur along the intertrochanteric line, i.e. the line that connects the greater and lesser trochanters of the femur, but may extend above or below the trochanters. These fractures are associated with osteoporosis as are femoral neck fractures and they occur at a comparable incidence to their more proximal counterparts [12, 14]. While several classification systems exist, the feature that is classically clinically relevant is the stability of the fracture as defined by Koval et al. [14] and Evans [58]. Indicators of instability are comminution of the posteromedial cortex preventing cortical apposition and fracture lines that extend distally from the lesser trochanter (reverse obliquity). Up to 60 % of intertrochanteric fractures have an unstable pattern, and are more likely in patients with increased age and low bone mineral density [59, 60]. As fracture instability increases, so does the likelihood of fixation failure [61, 62]. A wide area of extracapsular, well-perfused bone is involved, making nonunion less likely with proper reduction and internal fixation.

Much like femoral neck fractures, the treatment of intertrochanteric fractures is surgical. Early mobilization is the greatest concern when treatment options are considered, which minimizes medical complications. However, in contrast to their counterparts involving the femoral neck, intertrochanteric fractures will most likely undergo open or closed reduction and internal fixation, and not arthroplasty.

Surgical treatment commences with optimal reduction on the fracture table which is essential for stability and successful fixation. The most significant surgeon-controlled features of fixation in intertrochanteric fractures remain appropriate implant choice, proper reduction of the fracture and the tip-apex distance of the chosen implant. Defined by Baumgaertner et al. as the sum of distances from the apex of the femoral head to the tip of the lag screw in a DHS plate on anteroposterior and lateral radiographs (less than 25 mm minimizes implant failure), many studies have proven the tip-apex distance to apply for the spiral blade/lag screw in intramedullary (IM) devices as well [63–66].

Two kinds of constructs are commonly utilized for the fixation of intertrochanteric fractures: DHS plate or intramedullary implants (IMN). Although theoretically the IMN have advantages such as load-sharing and reduced moment arm over the DHS side-plate, the superiority of these implants is still a matter of debate. Studies have reported equivalently good outcomes in stable fractures with the DHS and IMN both [67, 68]. However, in unstable fractures, unacceptably high rates of failure with the DHS have resulted in the IMN becoming the preferred implant [61, 62, 69–71]. Another area of discussion is the length of the implant, i.e. short versus long IMN implants. Reports of 3–5 % incidence of intraoperative fracture comminution with short implants led to the preference of longer implants by some surgeons, although recent reports of second-generation short nails demonstrate similar rates of peri-implant fracture compared to their long counterparts, along with increased operative time and intraoperative blood loss values [72–75]. It should be kept in mind that these fractures take place in pathologic bone, and treatment should be focused on protecting the entire bone from possible future fractures, as is common practice in other kinds of pathologic fracture, such as metastatic disease.

Prosthetic replacement for intertrochanteric fractures is not considered to be a routine treatment option. Due to the location and orientation of the fracture line, calcar-replacement revision prostheses or total proximal femoral replacements are required for reconstruction, a procedure that is technically more challenging compared to hemiarthroplasty, and results in a great amount of bone loss. Arthroplasty options for intertrochanteric fractures are not considered standard treatment but may be reserved for the occasional patient with underlying disease precluding osteosynthesis, underlying arthritis, nonunion or fixation failure.

Femoral Head Fractures

Another fracture pattern in the geriatric, osteoporotic patient is the subchondral fracture of the femoral head [76]. In contrast to hip fractures, these generally have no clear inciting traumatic event. They are most often found in patients with secondary morbidities such as diabetes, or requirement for prolonged corticosteroid utilization. They are often confused with avascular necrosis, but differentiation is possible with careful analysis of magnetic resonance scans [77, 78]. Treatment of subchondral fractures consists of restriction of weight-bearing until healing of the fracture. Displaced fractures and those that heal with significant deformity of the femoral head are best treated with total hip arthroplasty [79, 80].

Pelvic Fractures

Pelvic fractures may have an insidious or acute onset and may or may not have a preceding traumatic event in severely osteoporotic patients [81]. Routine radiographs may be unrevealing, requiring a high index of clinical suspicion and advanced

imaging modalities (CT and/or MRI) for diagnosis. Most common locations for pelvic fractures are the sacrum and pubic rami. Current treatment of osteoporotic pelvic fractures consists of weight bearing as tolerated, usually with a walker, symptomatic care and, most importantly, the administration of anti-osteoporotic medications. There exists good data that the utilization of an anabolic agent will result in rapid healing of these fractures, as detailed below [82]. Bisphosphonates in the setting of long-term treatment may be prohibitive to fracture healing and should be discontinued until evidence of fracture healing exists [83]. However, in the bisphosphonate-naïve patient, these drugs may be initiated once early callus biology has been achieved, usually after 3 weeks [84, 85]. Treatment is focused purely on symptomatic control as even an unhealed fracture may become asymptomatic in time. Patients who have suffered a displaced fracture of the pelvis remain at increased risk for secondary fractures of the sacrum bilaterally and should utilize a walker for protection until disappearance of pain and return of their walking balance [86].

Drug Therapy

The treatment of osteoporotic fractures requires initiating an osteoporotic program at the time of diagnosis with calcium and vitamin D supplementation being first line treatment. Calcium requirements typically range from 800–1200 mg/day, and calcium citrate is preferred over calcium carbonate due to superior absorption properties [87, 88]. Daily requirements may be higher in patients with malabsorption conditions or histories of long-standing gastroesophageal reflux disease (GERD) medication [89]. With adequate supplementation, serum levels usually normalize in 1–2 weeks. When correcting for calcium levels, evaluation not only consists of serum but also of urinary content. In patients with a renal leak, the serum will be low and urinary content will be high. If both serum and urinary content are low, then there is an underlying calcium intake deficiency. Dosage can be evaluated by measuring intact PTH, with appropriate values ranging from 20 to 40 pg/mL [90]. When calcium levels fail to normalize, urinary losses should be considered. A 24-h urinary calcium test should be performed, and levels exceeding 200 mg/L, particularly in the face of low serum calcium, are strongly suggestive of renal pathology [91]. These situations can be medically managed with a di-hydrochlorothiazide to inhibit renal excretion, and a nephrologist may provide valuable assistance [92]. Correcting calcium deficiencies, regardless of cause, is the foremost step before proceeding with more intensive osteoporosis management.

As with calcium, vitamin D is frequently low in osteoporotic patients. Serum levels less than 15 ng/mL are considered “deficient,” and levels between 15 and 30 ng/mL are considered “insufficient.” Supplementation strategies differ, ranging from 4–6000 IU/day to 50,000 IU/week. In the setting of a fracture, a minimum of 2000 IU/day is a useful starting point [93]. A larger dose of 4000 IU/day may be more appropriate if initial serum levels are less than 25 ng/mL. Once levels rise greater than 30 ng/mL, the dose can be tapered to 2000 IU/day until final adjustments

are made. Normalizing and increasing vitamin D has been associated with enhanced functional and motor properties that could be critical during fracture recovery and underscores its importance as first-line therapy [87].

More intensive therapeutics fall into two classes: anti-catabolic and anabolic. Bisphosphonates are one of the oldest anti-catabolic agents. As non-degradable pyrophosphate analogs, they are specifically drawn to bone where they are taken up by osteoclasts and inhibit bone resorption [94]. The different bisphosphonates have similar mechanisms but varying binding affinity, bioactivity, and resident time, which range from 30 to 60 years. These agents provide strong fracture prophylaxis and reduce the risk of vertebral fracture by 70 %, subsequent hip fracture by 40 %, and distal wrist and ankle fracture by 20 % [95]. When administered following a fracture, bisphosphonates will concentrate at the fracture site and have reduced systemic anti-osteoporotic capacity. Consequently, delayed administration is recommended with 4–6 weeks post-fracture considered optimal for both healing and osteoporosis protection [96].

Denosumab is the second major anti-catabolic agent. These monoclonal antibodies bind to receptor activator of nuclear factor kappa-B ligand (RANKL) preventing it from reaching membrane receptors on osteoclasts and osteoclast precursor cells [97, 98]. Consequently, they inhibit bone resorption by inhibiting osteoclast maturation, recruitment, and activity. Because of structural differences, denosumab's half-life is only several weeks compared to the decades seen with bisphosphonates. Although denosumab interferes with bone remodeling, it does not have an impact on the early modeling involved in fracture healing and, like bisphosphonates, can be given in the setting of an acute fracture [99].

Contrasting with the anti-catabolic agents, anabolic agents stimulate osteoblasts to promote bone formation. PTH 1-34, commonly referred to as teriparatide, consists of the active component of the PTH molecule. It is a powerful anti-osteoporotic medication and is given on an intermittent dosing schedule to avoid the hyper-osteoclastic states seen in conditions with continuous PTH production. Although teriparatide offers the same protection as other medications in terms of fragility fracture prophylaxis, it is unique in its ability to enhance fracture healing. Studies have demonstrated PTH treatment to accelerate healing in distal radial fractures, pelvic fractures, and even spine fusion [100–103]. Because of its positive effects on healing and osteoporosis, PTH may be the ideal therapy for osteoporotic hip fracture patients when surgical intervention is uncertain. It may also be a suitable rescue drug in patients with a long history of bisphosphonate use, as it can reactivate bone turnover to restore bone volume and enhance trabecular properties [103, 104]. Bone markers can return to normal and bone histomorphometry can demonstrate more mineralized surface.

The different medications have optimal usage according to the clinical scenario. Although either anti-catabolic agent would suffice in the setting of a hip fracture treated with hemiarthroplasty, bisphosphonates would be ideal due to their ability to adhere to the bone surface, take residence, and prevent future osteolysis. In the setting of inadequate fixation, a femoral neck fracture (which have an 80 % nonunion rate), or a non-operatively managed fracture, an anabolic agent would be preferable for its effect on both bone healing and the underlying osteoporosis. Lastly, with an

intertrochanteric fracture and no prior drug intervention, intravenous bisphosphonates initiated at 6 weeks have been shown to effectively prevent additional fracture as well as decrease myocardial infarction risk by 25 % [105].

Atypical Fractures: The Diagnosis, Pathophysiology, and Treatment for Both Complete and Incomplete Fracture

Anti-resorptive agents such as bisphosphonates and denosumab have been associated with atypical fractures of the femur [106, 107]. These occur in the subtrochanteric area and have a very distinctive configuration as reported in detail by the American Society for Bone and Mineral Research Task Force on atypical femoral fractures. They have been noted largely in patients with 5 and more years of bisphosphonate therapy, but recent reports of atypical fractures in patients receiving denosumab have appeared, although most of these patients do also have a long-standing history of bisphosphonate use [108–110]. These are classical stress fractures that are thought to result from suppression of bone turnover and occur in the lateral cortex at the point of peak strain in the bone. They are commonly bilateral. There is usually a well-established history of prodromal thigh pain. Patients afflicted with these fractures are usually shorter, younger and more active than the general population [111]. The prodromal symptoms may often be missed and confused with sciatica. Thigh pain in a patient with long history (5 years and up) of bisphosphonate usage should raise the suspicion of impending atypical fracture and appropriate imaging should be obtained to rule it out. Radiographs are often obtained first and may demonstrate thickening of the lateral cortex with or without a discernible fracture line [112]. In patients with no radiographic evidence but strong clinical suspicion, MRI to rule out stress fracture is indicated [113].

In the patient presenting with thigh pain and evidence of impending fracture (the "dreaded black line" and marrow edema on MRI, thickening of lateral cortex and incomplete fracture line on plain radiography), cessation of bisphosphonate treatment and limitation of weight-bearing should be immediately instituted and prophylactic intramedullary nailing of the femur should be strongly considered. Reaming up to 2–2.5 mm larger than intended nail diameter may be required in these patients when fixation is undertaken [106]. If the fracture is complete and displaced, again bisphosphonates should be discontinued immediately and operative fixation should be undertaken in an expedient manner. Standard fixation of these fractures is generally reamed intramedullary nailing; however, a high complication rate exists, placing even more emphasis on avoidance of malreduction in varus [114]. Delayed healing should be expected in many atypical fractures of the femur [115]. If in the patient with thigh pain only marrow edema without evidence of fracture initiation is observed, nonoperative treatment with limitation of weight-bearing and a course of anabolic agents such as PTH 1-34 can be attempted. If symptoms and imaging findings do not improve after 6 weeks of conservative treatment, we consider prophylactic nailing. A limited percentage of patients will heal with conservative treatment, but complete resolution of evidence of a stress reaction will usually require over a year [104].

A Brief Discussion of the Fracture Liaison Service

At this point, studies have been shown that sending a letter to the primary care doctor only results in at best 25 % of patients being treated with an osteoporosis program [116]. It has also been shown that if the fracture service intervenes and starts the therapy there is a 55 % chance the patients will be on the long-term therapy. Therefore, the ideal arrangement is for the fracture team in its completeness before finishing the care of their patient initiate a program for anti-osteoporotic care. The most successful method that has been established to-date is the fracture liaison service, which consists of a group under the leadership of "bone caring" physicians. These can be physiatrists, geriatricians, internists, endocrinologists, rheumatologists, and orthopedists who have an interest in this area and will establish algorithms of care [117]. They would then oversee a group of physician helpers, often in the form of nurse practitioners or physician assistants, who would work under an algorithm. Initially they should oversee the laboratory testing and start the patient on calcium and vitamin D. After 4–6 weeks the Fracture Liaison Service showed initial osteoporotic drug therapy based on relative need for anti-resorptive or anabolic agents. The algorithm should be overseen by the physicians, and periodic checks and conferences should be carried out. This has been an extraordinarily successful treatment method and has, in addition, a major teaching function. The patients are identified while in the hospital and followed during the perioperative period. It is under the oversight of a separate service other than the actual trauma orthopedists. This service is called the metabolic bone disease team with a liaison service, which has their own financial billing as a consultative service. This has been found to be cost effective and has led to lower readmissions and appropriate care. The National Osteoporosis Foundation and several other groups will have models available to be used by physicians who are interested in setting up such a program. The Joint Commission on Accreditation of Healthcare Organizations mission has adopted this as the lead method to treat patients with hip fractures and will be looking forward to seeing that all hip fracture patients have an interaction with a defined fracture liaison team.

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Chapter 9
Preoperative Management of Paget's Disease

Joseph R. Tucci

Introduction/Epidemiology

Paget's disease (PD) originally referred to as osteitis deformans is the second most common bone disorder in man which affects an increasingly aging population in the United States after osteoporosis. It is a focal disorder that is associated with abnormal bone metabolism that involves one or more bones or many in severe cases. On the basis of 4614 unselected necropsies in Germany in individuals over 40 years of age Schmorl reported a 3 % incidence of PD [1]. In northern England, in a consecutive series of unselected necropsies in 650 individuals greater than 40 years of age, the incidence of PD was 3.7 % [2], nine out of ten were 55 years of age or older. On a limited radiologic survey of 9775 patients over 45 years of age in the United Kingdom, Pygott reported an incidence of PD of 3.5 % [3]. There are estimates of PD in 1–8 % of the elderly population in Italy and Great Britain, respectively [4, 5]. The prevalence of PD increases with age and is generally diagnosed after the age of 50 years [6]. In a survey of 800 patients with PD in the United States, the average age at diagnosis was 58 years [7]. In a series of 889 patients with PD, the diagnosis was made in 1.7 % of patients by age 39, in 6.6 % between 40 and 49 years, in 21 % between 50 and 59 years of age, in 32 % between 60 and 69 years of age, in 28 % between the ages of 70–80 years, and in 10 % between 80 and 89 years of age [8]. Earlier data indicated that 10 % of individuals over 80 years of age had pathological evidence of PD [1], while more recent data indicate a prevalence of 9–15 % in individuals in their 80s [2, 9]. Most reports are in keeping with a somewhat greater prevalence in men [1, 6, 10, 11].

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There are archeologic findings including that of a Neanderthal skull that suggest the possible presence of PD in prehistoric times and the existence of the disease in antiquity based on an ancient Egyptian skull with much more evidence dating back to the years between 900 and 1066 [10, 12, 13]. The geographic distribution of PD in ancient skeletons supports a northwest European origin of PD and its existence for at least 2000 years [14]. Epidemiologic data also suggest an origin of PD in the United Kingdom with an increased prevalence in other countries due to emigration by English colonists in the 1600s and 1700s [14, 15]. Thus, PD is most prevalent in the United Kingdom, North America, western and southern Europe, and countries to which those of European descent migrated such as New Zealand, Australia, South Africa, and South America [2, 10, 16–21]. It is uncommon in African blacks [22] and Asian Indians [23, 24] and rare in Scandinavia, Japan, and China [25–27]. In Europe the highest prevalence of 8.3 % was reported in Lancashire, England [19] and the lowest prevalence of 0.4 % in Sweden [18]. In the United States, the prevalence is highest in the northeast and lowest in the south [20]. A report based on pelvic X-rays revealed a prevalence of pagetic changes of 3.9 % in Brooklyn, New York, 0.9 % in Atlanta, Georgia, 1.1 % in Providence, Rhode Island, and a prevalence of zero in Lexington, Kentucky [28].

Recent reports in Great Britain and New Zealand have indicated a decrease in the frequency and severity of PD between the 1970s and 1990s despite an ever increasing aging population [6, 29–33]. In Olmsted County, Minnesota the incidence of PD seemed to increase from 1950 to 1979 and then decreased over the next 15 years [34]. On the other hand, in 2006 Rendina et al. reported an increase in the severity of familial and sporadic PD in southern Italy [35].

Etiology/Pathogenesis

Epidemiologic and extensive laboratory and genetic studies have implicated genetic and viral etiologic factors [36]. A strong genetic component appears to be an underlying factor in many patients with PD [37]. Fifteen to thirty percent of patients with PD have a positive family history of the disease [38]. Morales-Piga et al. [39] reported that 40 % of patients with PD had one of more first degree relatives with a pattern consistent with an autosomal dominant disorder. In many cases of familial PD, the disease is inherited as an autosomal dominant trait with high penetrance [40, 41]. Familial aggregation studies are in keeping with a seven to tenfold increased risk for the disease in first degree relatives of patients with PD [42, 43]. Galbraith et al. [44] suggested that those with more severe and extensive PD were more likely to have a family history of the disease. Twenty percent of patients initially enrolled in the New England Registry for PD had a positive family history [45].

In 2002 in patients with familial PD, genetic mutations were identified in the sequestosome1 (SQSTM1) gene that encodes p62, a scaffold protein that is involved in NFκB signaling [46–48]. Such mutations have been reported in 20–50 % of patients with familial PD and 5–15 % of patients with sporadic disease [46, 47, 49]. Missense or truncating mutations in the SQSTM1 (p62) gene have been described and most mutations are in or close to and affect the ubiquitin associated domain of the protein [49]. Patients with the SQSTM1 truncating mutations tend to have a high penetrance more clinically severe form of PD [46, 50, 51]. The majority of patients with PD do not have SQSTM1 mutations [36]. The p62 protein appears to have an important role in osteoclast differentiation and function through effects on signaling proteins including the RANKL/RANK axis [52]. The SQSTM1 p62 mutations may also affect the bone marrow microenvironment [53]. A number of genetic variants appear to increase the risk of PD [52, 54, 55]. Seven susceptibility loci for PD have been identified which contribute to the risk of PD in having a critical role in osteoclast differentiation and function and explain about 13 % of the familial risk of PD [55].

A viral etiology was suggested in the 1970s with the finding of cytoplasmic and nuclear inclusion bodies in pagetic osteoclasts that resembled viral particles or nucleocapsids [56, 57]. Ultrastructural studies demonstrated that nuclear and cytoplasmic inclusions similar to nucleocapsids from paramyxoviruses were present in pagetic osteoclasts [58]. Data supporting a viral etiology or environmental trigger have included immunohistochemical studies with positive staining with antibodies to measles and respiratory syncytial viruses in cultured osteoclast-like cells in patients with PD [59–62]. Mills et al. [63] reported finding measles and respiratory syncytial virus antigens in pagetic osteoclasts. Transfection of measles virus nucleocapsids into normal human osteoclast precursors resulted in pagetic-like osteoclasts [64]. With in situ hybridization studies, canine distemper virus nucleocapsid protein was reported in patients with PD [65]. With reverse-transcriptase in situ polymerase chain reaction techniques (PCR), Mee et al. found that osteoclasts in all 12 patients with PD expressed canine distemper virus nucleocapsid transcripts [66]. Yet, other studies using a variety of molecular, immunological, and ultrastructural studies have not confirmed evidence of paramyxoviral protein or nucleic acids in pagetic bone or peripheral blood cells [67]. Also, Matthews et al. [68] failed to detect measles virus RNA in cells cultured from pagetic bone. In a multicenter-blinded analysis of (RT-PCR) detection methods for paramyxoviruses, there was no evidence of paramyxovirus transcripts in samples of pagetic bone [69].

According to Mee, overwhelming evidence exists for the presence of paramyxoviruses in PD [70], while Ralston et al. indicate that available data do not support the unequivocal presence of paramyxovirus sequences in pagetic bone [69]. The identity of the osteoclast nuclear and cytoplasmic structures to this day remains unclear [71]. Evidence in favor of a viral etiology continues to be controversial [69, 72, 73]. At present, it remains possible that an environmental factor such as a viral infection may play a role in the ultimate development of PD in a genetically susceptible individual with SQSTM1 mutations [36, 49].

Histopathology

PD is a focal disorder of one or more bones in which bone remodeling is markedly accelerated [74–76]. In the early phases of pagetic activity, osteoclasts play a pivotal role in bone remodeling and in the acceleration of bone resorption [74]. Osteoclasts are numerous and may be increased up to 100-fold [77]. They are larger and contain more nuclei than normal osteoclasts, in some cases as many as 100 nuclei [77, 78]. Many osteoclasts have cytoplasmic and nuclear inclusion bodies [56, 57, 79]. In response to the increased osteoclastic activity and bone resorption, osteoblasts proliferate on the bone surface and rapidly lay down bone matrix that is initially woven with collagen fibers laid down haphazardly with an irregular orientation of lamellar bone and a mosaic pattern of woven and lamellar bone [74, 75]. The rapidity of new bone formation results in an increase in surface coverage in bone by osteoid [75, 80]. Mineralization generally is normal but may be less than optimal in areas of thickened osteoid [81]. Bone marrow is replaced by increasing amounts of fibrous connective tissue and blood vessels [75, 80, 82]. Osteoblasts have been thought to be intrinsically normal. However, there are data suggesting abnormalities in pagetic osteoblasts, bone marrow stromal cells, and marrow accessory cells that may contribute to the abnormal bone microenvironment [83–85]. Later in the course of the disease, pagetic bone may become less metabolically active, less hypercellular, and more sclerotic with bone marrow that is less vascular with less fibrous connective tissue giving rise ultimately to "inactive" or burned-out PD [75, 82]. The histopathological changes described commonly result in an increase in cortical and trabecular thickness and a change in the size and shape of involved bone. The end result is bone that despite an increase in size lacks normal structural integrity and is susceptible to deformation and pathological fracture [80].

Sites of Skeletal Involvement/Radiologic and Scintigraphic Findings

PD can affect any bone. In some cases, it may involve only one or two bones but in 75 % of patients it is polyostotic involving a number of bones in a typically asymmetric fashion [80, 86]. The most common sites of involvement are pelvis, femur, spine, skull, and tibia [81, 87]. Less commonly involved sites are the humerus, scapula, ribs, clavicle, sternum, calcaneus, and patella. The other bones of the foot, the hand, facial bones, fibula, radius, and ulna are rarely involved [10]. In those with monostotic disease, the most common sites of involvement include pelvis, tibia, and femur [87].

Typical radiologic findings include osteolytic areas as in osteoporosis circumscripta of the skull, "blade of grass" or a V-shaped osteolytic advancing resorption front in a long bone such as the tibia or femur, mixed lesions of osteolysis and osteosclerosis, or a predominance of osteosclerosis. The advancing osteolytic process

estimated from serial radiographs can progress at a rate of approximately 0.8 cm per year [88]. Other abnormal findings are cotton wool appearance of the skull, cortical and trabecular thickening, bone enlargement, hyperostosis, and bone deformation such as in skull, facial bones, clavicle and long bones of the lower extremities with anterior bowing of the tibia and lateral bowing of the femur.

The femur is the most frequently involved long bone [80]. Fissure or incomplete fractures are more likely to occur in the femur, tibia, and humerus. They typically occur on convex surfaces in approximately 8–31 % of patients with PD [80]. Fissure fractures frequently remain asymptomatic for many years but in some cases are associated with pain [80]. They may result in a complete transverse fracture especially in the femur and tibia [80]. According to Redden et al., 50 % of fissure fractures ultimately result in completed fractures [89]. The pelvis is the most common site involved with PD where there may be areas of sclerosis, sclerotic thickening of the ileopectineal line, pelvic deformation, protrusio acetabuli, acetabular thickening, and a relatively uniform narrowing of the joint space such as at the hip. It is important to note that progression of pagetic changes to a new skeletal site rarely, if ever, occurs [80].

Generally, a bone scan with technetium is the most sensitive way of visualizing the skeleton and in delineating the presence and extent of the PD [80, 81, 90]. There are a number of reports in which a comparison of scintography and radiography reveals that radiography underestimates pagetic sites of involvement [91–93]. However, radiographs can occasionally demonstrate pagetic changes at sites not seen on scan especially in cases of sclerotic or inactive PD [92, 94]. This is uncommon: radiographs are positive for scan-negative sites less than 3 % of the time [90, 91]. A bone scan is less specific as increased uptake may also occur in nonpagetic areas involving degenerative arthritis or metastatic disease [90]. Based on scintigraphic findings, appropriate X-rays can subsequently be directed to areas that on scan suggest PD for confirmation of the diagnosis and more exact characterization of lesions [81, 90]. When there is uncertainty as to the diagnosis, an MRI scan may be helpful in cases of sarcoma, metastatic disease, or giant cell tumor. Occasionally, a bone biopsy may be necessary for a definitive diagnosis or to exclude a neoplastic lesion [81].

Skeletal Blood Flow

Increased skeletal blood flow is a recognized feature of PD. Sir Paget [95] felt that the disease was inflammatory in nature and called it osteitis deformans. During the necropsy of his first patient, there was evidence of increased vascularity of affected bones [95]. Subsequently, in three of seven other patients with PD, he noted increased heat over the tibiae [96]. In 1908, Klippel and Weil demonstrated that the skin temperature over affected bone was higher than temperature over the rest of the body [97]. In 1922, Cone described the highly vascular state of affected bone in PD and the frequent association of PD with extensive cardiovascular disease [98]. In an arteriographic study Reboul documented in a case of osteitis deformans, considerable

vascularity of involved bones, very large caliber arteries, and numerous collateral vessels [99]. Subsequent arteriographic studies in three cases of osteitis deformans documented increased vascularity of affected bones with no definite evidence of arteriovenous fistulas [100]. In 1943, Snapper documented with an electric skin thermometer that the skin over an involved tibia was always 1.5–3.8 °C greater than the skin temperature over the normal tibia [101]. In a case of generalized PD with evidence of congestive heart failure, Edholm et al. documented an increased cardiac output of 13.3 L/min and a marked increase in bone blood flow of up to 20 times normal by a modified Lewis–Grant plethysmograph [102]. In two cases of localized PD, blood flow through the affected limbs was greatly increased. Howarth reported that in 12 patients with active osteitis deformans, cardiac output was increased in five patients [103]. A high cardiac output was not found in cases in which there was less than 35 % of skeletal involvement. In a subsequent study of 18 cases of osteitis deformans, Edholm and Howarth reported an increase in peripheral blood flow in 21 of 23 limbs in which the underlying bone was affected whereas blood flow was within normal limits in normal bone [104]. There was no increase in bone blood flow in a case of inactive osteitis deformans. On biopsy of an affected humerus, there was "considerable troublesome bleeding." Skin temperature was increased in areas over bones that were affected by active osteitis deformans. Dissection of affected limbs at autopsy revealed a marked increase in the size of blood vessels forming the periosteal plexus.

In a critical review of the literature with case studies, Sorenberger and Smedal found a much greater prevalence of cardiovascular disease evidenced by cardiac enlargement and marked arteriosclerosis in patients with extensive PD than among the general population [105]. The severity of both of these findings was related to the degree of skeletal involvement and the marked vascularity of pagetic bone. There was no convincing evidence of cardiac enlargement in patients with localized PD. In a study of circulatory dynamics, Lequime and Denolin reported that at rest, even in cases of generalized PD, cardiac output was normal but during exercise, there was a considerable increase in bone blood flow and cardiac output [106].

Interestingly, Heistad et al. [107] suggested on the basis of epinephrine iontophoresis and heating that in their study of three patients with PD involving one extremity increases in blood flow were a result of cutaneous vasodilatation. Wootton et al. [108] utilizing a new method for measuring blood flow to the skeleton by an intravenous radiofluorine clearance method reported in eight normal subjects values of 4.4–5.9 % of blood volume per minute with a mean value of 5.1 %. The blood flow to bone was approximately 300 mL/min, which was less than 5 % of the cardiac output. In six patients with severe untreated PD skeletal blood flow was significantly increased from 8.1 to 15.3 % of blood volume per minute. In a follow-up report, skeletal blood flow was significantly increased in 23 of 24 patients with untreated active PD at 6–18.9 % of blood volume per minute [109]. In one patient with inactive PD skeletal blood flow was normal at 4.4 %. Skeletal blood flow measurements correlated significantly with the extent and severity of the PD. After treatment of 14 patients for 7 days or for 7 weeks with parenteral calcitonin, skeletal blood flow, serum alkaline phosphatase (SAP), and urine hydroxyproline excretion fell toward normal in every

patient. Their data were in keeping with a more rapid fall in skeletal blood flow than in SAP. These results were not at all consistent with cutaneous vasodilatation suggested by Heistad et al. [107] but rather with changes in skeletal blood flow [109].

Six patients with symptomatic PD were treated with salmon calcitonin 50 units subcutaneously twice daily for up to 15 months [110]. Cardiac output which was increased in four of the six patients fell progressively in three of them during therapy. No change in cardiac output was noted in two patients with normal cardiac output throughout the study. In a study of the cardiovascular status of 39 patients with PD before and after therapy with calcitonin or etidronate, cardiovascular abnormalities were detected in 32 patients with an increase in the cardiac index in 27 of 39 patients that had moderate or severe PD [111]. Correlated with the cardiovascular abnormalities were biochemical measurements of pagetic activity and skeletal radiologic findings. After 24 weeks of treatment with either porcine calcitonin or etidronate, there was a decrease in the cardiac index in 17 of 18 patients. In those treated with calcitonin there was a mean decrease of 13 % in the cardiac index and in those treated with etidronate a mean decrease of 27 %. Walton et al. [112] reported that in ten patients with PD treated with etidronate for 3–4 months skeletal blood flow was decreased by a mean of 21 %. These results were similar to those seen in an earlier study in patients treated with calcitonin. However, in contrast to etidronate, calcitonin therapy was associated with an earlier reduction in blood flow [112]. Using infrared thermography, Ring and Davies reported elevated values in patients with tibial disease without pain and higher values in those with pain [113]. Treatment with etidronate for 4–6 months in three patients with PD resulted in a decrease in the thermal index. Treatment with parenteral calcitonin was associated with striking effects with relief of bone pain, a decrease in biochemical indices, and a reduction in the thermal index over a pagetic lesion during a 6-week period and a more marked effect during treatment for 6 months. In an open study with alendronate therapy in a small group of patients for 6 months, Ring et al. reported that there was a fall in the thermal index in six of seven patients [114]. The authors commented that the main source of temperature changes strongly associated with bone pain was related to osseous perfusion.

Clinical Features/Presentation

The diagnosis of PD is generally made after the age of 50 years but there are patients who present in their 40s and rarely in their 30s. The presentation of patients with PD varies considerably. The majority of patients are said to be asymptomatic at diagnosis [81, 115] with two reports indicating that at diagnosis 30–40 % of patients were symptomatic [34, 44]. In a review of 889 patients with PD from centers in the United Kingdom, 74 % of patients did present with symptoms [8]. Initial presentation varies from a finding of an abnormal SAP level on a blood screening chemical profile or of pagetic changes on an X-ray done for an unrelated reason. Pain is the most

common presenting complaint [80, 115] and most often is due to a secondary osteoarthritis [116]. It may also be due to pagetic disease per se, primary osteoarthritis, pagetic-related compressive central or peripheral neurological syndromes, fissure or completed fracture, and rarely osteosarcoma [115, 117–119]. Pain related to PD per se may be due to periosteal stretching [120], increased blood flow through pagetic bone [80], increased skin temperature over pagetic bone, or a fissure fracture [80, 81, 121]. Pagetic pain is likely to be an aching pain and is often present at rest and worse with weight bearing and physical activity [71]. Other complaints may be related to bone deformity, enlargement of the skull with prominent superficial vessels over the forehead, softening of the base of the skull with platybasia and basilar invagination, hearing and other cranial nerve deficits, and impaired gait and mobility. Patients with polyostotic disease are more likely to be symptomatic, although there are patients who may, for example, have one bone involved and have pain as with a pagetic calcaneus or scapula. Neurological complaints may be related to central or peripheral encroachment of nerves by pagetic bone, spinal stenosis and, in some cases, vascular steal syndrome. Complaints may result from enlargement and deformation of face, jaw bone, clavicle, and bowing of the femur or tibia. Atrophic and erythematous skin ulceration can occur with increased warmth overlying a pagetic tibia [80].

Joint pain is often related to enlarged and/or deformed bone adjacent to articular cartilage and surfaces and primary and secondary osteoarthritis with thinning of articular cartilage. At the hip, pain may be related to protrusio acetabuli. Osteoarthritis involving the acetabulum or proximal femur is common [122]. Such patients are three times more likely to need a hip replacement for osteoarthritis than are aged-matched controls [29]. As noted above, particularly in cases of extensive PD, there is an associated increase in cardiovascular disease including calcification of large vessels, heart valves and myocardium, high cardiac output, cardiac enlargement, and congestive heart failure at least in part related to the increase in bone blood flow [10].

Of the long bones, the femur is most commonly involved [80]. Fractures are more likely to occur in the long bones of the lower extremities and often occur with minimal or no preceding trauma [10, 80, 123]. In patients with PD, femoral fractures occur more frequently than tibial fractures [80]. In a personal series of 100 femoral fractures, Barry reported that 30 were subtrochanteric, 8 were cervical, and all the others occurred through the remainder of the shaft [124]. In these cases, trauma was usually slight and some fractures were preceded by fissure fractures. Redden et al. [89] reported that 50 % of patients with a fissure fracture ultimately developed a complete fracture. An incidence of femoral fracture nonunion of up to 10 % was reported by Barry [124], 25 % by Grundy [123], and 40 % by Dove [125]. In a review of 30 patients with PD who had 35 fractures through pagetic bone, there were 21 femoral fractures of which 6 were cervical, 7 were subtrochanteric, and 8 were at the upper and middle third of the femoral shaft [126]. All patients received bisphosphonates therapy and there was no gross delay in fracture union.

Although three of the first five patients seen by Paget developed a sarcoma, it is a rare complication of PD occurring in less than 0.5 % of cases [127, 128]. Common sites of involvement with sarcoma include femur, pelvis, skull, and tibia [129]. In an

interesting review of the literature, Porretta et al. reported that of 78 patients who had sarcoma in the long bones 14 had a recent fracture in the same area [130]. In a report of the incidence of osteogenic sarcoma in England, it was estimated there was a 30-fold increase in the risk of sarcoma in patients with PD and in those with extensive disease there was a further increased risk [131]. Benign giant cell tumors may also occur in pagetic bone and osteoclastomas in nonskeletal sites [81, 132].

Endocrine/Metabolic Features

Serum calcium and phosphorus levels are generally normal in patients with PD [10, 80]. Hypercalcemia and hypercalciuria may occur in patients with extensive disease when immobilized [117, 133]. In PD fasting urine calcium creatinine ratios have been reported to be increased despite normal 24-h calcium excretion [80]. This may be attributed to overnight immobilization and an associated decrease in osteoblastic activity and an increase in osteoclastic activity [80]. In keeping with secondary hyperparathyroidism, increases in serum PTH levels have been reported in patients with PD who have normal serum calcium levels [134–136]. Such increases may in many cases be related to vitamin D deficiency or insufficiency and/or diminished renal function which is more likely in older individuals who are also those that are more likely to be afflicted with PD [71, 137]. The occurrence of primary hyperparathyroidism in some patients with PD may simply be related to the coexistence of common clinical disorders [138]. In other cases, hypercalcemia may be due to any of a number of other causes including malignancy. Serum calcium levels may be intermittently normal in some patients with mild primary hyperparathyroidism and also in those with concomitant vitamin D deficiency [80]. Patients with PD who are vitamin D deficient may not respond optimally to pharmacotherapy [80, 139, 140]. Hypocalcemia may be a feature of severe vitamin D deficiency but may also occur within days of treatment with a potent bisphosphonate especially following intravenous pamidronate or zoledronic acid as a result of inhibition of osteoclastic activity and bone resorption [71].

Biochemical Parameters

Serum total alkaline phosphatase (SAP) remains an important clinical marker and index of pagetic activity [141, 142]. SAP is a composite derived from liver, intestinal tract, and bone. Generally, an increase in SAP without any biochemical evidence of liver or gastrointestinal disease is in keeping with bone derivation and related to excess osteoblastic activity. Significant liver source of SAP can be excluded by measurement of gammaglutamyl transferase or 5′ nucleotidase. For years, there has been a fractionation technique to determine the amount from intestinal tract, liver,

and bone. SAP from bone is heat labile, that is "bone burns" while SAP from liver and intestinal tract is not affected by application of heat. Now available is a bone-specific SAP which can be obtained in cases in which there may be a question as to its origin. In those patients with liver disease, a bone-specific alkaline phosphatase can be used in the assessment and monitoring of pagetic activity.

Generally, in patients with more extensive and more active PD the SAP levels are quite increased and in some cases up to 10–20 times the upper limit of normal. On the other hand, in patients with relatively limited bone involvement and activity, as in patients with monostotic disease, SAP levels may be within normal limits or only minimally increased [143]. In such cases a bone-specific alkaline phosphatase measurement may be more useful. Interestingly, pagetic involvement of the skull is often associated with marked increases in SAP [144]. Thus, SAP levels have been a diagnostic mainstay in assessing pagetic activity and an important parameter in monitoring the response to therapeutic intervention.

For many years, measurement of urinary hydroxyproline excretion was used in assessing osteoclastic activity and bone resorption with increased excretion correlating with the extent and activity of the pagetic process. That measurement has been replaced by measurement of more specific components of bone matrix such as C terminal-telopeptide of type I collagen (CTX) and urine N terminal-telopeptide of type I collagen (NTX). Current assessment of osteoclastic activity and bone resorption is accomplished by measurement of NTX and creatinine in a second morning urine specimen or a morning plasma CTX measurement. With therapy of the PD, these resorption markers fall rapidly within days to weeks followed by a slower decrease in SAP levels within weeks to months. With activation of the disease, resorption markers typically rise before there is any increase in SAP levels.

Antipagetic Medications

The first therapeutic agents effective in suppressing pagetic osteoclastic activity and bone turnover became available in the late 1960s and 1970s with the approval of parenteral salmon calcitonin and the first oral bisphosphonate, etidronate. Since then, more potent bisphosphonates have become available for clinical use that can result in long-standing remissions. Calcitonin is a 32-amino acid polypeptide that is synthesized and secreted by the parafollicular cells of the thyroid gland in response to an increase in serum calcium. Its physiologic role seems relatively insignificant clinically since total thyroidectomy in man has no effect on serum calcium levels nor is medullary cancer of the thyroid in which there is excessive calcitonin secretion associated with any clinical abnormality in serum calcium. Parenteral calcitonin administration can lower serum calcium by inhibiting osteoclastic resorption of bone and by increasing urinary excretion of calcium. In patients with PD, salmon calcitonin is subcutaneously injected in doses of 50–100 units every other day or on a daily basis. Such therapy decreases the number and activity of osteoclasts and bone turnover by up to 50 % in many patients over several months, and in a matter

of days or weeks, alleviates pagetic pain, neurocompressive syndromes, promotes healing of lytic lesions, and decreases bone blood flow and cardiac output [110, 145, 146]. Only in patients with limited disease is there a complete clinical and biochemical remission. Generally, despite continued therapy with calcitonin, there is no further fall in SAP levels, the so-called plateau response. Uninterrupted therapy with calcitonin can continue to suppress bone turnover in some but not in all patients. It can continue to alleviate pagetic pain and some neurologic deficits and decrease pagetic bone vascularity with a positive effect on lytic lesions and improvement in bone histopathology. Discontinuation of therapy rapidly results in a recurrence of pagetic activity. Today, due to its relatively weak antiresorptive effect and duration of effect its use is limited to patients intolerant to bisphosphonates or to patients with renal insufficiency with glomerular filtration rates of <35 mL/min. Therapy with parenteral calcitonin can be associated with transient symptoms including nausea, facial flushing, abdominal discomfort, and diarrhea.

A recent safety signal suggested a possible link between salmon calcitonin and prostate cancer. In 15 of 18 studies reviewed, the percentage of cases of malignancy was greater in those subjects treated with calcitonin suggesting an association between salmon calcitonin use and cancer. This was based on studies with poor quality cancer assessment methods [147]. On the basis of available data, short-term use of salmon calcitonin to facilitate an early decrease in pagetic activity and bone vascularity should not be a concern at this time.

Bisphosphonates are the treatment of choice for active PD. Bisphosphonates are analogs of pyrophosphates in which a carbon atom has replaced the oxygen atom resulting in compounds that are stable and resistant to enzymatic hydrolysis [148]. These compounds have a strong affinity for bone and inhibit osteoclastic activity and bone resorption [148]. Their binding to bone is related to the P-C-P structure with a hydroxyl group at the R^1 side chain and their antiresorptive potency is related to the diverse R^2 side chains [148, 149]. Non-nitrogen-containing bisphosphonates such as etidronate, tiludronate, and clodronate inhibit osteoclastic activity through formation of cytotoxic ATP analogs that have an adverse effect on osteoclast function and structure, decrease osteoclast recruitment, and promote osteoclast apoptosis [148, 150]. Nitrogen-containing bisphosphonates such as alendronate, risedronate, pamidronate, and zoledronic acid inhibit osteoclastic activity through inhibition of farnesyl pyrophosphate synthase of the mevalonate pathway [148, 151]. The subsequent inhibition of protein prenylation and formation of GTP-binding proteins results in disruption of osteoclast structure and function and induction of apoptosis of osteoclast precursors [149]. Bisphosphonate therapy decreases bone turnover, alleviates bone pain, promotes healing of osteolytic lesions, and can restore normal bone histology [152]. Potency in inhibiting bone resorption varies from a value of 1 for etidronate to 10 for tiludronate, 100 for pamidronate, 1000 for alendronate, >1000 for risedronate, and 10,000 for zoledronic acid [148]. Absorption rates for oral bisphosphonates are very low (0.7–2.5 %) and bio-availability is significantly diminished by concomitant intake of food, calcium, magnesium, and many other substances [153]. Therefore, oral bisphosphonates need to be taken with plain water only. Food, vitamins, medications or other substances should be taken no sooner than 30–60 min later.

Diminished responses with repeated therapy have been reported with etidronate and pamidronate in keeping with an acquired resistance [154–156]. However, such patients often respond to other bisphosphonates [157, 158]. Biochemical remission rates based on pivotal trials have varied from 15 % for etidronate [159], 63 % for alendronate [160], 35 % for tiludronate [161], 73 % for risedronate [162], and 89 % for zoledronic acid [163]. Remission rates have varied following therapy with pamidronate with diverse dosing regimens [156, 164]. Reported duration of remissions varies from months to as many as 6.5 years with zoledronic acid [165], and for more than 10 years in some patients treated with pamidronate [166]. Dosing regimens are as follows: alendronate 40 mg orally per day for 6 months, risedronate 30 mg orally per day for 2 months, and intravenous pamidronate with an FDA approved regimen of 30 mg intravenously in 500 mL of isotonic saline or 5 % D&W over 4 h each day for 3 days. Zoledronic acid is administered once intravenously as a 5 mg infusion over 15 or more minutes. Therapeutic response is monitored by measurement of bone turnover markers such as SAP at 3, 4, or 6 monthly intervals. Oral bisphosphonates can occasionally be associated with myalgia and bone pain as well as dyspepsia, abdominal pain, nausea, vomiting, and diarrhea. Oral and particularly parenteral bisphosphonates after the first infusion can give rise to an acute phase reaction in 10–25 % of patients with a flu-like illness lasting several days [159, 167]. Acetaminophen will often prevent or alleviate these symptoms. Uveitis is a rare complication of parenteral therapy.

Indications for therapy include extensive disease especially in those with cardiovascular disease, pain, long bone involvement with bone deformities and lytic lesions, fissure or complete fractures, areas of critical skeletal involvement even in asymptomatic patients, younger patients in an effort to prevent progression, preoperatively to prevent excess bleeding during an orthopedic procedure on pagetic bone, and immobilization hypercalcemia. Due to the greater potencies of the nitrogen-containing bisphosphonates over etidronate and tiludronate, a single infusion of zoledronic acid or oral risedronate on a daily basis for 2 months are the drugs of choice. Since early limited data have suggested a more rapid effect in terms of affecting bone blood flow with parenteral calcitonin [109], such therapy can also be considered together with intravenous zoledronic acid or oral risedronate, especially in cases where urgent surgery is necessary. Patients who are intolerant to oral or intravenous bisphosphonates or have glomerular filtration rates of less than 30–35 mL/min should be treated with parenteral calcitonin. Though nasal calcitonin appears to be as effective as parenteral calcitonin, it has not been approved in the United States for therapy of PD.

Pharmacotherapy Induced Hypocalcemia

Bisphosphonates are the most effective agents in the treatment of PD. As a result of their inhibition of osteoclastic activity, asymptomatic and symptomatic hypocalcemia can occur with the more potent nitrogen-containing compounds particularly

following intravenous therapy with pamidronate or zoledronic acid [81, 168–172]. Inadequate dietary calcium intake and limited sun exposure and vitamin D intake are common in the elderly and in those with PD [163, 173]. In addition, comorbid conditions or factors predisposing to hypocalcemia have been reported such as hypoparathyroidism, hypomagnesemia, renal insufficiency and gastrointestinal malabsorption [171, 174, 175]. In a randomized trial with oral alendronate and intravenous pamidronate in 72 patients with PD, greater increases in serum intact PTH and decreases in plasma ionized calcium were reported in those treated with alendronate [157]. In another study asymptomatic hypocalcemia following therapy was reported in all 26 patients treated with intravenous pamidronate [168]. Gutteridge et al. [169] reported a decrease in serum ionized calcium levels in 71 patients with PD between 4 and 10 days following intravenous pamidronate with more severe hypocalcemia in those with more active PD and treatment with larger doses of pamidronate. In a pivotal trial in which patients were treated with intravenous zoledronic acid or risedronate, asymptomatic hypocalcemia was reported in 8 of 177 patients in the zoledronic acid group [163]. Two of the eight patients were mildly symptomatic and had not taken their calcium and vitamin D supplements. One patient with polyostotic PD and an SAP of 1894 IU/L (31–110 IU/L) in the risedronate group had severe symptomatic hypocalcemia requiring intravenous calcium administration [176]. After 10 days of risedronate therapy, serum calcium had fallen from a baseline level of 9.3 to 5.4 mg/dL, baseline serum 25-OHD was 13 ng/mL in keeping with vitamin D deficiency and serum PTH was low-normal at 20 pg/mL (normal 12–72). These authors indicated the need for awareness of possible hypocalcemia following bisphosphonate therapy and the need for continuing optimal calcium intake and the critical importance of vitamin D sufficiency prior to initiation of bisphosphonate therapy. On the other hand, Merlotti et al. reported that in 90 patients with PD treated with intravenous pamidronate or zoledronic acid, asymptomatic hypocalcemia did not occur apparently because patients were supplemented with 1 gm of calcium and 800 IU of vitamin D [158]. However, mild hypocalcemia defined as an ionized serum calcium less than 1.21 mM occurred in 3 of 47 patients treated with intravenous zoledronic acid and in 1 of 60 patients treated with intravenous pamidronate.

Vitamin D

Vitamin D insufficiency and deficiency are important clinical problems in all segments of the population and especially in the elderly [137]. Vitamin D deficiency may result clinically in muscle weakness, bone pain, and vulnerability to fracture [177]. Biochemically, classical changes include hypocalcemia, hypophosphatemia, hypocalciuria, and an increase in SAP. Vitamin D deficiency in the elderly is often related to inadequate sun exposure, decreased synthesis of vitamin D in the skin with sun exposure as compared with the young, and poor intake of dietary or supplemental vitamin D [137]. Vitamin D deficiency is very common in patients with

hip fracture [178–180]. One alpha hydroxylase activity decreases with age and with age-related changes in renal function [181]. In patients with vitamin D deficiency, serum 25-OHD levels are low and production of 1,25-OHD may be diminished for lack of substrate [140, 178, 182].

The Institute of Medicine has defined vitamin D insufficiency as a serum 25-OHD level of 10 to <20 ng/mL and deficiency as a level of <10 ng/mL [183]. In contrast the Endocrine Society has defined insufficiency as a level of 20–29 ng/mL and deficiency as a level of <20 ng/mL [184]. Vitamin D facilitates calcium and phosphorus absorption [185]. Suboptimal vitamin D status and especially vitamin D deficiency can result in calcium malabsorption, secondary hyperparathyroidism, increase in bone turnover, bone loss, and hip fractures [137]. In those 75 years of age or older, decreases in renal function occur with blunting of synthesis of 1,25-OHD. Age-related decreases in calcium absorption have been reported even a decade earlier than the described decrease in serum 1,25 OHD levels. A low intake of dietary calcium adds to the problem by further increasing PTH secretion [186]. Even using a conservative definition of serum 25-OHD of 20 ng/mL, one-third of Caucasions have low serum levels especially during the winter time [187]. A decrease in dietary calcium and calcium absorption as in patients following a gastrectomy results in increases in serum PTH and 1,25-OHD. These increases are associated with increased metabolic clearance and catabolism of 25-OHD which may well make worse an already low level of serum 25-OHD [188]. Optimization of calcium and vitamin D intake results in a decrease in serum PTH levels and bone turnover, and decreases the risk of hip and other fractures [137]. Optimal calcium intake and vitamin D status are also critically important pre- and postoperatively in patients with PD to prevent postoperative hypocalcemia and secondary hyperparathyroidism and in facilitating optimal absorption of calcium and an optimal therapeutic response to antipagetic therapy [159, 163]. A total intake of 1200–1500 mg of elemental calcium per day is recommended [176]. Vitamin D therapy would depend on the serum 25-OHD level and the response of serum 25-OHD levels to supplementation. The goal would be a serum 25-OHD level of ≥30 ng/mL. Optimization of calcium intake and vitamin D status should be routinely recommended and discussed with patients prior to, during, and following bisphosphonate therapy [189].

Orthopedic Surgery of the Hip in Paget's Disease/Preoperative Assessment and Therapy

Orthopedic surgery may be necessary in the treatment of pagetic complications such as (1) unstable fissure or pathologic fractures, (2) secondary osteoarthritis, (3) hip replacement for intractable pain, stiffness, femoral deformity, and functional limitations, (4) osteotomy for long bone deformities, (5) bone biopsy, (6) surgery for spinal stenosis and osteosarcoma [190–192]. Pain in patients with PD can be a major complaint [193] and is often due to a rheumatologic complication such as osteoarthritis [116]. In patients with PD, the most common site for joint arthroplasty

is the hip [194]. After pain has been determined to be articular rather than osseous a total hip replacement is quite effective in relieving severe pain and restoring more normal mobility [192, 195].

In 1966, Machtey et al. noted that the problem of hip joint disease due to osteitis deformans had received relatively little attention in the American literature [196]. With increased awareness of the importance of hip disease in patients with PD, the records and X-rays of 98 unselected patients with PD were reviewed with particular emphasis on the occurrence of hip joint involvement [196]. Findings included the deepening of the acetabulum and ultimately protrusion due to pressure of the femoral head on the joint socket, development of osteophytes, weakening of subchondral bone leading to degeneration of articular cartilage and concentric narrowing of the joint space. The majority of patients with coxopathy were symptomatic with pain, limp, and limited motion at the hip joint. A subsequent report by Harris and Krane indicated that hip involvement in patients with PD was a common source of pain [197]. Graham and Harris [198] in a radiologic examination of 199 hips in 131 patients with PD reported the pattern of arthritis with pagetic involvement of femur, acetabulum or both. Protrusio acetabuli was present in 25 % of cases generally when both femur and acetabulum were involved. Stauffer and Sim reported their experience with total hip arthroplasty in 32 patients with symptomatic PD involving 35 hips with mechanical disruption of the hip joint, pain, and disability [199]. Protrusio acetabuli was very common. There was no excessive operative blood loss and no significantly increased risk as compared with their larger series of 2012 total hip arthroplasties in patients without PD. There was a high incidence of heterotopic bone formation.

In 21 patients with PD who had a total hip replacement for coxarthrosis, Merkow et al. reported good or excellent results in 18 patients [191]. Eight patients were treated preoperatively with etidronate and/or calcitonin. All but one of these patients had improvement in SAP levels to near normal values. The average operative time was 3 h (range 1.5–4 h) and the average blood loss was 1475 mL (510–3700 mL) versus an operative time of 2 h and blood loss of 687 mL in a group of nonpagetic patients similar in age and other characteristics who had had a total hip replacement. Preoperative treatment with calcitonin and/or a bisphosphonate resulted in a slight decrease in average blood loss of 1250 mL (range 510–3500 mL) as compared with the figures for the entire group. Therapeutic protocols varied in the eight patients treated medically and, therefore, definitive conclusions could not be made. The authors did recommend therapy with calcitonin beginning 1–3 months preoperatively followed by etidronate for 3–6 months in patients with active PD. Despite a 52 % incidence of heterotopic ossification there was no significant effect on function. Prior therapy with parenteral calcitonin or bisphosphonate did not reduce this complication.

Thirty-nine femoral procedures including total hip replacement in 27 patients with PD of the hip and osteoarthritis were associated with blood loss that was twice as much as that experienced with replacement of nonpagetic hips [200]. In a study of 80 patients with PD of the hip, symptomatic coxarthrosis led to total hip arthroplasty in 91 hips [201]. The average operative blood loss was 1390 mL (range 200–3500 ml) an amount that was not significantly greater than in their reported series of

2012 total hip arthroplasties in nonpagetic patients [202]. The overall result was good or excellent in 74 % of patients. Heterotopic bone formation occurred in 34 hips or 37 % overall in keeping with a reported range of 23–52 % in two other series [191, 199]. Total arthroplasty in 30 patients with PD for symptomatic coxarthrosis in 37 affected hips was associated with intraoperative difficulties in 9 of 37 operations [9]. The most common complications were excess bleeding, hard bone, and difficulty with exposure due to protrusio. Heterotopic ossification was seen in 24 hips (65 %). Sochart and Porter [203] in a report of 98 total hip arthroplasties in 76 patients with PD of the hip accurate blood loss measurements were available for 79 procedures. The average intraoperative blood loss was 388 mL (range 110–1730 mL) and total blood loss including postoperative drainage was 829 mL (200–2300 mL). In 17 cases, blood loss exceeded 500 mL and in 6 cases blood loss was greater than 750 mL with 2 patients losing more than 1 L of blood. SAP levels were not documented in these patients and the fact that intraoperative blood loss was not excessive suggested to the authors that there was no increased bone vascularity. Only 28 hips (29 %) had any evidence of ossification and in only four cases was it clinically significant.

A fracture is one of the most frequent complications of PD [123] and is a presenting feature in 6–16 % of patients [126]. The most frequent fracture is that of the femur and fractures of the femur, tibia, and humerus account for 92 % of all pathological fractures [204]. In a report of 48 patients with femoral fractures and a total of 63 fractures, despite progressive bone deformities, it was the femoral fracture in 40 patients that led to the diagnosis of PD [123]. In most patients, there was relatively mild trauma or no trauma with 17 patients reporting that the leg "just gave way." There was failure of union in all 11 patients with femoral neck fractures through pagetic bone. Most fractures occurred through the femoral shaft while neck fractures were much less common. In a personal series of 100 femoral fractures, Barry also reported that most fractures occurred through the shaft of the femur while neck fractures were infrequent [124]. Thus, the sites of femoral fractures in patients with PD differ from their usual anatomic locations in elderly patients without PD [124, 126]. Barry also reported that there was no abnormal operative bleeding [124]. Nonunion occurred in 10 % of cases. In a retrospective study of 35 femoral fractures, Bidner and Finnegan reported operative blood loss that was not significant when compared to operative blood loss with similar fractures in patients without PD except for a somewhat greater loss in the subtrochanteric group [205]. Again, femoral fractures in the pagetic patient were more likely to be in the trochanteric, subtrochanteric, and upper femoral shaft regions.

There is always the potential for excess blood loss during an operative procedure on pagetic bone [190, 192] and this varies from patient to patient and in different surgical sites [10]. Notwithstanding the fact that an increase in operative blood loss has not been universally reported with hip replacement [9, 124, 199, 203, 205], Kaplan has emphasized the importance preoperatively of reducing pagetic activity by approximately 50 % with drug therapy for minimizing potential excess blood loss [192]. Accordingly, before any urgent or non-urgent surgical procedure preoperative therapy should include a bisphosphonate and/or parenteral calcitonin [145,

146, 191, 206, 207]. Despite preoperative therapy, Stevens has indicated that pagetic bone may continue to bleed excessively necessitating blood transfusions [208]. In keeping with that possibility, Kaplan has also indicated that preoperative autologous blood donations should be considered [192] and others an intraoperative blood salvage system [190]. Thus far, there have been no controlled randomized studies to document the effect of pharmacologic preoperative therapy but such therapy has been common practice and has always been included in the indications for therapy in patients with PD [81, 145, 192]. In elective cases, Kaplan has suggested antipagetic therapy at least 6 weeks before surgery [192] while Urteaga has recommended 3 months of therapy prior to surgery [194]. For planned surgery, Martin has recommended 3–6 months of therapy with calcitonin [146]. Similar recommendations have been made by others [80, 81, 190, 191]. Such therapy will also prevent the development of post-immobilization hypercalcemia. The literature is now replete with the recommendation of antipagetic treatment prior to orthopedic surgery on pagetic bone. This appears to be a reasonable approach.

Preoperatively to determine surgical risk, patients with PD should have a thorough medical history, physical examination, and medical evaluation especially in those with polyostotic PD and a history of cardiovascular disease. A comprehensive blood chemistry panel is necessary to determine the status of serum electrolytes, renal and hepatic function, serum calcium, and SAP to determine the degree of pagetic activity. A second voided morning urine for measurement of NTX/creatinine ratio or measurement of plasma CTX may also be helpful in assessing pagetic activity. As already discussed in section IV, a bone scan and appropriate X-rays will demonstrate the location and severity of PD. A serum 25-OHD measurement will define vitamin D status and a serum intact PTH will determine the level of parathyroid activity. Prior to an orthopedic procedure on pagetic bone, Glaser and Kaplan have suggested that any anticipated dental or urologic procedure should be carried out before orthopedic surgery to minimize the risk of bacterial seeding of an endoprosthesis [195]. As indicated in section XI, a total intake of 1200–1500 mg of elemental calcium per day is recommended. This is inclusive of dietary intake and, when necessary, calcium supplementation. Vitamin D therapy will depend on the serum 25-OHD level and the response of serum 25-OHD to vitamin D supplementation to maintain a level of ≥30 ng/mL. There are available over-the-counter (OTC) vitamin D3 tablets of 1000, 2000, and 5000 IU. Generally, 1000 IU of vitamin D daily raises the serum 25-OHD level by approximately 10 ng/mL. Alternatively, patients with severe vitamin D deficiency could be treated by prescription with 50,000 IU of vitamin D2 once weekly for 8 weeks followed by a maintenance dose of 50,000 IU once or twice monthly. The preferred parenteral bisphosphonate is zoledronic acid at a dose of 5 mg administered as a single intravenous infusion over 15 or more minutes. The oral bisphosphonate of choice would be risedronate 30 mg daily for 2 months taken in the fasting state with tap water with no food for 30 and preferably 60 min for optimal absorption. For a more rapid antipagetic effect, salmon calcitonin is injected subcutaneously at a dose of 50–100 mcg every other day and, if tolerated, to a dose of up to 100 mcg daily. As indicated previously, those intolerant to oral and intravenous bisphosphonates or have renal insufficiency should be treated with parenteral calcitonin.

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Chapter 10
Metabolic Bone Disease Following Organ Transplantation

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Introduction

Solid organ transplantation offers a valuable therapeutic option to patients with terminal organ failure. Over the years, technical and therapeutic progress, especially the advent of new immunosuppressive agents, has significantly improved outcomes. The survival rate, for example, of a kidney transplant recipient at 1-year today exceeds 95 % [1]. Graft half-life has also increased dramatically almost to 10 years [2]. As transplant recipients live longer, patients and health care providers alike have become increasingly aware of complications related to transplantation.

Metabolic bone disease, such as osteoporosis and avascular necrosis (AVN), in post-transplant patients are ones that are most debilitating. They take a significant toll on wellbeing, with pain and discomfort. Another major issue is the high incidence of hip and vertebral fractures that increases both morbidity and mortality. Many epidemiologic studies have shown a strong association of the risk of fracture and solid organ transplantation. Organ transplant recipients were reported to have almost a fivefold increase in the risk of any fracture compared to general population [3]. Even when compared to the patients on the transplantation waiting list, the risk of fracture still remains significant. Of note is that the relative risk of hip fracture increased ~34 % following transplant, with the highest incidence in the

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early post-transplant period (3.3 fractures per 1000 person-year) [4]. Likewise, a longitudinal study (1997–2010) also showed a high hip fracture rate (3.8 fractures per 1000 person-years) [5].

It is important to note that in a post-transplant situation, fractures can, and do occur at relatively conserved, and often at near-normal bone mineral density (BMD) values. Fragility fractures, in themselves, in such cases initiate a formal diagnosis of severe osteoporosis. However, the diagnosis of osteoporosis or low bone mass (formerly termed osteopenia) based on BMD is equally common. A population-based study from Taiwanese National Transplant Registry reported significantly higher incidence of osteoporosis (and related fractures) in transplant patients compared with general population. The overall hazard ratio (HR) for osteoporosis and osteoporosis-related fractures was 5.14 (95 % CI, 3.13–8.43) and 5.76 (95 % CI, 3.80–8.74), respectively [6].

The risk of fracture in this population is clearly multifactorial. Decreased BMD from metabolic bone disease, a previous fracture, old age, a first-degree relative with fracture, low body weight, smoking, rheumatoid arthritis or celiac disease, glucocorticoid use, and excessive alcohol consumption are all considered risk factors for fracture. A meta-analysis of studies on renal transplant recipients suggested that advanced age, female gender, and a history of diabetes were compounded to increase fracture risk [7]. The higher rate of fracture in diabetes among renal transplant recipients was also noted in a separate study [8].

Metabolic Bone Disease After Transplantation

Pre-existing Bone Disease

Most transplant patients also have pre-existing bone disease, most prominently those with chronic kidney disease (CKD). Therefore, *albeit* challenging, it is imperative to assess, prevent, and treat metabolic bone disease in pre- and post-transplant period.

Renal Osteodystrophy

Renal osteodystrophy arises fundamentally from the disruption in calcium and phosphate homeostasis. The kidney is a principal organ that regulates blood calcium and phosphate levels. Parathyroid hormone (PTH) increases phosphate excretion by the inhibition of Type I/IIa sodium-phosphate co-transporter in renal proximal tubule. It also stimulates the activity of 1α-hydroxylase, which, in turn, hydroxylates 25-hydroxycholecalciferol to 1,25-dihydroxycholecalciferol. In a negative feedback loop, 1,25-dihydroxycholecalciferol produced in kidney inhibits PTH production. It is important to note that in addition to increasing calcium absorption from the gut, vitamin D also stimulates phosphate absorption, and in turn inhibits PTH secretion indirectly. The recent advance in the understanding of fibroblast growth factor FGF-23, FGFR and the klotho complex also helps to shed light on the

bone-kidney-parathyroid gland axis in calcium and phosphate homeostasis. Bone-derived FGF-23 suppresses Na/P co-transporter and excretes phosphate. Klotho, which is expressed in kidney and parathyroid gland, works as a cofactor promoting FGF-23 activity. FGF-23 level is high in CKD patients, and has been studied as a marker for CKD. Hyperphosphatemia is a hallmark of CKD despite elevated FGF-23 level, and it is postulated that FGF-23 does not exert its phosphaturic effect in the absence of klotho. As a matter of fact, marked reduction of urinary klotho was observed in early phase of CKD preceding FGF-23 elevation and electrolyte imbalance. To maintain the CaxP product within a normal range, elevated serum phosphate pushes serum calcium down; this causes the earliest elevations in serum PTH levels (secondary hyperparathyroidism). There is some evidence that hyperphosphatemia in CKD can directly stimulate PTH synthesis and contribute to parathyroid hyperplasia [9, 10].

As renal function deteriorates further, activity of 1α-hydroxylase in proximal tubules also decreases. With decreased enzyme activity and insufficient reserves of vitamin D, 1,25-dihydroxyvitamin D levels fall, which also stimulate the parathyroid gland contributing further to secondary hyperparathyroidism. Other cytokines such as IL-1, -6, and -11 also play a part in increased PTH expression [9]. Inasmuch as the mechanism of calcium and phosphate regulation is intricate, the characteristics of renal osteodystrophy vary among individuals. Renal osteodystrophy is, traditionally, classified into *four* different categories: osteitis fibrosa cystica, adynamic bone disease, osteomalacia, and mixed renal osteodystrophy [11].

Osteitis fibrosa cystica, or high turnover disease, is due to secondary hyperparathyroidism. Continuous exposure to PTH is key to the pathophysiology of high bone turnover [12]. At the same time, mesenchymal precursor cells differentiate into fibroblast-like cells, resulting in marrow fibrosis. However, and paradoxically, elevated PTH levels seem to be required to maintain normal rates of bone formation in patients with CKD. Uremia can itself cause PTH resistance, with the down-regulation of PTH receptors, increased levels osteoprotegerin and decreased bone morphogenetic proteins (BMPs) [13].

One of the tenants of CKD therapy is to reduce the effects of secondary hyperparathyroidism on the skeleton. This means that serum PTH must be suppressed therapeutically, using either phosphate-binding agents or calcium sensing receptor antagonists. Excessive suppression of PTH leads to *adynamic bone disease* (also termed low-turnover bone disease). Thus, *per* the Kidney Disease: Improving Global Outcomes (KDIGO) position statement, it is recommended that in patients with stage 5 CKD, serum PTH should be maintained at 2–9 times the upper limit if normal in order to prevent low-turnover disease [14]. Adynamic bone disease is more common in diabetic patients [11].

In addition to adynamic bone disease, CKD patients also display varying degrees of *osteomalacia.* In osteomalacia, mineralized bone volume is low because of an increase in mineralization lag time with relative osteoid excess and thick osteoid seams. This mineralization defect arises from vitamin D deficiency and resistance.

These subtypes of renal osteodystrophy tend to co-exist as *mixed renal osteodystrophy* and this ambiguous classification complicates management. In response, KDIGO released the bone turnover, mineralization, and bone volume (TMV) classification [15].

Malluche et al. [16] reported the histomorphometric analysis of 630 cases using TMV in CKD patients. They reported that 58 % of patients exhibited low bone turnover, with 18 % and 24 % patients exhibiting normal and high turnover respectively. This finding is consistent with Moe et al., who demonstrated that low-turnover bone disease was more prevalent in CKD patients [15]. Interestingly, Malluche et al. also found a racial difference, with whites exhibiting predominantly low-turnover disease (62 %), whereas blacks displayed mostly normal or high-turnover (68 %). Osteomalacia was observed in only 3 % of the study participants [16].

As expected, the risk of fractures in CKD patients on dialysis is many times higher than general population. Likewise, given their co-morbidities, mortality from hip fracture is also significantly higher in dialysis patients [17–19]. This has led to efforts to screen patients at risk of fracture. Notably, Coco et al. showed that patients with lower PTH levels were more likely to sustain hip fractures than patients with higher PTH levels [17]. However, this inverse relationship with PTH was not confirmed with other studies. Danese et al. [19] reported U-shaped relationship with risk of fracture and PTH level with the lowest risk observed at ~300 pg/mL, suggesting that the risk of fracture is high at both ends. So far the optimal PTH level in terms of skeletal health in CKD patients is still unclear.

Finally, renal osteodystrophy also causes heterotopic calcification, mainly arterial calcification, which is a major predictor of cardiovascular mortality. It is thought to be triggered by dyslipidemia, oxidative stress, advanced glycation end-products (AGEs), and hyperphosphatemia, which cause transformation of vascular smooth muscle cells to osteogenic cells. In vitro studies show that high phosphate levels directly stimulate vascular smooth muscle cell transformation to “osteoblast-like” cell [20, 21].

End-Stage Liver Disease

End-stage liver disease is the cause of pre-existing hepatic osteodystrophy in >80 % of patients undergoing liver transplantation evaluation [22]. It is more prevalent in patients with cholestatic liver disease, such as primary biliary cirrhosis (PBC) and primary sclerosing cholangitis (PSC) [23]. Histomorphometric analysis of bone biopsies from patients with PBC and PSC have shown decreases in bone volume and reduced bone formation. Osteoblast numbers, mean wall thickness, and mineralization rate are all reduced. Elevated bone resorption has also been documented with increased areas of eroded surface and osteoclast numbers [24].

The pathophysiology of hepatic osteodystrophy is not clearly understood. Unconjugated bilirubin reduces osteoblast proliferation in vitro [25]. Hyperbilirubinemia not only down-regulates *Runx2* expression, but also increases the RANKL/OPG ratio favoring bone resorption [26]. However, an association between serum bilirubin levels and BMD has not yet been established [27]. Finally, there are other risk factors in patients with chronic liver disease that contribute to bone disease; these include alcoholism, hypogonadism, vitamin D deficiency, and genetic factors [28].

End-Stage Heart Failure

About one third of heart transplantation candidates showed osteopenia and osteoporosis [29]. Intrinsic risk factors with heart failure, such as advanced age, vitamin D deficiency, CKD, and medication use (loop diuretics) can all contribute to the increased risk of osteoporosis in heart failure patients [30]. Furthermore, although unproven, immobilization and limited physical activity due to exercise intolerance are also considered to have a negative effect on skeletal health.

The pathophysiologic link between heart failure and osteoporosis is not well understood. A few studies have suggested that hyperparathyroidism in heart failure may be a contributor [31, 32]. Activation of the renin-angiotensin-aldosterone (RAA) system in congestive heart failure and hypertension has also been considered as a culprit. Osteoblasts and osteoclasts both express angiotensin II receptors. Angiotensin II induces the differentiation and activation of osteoclasts directly, and also increases *Rankl* expression in osteoblasts, which, in turn, stimulates osteoclast differentiation [33–35]. Leistner et al. [36] provided direct evidence for increased RANKL/OPG ratio in patients with systolic heart failure; this was repeated in the mouse following the induction of ischemic cardiomyopathy.

End-Stage Lung Disease

About 70 % of patients of lung failure have osteoporosis based on reports regardless of type of underlying lung disease [37, 38]. Hypoxia, hypercapnia, smoking history, and glucocorticoid exposure all contribute to bone disease [39]. Interestingly, Kneidinger et al. demonstrated that patients with COPD have decreased Wnt/β--catenin signaling; the latter pathway plays a key role in osteoblast differentiation [40].

Hematopoietic Disorders

About 70 % of 81 patients display normal BMD values prior to bone marrow transplantation. Although patients with high-dose chemotherapy tend to show lower BMD, only 4 % have documented osteoporosis [41]. However, a population-based cohort study of myeloproliferative disorders showed an increased risk of fracture [42]. Chemotherapy, steroid use, hypogonadism, and other co-morbidities likely contribute. In contrast, in pediatric patients with acute leukemia, 75 % of patients showed radiographic abnormalities, among which 40 % had osteoporosis, 20 % had pathologic fractures, and 1.2 % had AVN [43]. As expected, the incidence of fracture in children with acute lymphoblastic leukemia was very high [44]. Lean mass, age at diagnosis, systemic and/or intrathecal chemotherapy were found to predict bone loss [45].

Bone Disease in Diabetes Patients

Diabetes has an unequivocal and strong association with fracture risk, besides being a prevalent co-morbidity in patients with end-stage organ failure. Pre-transplant diabetes was found to be an independent risk factor for fracture (OR: 1.94, 95 % CI: 1.5–2.6) when adjusted for age, sex, previous fracture, and immunosuppressant (including glucocorticoid) use [46]. Furthermore, one of the most common etiologies of end-stage renal disease is diabetes, and patients with ischemic cardiomyopathy often have diabetes. One survey reported about 30 % of patients with liver cirrhosis had diabetes [47]. About 20 % of renal transplantation patients have type 1 diabetes mellitus, and a high rate of fracture (40 %) was noted in diabetes group compared to non-diabetes group. Of note, diabetic patients had fractures early in the post-transplant period, commonly in their appendicular skeleton, such as ankle and foot fractures [8]. The impact of diabetes on skeletal health after transplantation is therefore highly significant.

Transplantation-Related Risks

Immunosuppressant Use

Glucocorticoid-Induced Bone Loss and Osteonecrosis

Glucocorticoid use is strongly associated with the risk of vertebral and non-vertebral fracture. The risk of fracture is dose- and time-dependent, and is seen at doses as small as 2.5 mg prednisone per day when utilized for prolonged periods [48, 49]. Of note is that longer duration and continuous use shows an approximately fivefold increase in the risk of hip fracture [48].

The mechanism of glucocorticoid-induced osteoporosis is relatively well studied. The high fracture risk arises mainly from decreased bone formation. Histomorphometry shows decreased trabecular bone area and trabecular width. Bone formation rate (BFR) and mineral apposition rate (MAR) are consistently reduced in glucocorticoid users in a dose-dependent manner [50]. Glucocorticoids inhibit osteoblasts, but can also stimulate osteoclasts. Osteoblast differentiation is reduced with evidence for increased apoptosis [50]. Glucocorticoids also negatively affect osteocytes, resulting in the accumulation of micro-damage, which leads directly to impaired bone quality and a high fracture risk [50]. It has recently been shown that osteocytes can also undergo autophagy with low dose glucocorticoids [51]. Increased osteoclast perimeters, but with decreased osteoclast progenitor number has also been noted with glucocorticoid use [50]. An effect of glucocorticoids on osteoclasts was directly demonstrated in transgenic mice that over-expressed 11β-HSD2, an enzyme that converts cortisol to cortisone [52].

AVN is another debilitating skeletal complication in transplant recipients. Its prevalence has, however, decreased dramatically with introduction of newer immunosuppressants and reduced steroid doses. A recent epidemiologic study over

9 years reported the prevalence of AVN at 4.6 % in the transplant recipients. Male patients were more affected than females, and the femoral head was most commonly involved. Glucocorticoid usage is strongly associated with AVN [53]. A meta-analysis of 22 studies showed a strong correlation between daily total dose of glucocorticoid and AVN rate ($r = 0.61 - 0.80$) [54]. The cumulative steroid dose was statistically significantly higher in AVN group compared to control group [55].

The histopathology of AVN is characterized by osteocyte necrosis with or without loss of structural integrity [53]. On light microscopy, osteocyte necrosis is reflected by condensed nuclei and empty osteocyte lacunae. Hematopoietic marrow necrosis and surrounding interstitial edema are also commonly seen. With glucocorticoid use, fat emboli and lipid deposits increase intraosseous extravascular pressure, which compromise blood flow and cause ischemia [53]. The repair process with capillary angiogenesis and revascularization begins in the area of necrosis. Bone resorption occurs followed by bone formation; however, reduced bone formation due to glucocorticoid use leads to net bone loss. This net bone loss, *albeit* locally, leads to the loss of integrity and structural collapse [56].

Skeletal Effects of Calcineurin Inhibitors

Calcineurin inhibitors, a commonly used class of immunosuppressant drugs, notably cyclosporine (CsA) and tacrolimus (FK506), inhibit the activity of the enzyme calcium/calmodulin-sensitive phosphatase, calcineurin. Our group has shown that calcineurin plays a major important role in bone remodeling. The first evidence came from Epstein's group: cyclosporine injections in vivo were found to result in significantly elevated levels of bone resorption and trabecular bone loss [57]. This was shown to be T cell, dose, as well as duration dependent. Subsequent, histomorphometric studies in patients with cyclosporine monotherapy showed not only increases in osteoclast activity, but also decrements in osteoblastic bone formation [58]. CsA has been found to be more detrimental to bone than FK506 [59].

We found that calcineurin Aα, the target for both CsA and FK506, was expressed both in osteoblasts and osteoclasts [60]. We thereafter went on to characterize the skeletal phenotype of a mouse in which calcineurin Aα was deleted genetically [61]. We found that 6-week-old calcineurin $A\alpha^{-/-}$ mice were osteoporotic both at cancellous (lumbar spine) and cortical sites (femur and tibia). A marked reduction in cortical bone thickness and a modest reduction in trabecular bone were obvious upon histological examination. Labeling with tetracycline showed a (~60 %) reduction in MAR, which indicated attenuated bone formation [62]. Surprisingly, however, while there was little difference in resorbed surfaces in calcineurin $A\alpha^{-/-}$ mice, osteoclast formation from $A\alpha^{-/-}$ hematopoetic stem cells was markedly impaired ex vivo (~40 %). Overall, the studies confirmed that either the inhibition of calcineurin activity by chemical inhibitors, such as CsA or FK506, or genetic deletion of a predominant isoform, caused osteoporosis reflecting the clinical situation.

To substantiate this concept, we also performed gain-of-function studies using osteoblasts and osteoclasts. We created a fusion protein between calcineurin Aα and TAT, a 12 amino acid-long, HIV derived, Arg-rich sequence that was able to

traverse cell membranes [63]. We transduced mature osteoclasts, osteoclast precursor (RAW264.7) cells, and pre-osteoblastic (MC3T3.E1) cells in separate experiments, essentially with 100 % efficiency. The transduced protein stimulated the expression of the osteoblast differentiation markers *alkaline phosphatase*, *bone sialoprotein* and *osteocalcin* [62]. Likewise, it significantly enhanced osteoclast formation from both RAW-C3 cells and bone marrow precursors [64].

High turnover bone disease with elevated bone turnover markers have been noted clinically after the initial effect of glucocorticoids causing a low turnover, but when stopped the CsA effect becomes evident. This is accompanied by continuous bone loss at cortical bone sites the femur while the spine tends to recover. Histomorphometry performed years later in patients post-transplant only on CsA showed elements of high turnover [58]. Renal patients on CsA monotherapy post-transplant continued to lose BMD [65].

Finally, it is notable that calcineurin inhibitor-free immunosuppression protocols have worse outcomes with regard to long-term treatment outcome compared to steroid-free regimens.

Other Immunosuppressants

Sirolimus (rapamycin), an mTOR inhibitor, has not been studied in detail regarding its bone effects, but is considered safer. Rapamycin in vivo does not show significant loss of trabecular bone compared to CsA [66]. Bone turnover markers, including urine N-telopeptides and serum osteocalcin, were also consistently lower in sirolimus—compared with CsA-treated patients [67]. Consistent with this, patients on a sirolimus-based regimen showed reduced serum levels TRAP-5b and RANKL compared with calcineurin inhibitor-based regimens. In vitro studies have, however, shown reduced osteoclast differentiation and osteoclast precursor proliferation [68]. This anti-resorptive property of sirolimus might actually be beneficial in reducing the accelerated bone loss in the early transplant period. It allows the use of lower dose of glucocorticoids and calcineurin inhibitors without compromising organ survival. Everolimus, also an mTOR inhibitor, might have beneficial effects on bone, as mTOR inhibition is associated with decreased osteoclast survival and activity [69].

Another immunosuppressant, mycophenolate mofetil (MMF) did not show significant effects on histomorphometric parameters, although osteocalcin levels were suppressed in vivo [70]. The effects on bone of newer immunosuppressants, including monoclonal antibodies, such as alemtuzumab or basiliximab, have not been investigated.

Other Considerations in Renal Transplant Patients

Effect of Hypophosphatemia in Renal Transplant

Hypophosphatemia, a frequent accompaniment in the early phase after renal transplant, is multifactorial [71]. Persistently elevated PTH and/or FGF-23 will increase phosphate excretion from healthy transplanted kidneys. That said, there continues

to be relative 1,25-vitamin D deficiency as renal function may not be not fully restored—this will result in a persistent lowering of intestinal phosphate absorption. Immunosuppressant, such as glucocorticoids and CsA, can by themselves inhibit renal phosphate reabsorption [72, 73]. Persistent hypophosphatemia will invariably negatively affect bone mineralization, and result in skeletal complications that we have learned from diverse pathologies, such as X-linked hypophosphatemic rickets and oncogenic osteomalacia.

Persistent Secondary Hyperparathyroidism in Renal Transplant

PTH levels normalize during the first 3–6 months of transplant as renal function normalizes. Functional parathyroid gland mass is thereby reduced in most cases, except for those with monoclonal glandular hyperplasia [74, 75]. This category of patients normally has a highly elevated PTH level at the time of transplant [76]. Persistently increased PTH can result in hypercalcemia (and hypophosphatemia). However, bone turnover does not correlate well with PTH levels in transplant recipients. Histomorphometric parameters do not correlate with hypercalcemia in patients with post-transplant hyperparathyroidism [77], to the extent that PTH may not be the main determinant of bone turnover following transplant [78]. Recently, persistent hyperparathyroidism has been shown to be a major determinant of fractures 5 years post-transplantation [79].

Vitamin D Levels in Renal Transplant Patients

Vitamin D insufficiency and deficiency continues to be prevalent in patients with transplant [80–84]. 1,25-dihydroxyvitamin D levels often remain low, even after renal function improves. This could be caused, in part, by the normally insufficient vitamin D reserves in patients with renal transplant. Vitamin D deficiency could indeed be prolonged even after successful transplantation [85], particularly since other factors related to transplantation, such as immunosuppressant use, can also directly affect vitamin D metabolism.

Acute Rapid and Severe Bone Loss Post-transplantation

Rapid and acute bone loss may be promoted by secondary causes of osteoporosis, such as glucocorticoid-induced bone disease, immobilization, organ transplantation, and acute estrogen withdrawal. We have termed this as acute, rapid and severe bone loss (ARSBL) [86]. The etiology is multifactorial, arising from glucocorticoid and calcineurin inhibitor use, pre-existing osteodystrophy, hyperparathyroidism, poor nutrition, immobilization, and vitamin D deficiency.

BMD by dual energy X-ray absorptiometry (DXA) scan is, as of now, the most cost-effective and widely utilized non-invasive measurement of skeletal health. It is most generally accepted as a predictor of the risk of fracture in all population. The decrease of 1 standard deviation (SD) in BMD increases the relative risk of fracture about twofold [87]. DXA measures vertebral spine, radial shaft, and hip, respectively, representing mainly trabecular bone, cortical bone, or both types of bone. However, it is well known that BMD declines may not explain the high fracture risk noted, for example, with high dose glucocorticoid therapy. Patients can and do fracture with near-normal BMDs.

Longitudinal studies have shown a correlation between time-elapsed after transplantation and change in BMD. Regardless of type of organ, a significant decline occurs in early phase, mostly within 3–12 months; this is generally followed by BMD stabilization or even an increase at the spine [88–93]. Notably, Julian et al. showed that BMD at the lumbar spine decreased by 6.8 % from the time of transplantation, with more than half of their patients falling below the "fracture threshold." The bone loss during the first 6 months post-transplant contributed significantly to the overall bone loss of 8.8 % over 18 months. In this context, postmenopausal women may lose bone at the rate of 2 % per year in the early years of menopause, when such declines are most rapid. Thus, the bone loss in transplant patients is, by comparison, much more rapid and acute. Interestingly, however, BMD in radial shaft was near normal to begin with (*Z* score: −0.67) and there was no significant bone loss noted within 6 months [91]. This suggested that trabecular bone was more affected than cortical bone during post-transplantation period.

Yet another study looking at renal transplant recipients within first 5 months calculated an absolute mineral loss of 40 g (total skeleton has ~1 kg calcium). The bone was lost mainly in the trabecular bone compartment, with the rate of vertebral BMD loss at 1.6 ± 0.2 % per month [94]. This rate was significantly higher rate than that reported (1.7 % per year) in renal transplant recipients based on 8-year longitudinal study [95].

This pattern of ARSBL was also noted in other organ transplantation. Among patients with orthotopic liver transplantation, a high rate of bone loss at the lumbar spine (15.9 % per year) was observed in the first 4 months. Pre-transplant BMD at lumbar spine was in the osteopenic range (*Z*-score: −1.39), which further decreased (1.77) at the 4-month post-transplant time point. Almost 36 % of patients in this cohort developed fractures within 1 year following transplantation [96]. Interestingly, BMD slowly stabilized and even increased after 8 years follow-up [97]. Consistent with these dramatic declines, a cross-sectional study reported decreases in BMD by 8.6 ± 1.0 % at lumbar spine and by 11.3 ± 2.2 % at the femoral neck within 1 year [92]. Likewise, while patients undergoing bone marrow transplantation displayed normal pre-transplant BMDs at both lumbar spine and femoral neck, their femoral neck BMD declined whereas their lumbar spine remained conserved 3 months following transplantation [98, 99].

The noted decrements in BMD in transplant patients pose a significant risk of fracture [3, 5, 6, 100]. This risk is especially high in early period, due to the rapidity of bone loss over a short time [4]. Pre-transplant BMD and length of use of glucocorticoids are key determinants of the high risk of fracture [93].

Some studies have, however, questioned the association between BMD and fracture risk in transplant patients. Although BMD is most generally used as a surrogate for fracture risk, the association is relatively weaker in transplant recipients compared with general population [100, 101]. The insensitivity of areal BMD (aBMD) has been noted in patients treated with glucocorticoids and in patients with diabetes. Patients with type 2 diabetes tend to have higher BMDs, despite the increased risk of fracture [102].

It is well known that areal BMD (measured by DXA) is not able to assess bone quality, including its microarchitecture, which is as crucial as BMC in determining bone strength. Newly developed technologies like quantitative computed tomography (QCT), micro-MR imaging, finite element modeling (FEM), and microindentation allow us to examine cortical and trabecular bone compartments separately, as well as to assess mechanical properties of bone directly. Rehman et al. [103] demonstrated that volumetric BMD (vBMD) at the lumbar spine measured by QCT is a better predictor of vertebral fracture than areal BMD (by DXA) in postmenopausal women receiving long-term glucocorticoids. In renal transplant recipients, one study looked at bone stiffness and failure strength using micro-MR and FEM. Stiffness and failure strength declined in both cortical and trabecular compartments over the initial 6 months after transplantation. Importantly, these changes did not correlate with a change in areal BMD [104].

Serum bone turnover markers have also been studied as predictors of skeletal health in transplant patients, being non-invasive, readily available, and repeatable measures. Bone-specific alkaline phosphatase and osteocalcin reflects BFRs, whereas collagen degradation products, such as procollagen type 1, N-terminal pro-peptide, C-terminal telo-peptide, among others, are used as bone resorption surrogates. However, these markers are significantly affected by renal function [105], and studies to use these in transplant recipients have not been particularly useful [106–110].

Histologic features of post-transplant bone loss in renal transplant recipients vary. A cross-sectional study reported persistent high-turnover bone disease in renal transplant recipients, with ~50 % or more patients having osteitis fibrosa cystica [111]. A considerably smaller proportion displayed adynamic bone disease (5.3 %) or osteomalacia (3.5 %). Other studies, however, have demonstrated predominantly decreased bone formation, with high-to-normal bone resorption. Julian et al. reported decreased mean wall thickness and reduced MAR. Characteristics of secondary hyperparathyroidism, such as woven bone and marrow fibrosis, were shown to disappear as PTH levels normalized with renal allograft [91]. Consistent histomorphometric changes were noted using paired bone biopsies (pre- and post-transplant) at the 1- to 3-month time point. These showed evidence of reduced BFR, prolonged mineralization period, and importantly, an increased number of apoptotic osteoblasts [112]. Bone biopsies at 5.6 ± 0.8 years after transplantation similarly showed decreased BFRs in more than 50 % of patients, and prolonged mineralization in most patients [78]. Fortunately, these histologic changes do not seem to be persistent. After a period of 10 years, osteoid volume and surface became greater than normal, and BFRs and mineralization surfaces remained low, but almost approached normal values [113].

In liver transplantation, bone resorption compared to pre-transplant biopsies persisted. However, interestingly bone formation parameters increased, although mean wall thickness remained low at 4 months after transplant [24, 96]. Histomorphometric data on lung and cardiac transplantation are limited. A study of postmortem vertebral bone biopsy from post-transplanted, and non-transplanted patients with cystic fibrosis did not show any significant differences in terms of osteoblast and osteoclast activity, although cortical and trabecular bone mass was found to be somewhat lower in the transplantation group [114].

Management of Bone Disease After Transplant

Monitoring Bone Disease After Transplantation

The National Kidney Foundation recommends serial BMD measurements at time of transplant, 1 year, and 2 years post-transplant, and treat protocols according to *T*-score [115]. As BMD and other biomarkers cannot identify patients at a high risk of fracture, and the accelerated rate of bone loss occurs in early period, it is considered generally prudent to initiate preventive measures immediately following transplantation.

Preventive and Therapeutic Interventions

Exercise

There is evidence that structured exercise programs could potentially be helpful for maintaining skeletal health and increasing BMD in lung transplant patients [116]. Heart transplant recipients also regained BMD in axial and peripheral bones towards pre-transplantation levels with specific resistance exercise training [117]. Along the same lines, resistance exercise plus alendronate was more efficacious than alendronate alone in restoring BMD in heart transplant recipients [118]. These observations support the importance of physical activity and mechanical loading after organ transplantation.

Early Steroid Withdrawal or Avoidance

Because of the detrimental multisystem complications of glucocorticoid use, including skeletal fragility, attempts have been made to minimize their use in transplant patients. The skeletal benefit of early steroid withdrawal has recently been observed. Early steroid taper showed a significantly reduction in fracture risk, but that this was noted at the expense of a higher risk of graft rejection [119, 120]. Therefore, current

guidelines do not recommend early steroid withdrawal [115]. With the advent of newer immunosuppressant agents, such as MMF, sirolimus, and selective subsets of T cell inhibitors, non-glucocorticoid immunosuppressant regimes are being used more frequently and successfully to prevent organ rejection.

Anti-resorptive Agents

Bisphosphonates are currently the most effective therapies for post-transplant bone disease. These agents have been shown to prevent bone loss and increase BMD in transplant patients. The early generation intravenous bisphosphonate, pamidronate was studied in renal transplant recipients, being given at 1, 2, 3, and 6 months post-transplantation. Whereas spine BMD in the treatment group was preserved, the control group showed declines at 6 and 12 months (4.8 and 6.1 %, respectively) [121]. This preventive effect was also observed in different settings, where pamidronate was administered at the time of and 1 month following transplantation. At 12 months, the treatment group showed preserved BMD compared to a significant decrease at both lumbar spine and femoral neck in the control group [122]. Another bisphosphonate, ibandronate, was shown to be similarly effective in renal transplant patients [123–125]. Likewise, zoledronic acid, given two times within 3 month after transplantation, was shown stabilize or increase BMD at both sites [126]. Looking at fracture risk, a meta-analysis including nine studies showed that bisphosphonate use reduced number of subjects with fractures (OR: 0.53, 95 % CI: 0.31–0.91) [127].

Similar preventive effects were noted with transplant of other solid organs. Pamidronate increased BMD in lung transplant recipients [128]. Significantly less bone loss at the lumbar spine and femoral neck at 12 months was seen in cardiac transplant patients with ibandronate. The incidence of vertebral fracture also appeared to be lower in the ibandronate group, *albeit* not statistically significantly. However, in liver transplant recipients, a single dose of pamidronate before liver transplantation did not show skeletal preservation [129].

Although the preventive effect of bisphosphonate has been consistently observed in several clinical trials, there is still the concern that bisphosphonates might in fact exacerbate low bone turnover disease, occasionally prevalent in transplant recipients. Indeed, pamidronate use was actually associated with development of adynamic bone disease [121]. Another unanswered question is the duration and frequency of bisphosphonate use. Bisphosphonate might not continue to remain effective in the long-term, as the patients' BMD can stabilize (or declines very slowly) on its own after a significant early bone loss phase [90, 95].

For patients with AVN, anti-resorptive medications are possibly beneficial to prevent the loss of structural integrity, particularly as subchondral resorption can trigger femoral head collapse [56]. We have provided proof-of-concept that the pituitary hormone ACTH can, in a rabbit model, prevent steroid-induced AVN through its ability to enhance VEGF production and in turn stimulate angiogenesis [130, 131].

Anabolic Agents

Teriparatide, recombinant PTH (rPTH), is a compelling agent given its anabolic effect on bone remodeling. It is expected to counteract the early bone loss, which is characterized by decreased osteoblast differentiation and increased osteoblast apoptosis. Teriparatide has shown efficacy in the therapy of glucocorticoid-induced osteoporosis. Saag et al. [132] showed that treatment with teriparatide increased BMD and lowered vertebral fracture rate. Since glucocorticoid use plays a key role in early post-transplant bone loss, teriparatide mechanistically appears to be a logical choice, particularly if low bone turnover is the predominant feature. However, the protective effect of teriparatide has not been demonstrated yet. A small-sized randomized controlled trial comparing rPTH with placebo did not show any beneficial effect on BMD at lumbar spine or distal radius, although BMD at femoral neck was stable in teriparatide group and decreased in control group [133]. In the future the use of a sclerostin inhibitor potentially has the advantage of increasing bone formation and reducing fracture risk.

Vitamin D Supplements

Active vitamin D supplementation, not parent vitamin D, such as calcidiol, alfacalcidiol, and calcitriol showed an overall beneficial effect [134]. Calcidiol was compared to the non-nitrogen containing bisphosphonate etidronate in heart transplant recipients; an improvement in BMD was noted [135]. Two randomized trials have shown a protective effect of alfacalcidiol in renal transplant recipients [136, 137]. Calcitriol may be particularly beneficial in renal transplant since calcitriol production can remain persistently low even after renal function normalizes with allograft. A randomized, double blind study demonstrated that patients with renal transplant treated with calcitriol and calcium displayed increased or preserved BMDs at lumbar spine and femoral neck [59, 138]. In addition, there is possible additive benefit from the pleiotropic effects of vitamin D, since there is evidence that vitamin D can act as an immunomodulator. A retrospective cohort study reported less acute rejection in patients with renal transplant when treated with calcitriol [139].

Surgical Intervention for Skeletal Complication

Patients with AVN, osteoarthritis, and fractures oftentimes require and benefit from surgical intervention. In the case of AVN, hip preservation can be attempted depending on the presence of structural failure or collapse. There are several methods for surgical treatment for AVN of femoral head; core decompression with or without biologic augmentation, non-vascularized bone grafts, vascularized fibular grafts, intertrochanteric osteotomy, and cemented or un-cemented total hip replacement depending on the severity of bone loss [56]. Overall, total hip and knee arthroplasty can be safely performed and provides excellent functional outcomes in lung and

liver transplant recipients [140–142]. The patients with renal transplant also show good outcomes after total hip replacement, but a high rate of early failure was noted [142]. Indeed, there is ongoing concern for increased post-surgical complications, such as graft failure and infection because of co-morbidities, immunosuppressant use, and co-existing metabolic bone disease [141–143].

Conclusions

Skeletal complications after solid organ transplantation can compromise a patient's quality of life and increase mortality and morbidity. Pre-existing bone disease from underlying end-organ damage needs to be screened, and any reversible cause needs to be addressed before transplantation. Persistent pre-existing metabolic bone disease in addition to other factors specifically related to transplantation is the rule rather than an exception. Immunosuppressant use, especially high-dose glucocorticoids and calcineurin inhibitors, causes accelerated bone loss in the early post-transplant phase. The ensuring skeletal fragility is characterized predominantly by suppressed bone formation with mildly increased bone resorption. Decreased osteoblast differentiation and osteoblast apoptosis are key to the pathophysiology. Screening and diagnosing patients at high risk of fracture during pre- and post-transplantation thus becomes critical. It is recommended that BMD is measured at periodic intervals before and after transplant, notwithstanding the limitations of DXA. Newly developed technologies such as QCT, micro-MR, FEM and microindentation should provide more valuable information on bone quality. The most well-established preventive and therapeutic option, as of now, is a bisphosphonate. Although there is limited data in terms of fracture risk reduction, bisphosphonates have shown promise in increasing or stabilizing BMD at both trabecular and cortical sites. However, the optimal frequency and duration of treatment is unknown, and there is lingering concern that the drugs may exacerbate low turnover disease. Active vitamin D with calcium supplementation has shown beneficial effects on BMD. The only available anabolic agent, rPTH, as of yet has not shown a beneficial effect (in a preliminary study). Other newly developed therapeutics like RANK inhibitor and sclerostin inhibitor has not been fully studied.

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Chapter 11
Options for Primary Hip Arthroplasty

Aleksey Dvorzhinskiy and Mathias P.G. Bostrom

Introduction

Total hip arthroplasty (THA) is widely regarded as one of the most successful procedures in orthopedic surgery. It significantly reduces pain, increases mobility, and restores function to patients who are otherwise incapacitated by degenerative joint disease. In addition, THA has a cost/utility ratio that rivals treatments for hypertension and coronary artery disease making it one of the most cost-effective medical interventions known [1, 2]. Despite this, an ever-increasing life expectancy and greater patient expectations for post-surgical activity have spurred advances in design and surgical technique which seek to increase the longevity of the prosthesis while minimizing morbidity. Such developments are crucial to reducing revision rates in THA patients who are younger and may require multiple revisions in their lifetime.

This chapter will seek to provide an introduction to the rationale behind the design of the acetabular and femoral stem components as well as the articulating surfaces. We will also examine three surgical approaches commonly used in THA implantation and discuss the advantages and hazards of each.

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Implant Design

In its simplest form, the design of hip arthroplasty consists of two components: one acetabular and one femoral separated by a bearing surface. Ideally, these components are rigidly attached to the surrounding bone while maintaining a nearly frictionless articulation between them. Thus, the design choices available to orthopedic surgeons relate to one of three elements: the acetabular component, the femoral component, or the bearing surface. The femoral component is perhaps the most complex and has a multitude of different options that relate to its shape, fixation method, and modularity. The main options for the design of the acetabular component relate to its fixation method. Lastly, the bearing surface options relate to the materials used in the articulating interface.

Bearing Surfaces

The bearing surface is the articulation between the femoral and acetabular components of the prosthesis. The ideal bearing surface materials are those that exhibit low friction, minimize wear, and have sufficient toughness to resist fracture. Additionally, any debris produced by the bearing surfaces should be biocompatible, i.e. not evoke an immune response. To date, no perfect bearing surface exists and arguments can be made for each in certain circumstances. In general, the materials used as bearing surfaces can be broken down into metals, ceramics, and plastics. These materials are coupled with either a similar (e.g., metal-on-metal) or different material (e.g., metal-on-plastic).

Perhaps the most difficult problem to solve has been the excessive wear of the articulating surfaces. This phenomenon is an obstacle both because it serves to disrupt the shape of the articulation surface and because it produces a significant amount of particles over time. This wear debris can in turn cause catastrophic implant failure or a localized resorptive response at the bone–implant interface that leads to implant loosening. The osteolytic response to wear debris remains the most frequent cause of failure and subsequent revision in total hip arthroplasty [3, 4]. In addition to the material used in the bearing surfaces, the femoral head size can have a significant effect on the wear generated. As such, a balance must be reached between the increased stability that larger heads provide with the increased wear particles that they produce. As patients are both living longer and the incidence of early arthritis is increasing, the need to improve upon the wear properties of bearing surface materials is self-evident.

Ultra-High Molecular Weight Polyethylene (UHMWPE) and Highly Cross-Linked Modifications

Although the original articulation surfaces in THR devices were metal-on-metal (MoM), the true success of hip arthroplasty began with the adoption of polyethylene as part of the bearing couple [5]. Early prostheses made by one of the

originators of THR, John Charnley, incorporated a plastic bearing on the acetabular component coupled with a metallic femoral head. Eventually, Charnley settled on high molecular weight polyethylene as the bearing of choice and thus created the first metal-on-polyethylene (MoP) device. Since then, polyethylene has been coupled with numerous metal alloys (e.g., stainless steel, cobalt-chromium, and titanium alloys) as well as ceramics (e.g., aluminum and zirconium oxides). Metal-on-polyethylene (MoP) couples remain the bearing of choice in the majority of total hip replacements today.

Despite this success, UHMWPE was shown early on to result in high amounts of wear in both laboratory and clinical studies. As mentioned earlier, the debris produced by this wear can result in implant failure through the gradual process of osteolysis and implant loosening. There have been numerous studies which have examined the wear of the Charnley hip prosthesis and although the literature differs in many details, it can be combined to form a cohesive picture of the wear process. In general, the wear rate of the polyethylene is highest at the beginning of the lifetime of the prosthesis and subsequently decreases to a relative steady state in the long term (16–18 months) [6]. The precise reason for this is unknown but it is hypothesized that creep, bedding-in, and decreased patient activity over time play a role. This means that examinations of wear rate immediately after implantation should be taken with caution as long-term studies of the same subjects will show a decrease in this property. Data gathered from hip simulators have shown that volumetric wear rates typically range from 23.2 mm^3/million cycles to 32.8 mm^3/million cycles [7]. When examining the clinical ramifications of this process, other studies have noted that wear rates of 38.8 mm^3/million cycles have resulted in a high risk for revision [8, 9]. In practice, this means that there is a relatively small difference between the typical wear rate seen in a successful versus unsuccessful arthroplasty. Thus, poor surgical technique, non-ideal implant placement, and increased load on the prosthesis due to a variety of patient factors can all significantly increase the risk of revision.

The size of the femoral head is also an important factor when discussing the wear of a bearing surface. Increasing femoral head size is an enticing design decision because it is one way of reducing hip prosthetic dislocation rates. Unfortunately, increasing the diameter of the femoral head also increases the sliding distance of the bearing and therefore increases the volumetric wear in all types of bearing surfaces [10]. A hip simulator study performed by Clarke et al. found a proportional increase in volumetric wear of approximately 7.8 % for every millimeter that the head diameter increased in MoP implants [7]. An in vivo radiographic study found that there was a 74 % increase in volumetric wear when 28 and 32 mm MoP bearings were compared [11]. A revision retrieval study of loose MoP acetabular components found an increase of 5.1 mm^3/year for each millimeter increase in the radius of the head [12]. Thus a tradeoff exists between the reduced dislocations that larger femoral heads provide and the increased bearing surface wear that they produce.

In an attempt to improve the properties of UHMWPE, namely the wear rate, technologies were developed to cross link adjacent polyethylene molecules. The product, Highly Cross-Linked Polyethylene (HXLP), was designed for its resistance to wear, reduction in wear particle volume, and subsequently its theoretically reduced rate of implant loosening. It is produced by manipulation of ultra-high

molecular weight polyethylene with either an electron beam or gamma irradiation. This treatment leads to the creation of free radicals along the backbone of the polyethylene molecule which combines to form a cross link between two separate molecules and results in the production of HXLP. This new material has been shown to reduce volumetric wear between 70 and 90 % in vitro [13, 14]. Muratoglu et al. used a hip simulator to show that, compared to UHMWPE, HXLP had similar mechanical properties with greatly improved wear resistance [15]. In fact, initial results obtained from hip simulators were very encouraging and showed no increase in the rate of wear with increasing head size even when using 46 mm heads. In vivo studies however have shown mixed results in the short term (3 year follow-up). In one study, linear wear was not found to increase with increasing head size, however other studies with a medium length follow-up showed an increased volumetric wear with increasing head sizes [16–18].

Simulators are often imperfect models for the conditions seen in patients. Thus, despite the lower volume of wear debris produced from HXLP when tested in a laboratory, it is plausible that the true amount of wear produced by a bearing surface could be greater than predicted. Conditions in the human body are known to be more damaging to arthroplasty components and therefore could result in significantly more wear. Relevant factors that increase debris generation include third-bodies, microseparation, edge loading, and damaged femoral heads. More complex in vitro studies have been carried out which have attempted to mimic these effects and compare the rate of wear between UHMWPE and HXLP. A study examining the performance of HXLP in contact with scratched surfaces noted a tenfold increased rate of wear in HXLP as compared with UHMWPE (i.e., 30× versus 3× that of a surface contacting an undamaged femoral component) [19]. Polymethyl methacrylate debris was found to increase wear 80-fold in HXLP as opposed to sixfold in UHMWPE when compared to an articulation that was not subjected to this type of third body [20]. Other studies have contradicted this data. McKellop et al. found that HXLP interfacing with roughened surfaces had better wear resistance than UHMWPE but the clinical relevance of the study was limited by the fact that the hip simulator used higher than physiological concentrations of protein in the lubricant [21]. Another property that is often lacking in hip simulators is microseparation due to joint laxity. This phenomenon is described as the separation of the bearing surfaces with concentric relocation during normal gait and is also associated with significant edge loading [22]. Interestingly, microseparation and edge-loading are not known to have a detrimental effect on hard-on-soft bearing surfaces such as MoP [23–25]. Conversely, metal-on-metal and ceramic-on-ceramic bearings are negatively affected by these phenomena and the ramifications of this effect will be discussed later.

Other concerns include the differences in the sizes of debris particles produced by wear in HXLP versus UHMWPE. This property is a known determinant of the ability of the material to produce an immune response and therefore cause implant loosening. It has been noted that particles less than 0.5 μm in diameter have the greatest effect on response by macrophages and the subsequent release of inflammatory cytokines [26–28]. Endo et al. showed that while non-cross-linked UHMWPE produces larger debris volumes, the particles produced by HXLP were

smaller and in a more biologically active (smaller) size range [29]. A mouse model with identically sized particles of HXLP and UHMWPE implanted under the periosteum of the calvaria showed a greater osteolytic response in the HXLP group (35 % versus 9 %). The overall message of this data suggests that although there is great potential in the decreased volume of wear produced by HXLP, the beneficial clinical outcome of decreased wear debris may be offset by the increased tendency of HXLP particles to induce an immune response that leads to osteolysis and eventual loosening.

Current clinical outcomes data has demonstrated the superiority of HXLP over UHMWPE but suffers from a lack of studies looking at outcomes beyond 10 years after implantation, primarily because HXLP was adopted relatively recently. Studies have shown a risk ratio of 0.4 for radiological evidence of osteolysis when comparing HXLP with UHMWPE [30]. A systematic review of studies that looked at greater than 5-year follow-up also supported this trend and has encouraged the continued use of the cross-linked polymer in bearing surface designs [31]. More recent randomized controlled trials have also been favorable towards HXLP. A 7-year, double blind, randomized controlled trial by Thomas et al. compared femoral head penetration between HXLP and UHMWPE acetabular liners. It was demonstrated that HXLP has a significantly lower steady state wear rate compared to UHMWPE, with a mean of 0.33 mm compared to 0.55 mm [32]. Shaun et al. reviewed 46 primary THAs that used first generation HXLP liners with a mean follow-up of 9 years. It was found that the linear penetration rate was 0.037 mm/year, demonstrating a 74 % reduction in total penetration when compared to conventional polyethylene [33].

Although the vast majority of polyethylene bearing surfaces articulate with metal femoral components, ceramic-on-polyethylene (CoP) bearing couples also exist and are an enticing option due to the lower surface roughness of ceramic femoral heads when compared with metallic alloys. Once again, initial simulator data showed a 20-fold reduction in the volumetric wear of ceramic versus metallic heads [34]. Subsequent in vitro studies using joint lubricant with a more physiologic composition were less favorable but still showed a 50 % reduction in polyethylene wear when using ceramic versus metallic heads [35]. Clinical studies found that CoP had a linear wear rate that was two to four times less than a MoP bearing [36, 37]. A study of 31 matched pairs of a CoP and MoP with a follow-up of 15–20 years found a 37 % decrease in the mean wear rate, but found no statistically significant difference in patient functional scores, radiographic evidence of osteolysis, or revision [37]. Ceramic-metal composites have also been developed to combine the surface hardness and scratch resistance of ceramics with the fracture resistance of metals (e.g., oxidized zirconium, OxZr). Surface hardness studies have found that OxZr heads have more than twice the hardness of CoCr heads while retaining the same wear effects on polyethylene as ceramic heads in vitro. In vivo, a randomized study comparing wear and migration of CoCr and OxZr heads articulating with HXLP found no difference after 2 years [38]. Early retrieval case reports in patients found reduced resistance to surface damage of the OxZr [39, 40]. Hip simulator studies using damaged OxZr heads retrieved from patients found a 50-fold increase in polyethylene wear as compared with pristine implants of the same material [41].

Metal on Metal (MoM) Articulations

In 1938 Philip Wiles used a MoM articulation in what is thought to be the first THA [42]. Later, in 1953, George McKee of Norwich, England, adopted the MoM articulation in combination with a modified stem originally used for hemiarthroplasty. Whilst this device showed good functional outcomes, its use was gradually phased out due to the success of the Charnley MoP arthroplasty, which demonstrated reduced short-term loosening rates. Recently there has been a resurgence in the use of MoM articulations due to the increased resistance to wear they offer over conventional MoP bearings [43]. Today, MoM bearings are used in traditional total hip arthroplasties as well as hip resurfacings.

One of the main factors responsible for the loosening of prostheses is wear debris. Volumetric wear is inversely proportional to the hardness of the softest surface of a given bearing couple [10]. In a MoP articulation, this is clearly the polyethylene and so that natural design progression is to replace this surface with another metal and thus form a MoM bearing. Indeed, MoM bearings have shown significant in vitro reductions in volumetric wear. Studies in simulators have shown wear rates between 0.2 and 2.5 mm^3/million cycles for MoM bearings as compared with 32.8 mm^3/million cycles and 9 mm^3/million cycles for similarly sized heads in couples incorporating HMWPE and HXLP bearings, respectively [7, 44, 45]. Despite the lower volumetric wear rate of MoM bearings compared to metal-on-polyethylene bearings, the size of MoM wear particles has been shown to be around 50 nm in size (cobalt chromium alloy particles) compared to 500 nm for polyethylene [46]. As a result of this the actual number of particles and the surface area of debris generated by MoM wear is greater and may raise concerns regarding a greater tissue response per unit volume (3, 4) [46, 47].

The actual effects of metallic particles surrounding tissues is an area of intense research. Lohann et al. have shown that phagocytosis of metal particles leads to a decrease in cell osteoblastic activity, which may contribute to the cellular events that lead to aseptic loosening of the implant [48]. Additionally, adverse local tissue responses (ALTR) that are distinct from those seen in patients with MoP prostheses have been observed in patients with MoM implants [49–52]. One subtype of these adverse responses is termed aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL). In contrast to the primarily macrophage and giant cell response seen in MoP implants, this lymphocyte-dominated reaction is much more severe and can result in not only implant loosening but severe soft tissue necrosis and pseudotumor formation [53]. Mahendra et al. describe a spectrum of necrotic and inflammatory changes in response to the deposition of cobalt-chrome (Co-Cr) wear particles in periprosthetic tissues [54]. It appears that the incidence of pseudotumor formation in patients with MoM resurfacings is somewhat based on patient demographics [55]. Glyn-Jones et al. examined a cohort of 1419 patients who received hip resurfacings and found that age at implantation and the sex of the patient significantly affected the need for revision due to pseudotumor formation. The overall revision rate for women was 3.8 % compared to 0.5 % for men. Younger patients required revision for pseudotumor formation more often: 6 % for individuals less than 40 years old and 1.4 %

for patients older than 40. In women under 40 years of age, 13.1 % required revision for pseudotumor formation at 6 years of follow-up [55].

Other studies have noted systemic distribution of metal ions. Urban et al. demonstrated that metal particle migration can lead to metal deposition in the liver, spleen, and para-aortic lymph nodes [56]. Increased chromosomal aberrations in peripheral blood lymphocytes have also been noted [57]. In an effort to monitor the reaction of individual patients to MoM implants, blood monitoring analyses have been developed. At baseline, patients receiving MoM arthroplasties show increases in metal ion concentrations. Daniel et al. showed that the levels of cobalt and chromium significantly increased at 1 year, followed by a decreasing trend until the 6th year [58]. A 30-year follow-up of patients with MoM or MoP by Dunstan et al. showed that while the levels of all metals used in the bearing surface remained elevated during the duration of implantation, Co levels in the blood increased by up to 50-fold in patients with loose MoM implants compared to the stable group. These results suggest a role for Co blood monitoring in patients with MoM implants as a means of screening for loose prostheses [59].

Despite this, some long-term follow-up studies have been favorable towards MoM systems. As expected, the rate of osteolysis in patients with these implants has been lower than those with MoP, on the order of 0–3 % at 10 years [60–64]. The Metasul metal-on-metal hip system (Zimmer, Warsaw, Indiana) was studied by Saito et al. and showed excellent long-term results. 90 patients were monitored with a mean follow-up of 12.3 years. The survival rate with an endpoint defined as revision surgery and radiologic loosening was 94.4 %. In this study no adverse reactions due to excess metal debris were observed [64]. Other studies have noted a 0–5 % rate of ALTR in this implant type [65]. One theory for this discrepancy is that correct implant positioning is paramount in achieving optimal implant survival and lower levels of wear debris in implants with MoM bearings. In vitro analysis of acetabular component orientations supports this hypothesis. Angadji et al. used a hip simulator to demonstrate increased wear rates and total wear volume with cup angle orientations of over 50° [66]. Campbell et al. found that misalignment of the acetabular component led to mechanical problems including increased edge loading and failure rates in constructs that utilized MoM articulations, specifically Birmingham hip resurfacings [67]. This edge loading leads to increased wear and as a result, particle release. Hart et al. demonstrated that cup inclination of over 50° in Birmingham hip resurfacings leads to an increased whole blood level of cobalt and chromium, further suggesting that metal levels can be minimized by correct alignment of the acetabular component [68].

Higher rates of soft tissue reactions have been described in constructs with large-diameter heads [69]. At the 2011 British Hip Society Annual Conference, large diameter MoM bearings were discussed and it was concluded that their use should be avoided. It also recommended that patients with MoM bearings be followed up for the life of the implant, especially in the first 5 years after implantation. Any patients with MoM bearing presenting with pain should be investigated appropriately with proper three-dimensional imaging in order to detect the presence of ALTRs and respond accordingly [70].

More research is needed to elucidate the conditions which induce ALTR to occur. It is possible that certain factors leading to ALTRs are not inherent to MoM designs and are thus under the control of the designer, manufacturer, or surgeon. For instance, while correct implant alignment and surgical technique are crucial for the longevity and function of all THAs, it appears that the tolerances allowable when using MoM are more stringent. Additionally, certain implant designs have been found to be more prone to failure as evidenced by the recall by DePuy of its ASR and ASR XL arthroplasty systems which will be discussed later in the chapter. Ultimately, MoM replacements are promising in their theoretical ability to decrease the rate of loosening and expand the indications of arthroplasty to younger patients. Unfortunately, these replacements are currently plagued by setbacks that are unique to the environment of two articulating metals.

Ceramic on Ceramic Articulations

Ceramic-on-ceramic (CoC) bearings represent another approach taken to avoid the frequency of debris-induced osteolysis in MoP arthroplasty. Since the 1970s, CoC bearings have been used due to their very hard nature, scratch resistance, and improved sliding properties. In fact, CoC bearings display even lower volumetric wear rates than MoM bearing couples. Some studies have observed wear rates as low as 0.004 mm^3/million cycles, a rate approximately 6000 times less than similarly sized MoP bearings [35]. Others have noted wear rates between 0.05 and 0.1 mm^3/million cycles which is still considerably less than both MoP and MoM bearing couples [71–73]. The frictional properties of ceramics also appear to be superior to the other bearing couples. Excess friction has been hypothesized to contribute to sudden loosening of acetabular components and thus should be minimized if at all possible [74]. In a hip simulator study using 25 % calf serum as lubricant, Brockett et al. found CoC to exhibit the lowest friction factor of any combination tested (e.g., CoM, CoP, MoP, and MoM) [75]. Additionally, in vitro studies have shown that ceramic wear debris is significantly less inflammatory than UHMWPE debris with a minimum volume of 100 μm^3 needed to induce the production of TNF-alpha, an inflammatory marker. Thus, given the biocompatibility and low rate of wear production, the volume needed to induce osteolysis is unlikely to ever be reached in vivo and is therefore not clinically relevant.

The analysis of actual clinical outcomes of CoC bearings presents a complex picture. Early CoC bearings utilized alumina as the bearing surface and showed decreased osteolysis, loosening and inflammation in comparison with polyethylene [76]. The main drawback of the early generation of alumina-on-alumina (AoA) bearings was high levels of ceramic fracture. Long-term survival of the early generation of AoA bearings was between 45 and 68.3 % at 18 years [77]. Recent advances in ceramic design and production have led to significant reductions in ceramic fracture rates. Hannouche et al. reported 13 fractures (8 in the femoral head component and 5 in the acetabular component), in a cohort of 5500 alumina components (3300 in AoA and 1200 in alumina-on-polyethylene) [78]. Long-term data has favored the use of CoC implants. For instance, a minimum 20-year follow-up for 85

hips with CoC bearings showed a 1.2 and 7.1 % incidence of radiolucencies measuring >2 cm around the femoral and acetabular components, respectively [79]. In this series, 6/85 (7.1 %) required revision, all due to aseptic loosening of the acetabular component. A different comparative study of CoC versus MoP bearings with a mean 8-year follow-up demonstrated osteolysis in 1.4 % of CoC implanted hips and 30.5 % of MoP implanted hips [80]. This combination of low fracture rate, reduced wear volume, with reduced rates of osteolysis has led to a resurgence in implants with a CoC articulation especially in young patients.

Despite these advantages, CoC bearings have the disadvantage of producing an audible noise, described as a "squeak," in select patients. While squeaking is a phenomenon that occurs in all hard-on-hard bearings, it appears to be self-limiting in MoM bearings and usually resolves within the first 6 months [81, 82]. Conversely, the squeaking of CoC bearings occurs later in the lifetime of the prosthesis and usually persists [83, 84]. Many potential causes of this squeaking have been proposed including implant design, patient factors, and implant malposition. More specifically, edge-loading, third bodies, and certain stem designs have been associated with an increased risk of squeaking [85–87]. Interestingly, despite being a common cause for revision, squeaking is not known to contribute to implant loosening or even osteolysis as evidenced by two studies with minimum follow-ups of 2.5 and 10 years, respectively [88, 89]. Reports on the incidence of squeaking vary greatly between studies. A prospective observational study of 1486 CoC THAs with a mean follow-up of 5.5 years found that 6 % of patients suffered from an audible squeak [89]. The majority of squeaks in these patients occurred during walking, climbing stairs, and bending forward. A prospective, randomized, multicenter study by Capello et al. of 475 CoC THAs found that only 0.8 % of patients noticed an audible squeak, with a mean follow-up of 5 years [80]. Contrary to this, a smaller study of 43 CoC THA by Keurentjes et al. reported audible squeaks in 20 % of patients [90]. A meta-analysis revealed a mean incidence of 2.4 % (0.7–20 %) for CoC bearings [85]. Options for patients who find the squeaking intolerable include an exchange of all components or simply the liner. Before surgery is recommended patients should be counseled that there is a chance that the squeaking may reduce over time.

It is clear that CoC THA is a viable option for patients, especially the young, who remain increasingly active. However the risk of squeaking, while small, has dramatically reduced enthusiasm for this bearing. Still, if the incidence of this phenomenon can be minimized, it is possible that ceramics could become the bearing of choice in THA.

The Acetabular Component

The acetabular component represents the proximal articulation surface of the total hip replacement. Its function is to replace the native acetabulum with a synthetic bearing that interfaces with the femoral component. The types of acetabular components can loosely be divided into two groups: monoblock and modular. As the name implies monoblock components typically consist of a single piece of either polyethylene or

metal that is machined in such a way that it serves as an interface with the surrounding bone on the convex surface while articulating with the femoral head on the concave surface. By contrast modular cups consist of two pieces: a shell and a liner. The metallic shell contains interfaces with the surrounding bone and contains a locking mechanism on the concave surface that is able to accept the liner. Similarly to the mechanisms of femoral component fixation, the acetabular components can either utilize cement or osseointegration to provide rigid and lasting attachment to the surrounding bone.

Cemented Versus Uncemented Acetabular Components

The initial design of acetabular components utilized cement as the means of fixation between a monoblock polyethylene cup and the underlying bone. Cementless modular acetabular components were introduced in the 1980s as a response to the idea that cement was the principal cause of loosening of the acetabular component. The term "cement disease" was used to describe the process of microscopic cement particles inducing osteolysis and resulting in eventual loosening. Since then, this concept has been challenged by studies that demonstrated that the major causes of osteolysis are reactions to polyethylene wear particles and hydrostatic fluid flow [91, 92]. Additionally, the increased degree of osteolysis seen in cementless cups as compared with cemented ones has caused surgeons to re-examine the decision to move away from cemented acetabular fixation [93, 94]. Still, few studies have compared the long-term results of cemented versus uncemented acetabular and the optimal fixation method has not yet been decided.

It is important to note that there is a huge variety of cemented and cementless acetabular components that all have multiple aspects of their designs that can be either beneficial or detrimental to implant survivorship. Therefore, overarching conclusions are sometimes difficult to draw due to the confounding effect created when comparing two systems that differ in more than just their fixation method. Regardless of these factors, a thorough review of the literature can describe trends that are useful when deciding whether to use cement or osseointegration as the fixation method in a given patient.

Multiple meta-analyses exist that compare cemented and uncemented fixation for acetabular components. Many of these suffer from heterogeneities in patient cohorts, bearing surfaces used, and other aforementioned confounders which serve to limit the generalizability of this data. Early systematic reviews pooled studies with short- and long-term outcomes which can skew data. One meta-analysis of 20 articles included studies with follow-up of as little as 1 year. Another study used similar follow-up criteria to examine cemented and uncemented acetabular components at short and intermediate follow-up. Both meta-analyses failed to show a better survival of cementless as compared with cemented [95, 96]. A meta-analysis of the literature published by Toossi et al. in 2013 examined survivorship or revision rate of primary total hip arthroplasty at a minimum of 10 years follow-up [97]. It analyzed 81 articles that examined the outcomes of cementless, cemented or both types of acetabular components and ultimately included 13,509 cemented components and 13,067 uncemented acetabular components in its analysis. Initially, the study did not reveal any

effect of the type of acetabular component fixation on either survivorship or revision rate, however a regression analysis showed that the estimated odds ratio for survivorship of a cemented acetabular component was 1.6 (95 % CI 1.32–2.4 $p=0.002$) when adjusted for age, sex, and mean duration of follow-up [97].

Osseointegration of Uncemented Acetabular Components

Modern uncemented acetabular components rely on a type of biologic fixation known as osseointegration for adherence to the surrounding bone. The mechanism of osseointegration seen in uncemented implants is classified as either ongrowth or ingrowth. Traditionally, ingrowth is bone deposition in the interstices of a porous surface and ongrowth is bone attachment to a flat implant surface. The difficulty with these definitions is that ultimately porosity is an arbitrary definition and so ingrowth may exist in situations where it is smaller than the resolution of current imaging. Furthermore, even in porous-coated implants, there are flat surfaces which facilitate ongrowth. Thus, both ongrowth and ingrowth can play a role in the fixation of an acetabular component. One criterion commonly used to distinguish these two processes describes ingrowth as growth into pores which are visible under light microscopy and ongrowth as a situation in which "no surface macroporosity at the level of a light microscope is visible and the bone appears to be directly attached to the implant material" [98].

Interestingly, early uncemented acetabular components relied on neither ingrowth nor ongrowth for fixation and were plagued by failures. These designs utilized the geometric shape of the implant, large pegs, or threaded rings for mechanical fixation. In a retrieval study by Bobyn et al. it was found that there was radiographic and histological evidence of fibrous tissue filling the threaded grooves with as little as 9 % of the threaded (fixating) component surface area in contact with the bone [99]. It was concluded that the lack of "micro-interlock" or osseointegration among other reasons was the cause of acetabular component migration and eventual failure. These failures led to the development of the second-generation threaded cups which added design features meant to support ingrowth through the use of porous coated metallic surfaces or ongrowth using the rough surfaces of grit-blasted metals. The superiority of porous over first generation threaded implants was shown in a matched-pair analysis of otherwise identical cup designs. Porous threaded implants performed significantly better at 2–4 years of follow-up with a 0 % loosening/revision rate noted in the porous group compared with a 29 % incidence of loosening and a 10.7 rate of revision noted in the first generation design [100]. Other studies with longer follow-up supported these findings [101, 102].

Bony ingrowth requires more than just a porous surface to occur successfully. The surface must also be consist of a biocompatible material, have optimal pore size, be in intimate contact with viable bone, and have adequate initial stability for osseointegration to occur successfully. In several studies, the ideal diameter of the pores was found to be between 150 and 450 μm [103, 104]. Studies in canines have demonstrated that less than 20 μm of micromotion allowed for optimal bone ingrowth into a porous titanium mesh while over 150 μm of micromotion resulted

in fibrous tissue at the bone–implant interface [105]. This fibrous tissue contributes to osteolysis, implant instability, and eventual failure [106, 107]. Although initial apposition of a porous implant with the surrounding bone surface is not absolutely necessary for successful osseointegration, the rate and degree of mineralization is enhanced when the initial post-surgical gap width is less than 0.5 mm [108, 109].

These findings along with clinical data have prompted manufacturers to favor press-fit (under-reamed) acetabular fixation as opposed to line-to-line designs [110]. Additional fixation strength could also be achieved with the addition of supplemental screw fixation. One cadaveric study comparing line-to-line with press-fit both with and without screw fixation found that press fit with screw fixation resulted in the greatest stability [111]. Other designs have utilized hydroxyapatite (HA) coated components as an osteoconductive material to improve bone ingrowth and ongrowth. Although successful on femoral components, the results of HA coated acetabular components have been mixed. Smooth HA coated designs have proven to have high revision rates and porous HA-coated implants have shown identical clinical results to non-HA coated porous designs except for a decrease in polar radiolucencies at 2 years [102, 112–114]. An 8-year randomized controlled trial found no superior survival or rate of revision of HA-coated porous acetabular cups over similar non-HA-coated implants [115].

Femoral Stem Design

The femoral component is designed to mimic function of the proximal portion of the femur. This component is the most diverse in terms of design options available to the surgeon owing to the complexity and nuances encountered in human femoral anatomy. This section will discuss the effects of the use of cement, different implant geometries, modularity, femoral head size, and bone preserving hip replacement techniques, i.e. resurfacing.

Femoral Head Size and Dislocation Rates

Native femoral head sizes are typically larger than those used in total hip arthroplasty. Although total hip arthroplasty has largely been successful even when utilizing smaller heads, problems with impingement free range of motion and dislocation have left room for improvement. In vitro data prompted researchers to experiment with larger femoral head diameters in order to increase stability after arthroplasty [116–118]. These designers sought to decrease the rate of dislocation by increasing the head-to-neck ratio, the jump distance prior to dislocation, and the tension on the surrounding soft tissues. Cadaveric studies showed that the range of motion increased significantly when larger heads were employed and in samples with larger head sizes the limitation in range of motion was due to bone impingement rather than component impingement (Table 11.1) [119].

Table 11.1 Average range of motion in cadavers with 32, 40, and 44 mm femoral heads [Reprinted from Cross MB, Nam D, Mayman DJ. Ideal femoral head size in total hip arthroplasty balances stability and volumetric wear. HSS J. 2012;8(3):270–4. With permission from Springer-Verlag]

Head Size	Limitations to range of motion	Flexion	Extension	Internal rotation	External rotation	Abduction	Adduction	Flexed internal rotation	Flexed external rotation
32 mm	Component impingement	119.0 (±4.0)	50.7 (±1.3)	128.9 (±3.0)	55.1 (±2.7)	56.3 (±2.7)	54.3 (±3.2)	32.3 (±0.8)	92.4 (±1.4)
40 mm	Component impingement	124.7 (±4.6)	59.1 (±1.8)	137.1 (±3.7)	63.7 (±3.2)	60.3 (±2.7)	58.4 (±3.4)	39.9 (±0.4)	100.4 (±1.1)
44 mm	Component impingement	127.5 (±4.9)	62.0 (±1.4)	139.5 (±4.9)	66.5 (±4.9)	61.5 (±3.5)	60.5 (±3.5)	42.0 (±0.0)	102.5 (±0.7)
	Bone impingement	124.9 (±8.9)	108.0 (±18.5)	135.6 (±6.5)	40.7 (±9.4)	76.0 (±6.4)	24.6 (±7.6)	44.9 (±5.3)	105.7 (±7.6)

As a result of this research, there has been a trend towards increasing femoral head sizes in total hip arthroplasty in an effort to decrease dislocation rates and thus improve the stability. This has largely been successful, especially for surgeons who perform total hip arthroplasty through a posterior approach which has been traditionally associated with dislocation. Population based registry studies undertaken in Finland and Sweden found that larger diameter femoral heads resulted in a decreased dislocation rate. The Finnish study examined patients with femoral heads that were 32, 36, and greater than 36 mm and compared them with 28 mm heads. The results showed a significantly decreased relative risk of dislocation of 0.4, 0.4, and 0.09, respectively [120]. A Swedish registry study found similar results, noting that the relative risk of revision of 28 mm heads compared with 22 mm heads was 0.5 [121] A recent systematic review which incorporated 24 randomized controlled trials found that larger femoral head size (36 mm vs. 28 mm) was associated with a decreased risk of implant dislocation [122].

Unfortunately, larger femoral heads come at the cost of increased wear properties. As mentioned in the earlier section, larger femoral head sizes result in a greater volumetric wear and therefore increased osteolysis, implant loosening, and eventual failure. A hip simulator study performed by Clarke et al. focusing on UHMWPE found a proportional increase in volumetric wear of approximately 7.8 % for every millimeter that the head diameter increased in MoP implants [7]. An in vivo radiographic study found that there was a 74 % increase in volumetric wear when 28 and 32 mm MoP bearings were compared [11]. A revision retrieval study of loose MoP acetabular components found an increase of 5.1 mm^3/year for each millimeter increase in the radius of the head [12]. Studies comparing different sized femoral heads articulating with HXLP found no difference in linear wear but significantly increased volumetric wear associated with increasing head sizes [16–18]. Similarly, MoM bearings have all shown increased wear associated with larger head diameters [123]. MoM articulations have the added risk of producing severe adverse soft tissue reaction and releasing serum ions as a result of wear [49–52]. Thus, the use of large diameter heads in the context of MoM bearings is currently not recommended [70].

When considering what size femoral head to use in a total joint arthroplasty ultimately the improved range of motion and dislocation characteristics of the larger heads must be weighed against the propensity of these components to produce more wear. Johnson et al. found that in order to perform activities of daily living, one must have hip flexion of 120°, hip abduction of 20°, and hip external rotation of 20° [124]. The greatest range of motion was seen in cadaveric samples with a femoral head size of 44 mm, however a 32 mm head appears to be sufficiently large to provide adequate range of motion for day-to-day functioning. Thus one study concluded that for the average patient, a 28 or 32 mm cobalt chrome on highly cross-linked polyethylene is a safe, durable, and effective bearing surface that balances the risk of increased osteolysis with a decreased propensity to produce significant wear [119].

Cemented Femoral Components

The total hip arthroplasties popularized by Sir John Charnley utilized components that were fixed to the surrounding bone using a self-curing acrylic bone cement. In these early trials, there was a wide variability in the success of cemented femoral components [125, 126]. This inconsistency can at least partially be explained by the evolution of cementing techniques over the past half century. Originally the cement distribution technique involved finger packing the bone cement into an unplugged femoral canal. Modern cementing techniques involve cleansing the canal with pulsatile lavage, inserting cement in a retrograde fashion, porosity reduction via vacuum mixing, and cement pressurization within the canal. Additionally, the stem is centralized proximally and distally in order to ensure an adequate and symmetric stem mantle. Thus, when critically examining clinical data, it is important to determine which cement technique was used when placing the component.

The mechanisms of failure of cemented femoral components are typically the result of mechanical factors initiating femoral loosening. Debonding, or separation of the cement from the stem, occurs followed by high stresses produced in the cement mantle proximally and at the distal tip of the implant [127–130]. These stresses then initiate crack formation which further destabilizes the implant and produces debris which results in an inflammatory reaction, bone resorption, and a soft tissue membrane which is commonly encountered in aseptic loosening. Interestingly, unlike uncemented components, this fibrous membrane forms late in the loosening process of cemented components and is not thought to play a significant role in the initial loosening process [107, 131]. The factors that led to the initial debonding were examined in numerous studies. Radiolucencies in the cement mantle signifying poor distribution of cement were found to predict later failure [132]. Varus implant position was also found to be associated with a higher risk of aseptic loosening and was thought to result in adverse outcomes due to its propensity to create a poor cement mantle [133, 134]. Thus in an effort to evaluate cement mantles, a grading system was created by Barrack et al. [135] which distinguished complete filling of the proximal diaphysis (A), near complete filling (B), incomplete filling with either greater than 50 % demonstrating radiolucencies (C1) or less than 1 mm of mantle present (C2) and gross deficiencies in the mantle with no cement distal to the tip or multiple large voids (D). Aseptic loosening was associated with C and D mantles with the latter having the greatest amount of implant failures. Other variables that contributed to failure included increased weight of patient, younger age of patient, male sex, and patients with post-traumatic osteoarthritis. Interestingly, the type of implant and surgeon did not correlate with a change in incidence of revision in this study [136].

Clinical outcomes of cemented femoral components have improved with advances in cement techniques. Distal plugging of femoral canal, extensive lavage, and retrograde injection of bone cement resulted in reported mechanical failure rate of 1–5 % in studies performed by Ranawat et al., Madey et al., and Smith et al. at 15 years

follow-up [137–139]. Contradictory results were reported by Sanchez-Sotelo et al. who found that the mechanical failure rate was 10 %. Stratification revealed a 4.3 % failure rate in patients older than 50 years and a 27.7 % failure rate in patients younger than 50 years [140]. Further advances in cementing technique including pressurization and vacuum preparation of the cement have resulted in further decreases in failures. A 13.5-year follow-up of 204 THAs placed with this cementing technique showed only 4 revisions: one for osteolysis, two for recurrent dislocations, and one delayed infection [141].

Uncemented Femoral Components

Uncemented implants were originally created to deal with the issue of "cement disease" or the lysis of periprosthetic bone. Cementless femoral components rely on osseointegration, the structural and functional connection between bone and implant, without intervening soft tissue, for their fixation strength. The mechanism of osseointegration seen in uncemented implants is classified as either ongrowth or ingrowth. Traditionally, ingrowth is bone deposition in the interstices of a porous surface and ongrowth is bone attachment to a flat implant surface. As noted earlier, bony ingrowth requires more than just a porous surface to occur successfully. The surface must also be consist of a biocompatible material, have optimal pore size, be in intimate contact with viable bone, and have adequate initial stability for bony ingrowth to occur successfully [103–105, 108, 109]. The ideal values for these parameters are discussed earlier in the chapter when describing the osseointegration of uncemented acetabular components.

While uncemented components have enjoyed great success, it is currently recognized that "cement disease" is a misnomer and is instead referred to as osteolysis. This process is known to cause loosening and eventual failure in both cemented and uncemented implants. Osseointegration of cementless porous coated femoral stems has proven to be a reliable and successful form of fixation but some features of cementless stems such as stem geometry, surface properties of the porous surface, and the extent to which the porous surface is applied to the stem continue to be a source of debate. One way of categorizing femoral components is by stem geometry. The two most common types of geometries are anatomical and tapered. The differences between these include their shape, metallurgy, head-neck design, and ongrowth–ingrowth surface.

Anatomic and Tapered Designs Early hip arthroplasty designs featured anatomic stems. These designs were constructed from cobalt-chrome alloys and achieved fixation by osseointegration of the proximal femoral component. Unfortunately, patients receiving these replacements frequently complained of thigh pain due to some combination of modular mismatch, endosteal irritation, and lack of ingrowth. Efforts to improve this design have led to the development of tapered femoral components.

The design rationale behind tapered components is geared towards promoting long-lasting osseointegration between the component and the surrounding bone. This requires rigid initial fixation until full osseointegration can be achieved. This initial stability is provided by the taper when it is forced into the medullary canal thereby producing circumferential hoop stresses that do not allow an axially loaded tapered stem to advance any further [142]. Rotational stability is provided by a rectangular cross section of the tapered stem although circular cross sections also exist and have shown highly satisfactory results as well [143]. An advantage of the circular cross section over the rectangular one is the ability to correct femoral anteversion if necessary. The tapered design has been shown to reduce stress shielding and lead to a decreased prevalence of thigh pain [144–147]. Femoral fixation requires osseointegration of the femoral component, typically in the proximal stem because of the maximal contact between bone and implant afforded by this area. Once osseointegrated, the stem is rigidly and lastingly fixed to the surrounding bone.

Clinical studies have favored the use of tapered designs over anatomic ones. In one study of 311 Porous Coated Anatomic (PCA) stems the overall survival rate of the femoral component at 14 years was 95 %. Unfortunately this design also showed a 36 % prevalence of thigh pain and 42 % of individuals had significant amount of femoral osteolysis as evidenced by radiography [148]. One study with 10- to 13-year follow-up of tapered total hip replacements in 283 patients found a 99 % survival rate of the femoral component with osteolysis seen in only 6.2 % of cases [149]. Activity related thigh pain was also low, noted in only 3 % of patients [149]. Very long-term studies of greater than 20 years have also shown positive results for tapered designs. The 20- to 25-year survival rate for tapered total hip replacements with follow-up ranging from 20 to 25 years was found to be between 86 and 95 % [150–152]. A long-term study of 47 obese patients with 18- to 27-year follow-up found a 94 % survival [153]. Risks for failure in a study of 326 patients receiving tapered THA with a follow-up of 22 years were found to be undersized stems, and hips where the cup was already revised. This study had a high (38 %) rate of cup revision due to the use of smooth-threaded cementless sockets [151].

Proximal and Extensive Porosity Another point of contention among designers of femoral components is the ideal extent of porous coating that should be applied to a femoral implant. In general, uncemented press-fit designs fall into one of two categories: fully porous-coated cylindrical stems that achieve distal fixation and proximally porous-coated tapered stems that achieve proximal fixation.

Extensively porous coated prostheses are defined as those with porous coating of more than 80 % of the surface area of the stem. The most common of these is the Anatomic Medullary Locking (AML) stem produced by DePuy. A critical design feature of the AML is its straight, cylindrical, non-tapered distal stem geometry. Thus, the stem does not wedge in place and fixation depends on a "scratch fit" between the rough external surface of the implant and a similar shaped bone canal. The theoretical advantage of the extensive coating is that it allows for osseointegration over the entire length of the stem. In this design, distal porosity is particularly important because the distal part of the stem most consistently contacts with the

cortical bone. Interestingly, even in cases where successful osseointegration does not occur and a fibrous tissue membrane forms between the bone and stem, adequate fixation is still achieved and there is sufficient radiographic stability as well as patient satisfaction owing to the extensively coated surface [154]. Conversely, proximally porous coated femoral implants can be either tapered or cylindrical and were intended to achieve biologic fixation solely in the femoral metaphysis. This property was intended to reduce proximal stress shielding and preserve bone stock.

Both designs have proponents that cite multiple publications with reproducible long-term follow-up. The reported incidence of thigh pain in patients receiving THA with a fully coated femoral component has varied between 3 and 20 % [155–157]. Today, most surgeons presume that proximally coated stems and cemented stems are less predisposed to causing thigh pain than fully coated stems although this idea remains controversial [158–161]. Similarly, femoral bone loss as a result of stress shielding around well-fixed femoral components is thought to occur more frequently in extensively porous coated stems. In theory, bone loss in the femur could lead to greater and lesser trochanteric avulsion fractures and make future revisions more difficult. However, currently, it is important to note that stress shielding is more of a radiographic finding than a diagnosis and the clinical ramifications of this process have not yet been demonstrated. A prospective randomized blinded clinical trial followed 388 patients receiving either proximally porous coated and fully porous coated femoral components (Table 11.2). A minimum follow-up of 2 years with a mean of 6 years was used and found that post-operative clinical outcome scores were similar at all follow-up intervals. There were no differences in incidence of thigh pain at any time although bone density reduction was greater in the fully coated stem as compared with the proximally coated [162].

Modular Femoral Components

Despite the success of monoblock implants, these designs were limited by their inability to fine-tune two properties which can differ greatly between patients: offset and leg length. Since dislocations remain one of the most frequent post-operative complications after THA, designers sought to reduce the dislocation rate by allowing surgeons to make adjustments in the offset and neck length of implants. Thus modular femoral stems were intended to allow a more accurate reproduction of patient anatomy. The use of a modular head-neck junction allowed the surgeon greater freedom in adjusting for leg length discrepancies as well as optimizing the function of the abductors [163]. Modular head-neck components also allowed for easier revision of femoral components when the femoral stem is clearly fixed and requires no further fixation. Unfortunately, increased customizability came at a cost and these implants suffer from an increased risk of fatigue failure, fretting, and crevice corrosion.

There is a vast array of modular femoral stems that allow for retention and sacrifice of various components of hip anatomy. While most modular femoral components are used in revision total hip arthroplasty, some complex primary total hip

Table 11.2 Incidence and severity of thigh pain in Synergy™ (proximally coated) and Prodigy™ (fully porous coated) femoral stem groups [Reprinted from MacDonald SJ, Rosenzweig S, Guerin JS, McCalden RW, Bohm ER, Bourne RB et al. Proximally versus fully porous-coated femoral stems: a multicenter randomized trial. Clin Orthop Relat Res. 2010;468(2):424–32 with permission from Springer Verlag]

	Incidence			Severity*		
Time	Synergy™	Prodigy™	*p* Value	Synergy™	Prodigy™	*p* Value
Preoperative	71 %	69 %	0.75	80.74 (±20.24)	80.96 (±20.70)	0.84
6 months	11 %	15 %	0.254	38.67 (±31.96)	37.67 (±23.01)	0.94
1 year	11 %	14 %	0.512	42.82 (±25.06)	47.42 (±27.99)	0.683
2 years	9 %	6 %	0.527	42.25 (±34.76)	33 (±20.05)	0.661

[a]Values are expressed as mean ± SD on a 100-mm visual analog scale

arthroplasties can benefit from the use of these devices as well. Modularity can occur at various points throughout these femoral stems and great emphasis has been placed on the association between modularity positioning and implant failure. Systems such as the Zimmer ZMR utilize a mid stem modularity allowing independent selection of the sizing and positioning of the proximal and distal components. The DePuy S-ROM is a proximal modular femoral implant that utilizes a titanium stem with distal spines to achieve initial fit and rotational stability. Standard and calcar replacement options are available with variable offset options. A separate sleeve that incorporates a "step-like" geometry to convert shear to compressive forces is available in both porous and hydroxyapatite coated designs. Between the proximal and distal stem segments is a tapered section that engages this enveloping sleeve. The sleeve is positioned first and the stem is placed through the sleeve and engaged. This allows the S-ROM stem to separate hip biomechanics and component fixation. The sleeve achieves fixation whilst the stem allows for adjustments in length and offset. In all, the S-ROM design allows for 10,398 different reconstructive possibilities [164]. Unfortunately, stems with distal modularity have underperformed other systems and most have been withdrawn from the market.

Modular stems have produced good clinical outcomes in certain situations. Restrepo et al. examined initial distal fixation, femoral offset restoration, leg length equalization, and hip stability in 118 patients who underwent revision with Stryker Restoration Stem [165]. This system consists of a fluted, titanium conical distal stem, which attaches to a proximal body. Adequate bone ingrowth and fixation was obtained in 100 % of patients and the offset was corrected in 66 % while leg length discrepancy was corrected in 78 %. Ultimately, stability was achieved in 97 % of patients who received this implant. Initial concerns were raised regarding failure of the modular junction but in this study with a 4–7 years follow-up, no failure/fracture was observed in a total of 118 patients [165].

When two components lock into each other, wear and corrosion are an inevitable consequence. The production of wear particles can lead to osteolysis and corrosion can lead to implant failure. More alarmingly, metallosis and adverse local tissue responses (ALTR) similar to that seen in metal-on-metal bearing couples are being

reported in patients with modular hip arthroplasties [166]. One subtype of these adverse responses is termed aseptic lymphocyte-dominated vasculitis-associated lesions (ALVAL). This lymphocyte-dominated reaction is very severe and can result in not only implant loosening but also severe soft tissue necrosis and pseudotumor formation [53]. Modular stems that incorporate a double taper (head-neck and neck-stem) add additional sites for failure and corrosion, with the added risk of increased wear particles.

Kop et al. examined 57 retrieved modular stems of 7 different designs. Of these, three were cobalt-chromium-molybdenum based and four titanium based [167]. The aim of this retrieval study was to assess whether the same degradation mechanism was present at the head-neck and neck-stem junction, whether or not the additional junction contributed to the revision, if the implant alloy affected the extent of degradation, and if the trunion machine finish affected the degradation mechanisms. Corrosion and fretting were both lowest in the titanium components with 62 % of the Co-Cr-Mo components having corrosion of the trunion, and 90 % fretting. In contrast, 30 % of Ti-based components showed corrosion, with 50 % exhibiting fretting. However cold welding of the titanium components did occur. It was concluded that titanium modular components may reduce the amount of degradation, but at the expense of an increased risk of cold welding.

Kop et al. also used a retrieval study of 16 modular components to examine the relationship between corrosion, material, and implant time. Of the retrieved implants 6 tapers showed fretting corrosion, with the average implant time being 39 months. No corrosion was shown in the remaining 10 tapers, which had an average implantation time of 2.7 months. It was concluded that even with modern materials and taper designs corrosion is still a concern with added modularity [168].

Gilbert et al. examined 148 retrieved modular hip prostheses. Significant corrosion was noted on 16 % of necks and 35 % of heads [169]. Concerns have also been raised regarding the elevated serum metal ions levels produced due to corrosion of modular stems. Once implanted, a protective surface oxide layer forms on the implant (modular implants are typically composed of titanium or Cobalt-chrome). While this film provides added corrosion resistance to the implant, it is subjected to repeated disruption as a result of stresses applied to the prosthesis. As the film reforms it reduces oxygen in the surrounding soft tissue. This process repeats itself and results in a reduced ability of the film to protect the implant [29].

Jacobs et al. describe corrosion is also affecting the structural integrity of the implant. This has been implicated in isolated incidents of fracture. Wright et al. report a case of fracture of the modular neck in a 49-year-old man. The fracture occurred while bending forward to tie his shoes, in the context of a fall onto his hip 2 months previously. On examination with light microscopy marked fretting and corrosion were noted along with debris [170].

Despite the intra-operative advantages offered by modular stems, the added junctions with the implant can lead to increased corrosion and wear particle production. While implants such as the S-ROM and modular taper stems have revolutionized revision surgery the use of modularity in primary THA should be avoided due to the risk of fatigue fracture and corrosion.

Hip Resurfacing

While THA is the treatment of choice for osteoarthritis of the hip there is an increasing cohort of patients who are requiring replacements earlier in life in order to remain physically active. While THA offers good symptomatic relief for these patients, they are likely to require revision in the future as a result of the increased physical demands placed on the implants, their increased life expectancy, and the insufficient longevity of traditional total hip arthroplasty. Hip resurfacing was developed as one solution to this problem and involves the preservation of the femoral neck through the use of a cap over the femoral head. This approach conserves femoral bone and theoretically allows for easier revision in the future, should it be needed.

The results of early resurfacing procedures in the 1970s and 1980s were poor. Accelerated wear and large volumes of biologically active wear debris resulted from the combination of a large articulating surface with a thin polyethylene liner and led to high rates of implant loosening and bone loss. With the development of new, more wear resistant materials, resurfacing has been reintroduced, this time incorporating a metal-on-metal (MoM) articulating surface [171]. As such, the downsides of MoM bearing couples which have been discussed earlier in this chapter must be weighed when deciding whether to pursue this reconstruction option.

As the stability of the femoral head is a key component in the effectiveness of resurfacing, severe bone loss, cysts or osteonecrosis of the femoral head or neck are contraindications for resurfacing. Retention of the femoral neck also means that unlike THA, femoral neck fractures may occur. Marker et al. used a prospective cohort study to identify the incidence of femoral neck fracture. 550 resurfacings performed by a single surgeon were studied. It was shown that 14 (2.5 %) had resulted in fracture of the femoral neck. Of these, 12 had occurred in the first 69 resurfacings performed, with women and obese patients shown to have a higher cumulative incidence of fracture. It was concluded that the risk of femoral neck fracture is multifactorial, associated with both the surgical learning curve and patient selection [172].

In vitro studies have suggested more limitations to hip resurfacing. Bengs et al. and Kluess et al. have both demonstrated reduced range of motion (ROM) in resurfacing compared to THA. Kluess examined the ROM of eight resurfacing prosthetics using 3D CAD models. The ROM of the resurfacing systems was found to be substantially less than that of total hip prosthetics with the large diameter of the femoral neck leading to impingements in all maneuvers analyzed [173]. Bengs examined the ROM of eight different hip replacement designs implanted into composite femurs and pelvises. It was found that compared to the THA prosthetics, resurfacings showed reduced ranges of motion, with, once again, early impingement of the femoral neck [174]. This is important since hip resurfacing is largely being indicated for younger and more active patients who require an increased ROM for various activities. Fortunately, despite these studies demonstrating reduced ROM in resurfacing systems, these reductions have not been seen when applied to the clinical setting. Clinical studies have shown similar ROM for both resurfacing and THA systems. Le Duff et al. examined 35 patients who had undergone bilateral

surgery receiving THA on one side and resurfacing on the other, with a mean follow-up of 88 months. They found no difference in ROM between the two systems [175]. Shimmin et al. suggested that while THA shows greater ROM in laboratory studies, this cannot be recreated in patients with normal flexibility leading to similar ROM in both THA and resurfacing [176]. Shimmin also reports that of the nine papers comparing functional outcomes between THA and resurfacing, eight showed consistently similar outcomes [176].

Springer et al. used a large meta-analysis to compare the results of 3269 resurfacings with 6408 cementless THAs. Femoral revision for mechanical failure was used as an endpoint and was found to be 1.3 % in the THA group with a mean follow-up of 8.4 years compared to 2.6 % in the resurfacing group with a mean follow-up of 3.9 years [177]. Johanson et al. used the Nordic Arthroplasty Register Association database to examine the non-septic 2-year revision risk of 1638 resurfacings and compared to 172,554 THAs. By 2 years the revision rate for resurfacings was 2.4 % compared to 1.1 % for THA [178].

It is clear that not all resurfacing systems yield similar results. Seppanen et al. examined the Nordic Joint registry between 2001 and 2009. During this time 4401 hip resurfacings were performed. When comparing the Articulating Surface Replacement (ASR) Hip resurfacing system (DePuy Orthopedics, Warsaw, Indiana), to the Birmingham resurfacing system (BHR) it was found that the ASR had inferior outcomes to the BHR with a relative revision risk of 1.8 (CI: 1.2–2.7) [179]. The ASR Hip resurfacing system was recalled by DePuy voluntarily in August 2010, based on unpublished data from the National Joint Registry of England and Wales that showed a 12 % revision rate at 5 years [180]. In 2007, the Australian Orthopedic Association National Joint Replacement Registry (AOANJRR) reported that the ASR revision system had higher than expected revision rates (3.0 revisions per 100 observed component years), that were twice that of other resurfacing systems with a cumulative percent revision at 2 years of 5.16 % [181]. De Steiger et al. reviewed the AOANJRR between 2003 and December 2009 identifying 1167 ASR resurfacing procedures. It was found that the cumulative revision rate at 5 years for the ASR resurfacing system was 10.9 % compared to 4.0 % with all other hip resurfacing prosthesis [180].

While the literature shows that resurfacing is a viable alternative to THA, especially in younger patients, it is clear that adequate surgical experience must be combined with careful selection of the patient and prosthesis in order to achieve optimal results. Additionally, it is important to note that hip resurfacings utilize a MoM bearing couple which carries inherent issues as discussed earlier in the chapter.

Surgical Approaches in Hip Arthroplasty

Numerous surgical approaches to the hip exist for use in hip arthroplasty. Although evidence in the literature can be found for the use of certain approaches over others for given indications, realistically most surgeons will use the approach that they are

most comfortable with for the vast majority of their cases. In certain situations, however, there are definite advantages to either modifying the surgeon-preferred approach or using a different one altogether. The need to access a particular anatomic region either because of bony deficiency or in order to remove hardware from a previous surgery are two such examples. Additionally, modifications of existing approaches must be utilized in certain populations. Patients with difficult anatomy, such as obese or muscular patients, require larger incisions, longer retractors, and more surgical assistants in order to have a satisfactory clinical outcome.

Recently there has been a surge in interest within the orthopedic community to perform THAs using minimally invasive surgery (MIS). Mini-incisions are either smaller versions of conventional approaches or novel incisions which are used to gain access to the acetabulum and femur. *Ultimately, the invasiveness of a procedure is more dependent on the amount of soft tissue damage that it causes rather than the size of the incision*. MIS appears to be less disruptive to soft tissues and advocates point to the potential for reduced intra-operative blood loss, decreased muscle damage, shorter length of hospitalization, reduced post-operative pain, and improved cosmesis that these methods offer. Conversely, some believe that the current practices in THA already produce excellent results with low complication rate, significant improvement in patient function, and excellent long-term prognosis. They argue that smaller incisions impair intra-operative visualization and lead to implant malposition, increased risk of intra-operative fractures and the potential for increased muscle damage. Concerns have also been expressed over the risk of neurovascular injury and poor implant fixation [182].

Posterolateral

The posterior or Moore Southern approach is currently the most popular technique for total hip arthroplasty. Many surgeons favor the posterolateral approach as it is less technically demanding than other methods and results in limited muscle damage while allowing for simple extension of the incision if needed. This method does not violate the abductor mechanism and is therefore thought to result in a lower incidence of post-operative Trendelenberg gait [183–186]. The major disadvantage of this approach is the risk of posterior dislocation due to the need for the release of the external rotators. This risk can be minimized by utilizing a careful repair of the posterior soft tissue structures [187–191] or through the utilization of larger diameter femoral heads. Despite these modifications, dislocation remains the main post-operative concern of the posterolateral approach [192–194].

The approach is performed with a 10–15 cm curved incision centered on the posterior aspect of the greater trochanter. The fascia lata is split in line with the incision and the fibers of the gluteus maximus dissected bluntly to reveal the short external rotators. These are then detached close to the femoral insertion and reflected thus exposing the posterior aspect of the hip joint and capsule. An incision is then made in the joint capsule and internal rotation of the thigh is used to dislocate the

femoral head and thus expose the joint. Proximal and distal extensions are possible and can be used to visualize the ilium or middle-distal femur, respectively. In obese or muscular patients, this approach can be modified in order to obtain adequate exposure. Often, the release of either the quadratus femoris, gluteal sling, reflected head of the rectus femoris, or the anterior capsule can be used to mobilize the femur and provide adequate exposure to ream the acetabulum. Failure to do this in obese or muscular patients can result in excess retroversion and likely contributes to the increased incidence of dislocation that is associated with this approach [195]. The MIS adaptation of the posterolateral approach utilizes a smaller incision (8–10 cm) along with minimal quadratus femoris release and a less invasive dissection.

Studies on the clinical outcomes of the posterolateral approach, whether traditional or MIS as compared with other approaches have been difficult to interpret due to confounding variables and conflicting results. A Cochrane review by Jolles and Bogoch examining the merits of a posterior versus lateral surgical approach for total hip arthroplasty in adults with osteoarthritis found the quantity and quality of trials to be insufficient to make a recommendation [196]. One study of 1793 primary THRs performed by either the posterolateral or direct anterior approach found that the former resulted in a 1.2 % decrease in wound infection compared with the latter (7/505 vs. 3/1288) [197]. Studies have found a longer duration of rehabilitation, greater blood loss, increased use of transfusion, greater narcotic usage, and a longer hospital discharge associated with the posterolateral approach [198–201]. Other studies conducted to compare parameters such as gait have found similar results regardless of approach [202]. A prospective nonrandomized multicenter study of 1089 THAs found no difference in Oxford hip scores, dislocation rates, or revision rates between anterolateral versus posterior hip replacements at 5 years follow-up [203]. Unfortunately most of these studies were nonrandomized and so suffer from selection bias which limits the generalizability of the results.

Others have compared the traditional posterolateral approach to the MIS adaptation and have favored the adoption of the minimally invasive option. Sculco et al. reported on 1500 procedures that utilized the MIS adaptation and found that the complication rate for dislocation was 1.2 %, with femoral fracture and sciatic neuropraxia rates both at 0.3 % [204]. A randomized controlled trial found that patients who underwent a minimally invasive total hip arthroplasty demonstrated decreased blood loss and limped less at 6-week follow-up [205]. A systemic review by Cheng et al. compared the operative outcomes between standard and MIS in THA. It was found that operative time and blood loss were significantly reduced in the MIS group for patients with a posterolateral incision. There were no statistically significant differences reported in post-operative outcomes between the standard and MIS groups [206]. Berstock et al. conducted a systematic review and meta-analysis of the standard versus mini-incision posterior approach to total hip arthroplasty and found that the mini-incision posterior approach was associated with an early improvement in the Harris hip score, reduced operating time (by 5 min), reduced hospital stay (by 14 h), and reduced intra-operative and total blood loss (by 63 and 119 mL, respectively). There was no difference noted in the incidence of dislocation, nerve injury, infection, or venous thromboembolic events [207].

Direct Anterior

Recently there has been widespread interest in the direct anterior approach to the hip for THA partially due to the belief that it reduces the risk of posterior dislocation by preserving the external rotators. This approach is a minimally invasive modification of the Smith-Peterson method that begins with an 8–10 cm incision from the anterior superior iliac spine in the direction of the lateral patella. It then exploits the inter-muscular and inter-nervous plane between the tensor fasciae latae (supplied by the superior gluteal nerve), and the sartorius muscle (innervated by branches of the femoral nerve). The rectus femoris is retracted medially and the iliopsoas is dissected away from the joint capsule. An arthrotomy is then performed to gain access to the joint. The obvious benefit of this approach is that no muscles are incised including the posterior structures that are important in the stability of the hip. Concerns surrounding this approach relate to its limited exposure of the femur. Detractors contend that this may lead to malposition of femoral implants or the use of implant designs that offer less bone fixation as compared with the conventional posterior approaches.

The majority of approaches to the hip require resection/splitting of muscle. The theoretical benefits of the anterior approach come mainly as a result of muscle preservation. By preserving the posterior structures and external rotators post-operative dislocation rates are theoretically reduced. The high degree of soft tissue preservation means that the normal post-operative hip precautions are more relaxed and restoration of function is earlier. A comparison of minimally invasive direct anterior versus posterior total hip arthroplasty found that serum inflammation and muscle damage markers were decreased in the direct-anterior-approach group as compared with the posterolateral approach group [208]. Menghini et al. used 12 cadaver hips to compare the degree of muscle damage caused by the anterior and posterior approaches. While the posterior approach caused damage to the gluteus medius and minimus (18 % vs 8 %), the anterior approach demonstrated a high degree of damage to the tensor fasciae latae muscle (mean of 31 %). There was also a need to transect the piriformis or conjoined tendon in 50 % of the anterior approaches to mobilize the femur, thus causing damage to precisely those structures that the anterior approach is designed to avoid [209].

Clinical outcome data has been mixed and has suggested short-term outcome improvement associated with the use of the direct anterior approach as compared with other approaches. Nakata et al. used a clinical comparative study of the direct anterior with mini-posterior approach for 195 hips. It was found that patients who received the direct anterior approach had a quicker recovery for hip function and gait stability [198]. Other studies confirmed these findings and also found decreased blood loss, less narcotic use, decreased pain scores after surgery, and less use of walking aids with the direct approach [200, 201, 210–213]. Other studies have contradicted these findings and reported increased or equivalent operating time, blood loss, and length of recovery [214–216]. A prospective randomized study by Restrepo et al. of 100 patients compared a modified Smith-Peterson approach to the direct

lateral approach. It was found that at 1 year the anterior approach group showed significantly better improvement in mental and physical health dimensions for the Short Form-36 and Western Ontario McMaster Osteoarthritis Index, however at 2 years these results were the same for both groups [217]. No study to date has proven that the long-term functional results of the direct anterior approach are superior to any other approach.

Whilst the anterior approach to the hip reduces the risk of damage to the muscles and sciatic nerve, there is a high intra-operative risk of damage to the lateral femoral cutaneous nerve. Goulding et al. followed 132 patients who underwent an anterior approach to the hip and found that 81 % reported varying degrees of lateral femoral cutaneous nerve neuropraxia. There was a higher risk of neuropraxia in those undergoing hip resurfacing as opposed to THA: 91 % and 67 %, respectively. Whilst only a small number of patients reported complete resolution of the neuropraxia, no patients reported functional limitation and the symptoms of neuropraxia were eventually reduced over time [218].

Reports of hip dislocation vary. Matta et al. studied 437 patients (494 hips), undergoing an anterior approach to primary THA and found the dislocation rate to be 0.61 % [219]. Sariali et al. used a prospective study of 1764 primary THA using the anterior approach and found the dislocation rate to be 1.5 % [220]. These numbers are comparable to the reported dislocation rate when using the posterolateral approach (1.2 %) [204]. More data is needed before one can say with certainty that the anterior approach reduces dislocation rates.

Concerns have been raised with regard to the exposure attained when using the anterior approach. Femoral exposure is limited and one study noted that periprosthetic femoral fractures went unnoticed during 1.65 % of procedures utilizing the direct anterior approach [221]. The result is that the use of intra-operative fluoroscopy is recommended in some centers which has the potential to increase operative times and raises the risk of contamination of the surgical field. Additionally, specialist tables are recommended for this approach which are costly and not widely available [204].

Anterolateral

The anterolateral approach is also commonly utilized in THR. This method provides an inter-muscular plane between the tensor fasciae lata and the gluteus medius. It is important to note that both of these muscles are innervated by the superior gluteal nerve and therefore this is not a true inter-nervous approach. One study found that at a median of 9.3 months follow-up 74 % of patients exhibited either atrophy or hypertrophy of the tensor fasciae latae and 42 % exhibited fat replacement on MRI [222]. The approach begins with an incision starting posterior and distal to the anterior superior iliac spine and running distal to become centered over the tip of the greater trochanter. After incising the fascia, an interval is developed between the tensor fasciae lata and the gluteus medius. The abductor mechanism, and the reflected head of the rectus femoris are incised while the psoas

tendon is retracted after which a capsulotomy is performed and the joint visualized. The theoretical advantages of this approach include a decreased risk of dislocation owing to the limited disruption of posterior structures and good visualization of the acetabulum.

Clinical data has again failed to show clear superiority or inferiority compared with other approaches. A previously mentioned nonrandomized clinical trial comparing anterolateral and posterior hip approaches at 5 years follow-up failed to note any differences in Oxford hip scores, dislocation, or revision rates between groups [203]. A randomized clinical trial comparing anterolateral and lateral approaches found improved gait mechanics at 6 weeks post-surgery but no difference in functional outcomes after 12 weeks [223]. Other case series have shown similar results although one suggested that the risk of varus femoral stem malalignment was higher with anterolateral as compared with lateral approaches [224]. Lateral approaches are similar to anterolateral but result in a split in the gluteus medius rather than exploiting the inter-muscular plane between the gluteus medius and tensor fascia lata. Other studies noted an improvement in patient-reported outcomes such as pain and limping in patients undergoing the anterolateral approach as compared with the direct lateral approach [225]. The incidence of dislocation in a meta-analysis of studies comparing various approaches of studies was approximately 2.18 % for this approach which puts it in line with other approaches [190]. The anterolateral group showed increased range of motion as compared to the transtrochanteric approach [226]. One observational study of the Swedish Hip Arthroplasty Register noted an increased risk of revision due to aseptic loosening of THAs which were implanted using the anterolateral approach as compared with a posterolateral approach (RR 1.3 CI 1.0–1.6) [227]. Other studies have noted an increased risk for abductor muscle avulsion using this approach with a subsequent need for reattachment [228–230].

Similarly to other approaches, minimally invasive options exist for the anterolateral approach. Comparative studies of conventional versus minimally invasive options were conflicting with regard to surgical time and blood loss [231, 232]. Studies comparing functional outcomes found that during the first year after surgery, patients with the mini-incision THA had significantly better hip muscle strength, walking speed, and functional score but after 1 year, the performance characteristics studied were statistically equivalent [233–235]. A study of gait mechanics comparing direct lateral, posterior, and anterolateral approaches failed to find significant differences between groups in stride length, step length, peak hip extension, and walking speed after total hip arthroplasty at 6 weeks or 1 year after surgery [236, 237].

Studies comparing the various minimally invasive approaches (two-incision, mini- posterior, and mini-anterolateral found no difference between the three minimally invasive approaches in early hospital discharge or early functional recovery utilizing a rapid rehabilitation protocol [238]. Similarly a study comparing a mini-incision anterolateral and direct lateral approaches found differences in muscle strength recovery and blood inflammatory markers in short-term follow-up but did not find any difference in the Harris hip score, pain visual analog scale, the Western

Ontario and McMaster Universities Osteoarthritis Index, and Medical Outcomes Study Short Form 36 score between the two groups throughout the 1-year study period [239, 240].

Summary

Many approaches exist to gain access to the hip joint, with each having their own advantages and disadvantages. Some require steep learning curves and so operative results between surgeons in these approaches differ greatly. While each surgeon has their own views on each approach, the posterior approach remains the gold standard, as it is easier to master and allows for increased exposure to the hip. However it is clear that all approaches are successful in experienced hands, with surgical ability having a great effect on patient outcomes. Care must be taken to ensure that adequate exposure and familiarity to the procedure are attained so that complication risk and patient morbidity can be kept to minimal.

Conclusion

Hip reconstruction is the subject of ongoing efforts to improve clinical outcomes. It is especially challenging to improve on a treatment that has already produced excellent results. THA is successful in 85–95 % of cases. Given this finding, many will ask: why fix what isn't broken? One reason is that the surgical volume of hip replacements is staggering. Over 500,000 THAs are performed annually in the United States [241]. Even if only 5 % of these fail, the result is a significant amount of burden on the healthcare system but more importantly on those patients who are unlucky enough to have a poor clinical result. Secondly, implant failure that results in revision is costly, technically difficult, and more likely to fail than a primary procedure. Lastly, while THR is used often, there are many debilitated patients who are currently not candidates for this procedure due to their young age. Significant improvements in implant longevity can have a tremendous impact on the lives of these individuals by returning function to their joints earlier and allowing them to resume their normal way of life. Still, the multitude of new technological options that exist for total hip arthroplasty greatly exceed the evidence supporting their use. New designs should be tried but all should be tested rigorously in order to come to find the optimal combination of principal components. Lastly, despite the emphasis on technology, one of the main contributors to the success of THA is surgical ability. Component wear, soft tissue damage, and implant stability have all been shown to be affected by surgical technique. Thus, improvement in total hip arthroplasty must come from advances in implant design, biomechanics, and surgical technique.

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Chapter 12
Hip Sepsis and the Prevention of Perioperative Infections

Javad Parvizi and Fatih Küçükdurmaz

Introduction & Definition of Hip Sepsis

Total hip arthroplasty (THA) is currently one of the most frequently performed and most successful surgical procedures, greatly improving patient quality of life and functional status. However, periprosthetic joint infection (PJI) still remains as a devastating complication after THA.

The diagnosis of PJI remains challenging due to the lack of a "gold standard" and because of the infection existing in the form of a biofilm. However, in recent years much effort has been devoted to reach a standard definition of PJI. A workgroup convened by the Musculoskeletal Infection Society (MSIS) proposed a definition for PJI that has allowed the orthopedic community to use uniform criteria to define PJI. Recently the International Consensus Meeting on PJI, that convened more than 400 experts from around the world, also endorsed the MSIS definition and made slight modification [1] (Table 12.1).

The treatment of PJI often requires multiple surgical procedures and is associated with increased complications and morbidity. Prevention of PJI through implementation of effective strategies should be a priority. Several modifiable factors may influence the outcome of THA. Identification of modifiable risk factors is important, so that resources can be focused more effectively and greater attempts at risk reduction can be pursued. In this chapter the modifiable risk factors are assessed in sections of preoperative, surgical, and postoperative periods.

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Table 12.1 Definition of periprosthetic joint infection according to the International Consensus Group which is an adaptation of the Musculoskeletal Infection Society Definition of PJI

Major criteria
1. Two positive periprosthetic cultures with phenotypically identical organisms, OR
2. A sinus tract communicating with the joint, OR
Minor criteria
1. Elevated serum C-reactive protein (CRP) AND erythrocyte sedimentation rate (ESR)
2. Elevated synovial fluid white blood cell (WBC) count OR ++change on leukocyte esterase test strip
3. Elevated synovial fluid polymorphonuclear neutrophil percentage (PMN%)
4. Positive histological analysis of periprosthetic tissue
5. A single positive culture

PJI is present when one of the major criteria exists or three out of five minor criteria exist (Based on data from [1])

The Preoperative Care

Optimization of the Patient

Dental Clearance

Oral infections can harbor bacteria and serve as a source of hematogenous infection [2]. That is why active oral infections should be treated before joint replacement, and oral health should be maintained indefinitely. Because of this recognition, some authors propose routine dental screening before an arthroplasty to decrease the risk of bacteremia from the oral cavity. Some investigators have questioned the cost effectiveness of routine dental screening [3]. However, dental pathogens or procedures are responsible for only a small percentage of joint infections [4]. Barrington et al. [5] found that routine preoperative dental clearance revealed 23 % incidence of pathology, and none of these patients with pathology developed subsequent PJI. In addition, there is no official recommendation from the American Academy of Orthopedic Surgeons (AAOS) regarding dental clearance prior to TJA to prevent PJI [6].

Therefore, some authors advocated selective dental clearance prior to TJA based on patient profile. The risk factors that are associated with dental pathology are tobacco use, poor flossing habits, history of tooth extraction, older age, narcotic use, and lack of a dentist visit within 12 months [7]. As a result, surgeons must exercise their own clinical judgement in determining whether or not a dental clearance is necessary regarding the risk factors.

MRSA Decolonization

Studies have shown that the anterior nares are the most consistent site of reservoir for *Staphylococcus aureus* and high-level nasal carriage of *S. aureus* is an important risk factor for subsequent surgical site infection (SSI) [8]. Studies have attempted to

identify risk factors associated with nasal carriage of *S. aureus*. Male gender, obesity, a history of a cerebrovascular accident, multiple hospital admissions, and having a pet at home have all been identified as predisposing factor for *S. aureus* nasal carriage [9].

Three types of patient population with regard to *S. aureus* nasal carriage have been identified: persistent carriers, intermittent carriers, and non-carriers. Between 10 and 35 % of healthy individuals are thought to be persistent carriers as one or more strains of *S. aureus* are isolated from their nares [10]. Persistent nasal carriers are in particular risk of subsequent SSI [11].

Current literature supports the practice of screening for nasal carriers of *S. aureus* followed by decolonization with intranasal mupirocin and chlorhexidine gluconate (CHG) baths which has been shown to be associated with a decreased incidence of MRSA colonization and disease [12, 13]. There are, however, some logistic issues associated with this practice. The Center for Disease Control, in their revision of the SSI guidelines decided to table the issue of MRSA screening and decolonization because of the current issues surrounding this practice. One of the issues relates to the emergence of resistance to mupirocin that appears to be on the rise. Another issue relates to the recurrence or persistence of *S. aureus* in patients who have undergone decolonization [14]. The International Consensus group on PJI did also recognize the fact that screening and decolonization for MRSA leads to a lowering of SSI but did not endorse universal practice of screening in patients undergoing TJA because of the issues that have been highlighted previously.

Tobacco & Alcohol

Smoking is considered as one of the important modifiable risk factors for SSI. Smoking impairs the oxygenation of the surgical site due to nicotine-induced vasoconstriction, shift of oxyhemoglobin dissociation curve, and microthrombus formation by abnormal platelet aggregation.

Smoking is associated with postoperative morbidity and mortality. An effective smoking cessation program led to a fewer wound healing complications and postoperative morbidity [15, 16]. Although current smokers are under a higher risk, any history of smoking increases the risk of overall postoperative complications [16]. In a review that included total of 21 studies comparing nonsmokers to current smokers and former smokers found 24 % and 32 % higher risk of any postoperative complication in smokers after TKA or THA, respectively [17].

It is therefore paramount to encourage patients to halt smoking prior to undergoing TJA. The optimal time for cessation of smoking is not known but recommended to be at least 4–8 weeks prior to surgery. But each additional week of smoking cessation before the operation has a significant impact on the reduction of postoperative complications [18]. Also there is no consensus as to what constitutes as heavy smoking. It is, however, known that smoking more than one pack per day is significantly associated with PJI and other postoperative complications [19]. Thus, all efforts should be made to have all heavy smokers evaluated well in advance of TJA and cessation of smoking exercised at least 4–6 weeks prior to elective arthroplasty [20, 21].

An increased risk of postoperative complications, such as delirium, pneumonia, cognitive decline, and death has been linked to alcohol consumption [22, 23]. It was also shown that patients who discontinue drinking for 4 weeks prior to surgery have substantially reduced risk of postoperative complications [24]. Thus alcohol cessation before elective arthroplasty needs to be in place. If patients cannot stop alcohol consumption prior to surgery, a reduction in alcohol consumption should be attempted [25].

Diabetic Patients

Patients with diagnosis of diabetes mellitus (DM) are at an increased risk of adverse perioperative outcomes following total joint arthroplasty [26]. In addition, strict glycemic control (HbA1C levels <7 %) is associated with a decrease in infectious complications across a variety of surgical procedures [27].

As conflicting results are presented regarding the effect of the type of DM (IDDM vs NIDDM) in the surgical outcome [26, 28], additional studies are necessary to evaluate the effect of diabetes type on perioperative morbidity in patients managed with arthroplasty. Regardless of the diabetes type, patients with uncontrolled DM exhibit significantly increased odds of surgical and systemic complications, higher mortality, and increased length of hospital stay following lower extremity total joint arthroplasty [26]. Thus, preoperative optimization of patients with uncontrolled diabetes and strict glycemic control after arthroplasty are extremely important in minimizing the postoperative complications in general and PJI in particular.

Although the increased prevalence of adverse perioperative outcomes in patients with diagnosis of DM have been demonstrated indefinitely, the risk of uncontrolled or poorly controlled hyperglycemia in previously non-DM patients undergoing total joint arthroplasty has been unappreciated and underestimated. Stress-induced hyperglycemia is activated by the hypothalamic–pituitary axis in patients without a diagnosis of DM after major surgery and trauma. Hyperglycemia occurs in up to two thirds of surgical patients who are not known to have diabetes [29, 30]. And as glycemic control appears to be critical in patients undergoing total joint arthroplasty, a special attention should also be paid to non-DM patients for better control of postoperative glucose [31, 32]. Frisch et al. [33] found even an increased risk of 30-day mortality associated with hyperglycemia in non-DM patients when compared with those with well-controlled diabetes [30].

Liver and Kidney Disease

Patients with chronic liver failure undergoing major orthopedic procedures including hip surgery, spine fusions, and operations for long bone fractures have been shown to have a substantially higher incidence of perioperative complications and in particular infection [34].

The pathogenesis of increased incidence of infection in patients with chronic liver disease is likely multifactorial and related to:

1. An impaired removal capacity of the reticuloendothelial system, a consequence of hepatic failure.
2. A deficient neutrophil recruitment
3. An altered phagocytic activity of neutrophils and macrophages [35–37].

Beside the increased risk for infection, the success of surgical treatment of PJI in patients with chronic liver failure is reported to be poor. Hsieh et al. [37] reported a very high failure of two-stage exchange arthroplasty in ten patients with infection after THA. The authors recommended that the very high failure rate in these patients needs to be borne in mind when counseling these patients [37].

The mortality of patients with chronic liver failure is also reported to be high in patients undergoing non-hepatic surgery [38] including THA [39]. In a study by Cohen et al. the postoperative mortality was reported to be 15.8 % in patients with chronic liver failure who underwent THA.

The extent of hepatic dysfunction was the most important factor contributing to the development of infection in cirrhotic patients [40]. The risk of increased mortality was to a large extent determined by the preoperative Child-Turcotte-Pugh score [39, 41] (Table 12.2). Patients with Child's B and C class were found to have a significantly higher incidence of postoperative complications at 52.9 % compared to 10.2 % in patients with Child's A disease [39]. In addition, international normalized ratio (INR) greater than 1.6, presence of encephalopathy and prolonged prothrombin time were reported as poor prognostic factors [32, 36]. Because of these discoveries, some authors recommend aggressive correction of prolonged prothrombin time before surgery in order to avoid excessive bleeding [37].

The number of cirrhotic patients who need total joint arthroplasty will increase with improvement in the medical care of these patients in future [37]. The surgeons should be aware of the increased complications in these patients. The orthopedic surgeons should seek contact with the hepatologist caring for these patients prior to arthroplasty in an attempt to optimize their medical condition as much as possible. Patients should also be carefully monitored in the postoperative period with focus on minimizing complications such as infection, bleeding, and hepatic decompensation [39]. Patients with a higher Child-Turcotte-Pugh score should in particular be watched vigilantly and perhaps not subjected to elective arthroplasty if at all avoidable [42].

Patients with chronic renal failure (CRF) are also at risk of increased postoperative complications. Although there are some encouraging reports [43–47] patients with CRF who are on dialysis or received renal transplant undergoing THA had a relatively higher overall risk of developing early and late postoperative infection compared to patients without CRF. The risk of infection is particularly high in patients receiving hemodialysis [47–51]. Most of the CRF patients may also be carriers of MRSA and should receive an additional perioperative antibiotic, such as vancomycin, with activity against MRSA [46].

Table 12.2 Child-Turcotte-Pugh class

Measure	1 point	2 points	3 points
Total bilirubin [μmol/l (mg/dl)]	<34 (<2)	34–50 (2–3)	>50 (>3)
Serum albumin (g/dl)	>3.5	3.5–2.8	<2.8
PT INR	<1.7	1.71–2.30	>2.30
Ascites	None	Mild	Moderate to severe
Hepatic encephalopathy	None	Grade I–II (or medically controlled)	Grade III–IV (or refractory)

The exact reason for the increased risk of postoperative complications and in particular infection in patients with CRF remains unknown but attributed to a variety of factors, most of which relate to having a chronic disease state. For example, patients with CRF are usually anemic and may be in need of blood transfusion that by itself, and through immunomodulation, increases the risk of postoperative infection [46, 52, 53]. Patients with CRF also have a compromised immune system with impaired neutrophil function that can place them at higher risk of infection. Because of the higher risk of infection in patients with CRF, some authorities have advocated that femoral component fixation should be performed with antibiotic impregnated cement. Current literature does not, however, prove superiority for one mode of implant fixation in these patients [46, 53, 54].

THA in CFR patients can be considered a reliable surgical option with the awareness of the relatively high rates of early and late complications. Thus, elective arthroplasty must be performed within the framework of careful multidisciplinary patient management.

Inflammatory Joint Disease (IJD)

This group includes patients with rheumatoid arthritis (RA), juvenile inflammatory arthritis, and spondyloarthritis such as ankylosing spondylitis and psoriatic arthritis (PA). This patient population have been identified to have a higher baseline risk of infection compared with the general population [55].

In addition to the immune modulating effect of the disease itself, most of these patients who are on disease-modifying anti-rheumatic drugs (DMARDs) may be at added risk of infection [56]. The most commonly used medications are synthetic DMARDs such as methotrexate, hydroxychloroquine, and leflunomide; corticosteroids; and biologic agents, including the TNF blocking agents. As a general rule, disease-modifying agents should be stopped before the elective TJA. The cessation of these drugs should be performed in consultation of rheumatologist that can be arranged based on the specific medication and the individual patient. The International Consensus Group of PJI has proposed a drug cessation protocol based on the half-life of these biological drugs.

Rheumatoid Arthritis (RA)

According to the Scandinavian arthroplasty registry, 3–15 % of all prosthetic hip and knee replacements was performed in RA patients [57]. Patients with RA who undergo total hip or knee replacement are at increased risk of prosthetic joint infection due to the nature of the disease and because of receiving biological disease-modifying antirheumatic treatment [58]. The SSI rate among RA patients was found to be two to four times higher than in those with osteoarthritis [59]. Revisions have even higher risk, as expected, two-stage exchange (21 %) and resection arthroplasty (39 %) considerable risk of re-infection in this patient group [60]. In a mixed cohort of patients 9–14 % re-infection was reported after two-stage reimplantation [59, 61].

Psoriatic Arthritis

The diagnosis of psoriatic arthritis also places patients at increased risk of perioperative infection. SSI has been reported to be between 9 and 17 % in patients with psoriatic arthritis [55]. The main issue in patients with psoriatic arthritis is the presence of skin lesions. Although complete clearing of skin lesions is not always possible, it is advisable to optimize the condition of the skin, given the high level of bacterial colonization of psoriatic plaques. Colonization of the skin plaques with staphylococcal species has been confirmed, and more strikingly, enteric gram-negative organisms and Bacteroides species have also been seen to predominate the lesions present on the lower extremity and buttock region [62].

Because of the increased risk of infection, performing elective arthroplasty in patients with active and aggressive psoriatic arthritis and skin lesions is deemed to be inappropriate. The majority of these patients need to be treated for their psoriasis with the goal of eliminating or controlling the skin lesions prior to elective arthroplasty. It is agreed that incisions should not be placed through active skin lesions [63].

Although an antibiotic prophylaxis before dental procedures is not recommended in otherwise healthy patients, IJA patients are recommended to receive lifetime dental antibiotic prophylaxis after TJA, because they are immunocompromised and/or immunosuppressed and this places them at high risk of hematogenous infection.

The appreciation of significantly higher risk of PJI in patients with IJA by using all possible pre- and postoperative prophylactic interventions may help to reduce the infection rates in this high-risk group [59]. This includes proper timing of surgery, cessation of DMARDs, proper skin preparation, and antibiotic prophylaxis. Although there is no clear evidence, routine use of antibiotic-laden cement for fixation in IJA patients may be justified.

Anemia

The incidence of preoperative anemia in patients undergoing elective orthopedic procedures is reported to be as high as 35 % [64]. Preoperative anemia has also been shown to be an independent risk factor for PJI [65]. Patients who are anemic

preoperatively are expected to experience worsening of their anemia in the postoperative period due to surgical blood loss. Thus efforts should be made to treat preoperative anemia, if possible, that can then reduce the need for postoperative blood transfusion [66]. However, the first step in patients without an obvious cause for anemia should be the investigation for a possible primary etiology.

There are some treatment options for anemia such as autologous blood donation, iron replacement, and administration of erythropoietin (epoetin alfa). Autologous blood donation has well-known disadvantages including storage problems, increasing postoperative anemia and transfusion [67], transfusion reactions and, last but not least, contamination of the donated blood with blood-borne pathogens, either bacterial or viral [68]. Iron and erythropoietin treatments are safer strategies. The treatment of preoperative anemia with iron, with or without erythropoietin, was found to reduce the risk of transfusion in patients undergoing TJA [69].

Malnutrition

Although malnutrition has been understood as inadequate nutrition, according to the definition of the World Health Organization, under-nutrition, obesity, micronutrient deficiency are all different forms of malnutrition [70].

Malnutrition was found to be another common risk factor for SSI. Previous studies have found a close association between malnutrition and PJI [71, 72]. Malnutrition is defined as a serum total lymphocyte count <1500 cells/mm^3, a serum albumin concentration of <3.5 g/dl, low serum prealbumin and serum transferrin levels <200 mg/dl [72–74].

Malnutrition is thought to predispose patients to SSI by impairing wound healing, persistent wound drainage, inability to eradicate microorganisms and prolonging inflammation via several mechanisms, decreasing lymphocyte count, including impaired fibroblast proliferation and collagen synthesis [72, 75–77].

Thus screening patients contemplating elective arthroplasty may be a worthwhile endeavor. Patients with obesity, history of extreme weight loss, poor nutritional habits are in particular risk of malnutrition. The workup for malnutrition involves obtaining preoperative biochemical profile of the blood and complete blood counts with differential. Additional blood tests such as transferrin can also be ordered. Patients with malnutrition should be seen by nutrition specialists for possible nutritional optimization. As the malnutrition is a correctable risk factor, postponing the elective surgeries is strongly recommended until the patient's malnutrition has been corrected.

Obesity is a different form of malnutrition that affects more people compared to other forms of nutritional problems in developed countries. Approximately one-third of patients undergoing THA are obese [78, 79]. These patients must be aware of the higher complication rates before undergoing TJA. Patients with a BMI≥50.0 kg/m^2 reportedly have an 18.3 times higher odds of infection compared with non-obese [20].

The reason for increased risk may be related to an increase in operative time, greater need for allogeneic blood transfusion, presence of other comorbidities, traumatic tissue retraction, and increased risk of poor wound healing in the obese patients [18, 23]. Elective arthroplasty in morbidly obese patients with BMI≥40.0 kg/m^2 also significantly increases the risk of infection [80].

In some recent studies, the safety of weight loss is questioned which raise concerns for preoperative malnutrition as discussed later in this chapter [71, 81]. In the study of Inacio et al. patients who lost weight before a total hip replacement and kept it off post-operatively had a 3.77 times greater likelihood of deep SSIs compared with the reference group [81]. These findings emphasize the critical importance in respecting the balance between malnutrition and weight loss.

Another issue about obese patients is the preoperative dose adjustment of prophylactic antibiotics. Because of the relative unpredictability of pharmacokinetics in obese individuals, some antibiotics require adjustment based on patient weight in order to avoid under dosing of the preoperative prophylactic antibiotics [82–84]. The AAOS recommends to double the dose of cefazolin for patients >80 kg in IV antibiotic prophylaxis in primary TJA to optimize the efficacy of the therapy of antibiotic administration [85].

Prophylactic Perioperative Antibiotic

There are a number of studies that validate the importance of the preoperative dose of antibiotics in decreasing PJI and SSI in TJA. The goal of administering preoperative antibiotics is to allow for adequate tissue (blood, soft tissue, and bone) concentrations above the Minimal Inhibitory Concentrations (MIC) before surgical incision [86]. The optimal prophylactic antibiotic should be bactericidal (penicillin, cephalosporin, vancomycin, or aminoglycosides), and not simply bacteriostatic such as clindamycin.

In the current literature, a first or second-generation cephalosporin (cefazolin or cefuroxime) is recommended for routine perioperative surgical prophylaxis. Also isoxazolyl penicillin, such as cloxacillin, flucloxacillin, nafcillin, or oxacillin, can also be used. These have excellent distribution profiles in bone, synovium, muscle, and hematomas [87].

In a patient with a known allergy to penicillin, vancomycin or clindamycin is found to be effective agents for prophylaxis. However, vancomycin should not be used as a routine agent for prophylaxis, because of concern for emergence of resistance and also efficacy. Vancomycin is an inferior antibiotic against methicillin-sensitive staphylococcal species when compared to cephalosporin [86, 87]. Vancomycin should be reserved as a prophylaxis for patients with known colonization or infection with MRSA or in facilities with recent MRSA outbreaks [88, 89].

In surgical practice, there is a considerable variation in the timing of administration of prophylactic antibiotics. Some studies suggest that administration of antibiotics

within 2 h or [90] 1 h of incision is more effective [91] while others suggest an administration within 30 min prior to making the incision [92]. The timing of antibiotic administration depends largely on the type of antibiotic used [93, 94]. The preoperative dose of antibiotics should be administered within 1 h of surgical incision; this can be extended to 2 h for vancomycin and fluoroquinolones [89].

Prolonged postoperative antibiotic prophylaxis beyond 24 h has been found to have no additional benefit and possibly be harmful because of the possible added antimicrobial toxicity, potential for emergence of resistant organisms, and additional expense [95]. Thus, there is a good consensus in practice that recommends cessation of postoperative antibiotic within 24 h after surgery [89].

An additional intra-operative dose of antibiotic has been shown to reduce SSI rates after two half-lives of the prophylactic agent due to the reason mentioned above in this chapter [96]. This application was suggested in cases with large blood volume loss (>2000 cc) or high volume of fluid resuscitation (>2000 cc).

Preoperative Patient Hygiene

A whole body skin cleansing at-home one night before surgery appears to be a simple and cost-effective method to reduce PJI rates [97]. Also patients are advised to sleep in clean garments and bedding without the application of any topical products [63]. Although local body cleansing around the surgical field is an option, Wihlborg et al. demonstrated that preoperative whole body disinfection with chlorhexidine soap was significantly superior in reducing SSI to that of local washing and no washing at all [98].

The Surgical Factors

The Operating Room

Air Quality

The airborne transmission of bacteria within the operating room (OR) environment is perhaps the major cause of contamination of the wound during total joint arthroplasty and subsequent SSI [99]. There are mainly two routes of airborne bacteria. First is the direct contamination of the wound that occurs when airborne particles directly drop into the wound. Second is the indirect contamination, in which the airborne bacteria settle on sterile surfaces around the wound and then transferred into the wound via the surgeon's hands or the surgical instruments [100]. A study demonstrated that 70 % of contaminations are as a result of indirect fall out and 30 % from direct contamination by the way of the hands and instruments that are placed into the wound [101].

The number of airborne bacteria around the wound is correlated with the incidence of subsequent PJI [100]. The air quality is also affected by the traffic in the OR, as described in the next section of this chapter. In recent years many attempts have been made aimed at improving the air quality of the OR environment. Laminar flow is one of the most popular methods that aims to accomplish this objective. The efficacy and importance of laminar flow has been recently questioned. In fact the evidence seems to point to the contrary. A study using the New Zealand registry data has shown that the incidence of PJI was higher after THA that were performed in a laminar flow room [102]. At this point the efficacy and importance of laminar air flow in reducing SSI and PJI remains unproven.

Another strategy to improve the air quality in the OR related to the use of ultraviolet lighting. The rates of SSIs were reduced with the use of ultraviolet lighting in the operating rooms [103]. There is a major issue with the use of UV lighting in the OR, the most important of which relates to the hazard that UV may impart on the personnel present. In one study the exposure to ultraviolet lighting in the operating room was found to be 6–28 times greater than the recommended limits [104]. Another study demonstrated that 36 % of orthopedic operating-room personnel exposed to ultraviolet light reported eye and skin related symptoms due to the excessive exposure. Because of the safety concerns, the U.S. Centers for Disease Control and Prevention recommended against the routine use of ultraviolet lights in the operating rooms [105–107].

Surgical Team

An ongoing debate currently relates to the optimal surgical attire of the surgeon and the scrubbed personnel. In orthopedic surgery space suits have been used for many years. There is no conclusive evidence that proves the efficacy of the space suits in reducing SSI [108]. One study analyzing the 10-year results of 88,311 THAs or TKAs from the New Zealand Joint Registry demonstrated that the rate of revision for early deep infection has not been reduced by the use of laminar flow operating rooms and the space suits [109]. A recent study by Kapadia et al., in fact detected a higher infection rate with the use of laminar-flow operating rooms and body exhaust suits [110]. Also Hooper et al. [109] studying the rate of early infection identified an increased rate of early infection with the use of space suits both in conventional and in laminar flow theaters.

Another ongoing debate relates to what constitutes the most optimal antiseptic agent for skin preparation and hand washing prior to TJA. In a Cochrane Database review by Tanner et al. there was no significant difference among various antiseptic agents for hand scrub. Another issue relates to the optimal time for hand washing and skin preparation. Currently hand washing with a soap and antiseptic agent for a minimum of 2 min prior to surgery has been recommended [63].

The hospital and surgeon volume is also considered an important factor in influencing SSI rates. There is a reverse relationship between the rate of complications

and the surgical volume. The reason for this finding may relate to the fact that high volume surgeons may have an efficient protocol in place that minimized the risk of SSI and may be more expedient in executing the surgery [111]. No significant association was found between hospital volume and the rate of revisions of THAs. But the type of hospital was found to be associated with revision rates, non-teaching hospitals tended to have a higher revision risk, while nonprofit hospitals tended to be associated with a lower revision [112].

Room Traffic

The personnel are the major sources of bacteria in the OR. The amount of bacteria falling into the open wound is increased as the number of people in the room increases and the longer the wound is open [101]. It has been shown that an individual emits a few hundred-thousands of airborne particles carrying bacteria while wearing sterilized clothing in the operating room [113]. Also opening and closing of the OR doors can generate significantly marked air currents and subsequently reduces the quality of the OR air. Beside the traffic and the number of people present in the OR, a further finding suggests that there is a direct correlation between the activity level of OR personnel and the bacterial counts in the OR air [114, 115].

Thus, every effort should be made to minimize the number of personnel in the operating room and strictly control the OR traffic. In addition to limiting the OR traffic consideration should be given to the use of a sub-sterile hallway for entry and exit from the OR that helps improve the quality of room air. One strategy that helps reduce the OR traffic involves storage of implants and commonly used instruments inside the operating room. In addition the education of the personnel regarding the importance of keeping the traffic to a minimum is likely to help reduce bacterial counts in the OR environment.

Skin Preparation

Hair Removal

Clipping, as opposed to shaving, should be the preferred method for hair removal, when needed. Using razor may cause superficial skin abrasions or irritation and expose the bacteria from the deeper layers leading to a potential infection. A recent systematic review of randomized and quasi-randomized controlled trials showed that hair clipping lowered the rate of SSI when compared to shaving [116].

There is currently no evidence in the literature that shows the most appropriate setting and time in which to remove hair from the surgical site. Given the overall lack of research specific to the environment in which preoperative hair removal should take place, we recommend that hair removal be performed in the hospital as

close to the time of surgery as possible by either the surgical team or the trained nursing staff. Most surgeons prefer to perform hair removal prior to arrival of the patient in the OR to avoid having hair clipping around the surgical site.

One study investigated the effects of hair removal the night before surgery compared to hair removal on the day of surgery and found that clipping on the morning of surgery was associated with a lower SSI rate [117]. As a result, the preoperative hair removal, only those interfere with the incision, should be performed immediately prior to the operation and preferably with electric clippers [108].

Scrub Solutions

There are no prospective randomized studies comparing skin preps in patients undergoing TJA. The current literature provides conflicting results as to whether CHG or povidone-iodine provides superior skin antisepsis and lowers the rate of SSI. A study showed significant reduction in the rate of SSI when CHG in alcohol was used compared to aqueous povidone-iodine scrub and paint [118], while other found that when alcohol was used with povidone-iodine had a lower rate of SSI [119]. Sistla et al. [120] could not show a difference in the rate of SSI between patients prepped with either CHG or iodophors. What is clear is that alcohol should be part of any skin preparation. Alcohol is used as an antiseptic because of its rapid antimicrobial action. Thus, combination of antiseptic agents that contain alcohol is likely to be more effective and should be used. A Cochrane systematic review of published reports found that alcohol-containing products were most effective [121]. So in conclusion, while there is no clear evidence of superiority of CHG over iodine-based antiseptics, it is suggested that whichever agent is chosen, it should be dissolved in alcohol [63].

Draping

Incise drapes are intended to provide a sterile barrier between surgical site and the host flora during surgery [122–125]. There are some studies showing the decrease in recolonization of skin flora when impregnated incise drapes were used [126, 127]. Use of adhesive incise drapes impregnated with iodine should be avoided in patients with systemic or topical allergy to iodine.

Adhesion of drape and skin is important to minimize drape lifting. It has been shown that the lifting of drapes from the skin was associated with a significant increase in the infection rate compared with surgical procedures in which the incise drape was not lifted [128].

Although the studies demonstrating the decrease in contamination of the wound and recolonization of skin justifies the use of incision drapes, there are no high level studies to support this practice. There are a number of randomized prospective studies being conducted at this point which may provide better insight in the future.

Surgery

Implant/Fixation Method Selection

Data from the Norwegian registry showed that in over 97,344 primary THAs performed from 1987 to 2007, the 5-year revision rate due to deep infection was 0.54 % [129]. When compared to antibiotic-laden cemented fixation, both uncemented and cemented without antibiotics fixation had a higher risk of revision due to infection. A prospective study from Norwegian health registry comprising the period 2005–2009 reported the rate of SSI as 3 % in THAs and was not influenced by the type of fixation (cemented, uncemented, or hybrid). On the other hand, the rate of revision due to infection was 0.8 % and was influenced by the type of fixation. Cemented hips had a lower adjusted risk of revision compared to uncemented hips due to infection while the rate was the same in hybrid and cemented fixation arthroplasties. One has to keep in mind that, in Norway, nearly all cemented THAs are fixed with antibiotics-laden cement [57].

A study by the Nordic Arthroplasty Register Association (Denmark, Finland, Norway, and Sweden) stated that the implant-related risk factors that increase the relative risk of revision due to infection were hybrid fixation and fixation with plain cement [130].

A Cochrane review comparing hemiarthroplasty and hydroxyapatite-coated hemiarthroplasty for proximal femur bone fractures in adults found no difference in the rate of superficial or deep infections between the two groups [122].

Postoperative Care

Blood Management

Numerous studies have shown that allogeneic blood transfusion increases the risk of SSI through the mechanism of immunomodulation. Perioperative allogeneic transfusion was found to be associated with a higher rate of revisions for acute infection. In the same study of Newman et al., after adjustment for the total number of units transfused and an ASA score of >2, allogeneic exposure was not significantly predictive of a reoperation for infection, because patients with allogeneic exposure had already increased risk factors for infection [123]. Moreover, not only the wound infection rates but also lower or upper respiratory tract and lung infection were significantly increased after elective total hip or total knee arthroplasty in patients receiving allogeneic blood transfusion or no blood transfusion [124].

Wound Care

Suction Drain

There is ample evidence to suggest that routine use of surgical drains during TJA may not be indicated. A Cochrane review of 5697 patients undergoing various surgical procedures including hip and knee replacements was performed. Pooling of the data indicated no statistically significant difference in the incidence of wound infection, hematoma formation, wound dehiscence or re-operations between those who received drains and those without drains. However, the patients who received drains required more blood transfusions and the patients without drains needed more wound dressing reinforcement and were more likely to develop lower extremity bruising [125].

One of the concerns regarding the use of drains relates to the potential for contamination of drain tips and subsequent infection. A prior study examining the tip of a drain showed evidence of contamination between 41 and 54 % [131, 132]. Although there is evidence indicating that the tip of surgical suction drains can be a potential source of contamination, these results could not be able to correlate with a subsequent SSI/PJI.

Wound Closure

Complications associated with wound closure, such as delayed healing or infection may prolong recovery, resulting in increased morbidity, delayed discharge, increased costs, and reduced patient satisfaction [133]. However, there is lack of evidence supporting the superiority of one method over others for wound closure. In one study no significant difference was found between the outcomes of skin closure using an adhesive or staples in terms of cosmetic appearance of scars at 3 months, the occurrence of complications, or patient satisfaction. Closure with staples was quicker and less expensive than using adhesive [133].

In recent years, barbed sutures have been introduced for wound closure. A few studies evaluating the use of this technology have been conducted. One study by Ting et al. stated that the use of barbed sutures are likely to reduce operative time and may translate to potential for costs savings [134]. Another study found 9.72 min decrease in operative time with an average of $549.59 less cost for wound closure when barbed suture was used. However, an increased frequency and severity of wound complications were detected with the use of barbed sutures [135].

At this point the best method of wound closure remains unknown with all modalities being acceptable. There is no evidence to suggest that one method of wound closure leads to a higher incidence of SSI. One common practice that is based on some evidence is the use of monofilament sutures for closure of wound in patients with infection or undergoing reoperation, as monofilament sutures are believed to be less susceptible to bacterial growth and potential for subsequent infection [136].

Dressing

There is ample evidence to link wound related problems to a subsequent infection [137]. Thus, any effort that optimizes wound healing and prevents wound related complications is likely to reduce the incidence of SSI. An ongoing debate relates to what constitutes as the most optimal dressing for patients undergoing THA.

There are numerous available wound dressings that include materials such as passive fabric-based products, interactive vapor-permeable films, films plus fabric, hydrocolloids or hydrofiber dressings. The optimal dressing for wound after THA is believed to be one that allows for join movement without causing blistering. In addition, in recent years evidence has been mounting to suggest that occlusive dressings may result in lowering of SSI. An occlusive dressing placed on the wound in the operating room under sterile conditions and kept for a few days without regular wound inspections or dressing changes is believed to allow for better fibroblast proliferation and healing. In addition, the occlusive dressings may be more effective in preventing wound contamination during the early period of healing. In recent years the orthopedic community has been moving towards the use of occlusive dressings, particularly hydrofibers with silver impregnation, which appears to provide better wound care [138].

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Chapter 13
Venous Thromboembolism in Total Hip Arthroplasty

Jay Lieberman and Jessica Bear

Introduction

With the high prevalence of osteoarthritis and the aging population, surgery about the hip is becoming exceedingly more common particularly total hip arthroplasty. Despite growing advances in surgical techniques and technologies, complications do arise, one of the most common being venous thromboembolism (VTE). Although the signs and symptoms may be subtle, the consequences can be fatal. In this chapter, we will discuss the prevention of VTE and its sequelae, as well as the diagnosis and treatment of venous thromboembolic events.

Epidemiology

Venous thromboembolism is a national health concern resulting in significant morbidity and mortality. Pulmonary embolism is not only the third most common cause of hospital-related death, it is also the most common preventable cause of hospital-related death [1–3].

While the numbers vary considerably among different population groups, the incidence of deep vein thrombosis (DVT) is reported to be between 43.7 and 145.0 per 100,000, and the annual incidence of pulmonary embolism is estimated to range

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Table 13.1 Risk factors for venous thromboembolism

Genetic hypercoaguable states (Factor V Leiden deficiency, Protein C or S deficiency, lupus anticoagulant, thrombophilias)
History of prior DVT and/or PE
History of prior congestive heart failure, myocardial infarction, and/or stroke
Advanced age
Obesity
Smoking
Major or minor trauma
Pregnancy
Oral contraception
Malignancy
Prolonged immobilization
Recent surgery or hospitalization within 3 months

from 20.8 to 65.8 per 100,000 [4–6]. Some orthopedic patients are at significant risk of developing VTE. In patients who undergo total knee or hip arthroplasty this risk is particularly high, with studies demonstrating a risk of DVT of 3–12 %, and risks of fatal pulmonary embolism of 0.1 %, despite thromboprophylaxis [7–11]. The vast majority of the DVTs arise in the lower extremities, with only 4 % affecting the veins of the upper extremities [12]. Multiple hereditary and acquired factors have been associated with an increase risk of developing thrombosis, as seen in Table 13.1 [8, 13–17].

Pathophysiology

In order to understand the diagnosis and treatment of VTE, it is important to first understand how and why clots are formed. This begins with an appreciation of Virchow's triad: blood flow (stasis), blood vessel wall (endothelial damage), and blood clotting components (hypercoaguability). Thrombus formation occurs when there are abnormalities involving one or more of these elements, resulting from either hereditary or acquired factors. This leads to an imbalance in the normal homeostasis that exists between clot formation and degradation [18, 19].

Thrombi formation begins at a location with vessel damage and stagnant blood flow. Reduced blood flow in combination with the avascular nature of venous valves predisposes the epithelium at these sites to hypoxic damage [20]. This insult to the tissue then attracts tissue factor and activated factor VII, initiating the coagulation cascade, seen in Fig. 13.1. Red blood cells, and to a lesser extent platelets, become entrapped within the fibrin clot that forms as the product of the coagulation cascade [21].

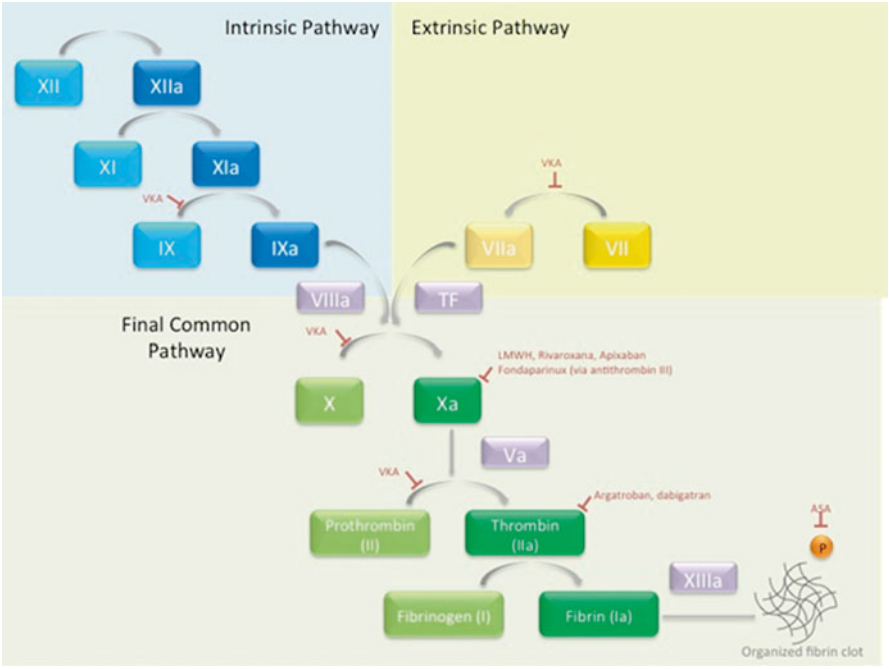

Fig. 13.1 Depiction of the coagulation cascade (*VKA* vitamin K antagonist, *LMWH* low molecular weight heparin, *P* platelets, *TF* tissue factor)

Once a thrombus has formed, the process of degradation begins. Fibrinolysis can lead to complete or partial resolution of the clot by converting plasminogen to plasmin, an enzyme that breaks down fibrin. If partial resolution occurs, one of three outcomes can ensue: clot organization, extension, or embolization. During *organization*, inflammatory cells cause remodeling and incorporation of the clot into the vessel wall. This allows for continued blood flow, but also, leads to scarring, damage to the venous valves, and venous reflux disease, which is associated with edema and varicose veins. This can result in chronic venous insufficiency or post-thrombotic syndrome [21]. Clot *extension* occurs as the thrombus propagates proximally, in the direction of blood flow. Traditionally it was thought that *embolization* occurred when a clot in the lower extremity migrated to the pulmonary arteries causing a pulmonary embolism [22]. However, this has become a point of contention, due to numerous studies demonstrating a low percentage of DVTs in patient with pulmonary embolism, leading to the argument that pulmonary embolism may in fact originate de novo in the lungs [23–25]. There is agreement that an embolus can obstruct the pulmonary bed and both respiratory and hemodynamic consequences can occur. The severity of the pulmonary embolism depends on a number of factors including the size and number of emboli, the underlying condition of the lungs, and the body's ability to respond to the insult. This can result in hypoxemia, pulmonary hypertension, right-sided heart failure, and even death [13].

Prophylaxis

Because VTE can have fatal consequences, and orthopedic patients are at a considerable risk, it is well accepted that patients undergoing surgery about the hip should receive some form of prophylaxis. A number of methods are used, including both mechanical and pharmacologic agents. The selection of which prophylactic agent to use is a balance between efficacy and safety.

Mechanical Prophylaxis

Intermittent pneumatic compression devices, which can be applied to the feet or calves, act by increasing venous return and decreasing stasis. There has been some evidence to support that they additionally stimulate fibrinolysis, although the clinical significance is still uncertain [26]. The benefit of compression devices is they do not carry the risk of bleeding that the pharmacologic agents do, however, the efficacy is dependent on patient compliance and appropriate usage. Therefore, it is essential that the patient and the nursing staff are educated regarding the importance of, and appropriate use of such devices [27]. Additionally, a recent study evaluated the efficacy of a portable compression device for home use following hospital discharge for a minimum of 10 days. This registry study demonstrated a non-inferior risk of symptomatic VTE when mechanical compression was used alone or in conjunction with aspirin when compared to multiple pharmacologic agents, including warfarin and enoxaparin [28].

Graduated compression devices are a second method of providing mechanical means to reduce stasis, and do so by creating a pressure gradient between the distal and proximal veins [29]. Although used commonly in addition to pneumatic compression and/or chemoprophylaxis, there is currently no data to support their use as an independent method of prophylaxis.

Another method of mechanical prophylaxis is the inferior vena cava (IVC) filter. IVC filters are metal implants that are inserted percutaneously, into the IVC, and act as a barrier to blood clots, while their porosity allows for continued blood flow. However, placement of the filters does carry risks, and this must be weighed against the benefits when determining their role in prophylaxis. In general, filter use is considered only in high-risk patients in which chemoprophylaxis is contraindicated, despite prior history of DVT and/or pulmonary embolism [30].

Chemoprophylaxis

Many pharmacological agents are now available for DVT prophylaxis (Table 13.2).

Aspirin, an antiplatelet agent, has been investigated in the prevention of VTE, due to its ease of administration and lack of required monitoring. The Pulmonary Embolism Prevention trial, a randomized control trial, evaluated the use of asprin

Table 13.2 Anticoagulation agents

	Advantages	Disadvantage
Aspirin	Oral, no monitoring needed	More data needed
Warfarin	Oral, ability to titrate, reversible	Frequent monitoring required, food/drug interactions
Low molecular weight heparin	No monitoring required	Subcutaneous, bleeding risks
Unfractionated heparin	No monitoring required	Subcutaneous, frequent dosing, risk of HIT
Fondaparinux	No monitoring required	Subcutaneous, bleeding risk
Rivroxaban	Oral, no monitoring needed	Ideal timing of administration unknown, bleeding risk
Apixaban	Oral, no monitoring needed	No FDA approved, bleeding risk
Dabigatran	Oral, no monitoring needed	Few studies

compared to placebo following both hip fracture surgery and hip arthroplasty [31]. Although aspirin was shown to decrease the rates of DVT and PE in patients with hip fractures when compared to placebo, this did not hold true for patients who underwent elective total hip arthroplasty. In regard to bleeding, however, there is no increased risk of bleeding with aspirin as compared to placebo [31–33]. A more recent British registry study comparing aspirin to low molecular weight heparin (LMWH) demonstrated no significant difference on venous thrombotic events or major bleeding. When this data was further analyzed using matched control groups, they noted a significant increase in 90-day mortality in patients receiving aspirin compared to those receiving LMWH [34]. In order to determine the relative efficacy and safety of aspirin, there needs to be multicenter randomized control trials comparing aspirin to other agents, such as LMWH or the newer oral anticoagulants.

Warfarin, a vitamin K antagonist, functions by preventing the activation of factors II, VII, IX, X, as well as protein C and S. While multiple randomized control trials have demonstrated inferiority in efficacy when compared LMWH in preventing overall clot formation [35, 36], a multicenter clinical trial comparing warfarin to enoxaparin showed no difference in symptomatic events after hospital discharge [37]. Additionally, trials have demonstrated lower bleeding rates with use of warfarin when compared to LMWH [32]. Many surgeons prefer the use of warfarin due to the ability to titrate dosing to a desired INR, its reversibility with administration of vitamin K, and its oral route of administration. However, the numerous food interactions and frequent lab monitoring can be difficult with respect to patient compliance.

LMWH, which includes agents such as fragmin and enoxaparin, acts by inhibiting factor Xa in the coagulation cascade. LMWHs are effective anticoagulants and no monitoring is required, but there has been concern among orthopedic surgeons about bleeding and wound drainage associated with LMWH prophylaxis. While numerous trials have demonstrated significant reduction in rates of DVT formation compared to warfarin, there has been no proven difference in rates of

symptomatic VTE events. In general, LMWH is initiated either 12 h prior to surgery or 12–24 h postoperatively, with either daily or twice a day dosing. While LMWH does not require any monitoring, there is some evidence of increased bleeding rates compared to warfarin [32, 33, 35, 37]. With that in mind, LMWH should not be used in patients with indwelling epidural catheters.

Fondaparinux, an indirect factor Xa inhibitor administered subcutaneously, has been shown to decrease the incidence of asymptomatic DVTs compared to enoxaparin (an LMWH) in patients with hip fractures. However, the increased incidence of bleeding risks in total knee arthroplasty patients has limited its use in the United States [38]. It is also not recommended in patients with renal insufficiency.

Two additional direct factor Xa inhibitors have been recently studied, rivaroxaban and apixaban. Both are oral agents that require no monitoring, and have been shown to be effective in VTE prophylaxis with decreased rates of thromboembolism and death when compared directly to enoxaparin in randomized trials. Apixaban was also noted to be associated with decreased bleeding complications [32, 33, 39], but has not yet been approved for use in VTE prophylaxis by the FDA. There are current concerns regarding bleeding risks with the use of rivaroxaban, as it is a potent anticoagulant. A recent systematic review of the literature comparing rivaroxaban and LMWH demonstrated a reduced risk of symptomatic events, but an increased risk of major bleeding [40]. In the randomized trials assessing rivaroxaban, the drug was administered approximately six hours after surgery. While it may be safe to administer the drug the morning after surgery, the efficacy of this regimen needs to be assessed.

Dabigatran is an oral direct thrombin inhibitor, which has previously used for atrial fibrillation and stroke prophylaxis, and was recently approved by the FDA for VTE prophylaxis. In the RE-COVER and RE-COVER II randomized trials, dabigatran was found to be non-inferior to warfarin in prevention of symptomatic events. Although it was not associated with decreased rates of overall bleeding, it was found to have higher rates of gastrointestinal bleeding [41, 42]. Additional studies comparing dabigatran to enoxaparin have shown non-inferiority and equivocal bleeding risks as LMWH [32].

Guidelines for VTE Prophylaxis

Guidelines have been developed by both the American Academy of Orthopedic Surgeons (AAOS) and the American College of Chest Physicians (ACCP) in order to enable clinicians to provide effective and safe prophylaxis regimens for their patients.

In 2011, AAOS published a guideline that contains ten recommendations related to VTE prophylaxis [43]. These recommendations were primarily aimed towards elective total hip and total knee arthroplasty, and were based on a systematic review of the literature. The goal is to reduce the rates of symptomatic events, while balancing bleeding risks. Each recommendation was graded individually by the level of

Table 13.3 AAOS guidelines for VTE prophylaxis

1.	Recommendation against screening for DVTs in postoperative patients who undergo elective hip or knee arthroplasty (**Grade: Strong**)
2.	Assessment of history of prior VTE (**Grade: Limited**)
3.	Assessment of bleeding disorders of liver disease which increase the risk of bleeding and associated complications in patients who undergo elective hip or knee arthroplasty (**Grade: Consensus**)
4.	Recommendation to discontinue the use of antiplatelet agents prior to elective hip or knee arthroplasty (**Grade: Moderate**)
5.	Recommendation for the use of mechanical compressive devices and/or systemic chemoprophylaxis for the prevention of VTE in patients who undergo elective hip or knee arthroplasty (**Grade: Moderate**)
6.	Recommendation for the use of mechanical compressive devices and systemic chemoprophylaxis for the prevention of VTE in patients who undergo elective hip or knee arthroplasty who have history of DVT/PE (**Grade: Consensus**)
7.	Recommendation for the use of mechanical compressive devices for the prevention of VTE in patients who undergo elective hip or knee arthroplasty who have acute liver disease and/or a bleeding disorder (**Grade: Consensus**)
8.	Recommendation for early mobilization in patients who undergo elective hip or knee arthroplasty (**Grade: Consensus**)
9.	Recommendation for neuraxial anesthesia in patients who undergo elective hip or knee arthroplasty to prevent blood loss (**Grade: Moderate**)
10.	Unable to recommend for or against the use of inferior vena cava filters to prevent pulmonary embolism in patients who undergo elective hip or knee arthroplasty and have a contraindication to systemic chemoprophylaxis or residual VTE disease (**Grade: Inconclusive**)

Summary of the 2011 American Academy of Orthopedic Surgeon's clinical practice guidelines for the prophylaxis of venous thromboembolism in patients undergoing elective hip or knee arthroplasty.

evidence supporting it. The guideline does not make a specific recommendation regarding the optimal prophylaxis regimen or duration of prophylaxis because of the limited number of randomized trials assessing the impact of prophylactic agents on symptomatic events. The guidelines did, however, make a strong recommendation against routine screening for VTE at the time of hospital discharge. A summary of the AAOS guidelines can be found in Table 13.3.

The ACCP published their most recent guidelines for VTE prophylaxis for total joint arthroplasty patients in 2012 [44]. In contrast to prior ACCP guidelines, the 2012 recommendations now focus on balancing efficacy and perioperative bleeding. These guidelines highlight the recommendations for a combination of systemic and mechanical modalities in elective arthroplasty (Table 13.4).

The Surgical Care Improvement Project (SCIP) guidelines [45] are a series of core measures aimed to reduce surgical complications. It is essential that surgeons adhere to these guidelines because they are a measure of quality with respect to hospital care. The guidelines, which are based on the ACCP guidelines, were recently revised in 2014, with one of the core measures being appropriate VTE prophylaxis initiated within 24 h before or after surgery.

Table 13.4 ACCP guidelines for VTE prophylaxis in orthopedic patients

Patients undergoing elective THA or TKA
Recommendation for the use of chemoprophylaxis for minimum of 10–14 days versus with one of the following: LMWH, fondaparinux, apixiban, dabigatran, rivaroxaban, low-dose unfractionated heparin, warfarin, or aspirin (**Grade: 1B**)
LMWH is recommended in preference to the remaining agents irrespective of mechanical compressive devices (**Grade: 2B**)
Recommendation for the use of mechanical compressive devices for minimum of 10–14 days rather than no prophylaxis (**Grade: 1C**)
Patients undergoing hip fracture surgery
Recommendation for the use of chemoprophylaxis for minimum of 10–14 days with one of the following: LMWH, fondaparinux, low-dose unfractionated heparin, warfarin, or aspirin (**Grade: 1B**)
LMWH is recommended in preference to unfractionated heparin or fondaparinux irrespective of mechanical compressive devices (**Grade: 2B**)
LMWH is recommended in preference to warfarin or aspirin irrespective of mechanical compressive devices (**Grade: 2C**)
Recommendation for the use of mechanical compressive devices for minimum of 10–14 days rather than no prophylaxis (**Grade: 1C**)
Patients undergoing major orthopedic surgery and receiving LMWH
Recommendation for the initiation of LMWH either ≥12 h preoperatively or ≥12 h postoperatively (**Grade: 1B**)
Patients undergoing major orthopedic surgery
Recommendation for concomitant systemic chemoprophylaxis and intermittent pneumatic compression devices throughout hospitalization (**Grade: 2C**)
Recommendation against the use of IVC filter in patients with contraindications to both mechanical and systemic prophylaxis (**Grade: 2C**)
Recommendation against the use of postoperative duplex ultrasound screening prior to discharge from hospital (**Grade: 1B**)
Patients undergoing major orthopedic surgery and high risk of bleeding
Recommendation for the use of intermittent pneumatic compression devices in the place of systemic chemoprophylaxis (**Grade: 2C**)
Patients undergoing major orthopedic surgery who are noncompliant with injections or intermittent pneumatic compression devices
Recommendation for the use of oral apixaban or dabigatran (rivaroxaban or warfarin if not available) (**Grade: 1B**)
Summary of the 2012 American College of Chest Physician's clinical practice guidelines for the prophylaxis of venous thromboembolism in orthopedic patients. Grade 1 is a strong recommendation, whereas Grade 2 equates to a weak recommendation. The qualifiers A, B, and C pertain to the basis for the recommendations being high, moderate, or low-quality evidence respectively.

Duration

As mentioned previously, the AAOS guidelines did not include specific recommendations for the duration of prophylaxis due to the scant number of placebo-controlled randomized trials. However, the ACCP guidelines recommend a minimum of 10–14 days of prophylaxis and suggest that 35 days should be considered [44].

Additionally, recent systematic reviews recommend extended prophylaxis of up to 28–35 days in patients undergoing total hip arthroplasty, as this has been shown to decrease the risk of post discharge VTE. Extended prophylaxis should also be considered in high-risk patients with known risk factors for VTE [46, 47].

Diagnosis of VTE

While VTE can have significant and often deleterious effects, there are no clinical signs specific for the diagnosis of DVT or pulmonary embolism. Many of the signs and symptoms associated with a VTE occur frequently during the postoperative period. Therefore, a high index of suspicion is imperative in early diagnosis. DVTs can often be asymptomatic, however, acute leg pain or swelling can be signs of an underlying DVT. A Homan's test (calf pain with passive dorsiflexion of the foot) and examination for any palpable cords should be performed; however, these are frequently negative even in the presence of a thrombus [48].

If clinical suspicion for DVT exists, further evaluation is warranted. While venography remains the gold standard, duplex ultrasonography has become more widely used as it has demonstrated high sensitivity and specificity for proximal thrombi involving the extremities [49]. However, the sensitivity for identifying thrombus involving the pelvic vessels is poor. Therefore, invasive venography should be considered in cases where pelvic DVT is suspected.

D-dimer levels have also been used in the workup of both DVT and pulmonary embolism, however this should be done with caution. As this test evaluates the level of fibrin degradation, elevated levels can indicate thromboembolism, but can also be a normal finding after recent surgery. Therefore, an elevated D-dimer is not diagnostic of DVT or pulmonary embolism. However, a low D-dimer level has a high negative predictive value, and is associated with low risk of DVT [50].

Small pulmonary emboli are frequently asymptomatic, however, larger emboli can cause fevers, tachycardia, cough, tachypnea, dyspnea, chest pain, oxygen desaturation, hemoptysis, and even death. When pulmonary embolism is suspected additional studies may be necessary. The Wells Criteria (Table 13.5) can be used to determine the probability of pulmonary embolism. A score less than or equal to 4 is unlikely to be associated with pulmonary embolism, whereas a score greater than 4 is likely a pulmonary embolism [51].

Although a chest radiograph is typically normal in pulmonary embolism, a pleural effusion, enlarged pulmonary arteries, Hampton hump, or a Westermark sign may be present [14]. It can also be useful in ruling out other underlying pathology. Electrocardiogram may demonstrate tachycardia, right heart strain, or the classic S1-Q3-T3 pattern [52]. Arterial blood gas can also be evaluated, and sample should be taken without any supplemental oxygen. Findings of hypoxemia, hypocapnea, respiratory alkalosis, and an increased arterial-alveolar gradient are consistent with

Table 13.5 Wells criteria

Clinical symptoms of DVT	3 points
Other diagnoses are less likely than PE	3 points
Heart rate >100	1.5 points
Prolonged immobilization (3 or more days) or recent surgery (within 4 weeks)	1.5 points
History of DVT/PE	1.5 points
Hemoptysis	1 point
Malignancy	1 point

a pulmonary embolism [14]. However, more recent evidence demonstrates that the specificity and sensitivity of an arterial blood gas is not sufficient to diagnose or exclude a pulmonary embolism alone [53].

Pulmonary angiography remains the gold standard for the diagnosis of pulmonary embolism, as it allows for direct visualization of the pulmonary vasculature. A negative test excludes a clinically significant pulmonary embolism. However due to its cost and invasive nature, other means of diagnosis have become more popular. Spiral, or helical, chest CT pulmonary angiography (CT-PA) has become the most widely used initial study for the evaluation of pulmonary embolism. The PIOPED II trial demonstrated an 83 % sensitivity and a 95 % specificity of CT-PA [54]. The other major advantage of CT-PA is that it allows for the diagnosis of any other pathology. However, the study does require contrast and radiation, making it contraindicated in patients with contrast allergy, renal insufficiency, or pregnancy.

Alternatively, the ventilation-perfusion (V/Q) scan can be used. The test is designed to identify regions of the lung in which there is ventilation without perfusion (i.e., mismatch defect). They are graded as normal, low, intermediate, or high probability of pulmonary embolism. According to the PIOPED trial, patients with high clinical probability of pulmonary embolism and a high-probability V/Q scan have a 95 % probability of having a pulmonary embolism, whereas patients with low clinical probability and a low-probability V/Q scan have 4 % chance of having a pulmonary embolism [55]. V/Q scan can also be safely used in patients with contrast allergy, renal insufficiency, or pregnancy. Additionally, a randomized trial directly comparing V/Q scans and CT-PA demonstrated that CT-PA was not inferior to V/Q scans, however a significantly larger number of patients were diagnosed with pulmonary embolism with the use of CT-PA. The leading explanation for this is that CT-PA is too sensitive, identifying small clots that are not clinically relevant. This has led to concerns regarding the over diagnosis of a pulmonary embolism with CT-PA and unnecessary treatment with prolonged anticoagulation [56, 57]. The senior author of this chapter will routinely review the results of the CT-PA with the radiologist in order to obtain an accurate interpretation of the study.

Treatment

Deep Vein Thrombosis

The goals of treating DVT are to prevent clot extension and embolization, as well as decreasing the risk of recurrence and sequelae including pulmonary hypertension and post-thrombotic syndrome. Systemic anticoagulation is the primary method of treatment with the immediate initiation of LMWH, unfractionated heparin, or fondaparinux. LMWH and fondaparinux are generally preferred to unfractionated heparin, as they can be administered on an outpatient basis and have established track records. In addition to being cost effective, patients treated as outpatients with LMWH have lower rates of recurrence compared to those treated as inpatients with either LMWH or UFH [37].

When unfractionated heparin is used, therapeutic levels with an aPTT of 1.5–2.5 should be accomplished within 24 h, as studies have shown this significantly reduces the risk of recurrent VTE [58]. However, unfractionated heparin boluses should be avoided due to bleeding risks. Direct thrombin and oral factor Xa inhibitors have also been recently studied in terms of efficacy and safety for the treatment of DVTs, with evidence demonstrating comparable efficacy to warfarin, but with lower rates of bleeding complications. At the present time, the use of LMWH and vitamin K antagonists are still advised over the use of dabigatran or rivaroxaban [59]. As new research emerges, these guidelines may change.

Along with parenteral anticoagulants, ACCP guidelines recommend early initiation of oral vitamin K antagonists, with overlap of the oral and parenteral therapies for a minimum of 5 days, and until an INR greater than 2 is achieved [44]. It is important to note that warfarin should not be started as a sole therapy in the initial phase. The target INR is between 2 and 3, and frequent monitoring with appropriate dose adjustments is imperative throughout the treatment course. In the early postoperative period, it may be prudent to achieve a target INR of 2.0 to avoid bleeding. The suggested duration of therapy is at least 3 months and the use of compressive stocking for 2 years is also recommended to prevent post-thrombotic syndrome [44].

While systemic thrombolytic therapy, catheter-directed thrombolysis, and surgical thrombectomy have been studied in the management of DVTs, the ACCP guidelines recommend systemic anticoagulation above these other methods of management. Additionally, they recommend the use of IVC filters in patients when anticoagulation therapy is contraindicated.

Pulmonary Embolism

Management of pulmonary embolism has many similarities to the treatment of DVT, but with several key differences. The most important factor is the determination of the patient's stability. As pulmonary embolism can cause acute respiratory

failure, cardiac failure, and sudden death, the initial assessment of the patient should begin with a primary survey of the ABCs (airway, breathing, circulation). Supplemental oxygen and even intubation with mechanic ventilation may be required to maintain adequate oxygenation. Intravenous fluids (typically 500–1000 cc normal saline) should be administered to patients with hypotension; however, this should be done prudently as fluids can worsen right heart failure [60, 61]. Additionally, vasopressors should be considered if the hemodynamic status does not improve with fluids alone.

In patients with hypotension, the ACCP has suggested systemic thrombolytic therapy, if the patient is not at high risk of bleeding [44]. They recommend that thrombolytics be administered using a peripheral vein with short infusion times. If there is a contraindication to, or the patient has failed, thrombolytic therapy, they suggest catheter-directed thrombus removal or surgical embolectomy.

In the presence of hemodynamic stability and confirmed pulmonary embolism, parenteral anticoagulation therapy with LMWH, fondaparinux, or unfractionated heparin should be immediately initiated. In patients with an intermediate or high clinical suspicion of pulmonary embolism, anticoagulation therapy is recommended while awaiting diagnostic results. The dosing of enoxaparin is 1 mg/kg every 12 h or 1.5 mg/kg daily. As with the treatment of DVTs, ACCP guidelines recommend early initiation of oral vitamin K antagonists, with overlap of the two anticoagulation agents for a minimum of 5 days, and until an INR greater than 2 is achieved. The ACCP again suggests a 3-month duration of therapy with a goal INR of 2–3 [44]. Following a 3-month period of treatment in patients with recurrent PE, the risks and benefits of continued anticoagulation must again be weighed [62]. In patients with low to moderate bleeding risks, lifelong anticoagulation is recommended. In contrast, patients with high risks of bleeding, the ACCP does not recommend extended anticoagulation beyond 3 months.

Summary

VTE remains a significant risk among orthopedic patients undergoing elective total hip arthroplasty, as many of these patients carry multiple risk factors for thrombotic events. For this reason, prevention of clot formation remains a high priority, with a combination of mechanical and pharmacologic anticoagulation. Because the signs and symptoms of both DVT and pulmonary embolism are non-specific, it is critical for clinicians to maintain a high suspicion and initiate early diagnostic studies and therapy when appropriate. Although the ideal therapy and duration of treatment remains controversial, the AAOS and ACCP have developed clinical guidelines to assist in the decision-making process.

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