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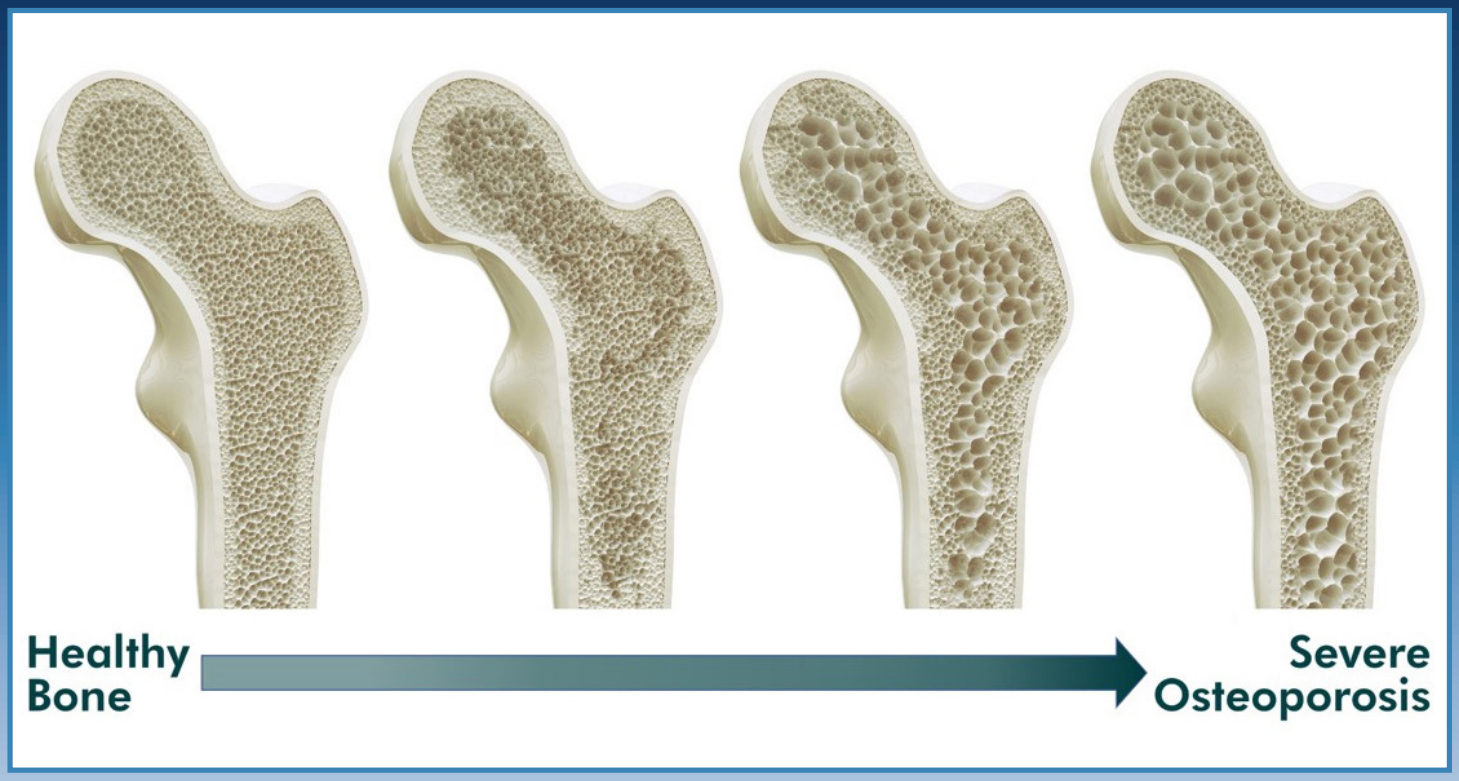

SPECIAL SECTION

OSTEOPOROSIS, METABOLIC BONE DISEASES, *and* FRAGILITY FRACTURES

GUEST EDITORS: JAKE LITTMAN, ScM, MPH; ROY K. AARON, MD

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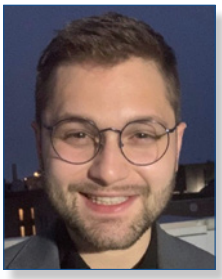

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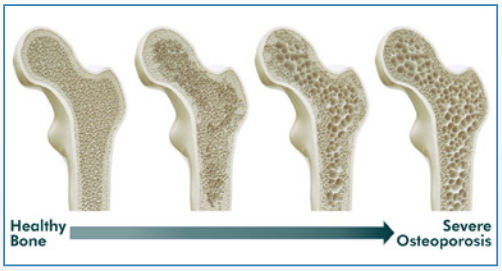

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RIMJ Special Section:
Osteoporosis, Metabolic Bone Diseases, and Fragility Fractures

Preface: The Fracture Liaison Service

JAKE LITTMAN, ScM, MPH; ROY K. AARON, MD
GUEST EDITORS

Enter Jane Doe: a 76-year-old woman with no known medical problems and no currently prescribed medications. She looks well for her age, is active in her community, and walks 3-5 miles per day. One day while out walking, she falls from standing height and suffers a displaced fracture of the femoral neck. Ms. Doe has just experienced one of the most common forms of low-energy fractures, also known as fragility fractures, in the elderly. She is taken by ambulance to her local emergency room where X-ray confirms her diagnosis, and she receives surgical treatment by way of total hip replacement. The surgery is performed without complication, and through subsequent physical therapy, she regains some of her mobility and independence. Within a year, however, she suffers a second fracture, leaving her permanently disabled and in need of home care.

Meanwhile, Ms. Doe's grandson suffers a wrist fracture while playing basketball. At 12 years old, this is the third fracture of his life. He complains of intermittent blurry vision, but his clinical examinations are otherwise normal, and his parents and physicians conclude that he is an overactive child who is prone to injury. His fracture is treated without complications, but months later he suffers bilateral retinal detachments leaving his vision permanently impaired.

Now, let us envision the contribution of a Fracture Liaison Service (FLS) to the care of these two patients. After receiving surgical treatment for her hip fracture, Ms. Doe is referred to an FLS where a comprehensive history is obtained, a physical examination with emphasis on the skeleton is performed, bone density is determined via dual-energy absorptiometry (DEXA) scanning, and laboratory analysis including investigation of bone turnover marker (BTM) levels is conducted. She is determined to have hyperparathyroidism and undergoes treatment with eventual normalization of her bone density. She regains most of her prior function and avoids subsequent fracturing.

Her grandson is evaluated at the FLS and is found to have a spinal DEXA scan Z-score of -2.5, an age-comparative measure indicating severely low bone density. Clinical suspicion of genetic pathology is raised, and a consult is obtained. NextGen whole exome sequencing reveals heterozygous LRP5 mutations, and an ensuing ophthalmologic workup confirms a diagnosis of familial exudative vitreoretinopathy (FEVR), a genetic disorder that can lead to low bone density, multiple fractures, retinal detachments, and permanent vision loss if not properly treated. He receives appropriate treatment and eventually graduates from high school with no further fractures and preserved vision.

In both cases, the identification of their fractures as signal events led to the detailed evaluation and specific diagnosis and treatment of their underlying pathology. This illustrates the main thematic approach an FLS takes in treating the fracture patient. Put simply, the FLS is a centralized hub for the complete management of fracture patients, including the exploration, diagnosis, and treatment of underlying pathologies that predispose to subsequent fractures. The FLS alleviates the fragmentation of care often found among orthopedic, endocrine, and primary care services regarding which is primarily responsible for the longitudinal evaluation and management of fracture patients. This was once aptly termed the "Bermuda Triangle of osteoporosis care of fractures," referring to the observed phenomenon of osteoporotic fracture patients disappearing from interdisciplinary care teams without proper management due to discordance on who is ultimately responsible for their long-term care.[1]

In **"The Roles of a Fracture Liaison Service,"** the framework for the evaluation and management of fragility fracture patients in the FLS is discussed in detail, including the history, physical examination, determination of bone density, and laboratory analysis. The clinical and economic benefits of FLS are explored, and a real-world application of the FLS paradigm, the Rhode Island Fracture Liaison Service, is detailed.

In **"Osteoporosis and Fragility Fractures,"** osteoporosis and fragility fractures are discussed as well as their relationship to each other and to the FLS. The epidemiology, pathophysiology, evaluation, and management of osteoporosis are explored, and the clinical importance, epidemiology, predisposing factors, outcomes, and preventative strategies for fragility fractures are elucidated.

In **"Osteomalacia and Renal Osteodystrophy,"** the clinical classifications, presentations, pathophysiologies, and treatment modalities for various osteomalacias are discussed as alternative bone diseases to osteoporosis producing low bone density. Renal osteodystrophy, a specific form of metabolic bone disease affecting chronic kidney disease and kidney transplant patients characterized by osteomalacia and hyperparathyroidism, is presented.

In **"Monoclonal Gammopathies in a Fracture Liaison Service,"** the spectrum of disorders characterized by the overproduction of plasma B-cells and immunoglobulin known as monoclonal gammopathies are discussed, with special emphasis on monoclonal gammopathy of uncertain significance (MGUS), a pre-malignant form of multiple myeloma. The clinical presentation of MGUS and its association with osteoporosis and fracture are explored and highlighted with data from the Rhode Island FLS, leading to the conclusion that the term "MGUS" be replaced with "MGSS," or "monoclonal gammopathy of skeletal significance."

In **"Hyperparathyroidism in a Fracture Population,"** the clinical presentation, diagnosis, and treatment of primary hyperparathyroidism (PHPT) are discussed, with special emphasis on its effects on the skeleton. Normocalcemic hyperparathyroidism (NPHPT), a variant of PHPT defined by normal serum calcium and persistently elevated parathyroid hormone levels, is also presented. Current evidence linking NPHPT to osteoporotic fractures, including observations from the Rhode Island FLS, is presented, raising the question if serum calcium measurements alone are sufficient to evaluate parathyroid function in the setting of osteoporotic fractures.

Finally, in **"Vertebral Compression Fractures,"** the epidemiology, clinical presentation, diagnosis, and treatment (including surgical and non-surgical management) of vertebral compression fractures (VCFs) are discussed. The susceptibility of VCF patients to subsequent fractures and their consequences is also described, as well as pharmacotherapy and the role an FLS can play in mitigating the sequelae of primary VCFs.

FLS MODELS

It is important to note that several types of bone health programs exist and an FLS is but one example. While the Rhode Island FLS specifically addresses patients who have already suffered a fracture, some alternative programs are designed to screen asymptomatic populations to find and treat low bone density in the hopes of decreasing fracture incidence. As might be expected, these programs are especially popular with closed panel models of health care delivery such as Accountable Care Organizations and Health Maintenance Organizations. Regardless of approach, the primary goal of all bone health programs should be the reduction of injury via multidisciplinary, comprehensive, high-quality, and cost-effective patient care. The recognition of the potential contributions of FLS programs is of importance to any medical groups serving elderly, osteoporotic, and fracture patients.

An FLS regards a fragility fracture as a signal symptom of metabolic bone loss, physical compromise, or environmental hazards, alerting clinicians to the presence of comorbidities and providing a framework for the identification of patients with a recent fracture, the diagnostic workup of the fragility fracture patient, the treatment of underlying contributors to the fracture, and follow-up to reduce sequelae. Because most patients in an FLS are defined as "symptomatic" by virtue of their fracture, the prevalence of intercurrent diseases and life circumstances in FLS patients is relatively greater than in the general population and offers the opportunity for study. Approaches and findings in our FLS are described in this volume. It is our hope that the findings of the FLS will find their way into screening programs and individual patient care.

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Acknowledgments

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The editors also owe a great debt of gratitude to the late Henry Mankin, MD, former chair of orthopedics at Harvard and the Massachusetts General Hospital, who taught metabolic bone diseases in an orthopedic context. Dr. Mankin sought to infuse orthopedic diagnoses and treatment with clinical medicine and its basic sciences for a fuller understanding of surgical pathology and treatment potential. He was a charismatic personality and brilliant teacher, and an anecdote serves as an illustration.

Using the biblical story of Lot's wife being turned into a pillar of salt, Dr. Mankin described the fate of an individual who consumed a high phosphate hamburger and a high calcium milkshake and then received a blast of vitamin D by going out into the sun as being turned into stone for exceeding the calcium-phosphorous solubility product. While Lot's wife's crystallization was due to her disobedience, the crystallization of Dr. Mankin's information was due to rapt attention.

Dr. Mankin could not know the long-term impact of his teaching in this community, and this could be a reminder to us all that we will most likely not realize the widespread effects of our teaching on our students and on the care of our patients.

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The Roles of a Fracture Liaison Service

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ABSTRACT

The roles of a fracture liaison service (FLS) are extensive and include, but are not limited to: 1) providing a standardized framework for the evaluation and management of low-energy fractures, also known as fragility fractures; 2) improving patient outcomes through the recognition of fragility fractures as signal events requiring further diagnostic explanation; and 3) lowering direct and indirect healthcare expenditures. One of the central tenets of the FLS is its recognition of fragility fractures as warning signs of underlying pathology, often osteoporosis or other metabolic bone diseases. This understanding, combined with the application of a multidisciplinary management team specialized in diagnosing and treating such pathologies, allows for better short- and long-term management of patients and concordant improvement in outcomes. This article should be viewed as a thematic introduction to the FLS, with others in this volume each illustrating specific examples of how FLS paradigms facilitate the roles described herein.

KEYWORDS: Fracture Liaison Service (FLS); osteoporosis; fractures; falls

INTRODUCTION

Fracture Liaison Services (FLSs) have emerged from two clinical observations. First, low-energy fractures, particularly in individuals over age 60, often result in significant functional morbidity, pain, loss of independence, and death. Second, low-energy fractures can be prevented by medical, physical, and environmental interventions, all dependent upon a sensitive understanding of the physiology of the fractures and their consequences. Low-energy fractures, also known as fragility fractures, are signal events, often the presenting symptoms of an underlying pathology requiring further diagnostic exploration. Therefore, in a very real sense, patients with low-energy fractures are not "asymptomatic." On the contrary, they are frequently found to have metabolic bone diseases such as osteomalacia, hyperparathyroidism, and especially osteoporosis that result in decreased bone density and disruption of bone micro-architecture leading to diminished ability to withstand applied stresses. Presentations in this volume will concentrate on metabolic contributions to fractures and on common fracture patterns that should be recognized for their association with functional impairment and secondary fractures. Thematically, the volume makes several points:

- The signal value of fragility fractures should not be ignored or minimized.
- Certain fractures, especially vertebral compression fractures, often signal an increased incidence of subsequent fractures.
- Screening bone density is only an initial step in the treatment of fractures. It does not yield a diagnosis, and, in itself, is not a basis for therapy. All patients with fragility fractures deserve a metabolic bone evaluation.
- The evaluation of bone density in the context of fractures frequently reveals medical conditions that contribute to decreased bone density and falls.
- Appropriate therapy depends upon accurate diagnosis of causal and contributory factors to the fracture history and bone density.
- Several medications are available for the treatment of decreased bone density depending upon the extent of bone loss, fracture history, and co-existing medical conditions.

CLINICAL FINDINGS IN THE RHODE ISLAND FRACTURE LIAISON SERVICE

By carrying out a metabolic bone investigatory program as described here, we have made some surprising findings that have enabled more targeted approaches to therapy. Reports of disease prevalence are particular to each FLS referral base. In our case, fractures are the triggering symptom. Renal and transplant patients are treated on those services, respectively, and are discussed in a later article in this volume. Nonetheless, some observations can reinforce the consensus on coordinated evaluation of fracture patients. Within the last 2 years, of 265 consecutive patients with osteoporosis and fractures on our service, we detected 28 patients with primary hyperparathyroidism and 27 patients with monoclonal gammopathy of uncertain significance (MGUS), both discussed in subsequent articles, as well as 10 patients with hematologic malignancies including multiple myeloma, Waldenström's macroglobulinemia, chronic lymphocytic

leukemia, mast cell leukemia, and lymphomas. In addition, the FLS has evaluated and treated osteoporosis associated with several genetic diseases including osteogenesis imperfecta, Marfan's syndrome, Ehlers-Danlos syndrome, and familial exudative vitreoretinopathy (FEVR), as well as neuromuscular conditions including muscular dystrophy and cerebral palsy. As discussed in an ensuing article, malabsorption-related osteomalacia has posed challenges to raising vitamin D levels depending upon the severity and cause of the malabsorption. Combined, 75/302 (25%) of patients referred for osteoporosis or osteoporotic fractures were diagnosed with another condition, usually serious, and therapy was targeted at those diseases. This reflects a major thematic approach of our FLS. Without a diagnostic approach such as that described below, these conditions could be missed and, therefore, mistreated.

CLINICAL APPROACH

A fragility fracture is often defined as one resulting from a fall from a standing height. However, there are other considerations such as the surface upon which one falls, the circumstances of the fall, etc. In general, the fractures of concern are low-energy fractures and ones with unusual injury mechanics. The clinical approach to the patient with a fragility fracture consists of a history focused on skeletal biology, a focused physical examination, occasional X-rays, determination of bone density, laboratory evaluation of skeletal biology, and a treatment plan that takes into account the patient's medical and fracture history, severity of bone loss, chemistry, and clinical diagnoses.

1. History – A general medical history with an emphasis on the skeleton inquires about the patient's fracture history, history of falls, acuity of vision and hearing, balance, loss of height, the home environment, diet (especially dairy intake or lactose intolerance), medications that may have an adverse effect on the skeleton, medical exposures such as corticosteroids, and general bone hygiene including caffeine intake, alcohol consumption, and smoking habits (**Table 1**). The physical and environmental contributions to fractures should be part of every screening conversation. Causes of secondary osteoporosis are described in the *Osteoporosis and Fragility Fractures* article in this volume.

2. Physical Examination – A focused skeletal examination includes gait and balance stability, core muscle strength, and spinal deformity (especially kyphosis) that might indicate previous fractures. Rapid, simple tests of lower extremity strength are available, such as "timed up and go" and rising from a chair, that suggest a need for physical therapy for muscle strengthening and gait stability to prevent falls.[1,2] In the kyphotic patient, lateral thoracic spine X-rays may be indicated to detect previous vertebral compression fractures since these fractures can be almost asymptomatic yet result in deformity and indicate risk for subsequent fractures.

Table 1. Static and Potentially Alterable Risk Factors for Osteoporotic Fractures

Static Factors	Potentially Alterable Factors
Demographic factors: old age, female sex, Asian or White race	Low bone density
Personal and/or family history of adult fracture	Lifestyle factors: low BMI, sedentary lifestyle, smoking, excessive alcohol consumption, low dietary calcium intake
Menopause onset prior to age 45	Iatrogenic contributions: glucocorticoids, sedatives, anti-hypertensives, polypharmacy
Physical frailty	Environmental factors: obstructed walkways, poor lighting, unequal surfaces, etc.
Deterioration in mental status	Estrogen deficiency

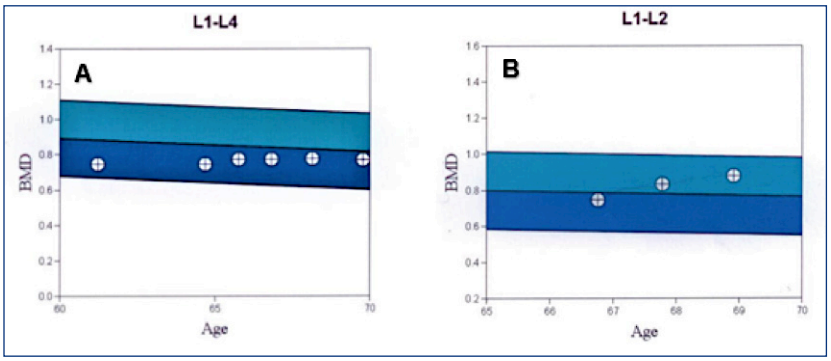
Sensitivity to loss of thoracic height can be important since vertebral compression fractures can result in the lower ribs abutting the pelvis, resulting in impaired sitting and loss of thoracic volume. Several studies have found that pulmonary function can be compromised in patients with osteoporotic vertebral compression fractures compared to patients with chronic low back pain without osteoporosis.[3] Reductions in both vital capacity and forced expiratory volume (FEV1) have been correlated with spinal osteoporotic fractures and resulting spinal deformity and decreased thoracic volume, indicating that reductions in pulmonary function can be correlated with osteoporotic spinal deformities that can be detected and quantified by clinical and radiographic assessment.

3. Determination of Bone Density – Dual-energy absorptiometry (DEXA) scanning has several major advantages in the evaluation of the skeleton. It is rapid, noninvasive, and non-enclosed. The radiation exposure is trivial (**Figure 1**). It provides 2-dimensional measurements of bone density which are reported in g/cm^2 and compares them to age-related norms (Z-score) and values at age 20 (T-score). The

Figure 1. Patient undergoing DEXA scan and technician
Bone mineral density or bone strength is measured with a type of low-energy X-ray called a DEXA scan. The scan is entirely noninvasive, non-enclosed, and takes approximately 15 minutes to complete. The measurement of an individual's bone mineral density is compared to values of the normal population to determine the extent of bone loss. Patients under active treatment should have follow-up DEXA scans at 1-2 year intervals.

Figure 2. DEXA scans of the lumbar spine

A: A patient with breast cancer, treated with tamoxifen, showing a steady increase in bone density. **B**: Documentation of treatment efficacy in another patient.



well-established, age-related normative values are based upon very large numbers of individuals. Graphic display of data is often helpful, particularly in serial studies following progression and treatment (**Figure 2**). It does have some limitations in that normative values are available for the spine, hips, and wrist/forearm only. While the output of DEXA appears simple, one has to interpret the data with sensitivity to the effects of deformity, arthritis, and previous fractures that can give spurious results, especially in the spine. Some vertebrae may need to be excluded from the analysis. Particular attention must be paid to the femoral neck density since this is a frequent site of hip fractures. Extrapolation of density from one anatomic site to another should be done in the total context of the patient's history. Additionally, not all DEXA machines are equally calibrated, and care has to be taken when comparing results between machines. Ideally, the patient would be serially scanned on the same well-calibrated machine. While DEXA is a safe and widely available clinical tool for monitoring bone density and can accurately determine areal (two-dimensional) bone mineral density, it cannot be extrapolated to a three-dimensional volumetric density. Additionally, it does not have the ability to accurately assess structural micro-architecture nor to differentiate between cortical and trabecular bone compartments. Collectively, these constraints limit the ability of DEXA to estimate bone strength and do not allow it to provide microstructural information which can be used to assess bone quality.[4]

It must be appreciated also that the DEXA scan measures only bone density and does not give a clinical diagnosis of osteoporosis. Other conditions can produce low bone density and are treated quite differently, so that a biochemical analysis of the patient with low bone density is important to make an accurate diagnosis and target therapy, with or without fractures.

4. Laboratory Analysis – In 1994, Henry Mankin, then chair of orthopedics at Harvard and Massachusetts General Hospital, wrote a seminal paper on metabolic bone diseases in the orthopedic setting and described the relevant comprehensive analysis of the skeleton.[5] While clinicians often have their individual preferences as to what constitutes core and supplementary studies, one well-targeted initial approach was described by Mankin and reviewed several times (**Table 2**). The laboratory approach to the skeleton consists of 1) exploring conditions other than osteoporosis that can be associated with decreased bone density such as hyperparathyroidism or hematologic malignancies, most commonly multiple myeloma; 2) identifying modifiable conditions, commonly low serum 25-hydroxy vitamin D, chronic renal failure, and secondary hyperparathyroidism; and 3) informing the appropriate choice of pharmacotherapy once primary osteoporosis is identified as the cause of low bone density. In this last category, bisphosphonates require adequate renal function, denosumab requires adequate serum calcium and vitamin D, and osteoanabolics require a normal, or at least explainable, bone-specific alkaline phosphatase.

Table 2. Routine Post-DEXA Diagnostic Procedures in Osteoporosis Evaluation

Goals	Procedures
Exclude non-osteoporotic causes of low bone mass and skeletal fragility	Laboratory tests: Serum calcium, creatinine, alkaline phosphatase, protein electrophoresis, 24-hour urine chemistry, serum 25-hydroxy vitamin D, serum parathyroid hormone, bone turnover markers
Identify modifiable conditions such as low serum 25-hydroxy vitamin D, chronic renal failure, secondary hyperparathyroidism	
Assess the presence of vertebral fractures when clinically indicated	X-ray of thoracic and/or lumbar spine for patients with loss of height and/or deformity

Bone turnover markers (BTMs) are a series of protein biomarkers released by osteoblasts and osteoclasts, or from bone matrix during bone remodeling. They can reflect the degree of bone formation or resorption and can provide prognostic information on the risk of fracture, progression of disease, and response to therapy. Many BTMs are under study with several currently in clinical use. Two clinically used BTMs are the C- and N-terminal telopeptides of type I collagen, the most common protein in bone matrix. The two terminal telopeptides, notated as CTX and NTX, respectively, are released by osteoclastic resorption of bone and are useful in identifying the degree of bone resorption. CTX is generally assayed in serum; NTX is assayed in urine. They have broadly similar clinical utility.[6] Two BTMs reflect bone formation in remodeling: bone-specific alkaline phosphatase and osteocalcin. There are several genetic isoforms of alkaline phosphatase produced by the liver, intestine, and

placenta, but it is the bone-specific isoform that reflects bone formation. Osteocalcin is the most abundant non-collagenous protein in bone matrix and is secreted by osteoblasts. While of investigatory interest, pre-analytic variables have kept it from routine clinical use. BTMs are clinically useful primarily to assess the resorptive component of bone turnover, predict the responses to anti-resorptive therapy, follow the response to, and compliance with, therapy, and assess increases in bone density and reduction of fracture risk.[6]

ROLE OF AN FLS IN OSTEOPOROTIC FRACTURE CARE

Care of patients with fragility fractures is often compromised by a lack of coordination and shared expertise. Active interventions in an FLS have been shown to result in a decreased incidence of second fractures.[7] Anti-osteoporotic therapy after a fragility fracture results in a 40% decrease in the 3-year risk of a subsequent fracture.[8] The advantages of a coordinated post-fracture program were demonstrated by an FLS that achieved accurate diagnosis and secondary fracture prevention in 414/430 (96%) of patients with an osteoporotic fracture.[9] Many other studies have demonstrated that coordinated care of osteoporotic fractures in organized FLS programs improves evaluation, treatment, and outcomes, and reduces fracture-related morbidity and mortality.[10-13] Coordinated care in an FLS program has also been shown to result in substantial reductions in secondary fractures.[14] As a consequence of these demonstrations, a consensus has developed around the clinical benefits of an organized FLS program. Evidence-based clinical guidelines for the evaluation and treatment of low-energy, geriatric, and fragility fractures have been developed by the American Society of Bone and Mineral Research, 39 stakeholder societies, and the NIH.[15] While these are subject to updating, the overarching recommendation is that the FLS care delivery model is the most effective means for treating patients with low-energy fractures (i.e., fragility fractures), and that FLS programs consistently initiate and comply with best practice diagnosis and treatment guidelines more often than do traditional models.[16]

EPIDEMIOLOGY AND ECONOMICS OF LOW-ENERGY FRACTURES

The FLS takes the position that a fracture is a signal event indicating a propensity for functional decline and reflecting underlying reduced bone density, increased fall risk, and the presence of environmental hazards. Importantly, a previous low-energy fracture is among the strongest risk factors for subsequent fractures.[5,17-20] More specifically, patients with a low-energy fracture of the wrist, hip, proximal humerus, or ankle have a 2- to 4-fold greater risk for subsequent fractures than do individuals who have never experienced a fracture.[17] Up to 30%-40% of patients with a vertebral compression fracture will experience additional vertebral fractures within 3 years.[21] Compared to individuals with no history of fracture, a patient with a vertebral fracture has nearly a 5-fold increased risk of a subsequent vertebral fracture and a 6-fold increased risk of non-vertebral fractures.[22] Notably, fractures of the spine and wrist are associated with an increased incidence of secondary hip fractures.[23] Hip fractures account for over 350,000 hospitalizations/year, or 30% of all fracture-related hospitalizations.[24] Outcomes after hip fractures in the elderly are often complicated by morbidity, disability, and death. Overall, 24% of these patients die within a year after fracture.[12,25] Half of hip fracture patients do not regain their pre-fracture function, and many lose their functional independence and require long-term care. Taken together, these data indicate that patients who have experienced a low-energy fracture of any type have a markedly greater risk of subsequent fractures with associated morbidity than do individuals who have not fractured.

The economics of low-energy fracture care are similarly compelling. It has been estimated that the annual medical cost of treating hip fracture patients in the US exceeds $10 billion.[25] Hip fractures are related to age and the geriatric population, and therefore as the population ages, the incidence of hip fractures can be expected to increase concurrently. As a consequence of demographic changes, medical costs related to hip fractures have been predicted to rise to $25.3 billion by 2025, and costs associated with all osteoporotic fractures are predicted to rise to over $95 billion by 2040.[26,27] Multiple cost-effectiveness analyses have demonstrated the potential for substantial savings resulting from increased use of FLSs within the US healthcare system, with one 2021 study concluding that per every 1 million patients with Medicare coverage receiving secondary fracture prevention after an osteoporotic fracture, $418 million dollars could be saved and 30,000 quality-adjusted life-years could be gained.[11,28,29] These data are especially compelling when observed in concert with the estimation that the annual incidence of osteoporotic fractures in the US is expected to rise to 3.2 million by 2040, indicating a potential cost savings of $1 billion or more per year by that time through the widespread implementation of FLSs.[27] Other studies have demonstrated that the potential for savings is not specific to the US.[30-33] Lastly, it is important to note that the economic benefits of the FLS model extend not only to direct health care expenses, but to patients and their families as well due to lifestyle changes, institutionalization, and family care often associated with the longitudinal effects of recurrent fractures, with one study estimating the indirect cost of fractures in 2018 to be $8.2 billion.[27] The extent to which social and economic factors burden patients and families can be minimized by the timely diagnosis and management of the underlying disease processes by an FLS.

CONCLUSIONS

An FLS provides a systematic approach to osteoporotic fracture care that 1) recognizes low-energy fractures as signal events requiring further inquiry; 2) provides a framework for the comprehensive evaluation of underlying and often unexpected pathology; 3) facilitates appropriate treatment; 4) reduces the risks of secondary fractures with their attendant morbidity and mortality; 5) lowers costs for patients and healthcare systems; and 6) improves patient outcomes. This article provides an entryway into the subsequent presentations in this volume that each highlight distinct yet interconnected roles an FLS plays in providing multidisciplinary, comprehensive, high-quality, and cost-effective patient care.

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Osteoporosis and Fragility Fractures

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ABSTRACT

Osteoporosis and fragility fractures (FFs) are closely intertwined as the former is a common predisposing factor to the latter. This causal relationship is due to low bone density of osteoporosis and compromised bone microarchitecture, leading to structural failure, decreased ability to withstand applied stresses, and increased propensity to fracture. Osteoporosis can be idiopathic or due to a variety of secondary causes, and numerous treatment strategies are available. FFs are common injuries among the elderly and are caused by factors both intrinsic and extrinsic to the patient. The clinical and economic significances of osteoporosis and FFs are substantial, with considerable associated morbidity and mortality, and billions spent on healthcare expenditures in the US annually. Osteoporosis and FFs are two of the most important topics related to fracture liaison services (FLSs), and their understanding is integral to appreciating the benefits an FLS can provide for patients and providers.

KEYWORDS: Osteoporosis; fragility fracture; pharmacotherapy; hip fracture; vertebral compression fracture

INTRODUCTION

Osteoporosis is the most common cause of low bone density. It derives its clinical significance from its predisposition to fractures, often caused by low energy injuries and termed "fragility fractures." Fractures of the spine and hips in osteoporotic individuals often result in deformity, loss of function, a variety of morbidities, and premature death. Osteoporosis is quite prevalent in the US with estimates of 40,000,000 adults suffering from low bone density.[1] Osteoporotic fractures, which are common, result in substantial morbidity and mortality, with a woman's lifetime risk of dying from a hip fracture roughly equivalent to her risk of dying from breast cancer.[2]

Secondary forms of osteoporosis can result from endocrine disorders, genetic mutations, and hematologic malignancies (**Table 1**). Other causes of secondary osteoporosis include physical immobilization, often from neuromuscular diseases, premature menopause, athletic amenorrhea, anorexia nervosa, and alcoholism. Common medications contributing to osteoporosis include glucocorticoids, oral hypoglycemics, anticonvulsants, proton pump inhibitors, and immune modulators. Adjuvant hormonal therapies for both breast and prostate cancer reduce bone density and increase the risk of fracture. Aromatase inhibitors deprive bone of estrogen. Gonadotropin-releasing hormone (GnRH) agonists produce androgen deprivation.[3]

Table 1. Common Causes of Secondary Osteoporosis

Endocrine	Genetic	Malignancies
Hypercortisolism	Marfan's Syndrome	Multiple Myeloma
Hyperparathyroidism	Ehlers-Danlos Syndrome	Monoclonal Gammopathies
Hyperthyroidism	Osteogenesis Imperfecta	Lymphomas
Diabetes	Fibrous Dysplasia	Leukemias
Hypogonadism	Pseudoglioma Syndrome	

Other important causes of secondary osteoporosis are related to end-stage organ failure and organ transplantation. The most rapid bone loss is observed in the first 3–6 months post-transplant and is multifactorial, with contributions from pre-transplant bone loss. Immunosuppressive agents, prominently glucocorticoids but also the calcineurin inhibitors, contribute to transplant-related bone loss. Cyclosporine and tacrolimus inhibit the enzyme calcineurin, which plays an important role in bone remodeling and whose inhibition results in increased bone resorption.[4] Other immunosuppressants such as rapamycin and mycophenolate mofetil (CellCept) do not contribute to post-transplant bone loss.[4,5] Post-transplant bone loss and fracture risk have been reported to range from 6–53% after cardiac, pulmonary, or liver transplantation.[6] Patients with chronic renal disease pre-transplant are especially prone to reduced bone density because of the decreased renal parenchyma and inability to convert cholecalciferol to the active form, 1,25 dihydroxy vitamin D. Bone density and fractures particular to specific organ transplantations have been described in detail.[4,6,7]

BONE STRUCTURE AND OSTEOPOROSIS

Bone is characterized, in part, by an ongoing remodeling process of resorption and formation of both osteoid, the organic

component of bone matrix, and mineral in the form of calcium hydroxyapatite. An imbalance in remodeling in favor of resorption results in the net reduction of bone tissue per unit volume. Osteoporosis is characterized histologically by low trabecular bone volume and number, cortical thinning due to endosteal reabsorption, increased bone porosity, and compromised bone microarchitecture. Notably observed are thin, discontinuous trabeculae that reduce the ability of bone to withstand applied stresses and predispose to structural failure or fracture (**Figure 1**). Structural compromises are due to bone resorption, reduced osteoid formation, and decreased mineralization.

The histopathologic characteristics of osteoporosis are reflected in conventional radiographic features that provide clues to reduced density of both cortical and trabecular bone and indicate the need for further investigation. Cortices normally occupy about 50% of the diameter of the diaphysis on the anteroposterior X-ray. Endosteal resorption, cortical thinning, and concomitant medullary canal widening reflect the presence of severe osteoporosis (**Figure 2**). Bone trabeculae normally align coincident with patterns of stress and loss of trabeculation can be an early indicator of decreased bone density. Tensile trabeculae are lost before compressive trabeculae. Loss of compressive trabeculae usually indicates severely reduced bone density (**Figure 3**).

Figure 1. Trichrome stain of trabecular bone

Metabolic bone histopathology can be highly characteristic and often diagnostic. **A:** Normal bone volume and trabecular thickness. **B:** Low bone volume (density) and thin discontinuous trabeculae.

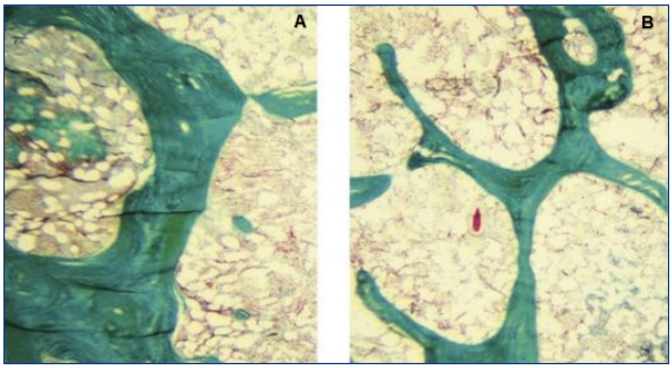

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Figure 2. AP X-rays of left hand

A: In normal bone, the two cortices of the third metacarpal occupy about ½ the width of the bone. **B**: Osteoporotic bone exhibits endosteal resorption of the cortices and widening of the medullary canal. An incidental distal radius fracture is seen.

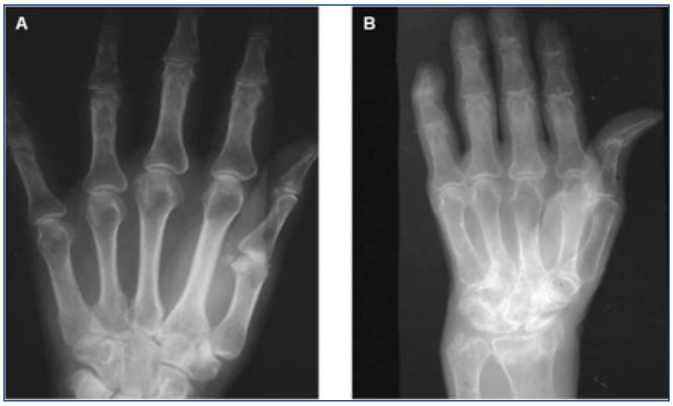

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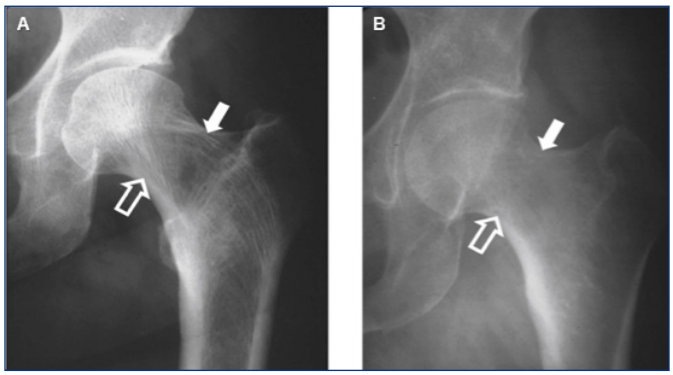
Figure 3. AP X-rays of left hip

A: In the normal proximal femur, thick cortices and well-defined tensile trabeculae (solid arrow) and compressive trabeculae (open arrow) are seen. **B**: In the osteoporotic proximal femur, trabeculae are not distinct due to resorption.



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CELL BIOLOGY

Osteoporosis results from an imbalance between osteoblastic bone formation and osteoclastic bone resorption in bone remodeling. Remodeling of bone consists of the coupled activity of osteoclasts and osteoblasts communicating by endocrine and paracrine signaling. In a remodeling cycle, osteoclasts first resorb bone matrix closely followed by osteoblastic new bone formation. Endocrine regulation by estrogen, thyroid and parathyroid hormones, glucocorticoids, and vitamin D acting through cell surface receptors is essential for maintenance of bone volume and structure. Receptors for bone morphogenic proteins and low-density lipoprotein receptor-related protein 5 (LRP5) have been found on osteoblast precursors. LRP5 functions as a Wnt receptor and is important for bone formation since deletion of LRP5 results in profound osteoporosis. The Wnt pathway is a complex, highly conserved signaling pathway that regulates cell fate commitment and is crucial in determining polarity and axis patterning in embryogenesis. The family of Wnt proteins regulate bone formation through the LRP5 receptor. Wnt signaling is regulated in part by sclerostin, a protein synthesized by osteocytes, that binds to the LRP5 receptor on osteoblasts and inhibits canonical Wnt signaling

resulting in a decrease in bone formation. Studies of the genetics of the osteoporosis pseudoglioma syndrome have shown mutations in the LRP5 gene.[8] Recently, biopharmaceuticals have been developed which inhibit sclerostin expression allowing greater Wnt binding to LRP5, resulting in enhanced activation of canonical Wnt signaling and preserving bone mass in the remodeling process.[8]

PATHOPHYSIOLOGY – BONE AS A CALCIUM DONOR

Maintenance of serum calcium concentration is a homeostatic priority because of the dependence upon it of cell membrane signal transmission including neuromuscular excitation-contraction coupling of skeletal and cardiac muscle. Responses to hormonal regulation, the conductivity of nerves, and the contractility of muscle are directly affected by cytosolic calcium concentration.[9] To accomplish this homeostatic regulation, parathyroid hormone and 1,25, dihydroxy vitamin D interact with three organ systems, renal, gastrointestinal, and skeletal, to regulate serum calcium concentration within appropriate levels to ensure both normal membrane transmission and the calcium-phosphorus solubility product. Among the organs maintaining serum calcium concentration, bone is unique in that its role as a calcium donor can compromise its structure and lead to decreased bone density and fractures. In fact, the role of bone as a calcium donor takes precedence over its structural roles of support, leading to the perspective that the primary function of bone is to act as the reservoir for serum calcium. Chronic, low-grade demand for serum calcium exerts a downward physiologic pressure on bone calcium stores and can lead to resorption of calcium from bone and osteoporosis. In response to serum calcium requirements, parathyroid hormone and vitamin D increase intestinal absorption of calcium, enhance renal tubular reabsorption of calcium, induce a phosphate diuresis, and produce osteolysis via osteocytic bone resorption. It is only bone that suffers a loss of structural integrity in this complex interaction to maintain serum calcium concentration.

DEXA SCANNING IN OSTEOPOROSIS

Bone density determination by dual-energy X-ray absorptiometry (DEXA) scanning is described in *The Roles of a Fracture Liaison Service* in this volume. The T-score is utilized as the DEXA criterion for osteoporosis. The World Health Organization has defined osteoporosis as either a T-score below -2.5 in men and postmenopausal women over 50, or a low-energy hip or spine fragility fracture regardless of bone mineral density. DEXA scanning is very useful in osteoporosis but, as pointed out, it must be appreciated that it does not provide a pathological cause of reduced bone density and needs to be interpreted in the whole patient context.

PHARMACOLOGIC TREATMENT OF OSTEOPOROSIS

Two therapeutic strategies are applied to the medical treatment of osteoporosis. Because bone loss is often due to overactive resorption, anti-resorptive agents are the first-line therapy, especially if excessive resorption is shown by bone turnover markers. Repairing microstructural damage requires the use of osteoanabolics. Prior to instituting pharmacotherapy, adequate serum calcium and vitamin D need to be assured and deficiencies corrected. Combining dietary and supplemental sources, about 1000–1200 mg/day of calcium and 1000–2000 IU/day of vitamin D for individuals with osteoporosis are recommended.

Pharmacotherapy needs to be tailored to the specific patient's medical condition, fracture history, DEXA scans, and laboratory evaluation. For example, oral agents may not be suitable for individuals with gastroesophageal reflux, Barrett's esophagitis, or bariatric surgery. Additionally, most medications have time limitations and long-term therapies are often complicated by the need for sequential prescriptions.

Oral bisphosphonates such as alendronate (Fosamax), risedronate (Actonel), and others, may be the agents of choice in mild to moderate osteoporosis. They exhibit different efficacies and durations of action but all are anti-resorptive.[3] They are analogues of pyrophosphate, bind to the surface of hydroxyapatite crystals, and inhibit osteoclastic bone resorption. Since they depend upon renal clearance, patients should have a creatinine clearance >30 ml/min. Bisphosphonates cannot be used for >5 years because of atypical femur fractures discussed in the section on fragility fractures below.

Denosumab (Prolia) is a human monoclonal antibody that acts as a decoy receptor for receptor activator of nuclear factor kappa-B ligand (RANKL) and inhibits the differentiation and activation of osteoclasts. It is an injectable anti-resorptive and may be a better choice for some patients who cannot take oral agents, assuming they can and will take adequate calcium supplements since it can lower serum calcium concentration. Denosumab increases the mineral density of the hip and spine and reduces resorptive bone markers to a greater degree than bisphosphonates. It has been shown to reduce hip and vertebral fractures by 40–60%. Denosumab is not dependent upon renal function and does not produce gastrointestinal symptoms. It has been associated with increased risks of a variety of infections, however, and should not be used in patients who are subject to recurrent infections, have impaired immune systems, or are on immunosuppressive agents.[10]

Two parathyroid hormone-related agents are of interest for their anabolic effects on building bone density. Parathyroid hormone (PTH) 1–34, teriparatide (Forteo) and the PTH-rP analogue, abaloparatide (Tymlos) produce both cortical and trabecular bone formation and reconnect discontinuous trabeculae. The parathyroid analog osteoanabolics should not

be used in individuals with risks of sarcomas. Patients need to be screened for possible bone malignancies and recommended usage is limited to 2 years.

FRAGILITY FRACTURES

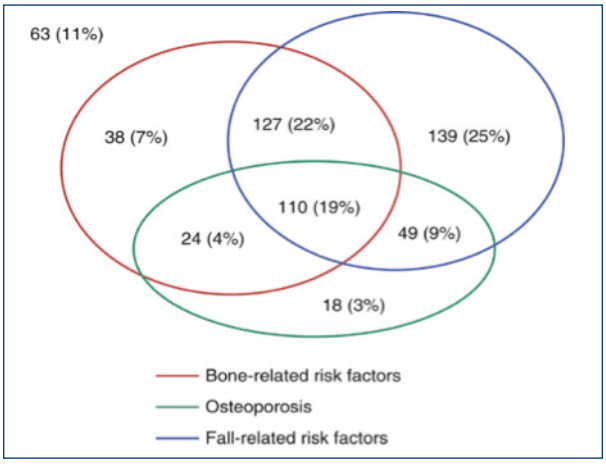
Fragility fractures, as defined by the International Osteoporosis Foundation, are fractures that result from low-energy trauma, such as a fall from standing height.[11] Common fragility fracture patterns include fractures of the distal radius, vertebrae, proximal humerus, hip, and pelvis.[12] Nine million fragility fractures occur annually worldwide, equating to one fracture every three seconds.[13,14] Approximately 1 in every 3 women and 1 in every 5 men over the age of 50 will experience an osteoporosis-related fracture during the course of their lifetimes, with these proportions anticipated to rise.[11,13,14] In 2010, there were an estimated 158 million individuals at high risk for fragility fracture and this figure is projected to double by 2040.[11,14,15] Individuals who experience fragility fractures incur an 86% increased risk of a subsequent fracture.[16] Among these individuals, between 5–10% of patients experience a subsequent hip fracture, with 23% occurring within a year of their first hip fracture and 70% within the first five years.[17] Patients with a history of vertebral osteoporotic fracture have a 2.3-fold increased risk of future hip fracture and a 1.4-fold increased risk of distal forearm fracture.[18] Given this data, it is important that primary care physicians and orthopedic surgeons collaborate to recognize, prevent, and treat osteoporosis.

THE IMPORTANCE OF FALLS IN FRAGILITY FRACTURES

Important associations with low-energy fractures are falls and poorly arranged living spaces contributing to falls. Falls are a major contributing cause of fractures and can be associated with muscle weakness, balance disturbances, and impaired vision and hearing that predispose to environmental distractions (**Figure 4**). One study identified bone-related and fall-related risk factors (**Table 2**) and, while these risk factors may overlap, the study points out the importance of falls in low-energy fractures.[19] Related contributions to falls and fractures are unsafe environments which can result from cluttered or obstructed walkways, poor lighting, insecure floor mats, unstable area rugs, unsafe bathrooms with slippery surfaces, and the absence of grab bars in showers and bathtubs. Iatrogenic contributions to propensity to fall center on medications such as sedatives and anti-hypertensives, as well as polypharmacy that leads to unsafe medication interactions. The physical and environmental contributions to fractures are not to be neglected and should be part of every screening conversation.

Figure 4. Illustration demonstrating the interactions of falls and low bone density in the fracture diathesis

Bone-related and fall-related risk factors interact with low bone density contributing to fractures.



(Adapted from reference 19 with permission.)

Table 2. Risk Factors for Fracture

Bone-Related Risk Factors	Fall-Related Risk Factors
Fracture history	>1 fall last year
Mother with fracture history	Psychoactive drugs
Body mass index (BMI) < 19	Low level of activities of daily living
Severe immobility	Articular symptoms
Glucocorticoids	Impaired vision
	Urinary incontinence
	Parkinson's Disease

(Adapted from reference 19 with permission.)

TREATMENT OF FRAGILITY FRACTURES

Several general principles exist among patterns of osteoporotic fracture presentations. For example, distal radius fractures, which are among the most common fragility fractures, can often be managed with closed reduction and splinting/casting as the first line of treatment.[20] Proximal humerus fractures can also often be managed nonoperatively when sufficiently well-aligned, with sling immobilization being a common first-line treatment modality.[21] Conversely, hip fractures are typically managed surgically with fracture fixation or replacement arthroplasty procedures to prevent complications related to immobility, such as deep venous thrombosis, pneumonias, and decubitus ulcers.[22] Specific patient characteristics, such as overall health, functional status, fracture morphology, and patient activity level, are essential to consider when deciding between operative or nonoperative management.

Fractures in the setting of osteoporosis are particularly challenging to treat for multiple reasons and require special consideration by the treating clinician. Osteoporotic bones are less dense than healthy bone, often leading to more comminuted, complex periarticular fracture patterns.[23] In addition to meticulous surgical technique, specialized implants (e.g., fixed angle or locking devices) and more robust implants may be required to obtain and maintain adequate fracture alignment in the operating room.[24] Due to the mechanical properties of osteoporotic bone resulting from porous cancellous and thin cortical bone, rigid implants must be used for added support and longevity. As such, implant loosening, implant retention, and peri-implant fractures are more common complications of osteoporotic fracture treatment.[25] Fragility fractures typically occur in elderly and metabolically depleted patients who have decreased capacity to manage their functional limitations and weight-bearing status, leading to increased falls and corresponding increased loading of the fixation constructs.[26] Additionally, elderly individuals often have marginal nutritional and hydrational status and other medical comorbidities making them more vulnerable to post-traumatic complications including infection, poor wound healing, and venous thrombosis. Brisk mobilization is desirable to counteract some of these morbidities adding to the challenges of stabilizing or replacing osteoporotic bone to facilitate early weight bearing.[27]

CONSIDERATIONS WHEN USING BISPHOSPHONATES

Bisphosphonates are first-line medications in the treatment of osteoporosis, but like most medications are associated with particular risks. Although concerns have been raised about retardation of fracture healing, studies have failed to detect differences in time to fracture healing and other outcomes with bisphosphonate use in surgically repaired hip and distal radius fractures.[13] Atypical femur fractures (AFFs) are an important clinical entity about which to be aware in patients treated with bisphosphonates, especially those patients treated for over 5 years. AFFs are defined by a characteristic type of subtrochanteric, short-oblique hip fracture originating in the lateral cortex of the proximal femur and occurring with no or minimal trauma (**Figure 5**).[28] AFFs may occur without prodromal symptoms or may be preceded by a dull, aching pain in the proximal thigh. This type of pain should not be disregarded. A high index of suspicion should be maintained for this fracture type in patients on long-term bisphosphonates, especially with thigh pain, and should stimulate imaging.[29] AFFs may appear as stress fractures on plain X-rays (**Figure 6**) but they also may be invisible on X-rays and seen only on MRIs. Therefore, patients presenting with proximal thigh pain and normal X-rays on long-term bisphosphonates should be studied with an MRI.

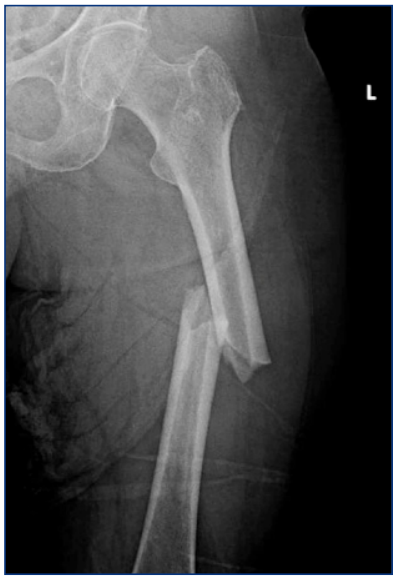
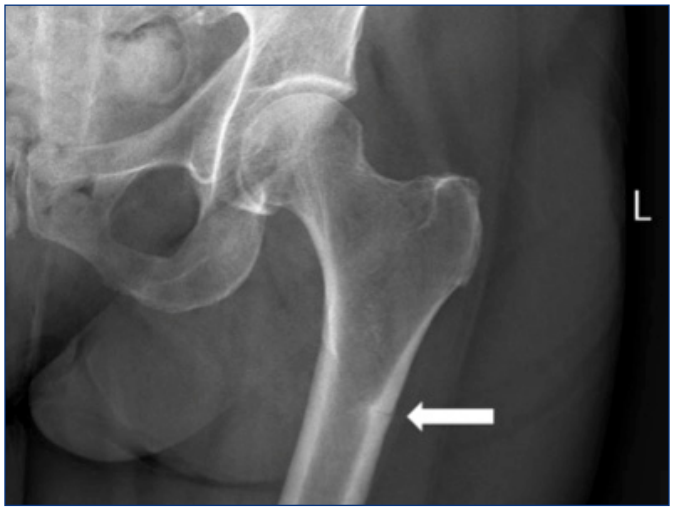


Figure 5.
AP X-ray of left femur
A short oblique atypical midshaft fracture with associated cortical thickening and beaking. Patient reported a history of antecedent left thigh pain and bisphosphonate therapy.

Figure 6. AP X-ray of left femur
Lateral proximal femoral cortical hypertrophy and a fracture line at the lateral cortex of the subtrochanteric region (arrow) observed in a patient with long-term bisphosphonate use. She presented with subtle, yet symptomatic, changes in her gait.



Although the relative risks of AFFs are high in patients on bisphosphonates, their absolute risk is extremely low, ranging from 3.2 to 50 cases per 100,000 person-years.[28] However, long-term use (>3 years) may be associated with higher risk (>100 per 100,000 person-years).[28] The risk-benefit ratio of bisphosphonates is highly supportive of their use assuming that the duration of use is kept below 5 years. An investigation of the cost-benefit of the risk of AFFs versus fragility fracture prevention with bisphosphonates analyzed 196,000 women who were aged 50 or older receiving bisphosphonates and concluded that reductions in the risk of osteoporotic hip fractures during 1–10 years of bisphosphonate use far outweighed the increased risk of AFF among White patients, with a less quantifiable effect among Asian patients.[30]

OUTCOMES OF FRAGILITY FRACTURES

Fragility fractures have a substantial impact on a patient's personal, family, and financial life. The impact of fragility fractures, particularly those of the hip, can lead to early morbidity and mortality. Patients often experience some degree of loss of function, primarily independent gait, and loss of overall personal and functional independence. Mortality in the first year after hip fracture surgery ranges between 15% and 36%.[31] Also, there are significant financial burdens placed on patients with fragility fractures, with those related to inpatient medical services, skilled nursing facilities, and homecare, comprising the highest expenses.[32]

PREVENTION OF FRAGILITY FRACTURES

Fragility fractures are, to a degree, preventable through assessment of risk and multimodal therapy. A full evaluation of risk factors should be carried out as described above. Antiresorptive agents are first-line medications that should be considered in patients identified as at-risk for fragility fractures. Certain modifiable factors, such as tobacco use and excessive alcohol intake, are detrimental to bone health. Therefore, cessation of tobacco use and limiting alcohol consumption should be recommended.[33] Adequate intake of calcium and vitamin D are important nutritional factors to consider. The National Osteoporosis Foundation recommends 1200 mg/day of calcium (from diet or supplement) as well as 800–1200 IU/day of Vitamin D for all adults over 50 years of age.[34] Weight-bearing exercise is another important consideration for high-risk patients.[33] A Cochrane review investigated the effect of exercise on prevention of bone loss and fractures in postmenopausal women and identified a statistically significant improvement of bone mineral density associated with exercise.[35] Since these fractures are commonly a result of falls, patient safety at home must be considered. Related recommendations include balance training exercises, avoiding central nervous system depressants, careful monitoring of hypertensive medication, and recommending visual corrective devices when needed.[36] Finally, the U.S. Preventive Services Task Force recommends bone mineral density testing in all women aged 65 years and older and in postmenopausal women younger than 65 years with increased risk as determined by a formal clinical risk assessment.[37] They currently do not recommend screening men due to insufficient evidence.

CONCLUSIONS

Osteoporosis is the most common cause of low bone density. It derives its clinical significance from its association with fragility fractures and their attendant morbidity and mortality. (1) Osteoporosis may be idiopathic, postmenopausal, or senile, and may result from multiple secondary causes as well; (2) cortical and trabecular resorption and porosity lead to structural weakness and predispose to fractures; (3) assuming appropriate causal diagnosis, pharmacologic treatments are available to increase bone density and decrease the risk of fractures; (4) falls are associated with osteoporotic fractures and can be due to both bone-related and fall-related factors as well as unsafe environments; (5) and despite state-of-the-art surgical therapy, fragility fractures often pose grave consequences in terms of morbidity and mortality, as well as economic, family, and personal costs.

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Osteomalacia and Renal Osteodystrophy

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ABSTRACT

Osteomalacia is defined by the undermineralization of newly formed bone due to a lack of available calcium, phosphorus, or vitamin D. Causative factors of osteomalacia include nutritional deficiency, diminished absorptive capabilities (often due to gastrointestinal disorders), and renal insufficiency. Renal osteodystrophy is a specific form of metabolic bone disease defined by the presence of osteomalacia and associated hyperparathyroidism secondary to a malfunction in, or absence of, renal parenchyma. This reduces the conversion of vitamin D to its active form, thus leading to a cascade of effects that negatively impact the stability of the skeleton. Osteomalacia occurs across a spectrum of severity and can produce severe consequences for specific populations, including patients with dietary, nutritional, and absorptive deficiencies. Renal osteodystrophy affects patients with chronic kidney disease, those undergoing dialysis, and renal transplant patients. Special considerations must be taken into account when assessing the bone health of patients fitting these criteria.

KEYWORDS: Osteomalacia; renal osteodystrophy; chronic kidney disease (CKD); reduced calcium absorption

INTRODUCTION

Osteomalacia is defined as "the lack of available calcium or phosphorus (or both) for mineralization of newly formed osteoid."[1] In classic papers, Henry Mankin, former chair of orthopedics at Harvard and Massachusetts General Hospital, reviewed the osteomalacias and the identification of vitamin D deficiency as the prototype of the disease.[2-4] He provided an etiological classification of the osteomalacias as deficiency, absorptive, and renal. In addition to vitamin D deficiency, osteomalacia can be produced by a variety of other conditions that impair mineralization (**Table 1**). The most common causes of osteomalacia are gastrointestinal disorders causing malabsorption, including enteric, hepatobiliary, and pancreatic diseases, short bowel syndrome, and some bariatric procedures. Less commonly these days, but still to be considered, are medications including the anticonvulsants phenobarbital, phenytoin, and carbamazepine, which can alter hepatic vitamin D metabolism. Renal osteodystrophy is a special case in which osteomalacia coexists with hyperparathyroidism.

Table 1. Etiological Classification of Rickets and Osteomalacia

I.	**Deficiency Rickets and Osteomalacia**
	A. Vitamin D deficiency
	B. Calcium deficiency
	C. Phosphorus deficiency
	D. Chelators in diet
II.	**Absorptive Rickets and Osteomalacia**
	A. Gastric abnormalities
	B. Biliary disease
	C. Enteric absorptive defects
III.	**Renal Tubular Rickets and Osteomalacia**
	A. Proximal tubular lesions
	B. Proximal and distal tubular lesions
	C. Distal tubular lesions (renal tubular acidosis)
	1. Primary
	2. Secondary
IV.	**Renal Osteodystrophy**

CLINICAL PRESENTATION

The clinical presentation of osteomalacia is often asymptomatic but, when severe, mainly reflects symptoms of hypocalcemia, including myalgias, muscle spasms, and bone pain. More severe symptoms related to hypocalcemia include tetany and seizures; chronic vitamin D deficiency can lead to long bone and limb angular deformities.[5]

Undermineralized newly formed bone is the hallmark of both osteomalacia and rickets, the juvenile form of osteomalacia. On radiographs, bones appear osteopenic often with a ground glass appearance and indistinct trabeculae. Stress fractures with radiodense lines adjacent to regions of radiolucency may be seen on the concave sides of bones. These are termed Looser lines, also called Milkman pseudofractures, after the aptly named radiologist, Louis Milkman, who described the radiological appearance of pseudofractures in osteomalacia (**Figure 1**). Characteristic osteomalacic

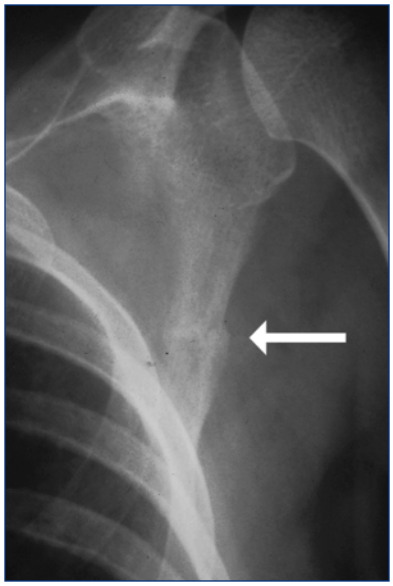

Figure 1. AP X-ray of left scapula
Looser line (Milkman pseudofracture) seen characteristically on the concave side of bone in osteomalacia (arrow).

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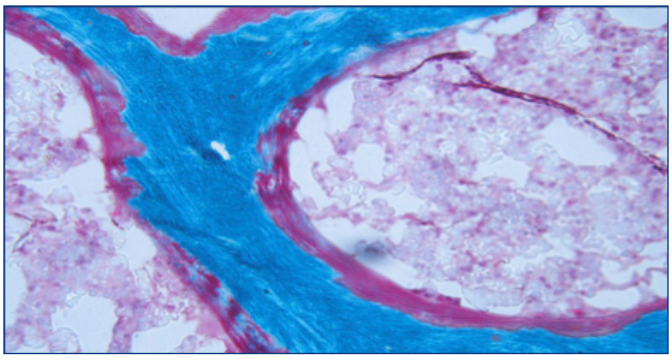
Figure 2. Histology and mineralization front in osteomalacia
Trichrome stain demonstrating unmineralized, thick osteoid borders (red) rimming the length of trabeculae.



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hip fractures resemble slipped femoral capital epiphyses and may occur over time with minimal symptoms. Stress fractures are common and may be seen by MRI and technetium bone scans; they may not be apparent radiographically until a healing callus is present. Histologic characteristics of osteomalacia are trabeculae covered with long, wide osteoid seams due to the lack of mineralization, contributing to the ground glass radiologic appearance of trabeculae (**Figure 2**). On bone biopsy with tetracycline labeling, smudged, indistinct tetracycline labels occur from the impaired mineralization.

PHYSIOLOGY OF DEFICIENCY OSTEOMALACIA

Apart from its structural function, bone serves as a reservoir for calcium.[1,4] Calcium plays a critical role in cell membrane signaling and neuromuscular signal transmission; there is a narrow range of safety for serum and cytosolic calcium concentrations. Hypercalcemia causes hypotonicity, hyporeflexia, obtundation, and coma, whereas hypocalcemia causes hypertonicity, hyperreflexia, and seizures. The homeostatic priority of maintaining soluble calcium concentration utilizes three organ systems to achieve rigorous control: the gastrointestinal, renal, and skeletal systems. The skeletal system is unique as a calcium donor because the downward pressure of transient calcium deficiency can lead to compromise of bone structure and increased fracture risk. In this context, bone resorption to maintain serum calcium homeostasis takes priority over the structural role of bone.[6]

Serum calcium exists in ionized and protein-bound forms, with the ionized form being metabolically active and critical for cell signaling. In states of decreased serum calcium, the body's homeostatic response includes regulation via PTH and vitamin D. Vitamin D is a fat-soluble vitamin which has two main sources: ergocalciferol is a plant-derived dietary source, and cholecalciferol, which derives from 7-dehydrocholesterol. After irradiation in the skin which opens these molecules' sterol rings, two hydroxylation steps take place.[7] The first occurs in the liver to form 25(OH)D, the storage form of vitamin D, and the second in the kidney to form 1,25 di(OH)D, the metabolically active form, or 24,25 di(OH) D which is less active and less regulatory. Active vitamin D raises serum calcium concentration by increasing intestinal calcium absorption, promoting a renal phosphate diuresis, increasing renal tubular reabsorption of calcium, and increasing the transfer of calcium from bone to serum. Parathyroid hormone stimulates the production of 1,25 di(OH) D, and both hormones increase serum ionized calcium concentration.[6] Vitamin D deficiency can be nutritional and has several other etiologies. Direct sunlight is required to irradiate dietary vitamin D and open its sterol rings. Individuals with reduced sunlight exposure, such as those who live in locations farther from the equator, can have lower serum vitamin D levels.[8] Additionally, heavily pigmented skin with high levels of melanin can affect the irradiation of vitamin D. Obesity and increased age can also result in reduced production of vitamin D to its active form.

DEFICIENCY RICKETS

Rickets is the juvenile form of osteomalacia and occurs in skeletons with open growth plates.[9] Because rickets and osteomalacia are failures of mineralization, it is not surprising that rickets is manifest largely in the physis (**Figure 3**). Deficiency in mineralization of the physis results in the growth of unmineralized cartilage reflected radiographically as cupping, widening, or flaring of the growth plate, with blurring of the mineralization front. Femoral neck fractures are characteristic of osteomalacia and resemble slipped capital femoral epiphyses. The prototype of the juvenile form is nutritional rickets, usually due to vitamin D or calcium

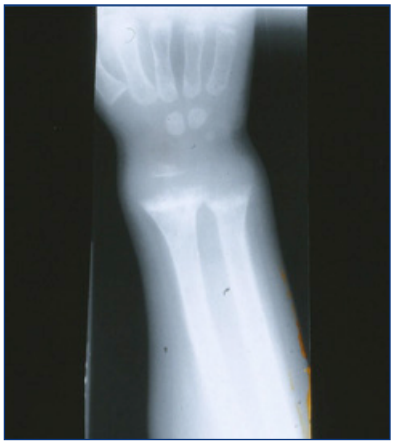

Figure 3. Epiphyseal plate in rickets
Radiograph of rachitic epiphyseal plate in the distal radius exhibiting cupping, flaring, and metaphyseal widening associated with deficient mineralization.

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deficiency. While rickets is less prevalent in the industrialized world, it is still present there in unusual situations. Rickets can be seen as a result of malnutrition in nutritionally deprived populations or as a result of individual dietary eccentricities and emotional eating disorders. Whether or not florid growth plate abnormalities are present, an index of suspicion should be maintained in children with the appropriate medical histories and atypical fractures. Bone density determination will assist in the diagnosis and detailed laboratory investigation is usually warranted.

ABSORPTIVE OSTEOMALACIA

A range of gastrointestinal conditions can cause malabsorption of nutrients and absorptive osteomalacia, decreased bone density, and fractures. Malabsorption of nutrients from the gastrointestinal tract has profound effects on the skeleton by depriving osteocytes of hormonal control and osteoid of its constituent calcium.[4] The subject of malabsorption is quite complex and, for our purposes, will be broadly considered in two forms.

(1) Pancreatic insufficiency, pancreatitis, cystic fibrosis, and hepatobiliary diseases, including cirrhosis and alcoholism, reduce the secretion of bile and pancreatic enzymes and impair the ability to digest and absorb fats including the fat-soluble vitamins, A, D, E, and K, contributing to an absorptive vitamin D-deficient osteomalacia and low serum 25(OH) D.

(2) Enteric malabsorption is due to the loss of absorptive surfaces of the duodenum and proximal jejunum. Loss of absorptive villi can be due to inflammatory diseases such as Crohn's disease, celiac disease, and sprue, surgical short bowel syndrome, or small intestinal bacterial overgrowth syndrome.

Other forms of absorptive osteomalacia occur due to intestinal binding of calcium. Calcium absorption from the gastrointestinal tract is regulated by vitamin D and PTH. Vitamin D is fat-soluble and is dependent on bile salts for absorption, which primarily takes place in the proximal duodenum and proximal jejunum. Chelating agents such as oxalate (in spinach), phytate (in coarse cereals), or excessive concentrations of phosphate or free fatty acids make calcium more difficult to absorb as calcium can bind to these molecules creating materials that are insoluble in body fluids.[3]

MALABSORPTION AND FRACTURES AFTER BARIATRIC SURGERY

Bariatric surgery has been very helpful to patients with morbid obesity. However, like many medical interventions, it has its risks and management challenges. Bariatric surgery can have negative consequences for the skeleton, including osteomalacia and increased risk of fractures.[10,11] Current procedures involve (1) Restriction or reduction in stomach size such as gastric banding and gastric sleeve procedures, and (2) Malabsorption procedures that bypass segments of the proximal stomach and small intestine such as the Roux-en-Y gastric bypass. The influences upon the skeleton that occur after surgery are specific to the procedure type, with the most pronounced metabolic abnormalities and bone loss seen after procedures that result in the most malabsorption.[12]

Bone disease among bariatric surgery patients is influenced by pre-operative abnormalities in bone and mineral metabolism related to morbid obesity. The effects of obesity on the skeleton can be profound and often center around vitamin D deficient osteomalacia secondary to sequestration of vitamin D in adipose tissue.[13] Vitamin D deficiency is often the source of hyperparathyroidism in obese individuals.

The hip is the most consistent site for bone loss after bariatric procedures. Measurements of hip bone density show losses in the range of 6–10% 1 year after bariatric procedures, and these can be seen for 10 years after surgery. The bone loss that occurs after bariatric surgery is likely multifactorial.[14,15] Proposed mechanisms include skeletal unloading, abnormalities in calciotropic hormones, and changes in gut hormones. Increased bone resorption can be assessed by elevated levels of the blood and urine bone resorption markers, NTX and CTX. Evaluation of bone biopsies up to 4 years after bariatric procedures have shown alterations in microarchitecture including decreased cortical thickness, declining mineralization, and increases in osteoid volume consistent with hypovitaminosis D and hyperparathyroidism.

The risk of fractures, including fragility fractures, in this clinical setting is increased at the hip, spine, and wrist (**Figure 4**). Management of nutritional deficiencies after bariatric procedures can often be done using high doses of ergocalciferol. After replacement, maintenance doses of calcium (1000-1200 mg/d) and vitamin D (2000 IU/d) can be used with monitoring of serum 25(OH)D, PTH, serum and urine calcium, and DEXA bone density with adjustment of supplements as necessary. Bone densities may decline but replacement therapy can often keep the densities out of the osteoporotic range.[16]

Figure 4. Vertebral compression fractures after bariatric surgery
X-ray showing multiple compression fractures (asterisks) and kyphoplasty (arrow).

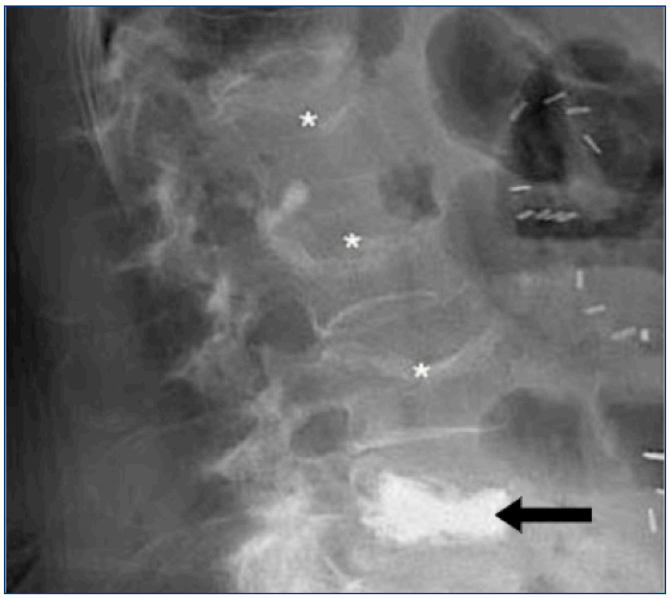
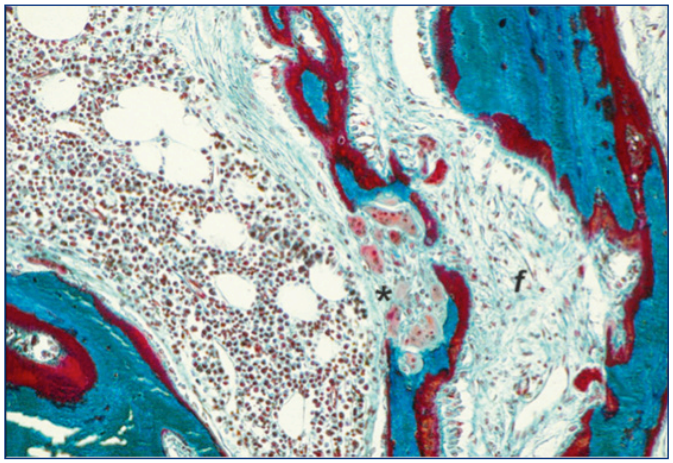


Figure 5. Histology in renal osteodystrophy
Osteitis fibrosa cystica comprised of (1) mineralization failure demonstrated by increased osteoid borders (red), (2) secondary hyperparathyroidism with osteoclastic resorption (asterisk), and (3) peritrabecular fibrosis ("f").



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RENAL OSTEODYSTROPHY

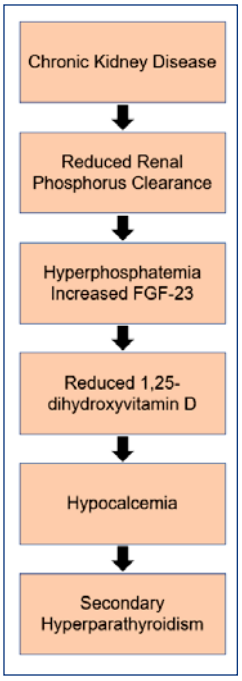
Patients with advanced kidney disease are at high risk of bone disorders that range from osteitis fibrosa to adynamic bone disease, also known as osteomalacia. Osteitis fibrosa is a result of overactivation of the parathyroid gland resulting in excess parathyroid hormone (PTH) release. This leads to increased bone turnover and, in advanced cases, brown tumor formation. Renal osteodystrophy denotes hyperparathyroidism, lack of osteoid mineralization (osteomalacia), and bone resorption, described previously as osteitis fibrosa cystica (**Figure 5**). Isolated osteomalacia is a result of over-suppression of the parathyroid gland decreasing PTH release. This results in decreased osteoclast and osteoblast activity and low bone turnover, leading to the formation of brittle bones that are prone to fractures. In addition to direct bone pathology, calcium, phosphorous, and PTH dysregulation leads to increased cardiovascular disease from vascular calcification. Hormones and minerals involved in the process include PTH, Fibroblast Growth Factor-23 (FGF-23), 1,25-dihydroxyvitamin D (calcitriol), calcium, and phosphorous (**Table 2**).

The nephron is the functional unit of the kidney, and each kidney is comprised of approximately one million nephrons. Nephrons are responsible for converting 25-hydroxy vitamin D, the inactive storage form, to 1,25-dihydroxyvitamin D (calcitriol), the metabolically active form of vitamin D. With a loss of renal parenchyma, the ability to produce active vitamin D decreases. Nephrons also regulate phosphorus homeostasis by excretion and reabsorption as needed. Nephrons are a target of FGF-23, PTH, and calcitriol. The exact mechanisms of interaction are not fully understood, but studies are ongoing. In chronic kidney disease (CKD), the number of functioning nephrons decreases over time. The physiology of CKD is summarized in Table 2. As the quantity of nephrons decreases in advanced CKD, phosphorous excretion diminishes, resulting in elevation of serum phosphorus concentration. Osteocytes sense this elevation in serum phosphorous and secrete FGF-23 which acts on the nephron and enhances phosphaturia. In addition to phosphaturia, FGF-23 also suppresses the synthesis of calcitriol. As the CKD progresses, phosphorous excretion

Table 2. Physiology & Actions of Hormones in CKD

Hormones/ Mineral	Phosphorus	FGF-23	1,25-DiOH-D (Calcitriol)	PTH
Physiology of CKD	Serum concentration increases as CKD progresses.	FGF-23 levels increase as serum phosphorus levels increase.	Calcitriol levels decrease as FGF-23 levels increase and nephron mass decreases. Calcium concentration decreases	Low serum calcium concentration and calcitriol leads to PTH secretion and increase bone resorption.
Resultant Action of Hormone	↑ FGF-23 ↑ PTH ↓ Calcitriol	↑ Phosphorous excretion in urine ↓ Serum phosphorus ↓ PTH ↓ Calcitriol	↑ Gut calcium absorption ↑ Gut phosphorus absorption	↑ Phosphorus excretion in urine ↑ Calcitriol

Figure 6. Mechanisms of CKD progression leading to secondary hyperparathyroidism.



is further impaired, FGF-23 secretion increases, and calcitriol levels decrease, ultimately resulting in hypocalcemia. These changes lead to a metabolic imbalance resulting in overactivation of the parathyroid gland and excess PTH secretion (**Figure 6**). Elevated PTH contributes to the release of calcium and phosphorous from bone, which further activates the FGF 23-vitamin D-PTH axis leading to osteitis fibrosa cystica, reduction in bone density, and resistance to fracture. Therefore, it is essential that patients with advanced CKD limit their phosphorous intake.[17] Patients on dialysis lose almost all of their ability to excrete daily phosphorous load. Even small amounts of dietary phosphorous intake will lead to significant serum accumulation.

Some degree of PTH elevation is thought to be protective of bone health by maintaining appropriate amounts of bone turnover in CKD.[18] Serum concentration above 80 pg/ml of intact PTH is diagnostic of hyperparathyroidism. Secondary hyperparathyroidism can be diagnosed if the PTH level is elevated above 80 pg/ml, advanced CKD is present, and serum calcium level is normal. Aggressive suppression of PTH to below 80 pg/ml in CKD leads to adynamic bone diseases and other adverse effects.[19] The target treatment range for elevated PTH is unclear, but expert guidelines suggest that PTH levels of 2–10 times the upper limit of normal are acceptable.[20] Progressive increase in serum PTH level, even if within the therapeutic range mentioned above, warrants intervention to prevent tertiary hyperparathyroidism. Intervention can be in the form of reducing serum phosphorus levels through dietary modification, starting patients on a phosphate binder with meals, using vitamin D analogs like paricalcitol and hectorol, or adding a calcimimetic such as cinacalcet if the PTH continues to rise. Parathyroidectomy is reserved for patients with tertiary hyperparathyroidism. Conversely, over-suppression of PTH by administering a vitamin D analog or a calcimimetic will lead to adynamic bone disease resulting in brittle bone and increased risk of fracture.

DIALYSIS

Patients on dialysis lose their ability to excrete the recommended dietary phosphate load and therefore are asked to limit phosphorous intake to less than 800 mg/day.[21] At times, this becomes challenging given the abundance of phosphorous in foods generally considered healthy, such as dairy products, beans, grains, and nuts. Phosphorous is cleared by dialysis mostly via diffusion. This clearance is limited to 800–1200 mg per dialysis session.[22,23] In our current dialysis delivery structure, patients receive dialysis three times a week. Based on this, patients are in a net positive phosphorus balance for 4 out of 7 days per week. Even with dietary phosphorus binders, it becomes challenging to regulate serum phosphorus concentration as there is active calcium and phosphorus release from bones driven by PTH secretion.[22,23] Therefore, an aggressive dietary phosphorous restriction is recommended to avoid hyperphosphatemia, elevated FGF-23, decreased serum calcium concentration, elevated PTH secretion, and increased bone resorption.

TRANSPLANTATION

Kidney transplant recipients may also experience calcium, phosphorus, and bone pathology due to adverse interactions among the parathyroid gland, kidney, and bone. Most transplant recipients with an adequately functioning transplanted kidney do not experience these pathologic interactions, but, depending on their transplanted kidney function, they may need to modify their dietary habits and regulate phosphorus intake. Studies have shown that hypophosphatemia leads to improved transplant graft survival and improved cardiovascular mortality.[24] This is thought to be due to enhanced phosphorus from functioning transplanted graft, leading to a reduction in FGF-23 level, which is linked to cardiovascular mortality.[24,25] Depending on the length of end-stage renal disease status, previous phosphorus control, and PTH levels, transplant patients are often at risk of tertiary hyperparathyroidism requiring parathyroidectomy. They are also at risk of severe hypocalcemia post parathyroidectomy due to hungry bone syndrome. In end-stage renal disease patients, persistently elevated PTH levels deplete bone of calcium and phosphorus stores. Once the parathyroid gland is removed, calcium and phosphorus are aggressively taken up by bone. This leads to a precipitous drop in serum calcium and phosphorus concentration risking acute arrhythmia and respiratory failure if unaddressed.

As kidney disease advances, either in the native or transplanted kidney, phosphorous excretion declines leading to hyperphosphatemia. This leads to elevation of FGF-23 and decreased calcitriol synthesis resulting in hypocalcemia. Hypocalcemia leads to increased elevation of PTH. Persistent, unregulated elevation of PTH can lead to tertiary hyperparathyroidism and osteitis fibrosa. Conversely, over-suppression of PTH via administration of calcitriol can also have negative consequences in the form of osteomalacia. Therefore, it is essential that patients regulate their phosphorus intake to prevent hyperparathyroidism and maintain good bone health.

CONCLUSIONS

Pathologically low serum vitamin D has profound effects on the skeleton including hormonal dysregulation of osteocytes and mineralization deficiency. (1) Reduced gastrointestinal calcium absorption exerts a downward pressure on serum calcium concentration that can lead to secondary hyperparathyroidism to maintain serum calcium but at the expense of bone calcium and resulting decreased bone density. (2) In all forms of osteomalacia, the structural function of the skeleton is sacrificed to maintain serum calcium concentration, resulting in loss of skeletal mass, reduced bone density, and elevated fracture risk. (3) Renal osteodystrophy consists of osteomalacia, secondary hyperparathyroidism, and bone resorption. The lack of renal parenchyma in CKD results in an inability to convert 25(OH)D to its active form and diminished phosphate excretion leading to hyperphosphatemia and hypocalcemia.

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Monoclonal Gammopathies in a Fracture Liaison Service

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ABSTRACT

Monoclonal gammopathies are a spectrum of disorders characterized by the overproduction of plasma B-cells and immunoglobulin. Monoclonal gammopathy of uncertain significance (MGUS), a pre-malignant form of multiple myeloma, is defined by relatively low bone marrow concentration of clonal plasma cells and asymptomatic clinical presentation. New evidence, however, points to an association of MGUS with osteoporosis, microarchitectural bone deficiency, and fractures, and it has been suggested that it be renamed "Monoclonal Gammopathy of Skeletal Significance." The prevalence of MGUS in the general geriatric population is estimated to be 3–8%, while the prevalence in geriatric vertebral fracture patients is 15%, and the prevalence in all fracture patients within the Rhode Island Fracture Liaison Service is 10%. Therefore, MGUS and other monoclonal gammopathies should be suspected in all patients diagnosed with osteoporosis or an osteoporotic fracture, and patients diagnosed with monoclonal gammopathies should be evaluated for osteoporosis and fracture risk and treated appropriately.

KEYWORDS: monoclonal gammopathy of undetermined significance; multiple myeloma; plasma cell neoplasms; fractures

INTRODUCTION

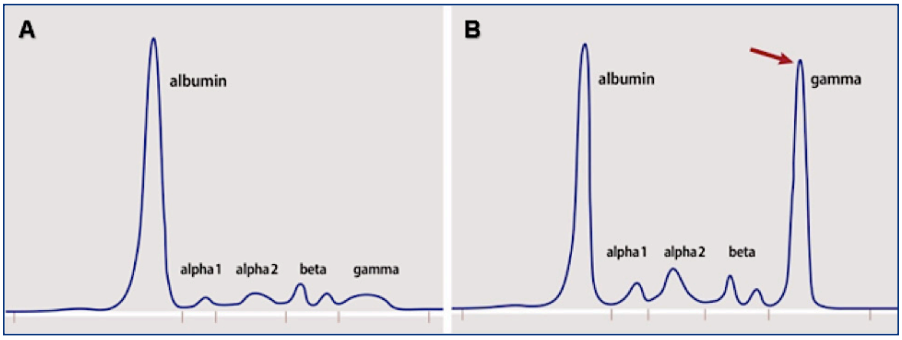
Monoclonal gammopathies represent a spectrum of bone marrow disorders caused by clonal expansion of plasma B-cells that overproduce an immunoglobulin, or monoclonal paraprotein, with consequences that are similarly variable. The most common resulting malignancy is multiple myeloma (MM), which is characterized by >10% of these plasma cells in the bone marrow with end-organ dysfunction such as hypercalcemia, renal dysfunction, anemia, and bone lesions, also known as "CRAB" signs. Multiple myeloma is the second most common hematologic malignancy, and will likely be diagnosed in over 30,000 Americans this year. At the other end of the monoclonal gammopathy continuum is monoclonal gammopathy of unknown significance (MGUS), a pre-malignant condition defined by low bone marrow concentrations of clonal plasma cells (<10%) and thus low circulating serum monoclonal protein. It is characterized by clinically asymptomatic disease without constitutional symptoms, anemia, lymphadenopathy or hepatosplenomegaly. It is becoming clearer that, despite its name, MGUS is rarely of no clinical significance, with subcategories including monoclonal gammopathy of renal significance (MGRS)[1], monoclonal gammopathy of neurological significance[2], and the proposed monoclonal gammopathy of skeletal significance, indicating that low circulating monoclonal protein concentrations may still have limited but important end-organ effects.[3,4] Blurring the line between the two extremes is smoldering multiple myeloma (SMM). Monoclonal gammopathies can also result in the development of solitary plasmacytoma of bone, solitary extramedullary plasmacytoma, light chain (AL) amyloidosis, or Waldenström Macroglobulinemia.

CLINICAL FEATURES OF MGUS

MGUS is the most common monoclonal gammopathy, found in approximately 3% of adults over age 50 and in 5% of adults older than the age of 70.[5] Interestingly, one study found the risk of MGUS to be 3.6% in patients with osteoporosis and 2% in those patients without osteoporosis.[6] Another study of patients with acute osteoporotic vertebral fractures found the risk of MGUS to be up to 15%.[7] The rate of progression from MGUS to MM over a lifetime varies, based on the amount of monoclonal paraprotein, the involved to uninvolved free light chain ratio, and the immunoglobulin isotype.[8] The average risk of progression is approximately 1% each year.[9] This is a linear risk as long as significant growth of the plasma cell clone does not move patients from the diagnosis of MGUS to smoldering multiple myeloma. Lifetime risk depends upon age at diagnosis. For a 65-year-old individual with an estimated life expectancy of 20 years, the risk can be considerable and justifies close follow-up.

Screening laboratory studies for monoclonal gammopathies should include serum protein electrophoresis (SPEP) with immunofixation (IFE), kappa and lambda free light chains with ratio, and quantitative immunoglobulins (IgG, IgA, IgM). If a patient has a non-IgG paraprotein, an abnormal serum free light chain ratio, a serum monoclonal protein of 1.5 g/dL or more, or a symptom concerning for multiple

Figure 1. Serum protein electrophoresis
A: Normal. **B**: M-spike in the gamma region (arrow).



myeloma, bone marrow assessment is recommended.[10] M protein spikes of over 3g/dL are more likely to be associated with malignancy while spikes under 3g/dL are usually not. However, a significant number of patients with myeloma may have a low M spike and, therefore, all patients with M spikes need oncologic evaluation. Most of the clinical interest is focused on the gamma region of the SPEP which contains primarily IgG immunoglobulins. **Figure 1** displays an SPEP with a large M spike in the gamma region representing a monoclonal gammopathy. Approximately 70% of MGUS is comprised of IgG, 15% of IgM and 12% of IgA.

MGUS, OSTEOPOROSIS AND FRACTURE

A consensus panel identified MGUS as a "non-malignant B-cell disorder (that) is the most common plasma cell dyscrasia and is associated with an increased risk of developing serious B-cell disorders."[11] This group pointed out that, from the perspective of the skeleton, individuals with MGUS have an increased risk of osteoporosis and osteopenia and an increased likelihood of developing fractures, especially in the vertebrae. Because of the prevalence of vertebral compression fractures, MGUS patients with significant back pain should be evaluated by MRI to rule out both vertebral fractures and myeloma. Given that MGUS is associated with a higher risk of osteoporosis/osteopenia and associated skeletal complications, especially fractures, it was recommended in the consensus statement that anyone with age-inappropriate or atypical bone loss undergo screening for the presence of a monoclonal gammopathy.[11] It was further recommended that MGUS patients who have evidence of vertebral compression fractures or who are osteoporotic be initiated on anti-resorptive therapy, and that MGUS patients with osteopenia be strongly considered for treatment as well. Bisphosphonates have been shown to improve bone density in the setting of monoclonal gammopathies. Other studies have confirmed that MGUS is a risk factor for fracture, particularly in the vertebrae, and have reported that vertebral compression fractures in patients with MGUS may be asymptomatic and may occur in patients without osteoporosis but still may be predictors of subsequent fractures. In one report, 18.4% of MGUS patients had at least one vertebral compression fracture and none were traumatic in nature.[12] Concordant data from US and European studies in largely Caucasian populations have suggested that overall fracture rates are increased approximately 1.7-fold, and vertebral fractures are increased up to approximately 6.3-fold in MGUS subjects when compared to the general population.[3] The observations that MGUS is associated with an increased risk of fractures has been supported by other studies showing that the risk of fracture at any anatomic site is 1.4–2.5 times greater in MGUS than in control populations.[13,14] Because of the propensity to fracture, the International Myeloma Working Group has recommended bisphosphonates for all MGUS patients with either osteopenia or osteoporosis.[15]

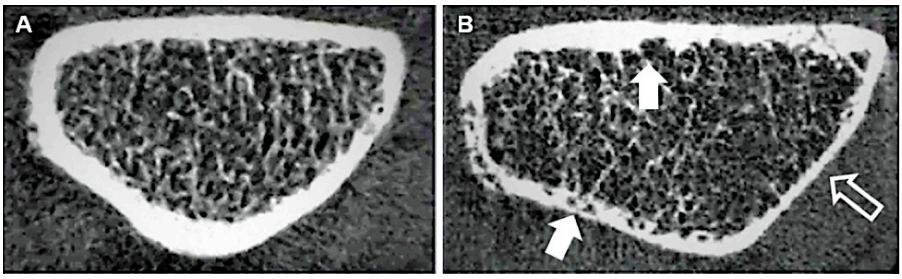
Having established the increased prevalence of fractures in MGUS patients, it is of substantial importance to examine the inverse: the prevalence of MGUS in the fracture population. Previously unrecognized MGUS is a relatively common finding in patients with fractures, as evidenced by a recent study which demonstrated that 6% of otherwise healthy subjects aged 50 years and older who sustained a hip fracture had MGUS.[16]

Understanding the mechanisms of bone loss in MGUS is of importance since the majority of these patients do not receive any therapy to increase bone density despite a substantially higher tendency to fracture. Monoclonal gammopathies are associated with excess bone resorption as assessed by increased levels of N-telopeptide of type I collagen. In one study of bone biopsies in 87 patients evaluated for MGUS, 45% of MGUS patients had criteria for excess bone resorption compared to 79% patients with indolent multiple myeloma and 93% of patients with overt myeloma.[17] Bone resorption was more frequent (52%) in MGUS patients that had progressive disease and subsequently developed myeloma. This study concluded that excessive bone resorption in MGUS is associated with progression and is an early sign of malignancy.

It has also been shown that MGUS patients have increased osteoclastogenesis and abnormally high bone resorption producing deterioration of skeletal microarchitecture and reduction in bone strength and ability to resist stress, leading to fracture.[3] Two studies have shown that patients with MGUS exhibit decreased bone mineral density at the proximal femur. High-resolution QCT has demonstrated decreased cortical and trabecular thickness, widening of the endosteal canal, increased cortical porosity, and increased bone width,

Figure 2. Distal radius showing trabecular and cortical bone

A: Normal. **B**: MGUS showing widening of the medullary canal, thinning of trabeculae, thinning of the cortex (open arrow), and porosity of the cortex (solid arrows).



all typical features of osteoporosis.[18,19] (**Figure 2**) The trabecular number and separation did not differ between the different groups. Micro-finite element analysis revealed that these microarchitectural alterations contributed to decreased biomechanical strength with an 8.9% reduction in the apparent modulus of elasticity.[3] Together, these observations characterize structural abnormalities in cortical and trabecular bone that result in decreased bone strength and contribute to the reduced ability of bone in MGUS to withstand applied stress and a heightened susceptibility to fracture.

Although over 20 cytokines that suppress osteoblast function or enhance osteoclast activity have been identified in multiple myeloma, few have been studied in MGUS. Two that are active in both myeloma and MGUS are macrophage inflammatory protein-1 alpha (CCL3/MIP-1α), a macrophage chemokine that, among other things, activates osteoclasts and is seen in inflammatory conditions associated with bone resorption (i.e., rheumatoid arthritis), and dickkopf-related protein 1 (DKK1) that inhibits the Wnt/β-catenin signaling pathway by blocking LRP6 receptor interactions and is seen in both myeloma and osteolysis. Circulating levels of the osteoclast activating factor, CCL3/MIP-1α, have been shown to be increased nearly 6-fold and circulating levels of the osteoblast-suppressive factor DKK1 are increased approximately 2-fold in MGUS patients compared to age, sex, and body mass matched control subjects.[18] These cytokines contribute to producing osteoporosis in monoclonal gammopathies. Since so few of the cytokines active in bone destruction in myeloma have been studied in MGUS, it may be that cytokines other than those described may also participate in reducing bone density and increasing fracture risk in MGUS.

MGUS IN THE RHODE ISLAND FRACTURE LIAISON SERVICE

The National Osteoporosis Foundation has reported that over 60% of American adults over the age of 50 will sustain fragility fractures.[20] Frequently, it is in the treatment of these fractures that monoclonal gammopathies are diagnosed. Accordingly, laboratory evaluation of low bone mass in our FLS will occasionally detect conditions that require further evaluation. SPEP is a useful screening test for identifying monoclonal gammopathies and is performed on patients evaluated for decreased bone mass and osteoporotic fractures. In our FLS, of 265 consecutive patients with osteoporosis and fracture, we diagnosed 27/265 (10%) with MGUS. This is compared to a report of 6% of fracture patients with MGUS.[16] Since about 1%/year of patients with MGUS develop multiple myeloma or other malignant monoclonal gammopathies, depending upon the patient's age at diagnosis, the lifetime cumulative risk can be substantial. The finding of MGUS requires oncologic evaluation and lifelong follow-up. Since MGUS has a higher risk of fractures than do age- and gender-matched cohorts without gammopathies, it is not surprising to find a higher prevalence of MGUS in fracture patients and in an FLS than in the general population. In addition to MGUS, the FLS has found 10 patients with a variety of hematologic malignancies including multiple myeloma, Waldenström macroglobulinemia, chronic lymphocytic leukemia, mast cell leukemia, and lymphomas.

MULTIPLE MYELOMA, OSTEOPOROSIS, AND FRACTURE

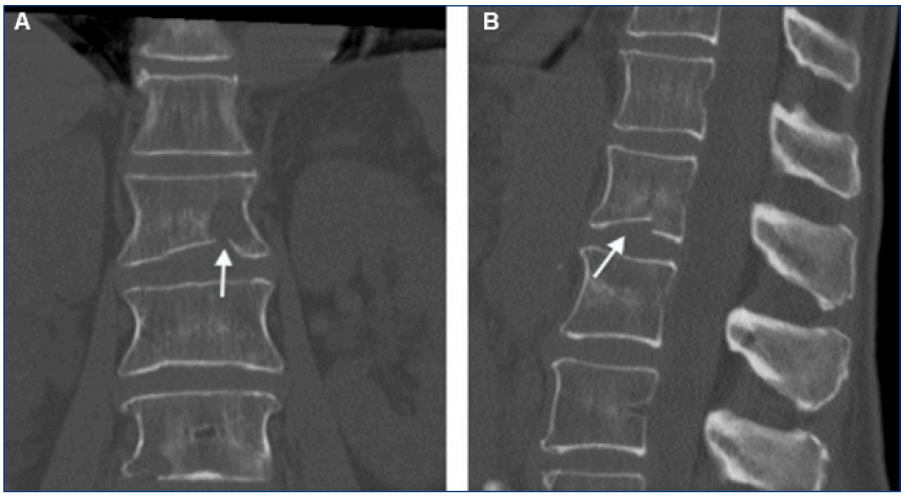
Multiple myeloma is one of several hematologic malignancies associated with decreased bone density, including lymphoproliferative diseases and Waldenström macroglobulinemia. Myeloma is a malignancy of plasma cells, which develop from B lymphocytes, and is characterized by IgG paraprotein. Decreased bone density can be diffuse in myelomatosis or localized in plasmacytomas. In a fracture liaison service, evaluation of decreased bone density by SPEP will usually detect abnormalities in the IgG region which can be explored in more detail with immunoelectrophoresis.

A typical antibody is characterized by 2 IgG heavy chains and 2 IgG light chains. Two types of light chains exist, kappa and lambda, each encoded by a separate gene. Monoclonal IgG light chains produced by malignant plasma cells are called Bence-Jones proteins and are associated with myeloma. Abnormal IgG proteins can be further characterized by immunoelectrophoresis and the concentration of kappa and lambda light chains can be quantified. The typical ratio of free kappa to lambda is 0.26:1.65. Alterations in this ratio are associated with malignancies.

Of the potential end malignancies associated with monoclonal gammopathies, the best studied for bone disease is MM. The complex pathophysiologic effects can be distilled into bone destruction and failure of bone formation.

Figure 3. CT of the spine in multiple myeloma

A: A lytic lesion can be seen on the AP view of the spine (arrow) and **B**: end-plate fracture on the lateral view (arrow).



Numerous factors have been described in this dynamic imbalance in bone homeostasis. The Notch signaling pathway influences the receptor activator of nuclear factor kappa-B ligand (RANKL) and the osteoprotegerin (OPG) system, activating osteoclasts and inhibiting osteoblasts. This signal is amplified by tumor necrosis factor (TNF) secreted by malignant plasma cells.[21] CCL3 (MIP-1α) has also been implicated as a chemokine that influences osteoclast differentiation and inhibition of osteoblast activity.[22] More recently, extracellular vesicles have been implicated in promoting this osteoblast/osteoclast imbalance, and represents a potential therapeutic target.[23] The results may include osteopenia, osteoporosis, lytic bony lesions, and fractures (**Figure 3**). These can be widespread but often have a predilection for the spine, skull, and long bones. Lytic lesions rarely appear in patients below the elbow or below the knee.

For adults in the United States over 50 years of age, the prevalence of osteoporosis and osteopenia is approximately 12% and 43%, respectively.[24] By comparison, bone lesions and bone density changes occur in 80% of patients with MM.[25] While there is a demonstrated increased fracture risk in MGUS, up to 74% in one study, the mechanism is not well understood, and recent studies have not found an associated decrease in bone mineral density or higher rate of progression to MM in patients with MGUS and fracture.[26]

Skeletal events have an important effect on mortality for patients with MM. One study found that patients diagnosed with MM at the time of a fracture have a 28% higher risk of death than patients with new MM and no fractures.[27] Another study found that patients requiring up-front radiation therapy for treatment of painful bony lesions have an increased risk of death compared to those patients who do not require radiation at diagnosis.[28] Even after MM diagnosis, patients who develop a fracture have a 2-fold increased risk of death compared to those without fractures, highlighting the importance of bone health in patients with monoclonal gammopathies.[27] The treatment of MM often involves bone strengthening measures including supplemental calcium and vitamin D. Aggressive use of bisphosphonates or RANKL inhibitors are recommended for patients with multiple myeloma to reduce risk of fracture.[29] Currently, there are no guidelines advocating for bone-modifying agents in patients with MGUS without concurrent fracture or reduced bone density.[30]

WALDENSTRÖM MACROGLOBULINEMIA

Waldenström macroglobulinemia is one of a closely related group of plasma cell malignancies that can present with osteoporosis and fractures. Plasma cells develop from B lymphocytes in bone marrow and lymph nodes and produce diverse groups of antibodies. Dysregulated plasma cell multiplication produces clonal expansion and the production of incomplete antibodies or, M-proteins (IgM), related to multiple myeloma and monoclonal gammopathies. Men are affected more than women and the average age of onset is 65 years. The etiology is unknown.

In addition to osteoporosis and fractures, patients with macroglobulinemia may have anemia, hyperviscosity syndrome, cryoglobulinemia, hepatosplenomegaly, lymphadenopathy, hemorrhage, and recurrent bacterial infections. In one study, 1/3 of patients' DEXA scans had hip T-scores of <–2.0 and 15/45 (33%) of patients had a vertebral compression fracture. In a study of 45 bone biopsies in patients with elevated IgM (36 men and 9 women), 2/3 of the abnormal antibodies were composed of kappa chains. Structurally, the bone abnormalities were comprised of both reduced formation and excessive resorption. Bone formation rates and mineralization surfaces were decreased and microresorptive osteoclastic surfaces were increased, contributing to bone fragility and inability to repair microdamage.

The initial diagnosis of Waldenström macroglobulinemia is suggested by an abnormal SPEP. Immunofixation studies will characterize the abnormal immunoglobulin. Treatment of Waldenström macroglobulinemia is with one of several chemotherapeutic agents, such as ibrutinib and rituximab, often in combination with corticosteroids. While helpful in controlling the clonal expansion of plasma cells, the treatment may not help, or even worsen, the osteoporosis.

CONCLUSIONS

Despite the original characterization of MGUS as a condition of "undetermined significance," there is now clear epidemiologic evidence that patients with MGUS have a significantly increased fracture risk and that the prevalence of MGUS is increased in patients with osteoporosis and fractures.[3] Because MGUS is associated with a significant prevalence of microarchitectural bone deficiency and a greater risk of fracture than age and gender-matched cohorts without gammopathies, it has been proposed that the term "MGUS" be replaced by the term, "monoclonal gammopathy of skeletal significance."[3] (1) The prevalence of MGUS in the geriatric population has been reported to be 3–8%; 15% in vertebral fractures, 6% in hip fractures, and, in our FLS, 10% of all fractures. (2) The prevalence of fractures in MGUS is 18% in vertebral fractures. Concordant data suggest that overall fracture rates are increased approximately 1.7-fold, and vertebral fractures are increased to approximately 6-fold.[3] (3) MGUS should be suspected in patients referred to an FLS, or those with osteoporosis on DEXA, and patients should not just be given treatment for osteoporosis without an evaluation including for MGUS. (4) Orthopedic surgeons, and FLS programs, are in unique positions to screen for and identify metabolic bone diseases that have substantial implications for appropriate skeletal therapy. Identification of MGUS is a contribution to bone health, and even longevity, that evaluation of osteoporosis and fractures should not ignore.

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Hyperparathyroidism in a Fracture Population

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ABSTRACT

Primary hyperparathyroidism (PHPT) is a common endocrine disorder that results in excess parathyroid hormone (PTH) secretion and hypercalcemia. PHPT is usually caused by an adenoma and its presentation is often asymptomatic, though it can negatively impact the skeleton via osteoporosis mostly affecting cortical bone and fracture. The diagnosis of PHPT is made by clinical presentation and biochemical and hormonal assessment. Surgical treatment guided by ultrasound sonography and/or ^{99}mTc-sestamibi scintigraphy is generally curative. Normocalcemic hyperparathyroidism (NPHPT) is a variant of hyperparathyroidism defined by normal serum calcium and persistently elevated serum PTH levels. Limited data exist on NPHPT's effects on the skeleton, though current evidence suggests a positive correlation between the disorder and the presence of osteoporotic fractures. Taken together, patients affected by the various manifestations of hyperparathyroidism and their associated homeostatic disturbances represent a not insignificant portion of fracture patients seen in a fracture liaison service.

KEYWORDS: hyperparathyroidism; bone density; osteoporosis; fracture

INTRODUCTION

Primary hyperparathyroidism (PHPT) is an endocrine disorder that is associated with hypercalcemia as a result of overactive or unsuppressed parathyroid hormone (PTH) secretion. It is among the most common endocrine disorders and affects three times as many women than men with a peak incidence in the sixth decade. It has an estimated prevalence of 1 per 1000 males and 2–3 per 1000 females. PHPT classically affects the skeleton and the kidneys can also have nontraditional PTH-related disorders and complaints with an effect on the quality of life. It is readily diagnosed with biochemical and hormonal studies and when indicated can be cured with surgery. In more recent years, patients with normocalcemic PHPT have been described and reported.

CLINICAL PRESENTATION

With the introduction of widespread biochemical screening, the most common clinical presentation of PHPT is that of asymptomatic hypercalcemia found on routine laboratory testing. Patients may develop traditional target organ manifestations such as osteoporosis, skeletal fractures, nephrolithiasis, and nephrocalcinosis. Many other patients have non-traditional problems that may include peptic ulcer disease, pancreatitis, constipation, fatigue, lethargy, muscle aches, and brain fog, which are well described in the literature.[1] Although renal disease occurs in less than 20% of patients, nephrocalcinosis and reduced renal function are easily appreciable both clinically and biochemically.[2] Neurocognitive symptoms of anxiety, poor concentration, and cognitive decline are more subtle and not often attributable to the PHPT.

NORMOCALCEMIC HYPERPARATHYROIDISM

Normocalcemic hyperparathyroidism (NPHPT) is a variant in which total and ionized serum calcium levels are normal despite elevated serum PTH levels. This diagnosis can be made only when calcium and PTH levels have been confirmed on several occasions and causes of secondary hyperparathyroidism have been excluded such as medications, vitamin D insufficiency, chronic kidney disease, renal calcium loss, and gastrointestinal disorders which affect calcium absorption.[3,4] Vitamin D deficiency or insufficiency is particularly common in northern latitudes including the New England area. Diminished vitamin D levels can cause an elevation in serum PTH levels. A serum 25-hydroxyvitamin D of ≥30 ng/ml is necessary for a diagnosis of NPHPT. If the 25-hydroxyvitamin D level is <30 ng/ml, patients should be supplemented with vitamin D and repeat measurements should be obtained at an appropriate time. A well-documented 7-year case study of an osteoporotic patient with NPHPT describes the pathophysiology in clinical detail. The study revealed a rising PTH with normal ionized calcium and a progressive decrease in cortical bone density manifested at the distal radius.[5]

CLINICAL EFFECTS OF PTH ON THE SKELETON

The skeletal impact of PHPT differs from post-menopausal osteoporosis in that cortical bone is mostly affected while trabecular bone is relatively preserved.[6] The pattern of bone loss is measured by dual-energy X-ray absorptiometry (DEXA). Because bone loss in PHPT is largely from cortical bone, bone mineral density (BMD) is most affected at the distal one-third of the radius, least at the lumbar spine with its high component of trabecular bone, and intermediately at the hip.[6] This is inverse to what would be expected to be seen in idiopathic osteoporotic bone loss, which centers around loss of trabecular bone in the vertebrae and hip. As such, 3-site DEXA is advised in all patients with PHPT. More sophisticated bone imaging such as trabecular bone score (TBS) have also shown reduced trabecular bone in PHPT, likely due to deterioration of bone microarchitecture. Even in mild PHPT, catabolic skeletal effects of PTH can increase the risk of fragility fractures.[7] There is clear evidence of increased fracture risk in a variety of locations including the forearm, rib, hip, and vertebrae.[8-10] In addition, severe and longstanding disease can cause progression to osteitis fibrosa cystica, with subperiosteal resorption of distal phalanges, tapering of distal clavicles, salt-and-pepper degranulation of the skull, bone cysts, and brown tumors.

There are limited data regarding bone disease associated with NPHPT, although there is evidence of its overall negative impact on the skeletal system.[11] An undefined fraction of patients with NPHPT may exhibit cortical bone loss in the distal forearm, and patients need to be followed for some time to document the stability of cortical bone.[5]

PRIMARY HYPERPARATHYROIDISM IN THE RHODE ISLAND FRACTURE LIAISON SERVICE

Of a consecutive series of 265 patients diagnosed in the Fracture Liaison Service (FLS) with a fracture and reduced bone density measurement, 28/265 (10.6%) patients had an elevated serum PTH level, in keeping with a substantially higher prevalence than in the general population. This is compared to a study of 444 patients with hip fractures and 444 non-fractured controls.[12] In that study, 21/444 (4.7%) of the patients with fractures had elevated serum PTH and calcium levels compared to 5/444 (1.1%) of non-fracture controls fulfilling the criteria for PHPT suggesting that PHPT enhances fracture risk ($p<0.01$).[12] However, of the patients in the FLS, only one had an elevated serum calcium. The creatinine levels were normal in all patients. These data are in keeping with a report of 156 women screened for osteoporosis in whom 14/156 (9.0%) had NPHPT.[13] Of patients with NPHPT, 21.4% experienced a fracture. These observations suggest a relatively high prevalence of PHPT and possibly NPHPT in an osteoporotic fracture population, and an association of NPHPT with structural bone loss and pathological fracture. While the prevalence of NPHPT in a fracture population is not definitively known, our observations would suggest a substantial prevalence. This observation suggests that serum calcium levels alone may not be an adequate screening marker of hyperparathyroidism in the fracture population, and that serum PTH levels should be assessed.

DIAGNOSIS

The diagnosis of PHPT is made biochemically, with workup including albumin-corrected serum calcium and ionized calcium, phosphorus, PTH, 25-hydroxyvitamin D, and creatinine levels. If albumin-corrected calcium, calculated as measured total serum calcium in mg/dL + 0.8 x (4.0 – serum albumin concentration in g/dL), and/or ionized calcium are found to be persistently elevated with serum PTH levels above the upper limit of normal of 65 pg/mL, the diagnosis of primary hyperparathyroidism can be established.[14] The serum phosphorus concentration is typically in the lower limit of the normal range.[2]

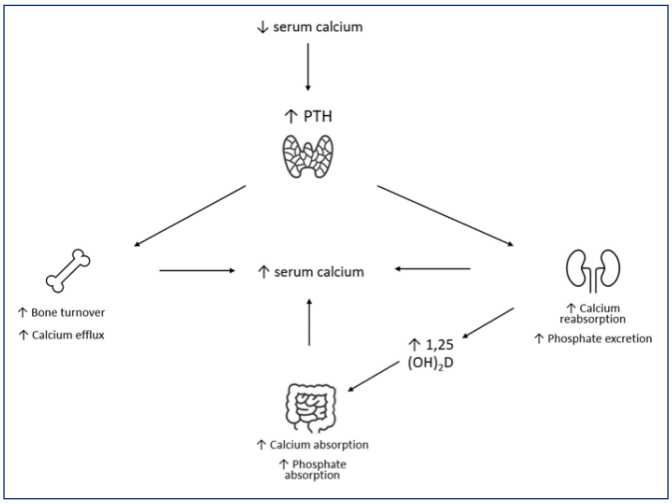
PTH plays a complex role in calcium and phosphate homeostasis, and as such, its levels can fluctuate across a wide range. In a patient with hypercalcemia, an elevated serum PTH level or an unsuppressed level would be in keeping with a diagnosis of PHPT. 24-hour urine calcium excretion greater than 300 mg in males and greater than 250 mg in females are consistent with hypercalcemia. Hypercalciuria in patients with PHPT may or may not be associated with calcium stone disease. Generally, normal calcium/creatinine ratios vary from 0.05 to 0.25 and ratios greater than 0.25 are in keeping with hypercalciuria. Urinary calcium measurements can also be used to distinguish PHPT from familial hypocalciuric hypercalcemia, which is characterized by urinary calcium excretion of less than 100 mg/24 hours, and a calcium to creatinine ratio less than 0.01.[15]

Serum 25-hydroxyvitamin D levels should be checked in all patients as vitamin D deficiency or insufficiency is common in patients with PHPT and may be associated with more severe skeletal disease. There is also evidence that reductions in serum PTH levels can occur when insufficient or deficient vitamin D levels are repleted. There is a greater percentage of patients with serum PTH levels that fall within the normal reference range when serum 25-hydroxyvitamin D levels are normal. Vitamin D repletion is appropriate when serum levels are less than 30 ng/ml. There are currently no specific recommendations for therapeutic regimens to replete 25-hydroxyvitamin D nor specific goals for repletion established in PHPT. This is an area that was recommended for future research by the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism.[14] A number of studies of vitamin D repletion in patients with PHPT have indicated no deleterious or negative effects.[16]

PATHOPHYSIOLOGY

PTH is an essential polypeptide that maintains calcium and phosphate homeostasis. Its secretion is regulated by the serum ionized calcium concentration. Normally, elevated serum calcium levels would suppress PTH secretion while a lowered serum calcium would stimulate its secretion. In the kidneys, PTH acts on the proximal renal tubules to enhance calcium reabsorption and phosphate excretion. Assuming intact renal parenchyma, PTH also facilitates the second hydroxylation step of vitamin D and synthesizes the metabolically active form, 1,25-dihydroxy vitamin D, which in turn increases calcium absorption from the intestine.[2] Together, PTH and 1,25-dihydroxy vitamin D raise serum calcium levels by increasing renal tubular reabsorption of calcium, increasing calcium absorption in the small intestine, and mobilizing calcium from bone. PTH also promotes an increase in phosphate excretion by decreasing renotubular reabsorption of phosphate. In bone, PTH acts on osteoblasts, osteoclasts, and osteocytes. The ultimate effect of calcium and phosphate in bone depends on PTH levels and whether secretion is chronic or intermittent, with chronic PTH secretion resulting in bone loss (**Figure 1**).[17] While the kidneys and small bowel suffer no structural damage from their participation in maintaining serum calcium concentration, bone experiences decreased calcium density and structural weakness predisposing to fracture.

Figure 1. Calcium-parathyroid hormone-vitamin D axis.



CELL BIOLOGY

PTH produces bone resorption and hypercalcemia by acting directly on osteoblast and mesenchymal stromal precursor cells, which secondarily increase the differentiation and function of osteoclasts. Osteoclasts themselves do not have receptors for PTH, but cells of the osteoblastic lineage, among others, express the receptor activator of NF-kB ligand (RANKL). RANKL attaches to RANK, a receptor on the cell surface of osteoclasts and osteoclast precursors, to stimulate cell differentiation to the osteoclast phenotype. This process can be modified by osteoprotegerin, a soluble decoy receptor produced by osteoblasts and marrow stromal cells which modifies the effects of RANKL by inhibiting the interaction of RANKL and RANK.[18] The hallmark of an activated osteoclast is the ruffled border which represents invaginations of the cell membrane that increase the surface area of the osteoclasts and seals the cells to bone. The osteoclasts then acidify the bone under the seal and dissolve the mineral phase of the bone. Lysosomal cathepsins erode the organic phase of bone (**Figure 2**). The combined process of dissolution of the inorganic and organic phases of bone, especially under the direction of PTH, produce erosions in bone known as Howship's lacunae and tunneling or, a "cutting cone" (**Figure 3**).

Figure 2. Osteoclast in Howship's Lacunae (asterisk)

Hyperparathyroidism creates porosity in bone by indirectly stimulating osteoclastic resorption of both the organic and inorganic phases of bone.

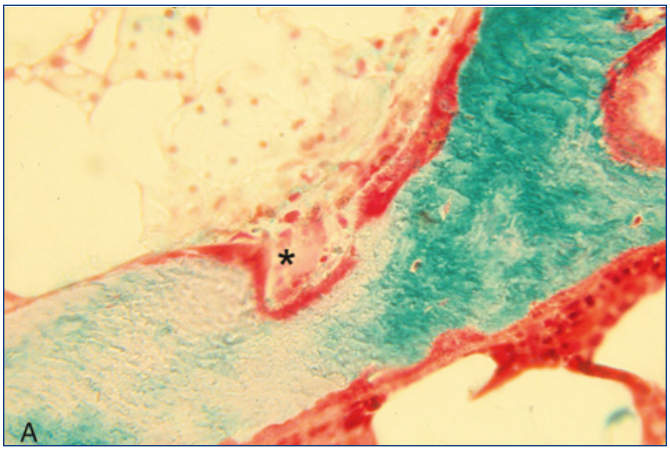


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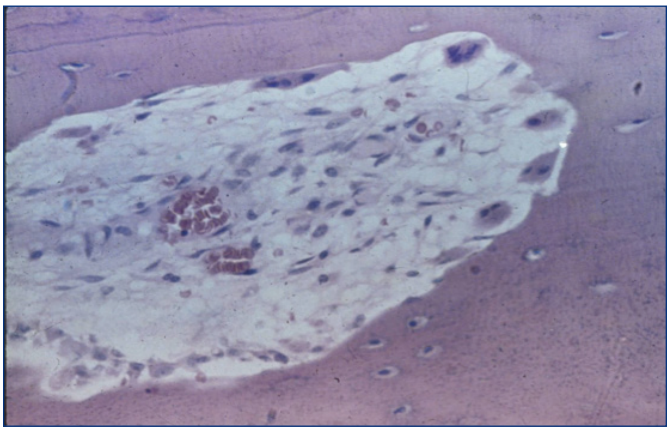
Figure 3. Osteoclastic cutting cone

Activated osteoclasts create a tunneling effect, resorbing bone, increasing porosity, and leading to mechanical weakening of bone under stress.



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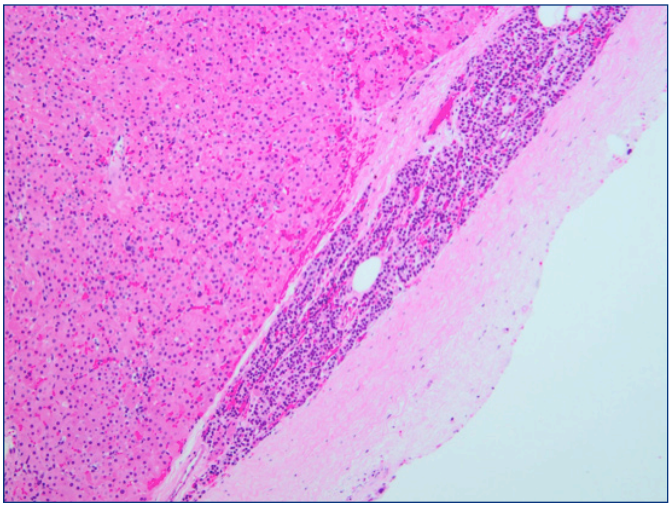
HISTOPATHOLOGY

Normal parathyroid glands each weigh 30–40 mg and are grey-tan to grey-yellow in color. Each person typically has four glands, with the superior pair of parathyroid glands arising from the fourth brachial pouches in embryo while the inferior parathyroid glands develop from the third brachial pouch along with the thymus gland. Parathyroid glands are composed of three different cell types: chief cells, clear cells, and oxyphil cells. Chief cells (4–8 µm diameter) primarily produce PTH, which is synthesized within prominent endoplasmic reticula and dense Golgi regions. Clear cells are chief cells with increased glycogen content. Oxyphil cells are larger than chief cells (6–10 µm) and increase in number with age. Their role is currently unclear, but they may derive from chief cells and may secrete PTH. The proportion of fat to glandular mass increases with age and may reach up to 60–70% of total volume.[19]

PHPT can be caused by a single gland adenoma (approximately 80% of cases) or parathyroid hyperplasia (15–20%).[2,20] Most adenomas are composed of chief cells, with a smaller portion comprised of oxyphilic cells, clear cells, and, least commonly, lipoadenomas. Typically, adenomas are separated from the adjacent rim of normocellular parathyroid gland by a fibrous capsule (**Figure 4**). The component cells may be arranged in cords, nests, sheets, and follicles, and center around blood vessels. Chief cells in adenomas have larger nuclei that stain hyperchromic and are pleomorphic. Parathyroid hyperplasia is due to an increase in parenchymal cell mass in all four glands. The enlargement of glands is relatively symmetric in most cases.[20] The glandular fat content decreases significantly, and chief cell hyperplasia typically predominates with some foci of clear cells.[21] At the cellular level, there is both an increase in cellularity as well as a change in secretion function. There is typically a reduced sensitivity to the calcium set-point which leads to over-secretion of PTH.

Figure 4. Parathyroid adenoma

Hematoxylin-Eosin stain of enlarged parathyroid gland. Many chief cells, without stromal fat, and a rim of normal parathyroid tissue can be seen.



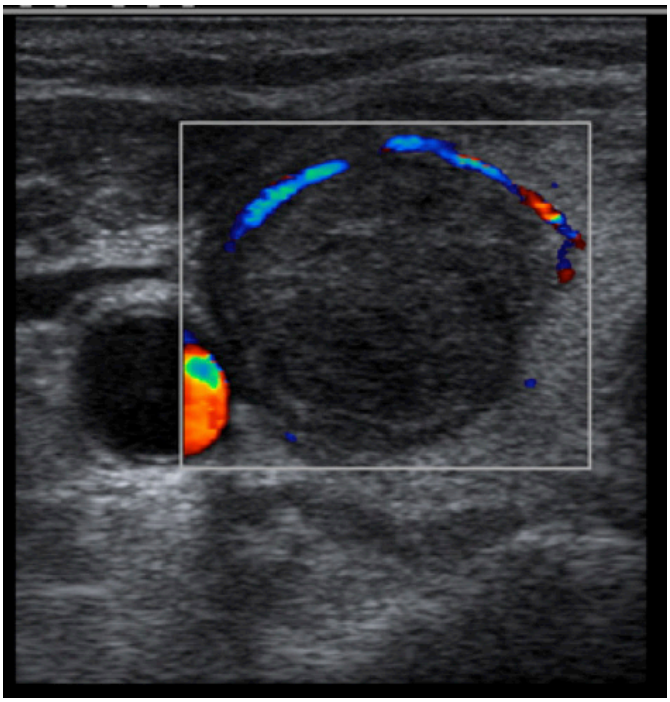
(Courtesy of Dr. Diana Murro Lin and PathologyOutlines.com)

IMAGING

Ultrasound sonography and ^{99}mTc-sestamibi scintigraphy are the most common imaging techniques used to localize parathyroid adenomas. On ultrasound examination, parathyroid glands are homogeneously hypoechoic and anatomically separate from the thyroid gland. Internal vascularity as seen by Color Doppler is typically in a peripheral distribution (**Figure 5**).[22] By scintigraphy, a radiotracer is preferentially absorbed by overactive parathyroid glands to assist surgeons with preoperative planning. The ^{99}mTc-sestamibi scintigraphy is typically combined with single photon emission computed tomography (SPECT) to provide additional detail and anatomical relationships (**Figure 6**). Sestamibi scans are typically positive with the presence of an adenoma and generally negative in patients with hyperplasia. In addition, 4-dimensional CT scan (4-D CT) can be a helpful adjunct in reoperative cases and is preferred by some surgeons for initial localization.[23] It is important to note that imaging plays no role in making the diagnosis of PHPT. The diagnosis and indication for surgery are based on biochemical findings and the traditional or classical parathyroid clinical findings.

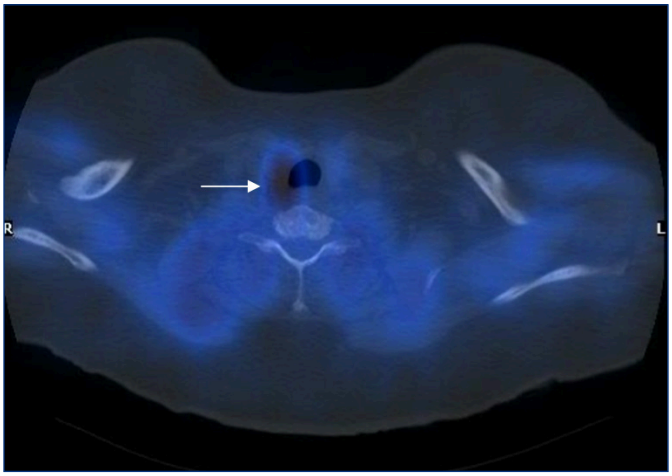
Figure 5. Adenoma seen on sonogram

Color Doppler sonogram showing a typical hypoechoic adenoma deep in relation to the lower pole of the thyroid with ring-pattern vascularity.



(Adapted from reference 22 with permission.)

Figure 6. SPECT with right superior parathyroid adenoma localization (arrow)



TREATMENT

Surgery is indicated for all patients with symptomatic PHPT including polydipsia, nephrolithiasis, diminished GFR, osteoporosis, or neurocognitive dysfunction. The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism guidelines also recommend surgery for asymptomatic patients with age less than 50, a substantially elevated calcium (more than a point above the upper limit of normal), underlying renal disease, or osteoporosis at any site.[8] Parathyroidectomy is low-risk surgery performed by identifying and resecting the diseased parathyroid glands. Intraoperative serum PTH levels are routinely measured after resection of a lesion or lesions to confirm operative success. A calcimimetic is a compound that reduces serum PTH and calcium levels by an inhibitory effect on calcium sensing receptors. This therapy can be used in patients with symptomatic or severe hypercalcemia who are poor surgical candidates. Though not a treatment, vitamin D should be appropriately supplemented during observation or while awaiting surgery as insufficiency is associated with more severe and progressive disease.[14] In a double-blinded randomized trial, hyperparathyroid patients who received daily vitamin D supplementation before parathyroidectomy had a 2.5% increase in lumbar spine BMD compared to the placebo. After parathyroidectomy, BMD increased significantly at the total hip and femoral neck within the vitamin D group.[24] Several studies have shown significant increases in T-scores after parathyroidectomy in the lumbar spine, total hip, and femoral neck up to two years after parathyroidectomy as a result of normalized calcium and PTH levels.[25,26] A study using the FRAX fracture risk assessment tool has shown an improvement in the 10-year risk for both hip and major osteoporotic fractures in patients who undergo parathyroidectomy compared to those who are managed with observation.[27] Overall, improvements in BMD and reduced fracture risk demonstrate a clear benefit of parathyroidectomy in patients with PHPT or NPHPT. Given that surgery is the only curative treatment option for PHPT, both symptomatic and asymptomatic patients should be evaluated by an experienced endocrinologist and an experienced parathyroid surgeon once the diagnosis been made.

There are no formal recommendations for management of pre-existing osteoporosis after successful parathyroidectomy given the limited data. A study of 30 patients with moderate to severe PHPT found a change in mean lumbar spine T-scores from –3.4 before parathyroidectomy to –0.43 one year after surgery and a +1.2 two years after the surgery. The mean total hip T-scores improved from –3.19 preoperatively to –0.90 at one year, and –0.40 at two years, after parathyroidectomy. The total hip had significant improvements in T-score at consecutive time intervals of 6 months, 1 year, and 2 years after parathyroidectomy.[28] These data suggest that surgery can lead to an eventual resolution of osteoporosis or at least an improvement without further medication over a period of time. A retrospective cohort study evaluated bisphosphonates for the treatment of osteoporotic patients after parathyroidectomy and found no reduction in fracture risk compared to patients who were managed with observation alone, while parathyroidectomy alone demonstrated improvements.[29] It may be that pharmacological management of osteoporosis post-parathyroidectomy may not be necessary. However, close follow-up of bone density, biochemical markers, and vitamin D repletion is recommended. Data on best post parathyroidectomy osteoporotic treatments are not yet clear and should be determined on a case-by-case basis.

CONCLUSIONS

PHPT is a common endocrine disorder diagnosable by clinical features but more commonly by screening serum studies. PTH regulates, and is regulated by, serum calcium concentration. (1) Regulation of serum calcium concentration by PTH occurs by controlling renal calcium reabsorption, vitamin D hydroxylation, gastrointestinal calcium absorption, serum phosphate concentration, and bone calcium content. (2) Of these mechanisms, only bone suffers structural compromise in its role as a calcium donor. (3) PHPT has specific imaging characteristics that guide surgical approach. (4) Surgery is generally curative. (5) NPHPT is a distinct variant of PHPT that may be more prevalent in the fracture population.

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Vertebral Compression Fractures

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ABSTRACT

Fragility fractures, particularly in the hip and spine, are the most common complication of osteoporosis. In the US, approximately 1–1.5 million vertebral compression fractures (VCFs) occur annually. While patients may present with sudden onset of low back pain and limited mobility, more than two-thirds of VCFs are asymptomatic and are detected incidentally. X-rays are the standard imaging modality for diagnosis, with CT and MRI indicated if neurological deficits are present or a malignant cause is considered. Initial management is often non-surgical, with medications, physical therapy, and bracing. Surgical management in the form of cement augmentation (kyphoplasty or vertebroplasty) or instrumented fusion can be considered after failure of non-operative treatment, cases of deformity, or neurologic deficits. Subsequent VCFs occur frequently, and risk factors for refracture include advanced age, low bone mineral density, and low BMI. Treatment of primary VCFs with anti-resorptive medication is essential to reduce the risk of subsequent fractures.

KEYWORDS: vertebral compression fractures; osteoporosis; secondary fractures

INTRODUCTION

Osteoporosis is the most commonly encountered metabolic bone disease, which affects 200 million people worldwide.[1] The disease is defined as a progressive loss of bone mineral density (BMD) as measured by dual-energy x-ray absorptiometry (DEXA). A score more than 2.5 standard deviations below the population average (T-score) indicates osteoporosis.[2] Due to the drop in estrogen after menopause and the consequent imbalance between bone resorption and formation, postmenopausal women have the greatest risk of developing osteoporosis.[3–5] Other risk factors include malignancy, low BMI, use of steroid medication, use of alcohol or tobacco, physical inactivity, and calcium deficiency.[2,6–8]

VCFs are the most reported fragility fracture in patients with osteoporosis. Approximately 1 to 1.5 million VCFs occur each year in the US, with an incidence rate of 40% in women over 80 years old.[9,10] With an aging population, the incidence of VCF will continue to grow, and therefore clinicians should be mindful of the presentation and management of these patients. Furthermore, patients with VCFs are at high risk of subsequent fractures, and it is important to consider bone density optimization for these patients and reduction of the risk factors for the development of additional fragility fractures. Previous studies have demonstrated that one prior VCF increases the risk of subsequent VCFs by 5-fold, and 2 previous VCFs increases the risk of future VCFs by 12-fold.[11] Analysis of data across 373 centers found that among 381 patients who had a VCF, the incidence of a new VCF in the following year was 19.2%.[12] A systematic review investigated the risk factors of secondary fractures after vertebroplasty, which included history of prior fractures, advanced age, reduced bone marrow density, and bone cement leakage.[13] Low BMI and the number of treated vertebrae were also established as moderate risk factors for refracture in another systematic review.[14]

CLINICAL FEATURES

The most common cause of a VCF is osteoporosis, although a diagnosis of malignancy should be considered in patients under 50 years old without history of trauma.[15] Patients with osteoporosis may develop a VCF after minor events, including coughing, sneezing, and lifting. In patients with severe osteoporosis, an estimated 30% of fractures occur when the patient is in bed.[11,16]

Risk factors for VCF can be modifiable or non-modifiable, which can guide clinicians in lifestyle optimization and identifying higher-risk patient groups. Nonmodifiable factors include advanced age greater than 70 years, female sex, history of steroid use, and Caucasian race. Modifiable factors include alcohol and tobacco use, physical inactivity, low BMI, and dietary deficiency of calcium and vitamin D.[11] The first step in preventing VCFs is the management of modifiable risk factors including treatment for osteoporosis.

The classically described symptom of a VCF is sharp or dull pain that is aggravated by movement or positional changes.[11] In many patients, this pain can be mild and attributed to another cause. Furthermore, 66% of patients with osteoporotic VCFs are asymptomatic, and their VCFs are discovered incidentally when imaging studies are performed for other reasons.[17] Red flags which may suggest a pathological

fracture (e.g., due to malignancy) include weight loss, other systemic symptoms, and persistent non-resolving pain.[18] The physical examination is often normal in patients, but midline tenderness with percussion over the spine and excessive thoracic kyphosis can indicate the presence of a VCF.[19] Kyphotic deformity with loss of height is more commonly seen with multiple fractures.[20] Neurological deficits, such as sensory or motor deficits, tend to be rare in osteoporotic VCF patients with minimal trauma as these fractures do not typically cause retropulsion of bony fragments into the vertebral canal.[11] The presence of neurological deficits should prompt evaluation with an MRI and possibly CT, and consideration of a more severe fracture or pathologic process.

The majority of VCFs occur in the mid-thoracic or thoracolumbar zone of the spine.[20] In patients with severe kyphotic deformity, pressure of the thoracic cavity on the pelvis and abdomen can result in reduced pulmonary function, atelectasis and pneumonia, and decreased appetite resulting in poor nutrition.[11] The osteoporotic thoracic kyphotic deformity frequently results in a restrictive pattern of pulmonary function. Lombardi et al reported that, when compared to women with osteoporosis alone, women with osteoporotic vertebral compression fractures had a lower forced vital capacity (FVC) and forced expiratory volume in 1 second (FEV1).[21] Furthermore, the severity of the kyphotic angle has been demonstrated to negatively correlate with predicted FVC and FEV1.[22] One study revealed that patients with osteoporosis had a lower FVC when compared to a control group of patients with chronic low back pain, with the reduction in lung function correlating with clinical measures of osteoporosis including height reduction.[23] A systematic review by Harrison et al identified four case-control studies that established an association between osteoporosis-related kyphosis and reduction in vital capacity.[24] These studies had several limitations, however, and the authors recommended future investigation with standardized outcome measures and longitudinal follow-up. Harrison et al note that pulmonary function tests are reported in comparison to reference values (based upon age, gender, and height) which can have variations depending on the formulas utilized. Additionally, kyphosis can be measured by height, rib-pelvic, or wall-occiput measurements, as well as radiographically.[24]

The restrictive component of thoracic kyphosis may lead to detrimental respiratory complications. Lee et al performed a retrospective review of 51 patients with thoracic hyper-kyphosis who visited the respiratory department.[22] Of these patients, 35 were hospitalized due to respiratory complications including lower respiratory tract infection, acute respiratory failure, and exacerbation of a chronic airway disease. For patients with severe hyperkyphosis, surgical intervention may improve pulmonary function with younger patients exhibiting greater improvements in FEV1 compared to older patients.[25] Similarly, patients with osteoporotic vertebral compression fractures demonstrated partial improvement in lung function subsequent to kyphoplasty.[26]

Other complications of vertebral compression fractures include chronic pain, constipation, increased risk of venous thrombosis, and prolonged immobility, which can result in reduced functional ability and psychological issues.[10,16,27,28] In addition to these complications, VCFs also have a detrimental burden on healthcare expenditure, with an annual medical cost of $746 million per year in the United States (**Table 1**).[11]

Table 1. Symptoms and complications of vertebral compression fractures

Symptoms
• Sudden onset low back pain, which can occur after a low energy event such as sneezing or turning in bed
• Increased pain while walking or standing
• Limited spinal mobility
Complications
• Chronic pain
• Kyphosis, predominantly thoracic
• Height loss
• Loss of mobility: Resulting in pressure sores, risk of deep venous thrombosis, pneumonia, and psychological distress
• Gastrointestinal complications: Including constipation which can cause subsequent decreased appetite, nausea, and poor nutrition
• Decreased pulmonary function: Leading to pneumonia and exacerbation of chronic airway disease

(Adapted from reference 28 with permission.)

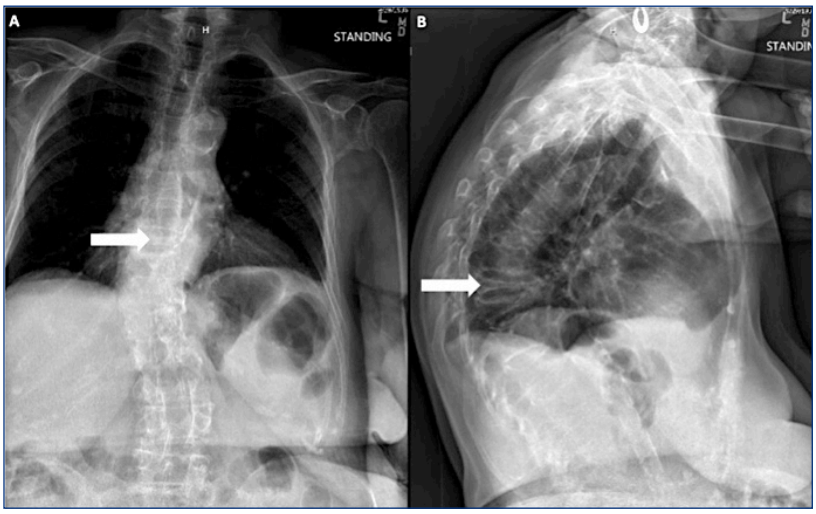
IMAGING

History and physical examinations, including a neurological assessment to evaluate arms, legs, and bladder and bowel function are the initial steps in evaluation, followed by imaging. Compression fractures can often be diagnosed with plain radiography, including lateral and anteroposterior views.[27] Clinicians should have a low threshold for imaging studies since inciting events are often low-energy and more than two-thirds of patients are asymptomatic.[27] If not previously recorded, DEXA scans should be acquired soon after the diagnosis of a VCF to evaluate for underlying osteoporosis and determine disease severity.[27]

A normal radiograph of the vertebral column should demonstrate a similar size and shape of the vertebrae across adjoining levels with horizontal endplates. A VCF is characterized by a reduction in vertebral height of 20%, or 4-mm loss from the baseline.[27] The Genant classification is commonly utilized to grade vertebral fractures based upon their morphology and height loss. Loss of height is graded from 0 (normal) to 3 (severe fracture), and morphology is reported as wedge, biconcave, or crush (**Figure 1**).[29]

Advanced imaging (CT or MRI) is rarely required but may be indicated to differentiate between benign versus malignant and acute versus chronic fractures.[15,27] Patients with

Figure 1. A: AP and **B**: lateral radiographs showing an osteoporotic compression fracture (arrows).



new or progressing neurological deficits merit advanced imaging to identify a retropulsed fracture where a bony fragment extends to the spinal column causing compression. MRI is typically the imaging of choice, as the characteristic signal intensities and enhancement patterns are well described for malignancy and a more recent fracture will demonstrate edematous changes. Radiological guidance should be sought when there are diagnostic concerns. For example, the intra-trabecular hemorrhage in an acute fracture may mimic a malignant cause and require further interpretation.

MANAGEMENT

Treatment for a VCF can be non-surgical or surgical. The goals of management are to achieve adequate pain relief, restore mobility, and prevent future fractures through addressing the underlying cause. In most cases, this involves careful evaluation of bone health and optimization of osteoporosis. Clinicians should discuss the benefits and risks of non-surgical and surgical treatment with a consideration for patient preferences and co-morbidities.

Non-surgical

Pain is a common presenting symptom of VCFs, and patients can describe this as intense.[30] Achieving adequate pain relief is important to prevent prolonged bed rest and encourage early mobility.[20] Although many patients experience pain relief over the first 6–8 weeks as fracture healing occurs, some patients have chronic pain.[31]

Subsequent to a VCF, a number of different medications can be used for pain relief including non-steroidal anti-inflammatory drugs (NSAIDs), opioids, calcitonin, and muscle relaxants.[27] NSAIDs are a common first-line therapy due to their ease of accessibility and low cost. Despite their effectiveness and overall safety, patients should be aware of risks, including peptic ulceration, gastrointestinal bleeding, and kidney disease.[20,27] This class of medication should also be used carefully in the elder population who generally have reduced creatinine clearance and are less tolerant of NSAIDs. Whenever possible, the patient's primary physician should be involved in the decision to use this class of medication. When NSAIDs are insufficient or contraindicated, opioids and muscle relaxants can be beneficial, but their use in the geriatric population is also cautioned due to sedative effects, constipation, nausea, and potential for dependency.[20,27] Calcitonin is a medication that has been used in the past for osteoporosis treatment, but also can provide acute relief of bone pain. A systematic review investigating its use in VCFs found strong efficacy for the management of acute back pain, but insufficient evidence for chronic pain due to older fractures.[30] Calcitonin is available intranasally and adverse effects include dizziness, flushing, and gastrointestinal disturbance.[27] Additionally, the use of calcitonin may be limited due to its relatively higher cost.[32] A review of US, UK, and Canadian national guidelines found inconsistent guidance on the use of these medications, with several stating weak evidence.[10]

For non-pharmacologic options, patients pursuing non-surgical management may consider the use of bracing, physical therapy, and nerve root blocks.[27] Physical therapy can strengthen the axial musculature and improve posture, which will assist with early mobilization and reduce the long-term likelihood of falls.[20] Rehabilitative exercise is also beneficial for all osteoporotic patients. Bracing can be used for a period of 4–12 weeks, although the evidence for its effectiveness is limited.[9,27] Braces are also not without risks and can cause muscular atrophy and deconditioning when used for an extended period.[20]

Patients may commence with a trial of non-surgical management, but careful follow-up should ensue to monitor for pain relief or progression of symptoms, as well as to observe for adverse effects.

Surgical

Although patients may commence with non-surgical treatment, clinicians must be aware of the indications for surgical management. An immediate referral to a surgeon is merited if a patient complains of leg weakness or pain, which indicates neurological deficit and demands further evaluation.[33] Furthermore, if patients exhibit no improvement in their pain level and disability over 6 weeks of conservative therapy, then surgical management should be considered.[27,33]

Kyphoplasty and vertebroplasty are percutaneous cement-augmentation techniques to manage symptomatic

VCFs. These are both minimally invasive procedures where bone cement is injected into the fractured vertebral body.[9] The procedure can be performed either inpatient or outpatient depending on individual patient characteristics. Several specialties can perform kyphoplasty and vertebroplasty, including surgical specialties (orthopedic surgery and neurosurgery) and non-surgical specialties (anesthesia, pain medicine, and radiology). Recent trends suggest that cement-augmentation procedures are being performed increasingly by non-surgeons.[34] The indication for these procedures in osteoporotic VCF is intense and sustained pain adjacent to the fracture with failure of conservative management for a minimum of 3 weeks. These procedures can also be used for pain relief in patients with osteolytic bony metastases.[35] Hirsch et al published a clinical care pathway using the RAND/UCLA Appropriateness Method. The multidisciplinary expert panel recommended that cement augmentation procedures be considered in patients with positive findings on advanced imaging (preferably MRI) and worsening symptoms, and in patients with 2–4 of the following unfavorable characteristics: progressive height loss, vertebral body height loss greater than 25%, kyphotic deformity, or severe impact on daily functioning.[36] Contraindications for these procedures include coagulation disorders, infection, allergy to bone cement, tumor involving the spinal canal, and unstable fractures.[20,35]

In a vertebroplasty, fluoroscopic guidance is used to inject cement into the fractured cancellous bone. This can alleviate pain and prevent further loss of height (**Figure 2**).[33,37] A kyphoplasty is similar to a vertebroplasty but involves an inflated balloon tamponade to restore vertebral height and create a cavity which can be subsequently filled with cement. This has theoretical advantages over vertebroplasty since it minimizes cement extravasation, restores vertebral height, and reduces kyphosis. In practice, clinical studies have found both procedures to be effective with no differences between patient-reported outcome measures.[37,38]

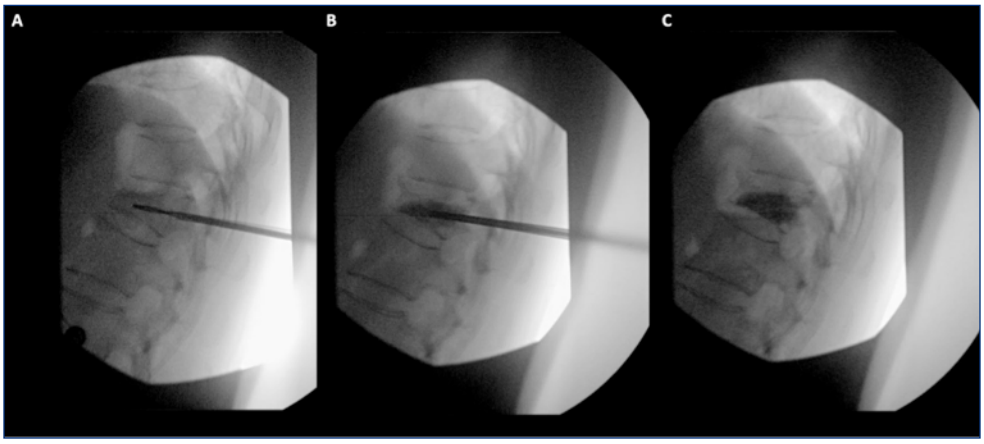
Complications of cement-augmentation procedures are low but include bleeding, infection, and neurological injury.[27] Cement extravasation is a rare yet catastrophic complication which can lead to arterial embolization or compression of neural elements. This complication is more common in vertebroplasty where cement is injected at higher pressure.[38] A systematic review and meta-analysis comparing cement-augmentation procedures to non-surgical management of osteoporotic VCF found superior pain outcomes in the surgically treated patients, demonstrating their efficacy.[39]

SECONDARY FRACTURES

One of the challenges following cement augmentation procedures is the risk of a subsequent VCF, which often happens at the adjacent vertebral levels to cement injection.[40] In a radiological study, new VCFs occurred in approximately one-third of patients, and in more than half of these the fracture occurred within 3 months of vertebroplasty at the adjacent vertebral level.[41] Several studies have considered if novel VCFs are the result of osteoporotic progression or the consequence of vertebral stiffness by cement augmentation. Several biomechanical studies have reported minimal changes in stresses and strains at adjacent levels to the kyphoplasty and conclude that adjacent segment fractures are more likely due to progression of osteoporosis rather than the intervention.[42,43]

Moon et al followed 111 female patients with osteoporotic VCFs who underwent kyphoplasty. The 1-year incidence rate of new compression fractures was 15.5% which is lower than the rate in natural osteoporotic progression.[40] The authors conclude that the lower incidence rate observed in their study sample could be related to a higher percentage of patients who were receiving medication for osteoporosis and recommend that spine surgeons should consider postoperative utilization of anti-osteoporotic medication to prevent novel fractures. This is supported by a meta-analysis which found that low BMD is a high-risk factor for refracture.[14] In fact, a 1% increase in BMD has been associated with a 3% reduction in risk of VCF.[13] This evidence emphasizes the role of metabolic treatment for primary VCFs to optimize treatment outcomes and reduce the risk of subsequent fractures. Furthermore, Moon et al found that one third of patients with subsequent VCFs were clinically asymptomatic, which emphasizes the importance of careful

Figure 2. A: Intraoperative image of a kyphoplasty demonstrating vertebral body access, **B**: balloon inflation, and **C**: cement injection.



follow-up. In patients with a primary VCF, follow-up imaging should be considered. This can include AP and lateral radiographs to detect progressive kyphosis or coronal plane deformity 2-4 weeks after diagnosis. A repeat MRI should be considered in the presence of new or progressing neurological symptoms, which may indicate an additional fracture, infection, or tumor.[44,41]

Due to the high likelihood of additional fragility fractures after a primary VCF is identified, such as distal radius fractures, geriatric hip fractures, or additional VCFs, many institutions have implemented the concept of a fracture liaison service to identify high-risk patients and pursue early diagnostics and potential intervention. These services have shown benefit in improving patient outcomes, and early referral should be considered if one of these services is available to patients with the new diagnosis of a VCF.[45]

CONCLUSIONS

VCFs are the most common fragility fracture affecting patients with osteoporosis. (1) Patients can present with acute pain although many are diagnosed asymptomatically after incidental imaging. (2) Plain radiographs are the modality of choice for diagnosis, while CT and MRI imaging may be required if a patient has neurological deficits, or a malignancy is a considered cause for the fracture. (3) Initial management is often non-surgical for at least 3 weeks before cement-augmentation procedures are considered. (4) A critical component in the management of VCF is the initiation of strategies for fracture prevention. If not performed recently, a DEXA scan should be ordered to monitor BMD. Patients should be educated on lifestyle changes such as smoking cessation and exercise, with referral to physiotherapy if assistance is needed to promote a regular program. (5) Pharmacologic treatment should be strongly considered for treatment of osteoporosis and fracture prevention. Medications to treat osteoporosis include bisphosphates (which are common first-line therapeutics), denosumab (a RANK ligand inhibitor), selective estrogen receptor modulators (raloxifene), and recombinant human parathyroid hormone (teriparatide). To prevent the progression of osteoporosis, it is also crucial to normalize calcium and vitamin D levels and provide dietary supplementation. (6) Early referral to a fracture liaison service or other provider who manages osteoporosis may improve outcomes in these patients and reduce risk of future fragility fractures. (7) An individual who experiences a VCF has a 5-fold increased risk of having a subsequent one, thereby justifying treatment regardless of bone mineral density.

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