Recent Management Controversies in Osteoporosis

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Abstract

Osteoporosis is an important health concern that leads to significant morbidity for millions of Americans. Most recently, several areas of osteoporosis treatment have been debated, including calcium and vitamin D supplementation, duration of bisphosphonate therapy, and frequency of bone mineral density measurement. This article reviews the recent studies on these controversial topics and presents the current practice guidelines.

Keywords

Osteoporosis, vitamin D, calcium, bisphosphonates

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Osteoporosis is a significant health concern that currently affects more than 10 million Americans, with an additional 34 million Americans at risk due to low bone mass. Osteoporotic fractures can lead to disabling pain, and nearly 30 % of patients with hip fractures require nursing home admission. In addition, 20 % of patients with hip fractures are no longer living one year after fracture. In 2011, the World Health Organization (WHO) defined osteoporosis as a skeletal disorder characterized by decreased bone strength, which is due to compromised bone strength and bone quality. However, bone quality remains difficult to measure therefore osteoporosis is diagnosed based in 1994 WHO guidelines using T-score based on bone mineral density (BMD). Osteoporosis is present when BMD lies 2.5 standard deviations (SDs) or more below the mean value for young healthy women (i.e., a T-score of <-2.5 SDs). Osteoporosis is further defined by the American Association of Clinical Endocrinologists (AACE) as a T-score of -2.5 or below in the spine (anteroposterior), femoral neck, or total hip, or the presence of fracture of the hip or spine (in the absence of other bone conditions).[1] Once osteoporosis has been diagnosed it is classified as either primary or secondary. Primary osteoporosis occurs later in life, in women often following the menopause. Secondary osteoporosis results from medications, concomitant conditions or disease processes[2] (a list of secondary causes can be seen in *Table 1*).[1] These secondary causes must be fully evaluated and excluded prior to initiating treatment.[1] There are several topics for debate in the current treatment of osteoporosis, which will be addressed in this article. These include the use of calcium and vitamin D supplements, duration of pharmacologic therapy, and the appropriate method for monitoring therapy.

Calcium Supplementation

Calcium and vitamin D are important in successful osteoporosis treatment. Randomized clinical trials have demonstrated that adequate calcium intake increased BMD and decreased the incidence of fractures.[3,4] In these trials, women who received calcium supplements of 1,000–1,200mg/day had fewer fractures than women who did not receive calcium supplementation. Guidelines therefore recommend a daily calcium intake of 800–1,200 mg/day, depending on age group, for adequate bone health.[5] Over the past several years, however, research studies have demonstrated a possible link between calcium supplementation and increased risk of cardiovascular disease,[6] making the choice of an appropriate dose of calcium the subject of increasing controversy.

In a randomized controlled trial designed to evaluate the effect of calcium supplementation on the risk of cardiovascular disease, 1,471 postmenopausal women were recruited and randomized to receive either 1,000 mg elemental calcium or placebo. After five years of follow-up, the women randomized to calcium were found to have a statistically significant (p=0.0099) increased incidence of myocardial infarction (MI).[7] Following the results of this study, a meta-analysis was performed to evaluate the risk of calcium supplements on cardiovascular events.[8] It included 15 studies in which patients received >500 mg calcium per day. The mean intake of calcium was 1,800 mg/day, patients were followed for a minimum of two years, and mean follow-up was 45 months. Cardiovascular outcomes were taken from self reports and hospital records. This analysis revealed an increased risk of MI in patients who received calcium supplementation;[8] however, the studies included did not have cardiovascular outcomes as primary or secondary outcomes, nor did patients receive vitamin D supplementation. Therefore, a repeat meta-analysis was performed that included two further randomized controlled studies in which patients had received calcium and vitamin D plus Women's Health Initiative (WHI) data. This meta-analysis also demonstrated a statistically significant (p=0.05) increase in the risk of MI in

Table 1: Secondary Causes of Osteoporosis[1]

Endocrine or Metabolic Causes	Nutritional/GI Conditions	Drugs	Collagen Disorders	Other
• Acromegaly	• Alcoholism	• Antiepileptics	• Ehlers–Danlos syndrome	• AIDS/HIV
• Diabetes mellitus types 1 and 2	• Anorexia nervosa	• Aromatase inhibitors	• Homocystinuria due to cystathionine deficiency	• Ankylosing spondylitis
• Growth hormone deficiency	• Calcium deficiency	• Chemotherapy	• Marfan syndrome	• Chronic obstructive pulmonary disease
• Hypercortisolism	• Chronic liver disease	• Immunosuppresants	• Osteogenesis imperfecta	• Gaucher's disease
• Hyperparthyroidism	• Malabsorption syndromes/ malnutrition	• Depo-Provera®		• Hemophilia
• Hyperthyroidism	• Total parenteral nutrition	• Glucocorticoids		• Immobilization
• Hypogonadism	• Vitamin D deficiency	• Gonadotropin-releasing hormone agonists		• Major depression
• Hypophosphatasia		• Heparin		• Myeloma
• Porphyria		• Lithium		• Organ transplantation
• Pregnancy		• Proton pump inhibitors		• Renal failure
		• Selective serotonin reuptake inhibitors		• Renal tubular acidosis
		• Thiazolidinediones		• Rheumatoid arthritis
		• Thyroid hormone (supraphysiologic doses)		• Systemic mastocytosis
		• Warfarin		• Thalassemia

GI = gastrointestinal. Source: Watts, et al., 2010.[1]

Table 2: Daily Calcium Intakes Recommended by the Institute of Medicine

Age	Sex	RDA	Upper Limit
19–50	Male and female	1,000 mg/day	2,500 mg/day
51–70	Male	1,000 mg/day	2,000 mg/day
51–70	Female	1,200 mg/day	2,000 mg/day
71 and above	Male and female	1,200 mg/day	2,000 mg/day

RDA = recommended daily amount. Source: Ross, et al., 2011.[5]

Table 3: Daily Vitamin D Intakes Recommended by the Institute of Medicine

Age	Gender	RDA	Serum Level	Upper Limit
19–70	Male and female	600 IU/day	20 ng/ml	4,000 IU/day
71 and above	Male and female	800 IU/day	20 ng/ml	4,000 IU/day

IU = international unit; RDA = recommended daily amount. Source: Ross, et al., 2011.[5]

the calcium group versus placebo. This study was limited by the WHI data, which were obtained from a publicly-accessible dataset and accounted for the majority (75–80 %) of the data included in the meta-analysis.[9] In the WHI trial, 36,282 post-menopausal women were randomized to calcium carbonate 1,000 mg/day plus vitamin D 800 units daily versus placebo. Cardiovascular outcomes were followed as a secondary endpoint. After seven years of follow-up, there was no difference in the number of myocardial infarctions or cerebrovascular events between the groups.[10] This study has been criticized for several reasons: only 50 % of women in the treatment group were taking more than 80 % of the calcium prescribed, and 46 % of the women were already taking calcium supplements prior to randomization, which may account for the lack of difference at the end of the study. When the study data were re-evaluated, excluding the 46 % of women taking calcium prior to randomization, there was a statistically significant (p=0.05) increase in clinical MI/stroke in the calcium group.[9] This analysis is limited by the low incidence of cardiovascular events in the WHI trial and by statistically meaningful differences in the baseline characteristics of the members in the placebo and calcium supplementation groups.[9] The Calcium intake fracture outcome study (CAIFOS) was a randomized, controlled trial involving 1,460 women who were randomized to calcium carbonate 1,200 mg/day or placebo for five years with observational follow-up for an additional 4.5 years.[8] These patients were evaluated for atherosclerotic vascular mortality or time of first hospitalization for a cardiovascular event. No differences were found between the calcium and placebo groups. In addition, there were no differences in the incidence of MI in the two groups.[8]

The debate over the effect of calcium on cardiovascular disease remains: currently there are insufficient data on the harm of calcium supplementation to change the daily allowances recommended by the Institute of Medicine (IOM), which are shown in *Table 2*).[5] Patients should not receive more than the recommended daily dose, which means that doctors should ask patients about their dietary intake prior to recommending calcium supplementation.

Vitamin D Supplementation

Vitamin D insufficiency has become an increasingly common problem due to lack of exposure to sunlight and lack of dietary sources rich in vitamin D. Currently, 41 % of men and 52 % of women in the USA are vitamin D deficient.[11] Previously, insufficiency had been defined as 25-hydroxyvitamin D (25(OH)D) <30 ng/ml, because this is the level that is associated with maximal suppression of parathyroid hormone (PTH).[12] However, in the recent IOM report on dietary reference intakes for calcium and vitamin D, the committee determined that 20 ng/ml is sufficient for 97.5 % of the population, and that levels above 50 ng/ml may have adverse effects.[5] The report also states that 600 IU/day of vitamin D is sufficient to enable the general population to reach the goal of 20 ng/ml (the IOM's recommendations are shown in *Table 3*).[5]

These IOM recommendations have led to significant debate on appropriate serum levels of 25(OH)D and appropriate daily dose levels.

They may be insufficient in terms of both the recommended daily allowance and the appropriate serum level.[13] Several large clinical trials have proven that a serum level of 30 ng/l is appropriate. In the UK, 2,686 men and women aged 65–85 were randomized to received vitamin D 100,000 IU every month for five years versus placebo to determine the effect of vitamin D on fracture rates. After five years of follow-up, the treatment group demonstrated an increase in 25(OH)D level from 21 to 29 ng/ml, which led to a statistically significant (p=0.04) decrease in the number of fractures.[14] Furthermore, several meta-analyses have demonstrated that the risk of fracture does not decrease until 25(OH)D levels are above 30 ng/ml,[13] and studies of optimal levels of 25(OH)D for maximizing intestinal calcium absorption have demonstrated that optimal calcium absorption occurs with 25(OH)D levels >32 ng/ml.[15]

The IOM's recommended upper limit of 50 ng/ml for serum 25(OH)D was supported by a randomized, placebo-controlled trial in elderly women that evaluated the effect of high dose vitamin D on falls and fractures. In this trial, women were randomized to cholecalciferol 500,000 IU/year or placebo for 3–5 years. The study found a statistically significant increase in both falls and fractures in the group treated with vitamin D. Interestingly, a *post hoc* analysis demonstrated that the risk of falls and fractures was exacerbated in the first three months after vitamin D dosing when 25(OH)D levels exceeded 48 ng/ml.[16] The large yearly dose that was used in this study is not currently used in the USA, therefore the fall risk demonstrated in this study is not applicable to US patients undergoing vitamin D therapy. In contrast to this study, a meta-analysis was performed to evaluate the effect of vitamin D on fall prevention. This meta-analysis included eight randomized controlled trials, in which the mean dose of cholecalciferol was 700–1,000 IU/day. The authors found that vitamin D supplementation decreased the risk of falling by 19 %, and patients who reached 25(OH)D levels of 60 ng/ml experienced 23 % fewer falls.[17] Given these data, the AACE recommends using vitamin D supplementation to maintain 25(OH)D levels of 30–60 ng/ml.[1]

Duration of Pharmacologic Therapy

Pharmacologic therapy is recommended for patients with a history of hip or spine fracture and a BMD of 2.5 SDs below the young adult mean (as measured by dual-energy X-ray absorptiometry [DXA]), as well as for patients with a high probability of fractures as determined using the FRAX® tool. The FRAX tool was developed by the WHO to determine the 10-year risk of fracture (www.shef.ac.uk/FRAX). It considers multiple factors, including previous fracture, BMD, body mass index (BMI), secondary causes of osteoporosis, and family history. Patients should be considered for treatment if the 10-year risk of hip fracture is greater than 3 % or if the 10-year risk of major osteoporotic fracture is greater than 20 %.[1]

Pharmacologic therapy should be initiated with a first-line agent such as alendronate, risedronate, zoledronic acid, or denosumab. These agents have been shown to decrease the risk of hip and non-vertebral fractures in randomized, prospective trials.[1] The majority of first-line agents are bisphosphonates, which are the most widely used drugs for treatment of osteoporosis. However, recent studies have questioned the long-term treatment of osteoporosis with bisphosphonates due to an association with atypical fractures. In particular, alendronate has been associated with subtrochanteric fracture.[18]

Several case series have been reported that demonstrate a possible relationship between long-term bisphosphonate therapy and atypical subtrochanteric fractures. The earliest series to be published demonstrated that a small number of patients had low energy non-vertebral fractures while on alendronate. Bone biopsies in these patients revealed severely suppressed bone turnover,[18] therefore it was postulated that, since bisphosphonates reduce bone remodeling, they might lead to 'frozen' bone or over-suppressed bone that is susceptible to stress fractures. These atypical fractures have been defined by a task force of the American Society for Bone and Mineral Research (ASBMR) (see *Table 4*).[19]

Table 4: Features of Atypical Femoral Fracture[19]

Major Features
• Located along the femur, most commonly proximal one-third
• Associated with little trauma, fall from standing height or less
• Transverse or oblique configuration
• Non-comminuted
• Complete fractures extend through both cortices and may be associated with medial spike; incomplete fractures only involve lateral cortex
Minor Features
• Localized periosteal reaction of lateral cortex
• Generalized increase in cortical thickness of diaphysis
• Prodromal symptoms, dull or aching pain
• Bilateral fractures
• Delayed healing
• Comorbid conditions (vitamin D deficiency, hypophosphatasia)
• Use of pharmaceutical agents (BPs, PPIs, GCs)

BPs = bisphosphonates; GCs = glucocorticoids; PPIs = proton pump inhibitors.
Source: Shane, et al., 2010.[19]

Since the publication of these initial case series involving atypical fractures, several larger studies have reviewed data on such fractures. A registry-based, cross-sectional study did not find an increased incidence of fractures in patients receiving alendronate.[20] In addition, a secondary analysis was performed of three large, randomized bisphosphonate trials—the Fracture intervention trial (FIT), the FIT long-term extension (FLEX) trial and the Health outcomes and reduced incidence with zoledronic acid once yearly pivotal fracture trial (HORIZON PFT). A total of 14,195 women were enrolled in these studies and 134 hip or femur fractures qualified for inclusion in the analysis. Of these fractures, 12 occurred in the subtrochanteric or diaphyseal femur, equivalent to a fracture rate of 2.3 per 10,000 patient-years. This represents an extremely low risk for atypical fractures even in patients who received alendronate therapy for 10 years.[21]

A Swedish population-based case-control study analyzed all femoral subtrochanteric and shaft fractures that occurred in one year. This study identified 59 patients with atypical fractures, of which 46 occured in patients on bisphosphonate therapy, equivalent to an absolute risk of 0.0005 or an incidence of five per 10,000 patient years.[22] This supports the findings of low incidence rates for atypical fractures in the randomized bisphosphonate trials, and confirms that the absolute risk of atypical fractures is small compared with the high risk of osteoporotic fractures if patients are not treated. In addition, the task force of the ASBMR did not find any data to support a causal relationship between bisphosphonate therapy and atypical fractures.[19]

The Swedish population-based study did demonstrate an increased risk of atypical fracture with duration of bisphosphonate use (odds ratio 1.3

per 100 prescribed daily doses),[22] indicating that it is reasonable to limit the duration of bisphosphonate therapy. The task force of the ASBMR reviewed the literature and found that atypical fractures occur after a median length of treatment with bisphosphonates of seven years. The task force recommends continuing therapy for five years and then determining the need for further therapy on a yearly basis according to the clinical scenario. It is reasonable to consider a holiday from bisphosphonates after five years of treatment, but currently there are no data indicating a decrease in atypical fractures for these patients.[20] The AACE recommends considering a 1–2-year drug holiday after 4–5 years of treatment with alendronate in patients with mild osteoporosis. During this holiday, bone turnover markers and DXA scans should be monitored and drug therapy restarted when bone loss is detected. In patients at high risk of fractures, a 1–2-year drug holiday should be considered after 10 years of treatment. During the drug holiday, high risk patients may benefit from treatment with teriparatide or raloxifene.[1]

Monitoring Therapy

Osteoporosis is in part defined by low bone mass, as measured by DXA scan. The measurement of BMD also can be used to determine the need for pharmacologic therapy; however, once patients are started on pharmacologic therapy, the need for follow-up DXA scans is not clearly established. A secondary analysis of data from FIT—a randomized, controlled trial evaluating the fracture benefit of alendronate therapy—was conducted to determine the need for maintenance DXA.[22] Patients underwent baseline DXA and yearly follow-up measurements to monitor the effects of therapy. These serial measurements were made with the same type of machine at all the clinical centers. The secondary analysis used a series of mixed models to determine the benefit of serial DXA scans. The study found a BMD increase of more than 0.019 g/cm^2 in 97.5 % of patients taking alendronate, and the authors therefore argue that there is no need for routine monitoring, because BMD increases sufficiently to justify continuing bisphosphonate therapy in all osteoporotic women in the first three years.[22]

By contrast, in their perspective on the benefits of routine DXA scans during bisphosphonate therapy, Watts and colleagues disagree with the findings of the previous analysis on several key points.[23] They argue that patients whose BMD decreases while on bisphosphonate therapy are at increased risk of fracture, and that it is therefore necessary to identify these patients. They also point out that patients enrolled in large clinical trials are more likely to be compliant with medication than patients in everyday practice, and that patients in clinical trials undergo extensive screening for secondary causes of osteoporosis that are often missed in clinical practice. (A recent study demonstrated that, in clinical practice, 10 % of patients treated with bisphosphonates lost BMD in the first 1–2 years, which was often due to an unrecognized secondary cause of osteoporosis.[14]) Watts et al. also note that the secondary analysis of the alendronate trial was extrapolated to include all bisphosphonates, which is inappropriate.[23] In the risedronate trial,[24,25] a greater percentage of patients had reduced BMD after one year than in FIT. Watts and colleague's final conclusion is that routine DXA screening is not essential to document increased BMD but to identify the subset of patients with declining BMD on therapy in order that the causes of this decline can be identified.[23]

The AACE recommends baseline and repeat DXA scans every 1–2 years until findings are stable and then follow-up scans every two years. These scans should be performed at the same facility, using the same machine and, if possible, the same technician, to decrease technical variability. To determine if there has been a change in BMD, the testing facility calculates the least significant change (LSC), which is determined by the facilities' technologists after performing a precision analysis, and set at 95 % confidence interval for change.[1]

Conclusion

Osteoporosis is a significant health concern that needs to be appropriately evaluated and treated to prevent morbidity and mortality associated with fractures. Calcium and vitamin D supplementation are the cornerstones of therapy despite recent concerns. Patients should be maintained on 1,200 mg/day of elemental calcium to prevent fractures and sufficient vitamin D to maintain serum 25(OH)D levels at >30 ng/ml. They should be considered for pharmacologic therapy based on their individual fracture risk, and if an antiresorptive drug is used a drug holiday after 5–10 years on treatment should be considered. Treatment should be evaluated with routine measurements of BMD to assess bone loss that would require further intervention. ■

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