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Osteoporosis Management Update: Comparing the 2010 and 2013 National Osteoporosis Foundation Guidelines

Emily J. McCleary, Pharm.D. Candidate

Osteoporosis is a bone disorder characterized by low bone density, impaired bone architecture, and compromised bone strength which predisposes the patient to increased fracture risk.[1] It is estimated that 9 million Americans have osteoporosis and approximately 48 million have osteopenia, or low bone density. Of those with osteoporosis, 40% of women and 15-30% of men will develop at least one fragility fracture in their lifetime.[2,3] Unfortunately, once an initial fracture occurs, there is an 86% increased risk for future fractures.[4]

Osteoporosis and resulting fractures often result in significant morbidity, mortality, and economic burden. In a study of patients 65 and older, 27.3% of patients died within one year after hip fracture.[5] Additionally, hip fracture significantly increases both the likelihood and duration of subsequent hospitalizations.[6] This increased use of healthcare resources creates potential for serious economic burden. In 2005, the total burden of osteoporosis in the United States was estimated as an occurrence of 2 million fractures costing nearly $17 billion dollars.[7] The negative consequences associated with osteoporosis emphasize the need for evidence based guidance on appropriate prevention and treatment.

Evidence based guidelines for osteoporosis prevention and management are developed by the National Osteoporosis Foundation (NOF). For the last three years, the 2010 guideline has highlighted the standard of osteoporosis care. In 2013, the guideline was updated to include new information on calcium, vitamin D, and osteoporosis medications. New recommendations were put forth regarding duration of treatment and screening for vertebral fractures. The purpose of this article is to discuss the differences between the 2010 and 2013 versions of the NOF Osteoporosis guidelines and to understand the rationale behind such changes. A direct comparison of the guidelines is found in Table 1.

Calcium

In 2010, the NOF guidelines recommended that all women and men aged 50 years and older receive at least 1,200 mg of elemental calcium daily. This recommendation has changed, as the 2013 guidelines recommend an intake of 1,000 mg elemental calcium daily for women aged 19-50 and men aged 50-70 years. Intake of 1,200 mg of elemental calcium daily is reserved for women aged 51 and older and men aged 71 and older.

The rationale for the update primarily

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Table 1 | 2010 and 2013 NOF Guideline Comparisons

Recommendation	2010[8]	2013[9]
Calcium	All women and men aged 50 years and older: intake 1,200 mg daily	Women 19-50 years old. and men 50-70 years old: 1,000 mg daily. Women ≥ 51 years old and men ≥ 71 years old: 1,200 mg daily
Treatment of Low Vitamin D	No recommendation	50,000 IU of vitamin D_2 or vitamin D_3 once weekly x 8-12 weeks. *or* 6,000 IU daily x 8-12 weeks. Goal 25(OH)D level is about 30ng/ml. Following maintenance therapy is 1500-2000 IU/day.
Duration of Treatment	No recommendation	May discontinue bisphosphonate treatment after 3-5 years if fracture risk is modest. Continue therapy past 3-5 years in patients with a femoral neck T-score below −2.5, or with a preexisting vertebral fracture and T-score < -2.0.
Vertebral Imaging	No recommendation	Perform in all women age ≥70 and all men age ≥80, in women age 65-69 and men age 75-79 with BMD T-score ≤ -1.5, and in post-menopausal women age 50-64 and men 50-69 with specific risk factors. Risk factors include low trauma fracture, historical height loss of ≥1.5 inches, prospective height loss of ≥0.8 inches, or recent/ongoing long term glucocorticoid treatment.
New Medications Since the 2010 Guideline	n/a	Prolia (denosumab): FDA approved injectable osteoporosis treatment for postmenopausal women, men at high risk for fracture, men receiving androgen deprivation therapy (ADT) for non-metastatic prostate cancer, and women receiving aromatase inhibitors (AI) for breast cancer treatment. MOA: Binds RANKL to inhibit osteoclast for-mation and bone turnover.

stem from a study by Hunt and Johnson, which expanded data on calcium balance to generate better estimates of the adult requirement. They collected calcium balance data by examining [calcium intake – (fecal calcium + urinary calcium)] of 155 subjects; men (n=82) and women (n=73) ranging from 19-75 years old. Interestingly, no significant relationship between calcium balance (mg/day) and age was found (P=0.4). Neutral calcium balance was predicted to be 741 mg/d for healthy individuals regardless of age or sex. Dietary allowance was predicted to be 1035 mg/d for all adults.[10] This value is significantly lower than the recommended elemental calcium intake of 1200 mg/day.

The information by Hunt and Johnson seem to suggest a universal recommendation of 1,000 mg/day of elemental calcium for all men and women over 19 years old. This however, is not the recommendation from the NOF. To explain, the recommended elemental calcium intake of 1,000 mg/day is adequate for younger individuals because the goal is to maintain bone and calcium balance.[11] Once women reach 50-55 years, the natural process of bone loss is evidenced by a higher proportion of women with low bone mineral density (BMD). Patients with low BMD have a greater calcium requirement because the goal of calcium supplementation is to lessen the degree of bone loss.[12] It is unclear what proportion of women aged 50-55 will benefit from a higher calcium intake, but to err on the side of caution, preference is given to the higher value of 1,200 mg / day. This recommendation is supported by the results of a meta-analysis by Tang et al. This analysis included women 50 to 85 years old and found that total calcium intake equal to 1,200 mg or more per day had a positive effect on bone mineral density (BMD) and a significant fracture reduction (relative risk [RR] = 0.88; 95% CI: 0.83-0.95).[13] Thus, it is still recommended that women older than 50 intake a greater amount of calcium than younger women.

On the other hand, the 2013 NOF guidelines lower the calcium requirement for men younger than 70 years old. There is a general lack of data on age related bone changes in men, but it does appear that men have a substantially slower rate of bone loss and fracture incidence compared to women.[14] Hunt and Johnson did not find any difference in calcium requirement between sexes, though there were only two men over 50 years old included. Still, there is no evidence implicating significant BMD changes in men under 70 and the assumption holds that men aged 51-70 years will require less calcium than women of the same age.[15,16]

Vitamin D

The 2010 guidelines did not make specific recommendations regarding treatment of vitamin D deficiency. On the other hand, the 2013 guidelines recommend treating adults with vitamin D2 or vitamin D3 at a dose of either 50,000 IU weekly or 6,000 IU daily for 8-12 weeks to reach a goal 25(OH)D level of about 30ng/ml. After the goal 25(OH)D level is reached, maintenance therapy consists of 1500-2000 IU/day of vitamin D2 or vitamin D3.

The 2013 NOF recommendation echoes the Endocrine Society Clinical Practice Guideline on vitamin D deficiency evaluation, treatment, and prevention. They were published in 2011 and are the first of their kind.[17] Interestingly, the evidence for treatment of vitamin D deficiency has been available since 2007 and has not changed.[18] Therefore, it is unclear why direct guidance was not included in the 2010 NOF guidelines. Perhaps the new Endocrine Society guidelines carry extra weight, hence the new inclusion of direct recommendations.

Additionally, the safe upper limit of vitamin D intake has been raised from 2,000 IU/day in the 2010 NOF guidelines to 4,000 IU/day in the 2013 guidelines. This reflects an update by the National Research Council. Toxicity has been associated with a serum 25OHD levels as little as 60nmol/L, but most often involve values greater than 350nmol/L.[19] Since studies evaluating serum levels after maximal sun exposure found levels to be no greater than 150 nmol/L, the National Research Council conservatively recommends against attaining serum levels above 125-150 nmol/L. In a study by Heaney et al, vitamin D intake of 5,000 IU/day resulted in serum 25OHD levels between 100 and 150 nmol/L after 160 days of administration.[20] Therefore, the National

Research Council conservatively recommends 4,000 IU/day as the upper limit.

Medications Approved Since 2010 Guideline

On June 1, 2010, the FDA approved Prolia (denosumab) as a new injectable osteoporosis treatment for postmenopausal women. Denosumab has also been approved for treatment of osteoporosis in men at high risk for fracture, treatment of bone loss in men receiving androgen deprivation therapy (ADT) for nonmetastatic prostate cancer, and treatment of bone loss in women receiving aromatase inhibitors (AI) for breast cancer treatment.[21,22]

Denosumab is a monoclonal antibody that binds to nuclear factor-kappa ligand (RANKL). Osteoblasts secrete RANKL, which in turn activate osteoclast precursors to promote osteoclast formation. Denosumab binds RANKL to prevent osteoclast formation, leading to decreased bone resorption and increased bone mass.[23]

Denosumab was evaluated in a 3 year randomized, double blind, placebo controlled trial of 7,808 postmenopausal women with osteoporosis, aged 60-91 years old. 3,886 women were given denosumab 60mg every 6 months for 36 months, while 3876 women received placebo.[24] Results showed that denosumab significantly reduced the risk of new radiographic vertebral fracture (95% CI, 0.26 to 0.41; P<0.001), hip fracture (HR 0.60; 95% CI, 0.37 to 0.97; P=0.04), and nonvertebral fracture (0.80; 95% CI; 0.67 to 0.95; P=0.01). The authors concluded that denosumab is superior to placebo.

To truly understand denosumab's place in therapy, it was compared to alendronate 70 mg weekly in a phase 3, multicenter, double blind, randomized controlled trial. The study included 1,189 postmenopausal women with T scores ≤ -2.0 at the lumbar spine or total hip. After 12 months of therapy, denosumab significantly increased BMD compared to alendronate (3.5% vs. 2.6%; p < 0.0001).[25] This difference was based on mean percentage change from baseline T-score. Additionally, no significant difference between denosumab and alendronate was observed in the overall incidence of adverse events. The main criticism of this study is that no conclusions can be drawn regarding fracture incidence, as it was not powered for that endpoint. These findings are interesting, as alendronate is the current standard of care for osteoporosis treatment.

Denosumab is also effective in postmenopausal women previously treated with bisphosphonates. In a trial by Kendler et al, 500 postmenopausal women (T-scores between -2.0 and -4.0) who had previously taken alendronate were randomized to either continue therapy or switch to denosumab. After 12 months, denosumab produced small, yet significantly greater increases in BMD than those on alendronate (Total hip 1.9 vs. 1.0%, Lumbar spine 3.0 vs. 1.8%).[26] A criticism of this trial is that it did not evaluate comparative effects on fracture reduction efficacy. Nevertheless, this study suggests that patients can be transitioned successfully from alendronate to denosumab, where they are likely to experience an even greater increase in BMD.

Despite the positive clinical trial data, denosumab is not considered first line treatment for postmenopausal women with osteoporosis. Advantages of denosumab include increases in BMD, possibly more so than alendronate, and frequency of administration at every 6 months. Disadvantages include risk for osteonecrosis of the jaw, hypophosphatemia, hypocalcemia, new malignancies, infections, and dermatologic reactions. While agents for treating osteoporosis may come with similar side effects, long term adverse events data for denosumab is not as robust because it is the newest agent. Another negative point is a lack of conclusive data regarding fracture risk compared to alendronate. Finally, denosumab effects wane significantly upon discontinuation, making it inferior to bisphosphonates.

Denosumab is an option for patients, but use likely depends on clinician comfort and patient preferences. Denosumab is an excellent choice for those who prefer the convenience of an injectable medication that is only taken every 6 months and for those who desire a greater increase in BMD compared taking alendronate. Caution should be used, as this increase in BMD does not necessarily confer reduced fracture risk.

Duration

While the 2010 NOF guidelines did not provide guidance on duration of therapy, the 2013 guidelines specifically state that therapy is not indefinite. They go on to recommend that a comprehensive risk assessment be performed after the initial three to five years of treatment. This assessment should take into account fracture history, new chronic disease or medications, height measurement, BMD testing, and vertebral imaging. The guidelines state that it is reasonable to discontinue treatment in those with modest fracture risk, but continuation is needed in those with high fracture risk. New data strengthening the evidence regarding bisphosphonate therapy duration has been published since the 2010 guidelines.

Most of the data regarding continuation of bisphosphonates after 3 to 5 years comes from the FLEX and HORIZON trials, published in 2006 and 2012 respectively. The FLEX trial is a randomized, double blind controlled trial that evaluated the optimal duration of treatment for women with postmenopausal osteoporosis. 1,099 postmenopausal women who had taken alendronate for an average of 5 years were randomized to either alendronate 5mg daily, 10 mg daily, or placebo for an additional five years. The HORIZON trial was a similar study that evaluated the effect of 3 years versus 6 years of zolendronic acid treatment for osteoporosis.[27] Both FLEX and HORIZON studies showed significant reduction in the risk of vertebral fracture with continuation of bisphosphonate treatment. In FLEX, continued therapy reduced risk of symptomatic vertebral fractures (relative risk 0.45; 95% CI, 0.24 to 0.85), but showed no reduction in risk of morphometric fractures.[28] HORIZON showed a reduced risk of vertebral fractures detected on paired radiographs (relative risk 0.45; 95% CI, 0.24 to 0.85). Both studies found that cumulative risk of nonvertebral fractures was not significantly different between those continuing or discontinuing therapy.

Both studies showed an association between clinical vertebral fracture in patients receiving placebo and bone mineral density at the femoral neck at the time of bisphosphonate discontinuation. FLEX found an increased risk of clinical vertebral fracture in patients with vertebral fractures at the time of alendronate discontinuation.[29] Black et al used data from FLEX to estimate the number needed to treat (for an additional 5 years) to prevent one clinical vertebral fracture. The assessment showed highest risk of vertebral fracture and lowest numbers needed to treat for patients with a femoral neck T-score below −2.5. This suggests that such patients are high risk and are expected to benefit from continuing bisphosphonate therapy. In addition, patients with a preexisting vertebral facture and T-score < -2.0 may also benefit from continuation.[30]

Although evidence is limited regarding fracture risk and continuation of bisphosphonates past 3 to 5 years, the data from FLEX and HORIZON suggest that the risk of vertebral fractures is reduced. On the other hand, there is no evidence that continuation of therapy significantly reduces the risk of nonvertebral fractures. Based on subgroup analysis, it appears that patients with low femoral neck BMD after 3-5 years of treatment are at highest risk for vertebral fracture and should be treated for a longer duration. Extended treatment should be considered for patients with existing vertebral fracture and lower BMD (T-score < 2.0). Patients who do not meet these criteria may stop bisphosphonate therapy at the clinician's discretion.[31]

Vertebral Imaging

The 2010 NOF guidelines did not provide a recommendation regarding vertebral imaging. New data has emerged to support the use of vertebral imaging in certain populations. The 2013 NOF guidelines recommend vertebral imaging be performed in all women age ≥70 and all men age ≥80, in women age 65-69 and men age 75-79 with BMD T-score ≤ -1.5, and in postmenopausal women age 50-64 and men 50-69 with specific risk factors. The risk factors include low trauma fracture, historical height loss of ≥1.5 inches, prospective height loss of ≥0.8 inches, or recent/ongoing long term glucocorticoid treatment. In order to determine disease severity, vertebral imaging is recommended in patients who have had a fracture.

A vertebral fracture warrants diagnosis of osteoporosis and pharmacologic treatment, even if the patient does not have a BMD diagnosis.[32] This is a serious concern, as a history of vertebral fractures increases risk of future hip fracture by 2.3 fold.[33] Most vertebral fractures are asymptomatic and often undiagnosed for years. This is evidenced by the STOP Fracture study published in 2010. The investigators performed a lateral chest x-ray on 96 postmenopausal women presenting to a hospital for unrelated health concerns. Alarmingly, vertebral fractures were found in 55% of women. Of the women with fractures, 58% were unaware of their condition and many were not on osteoporosis pharmacotherapy.[34] Often times, patients with vertebral fractures do not have T-scores that would indicate need for therapy.[35] With the high percentage of asymptomatic and undiagnosed individuals, many patients in need of therapy are likely to be overlooked.

The only way to diagnose an unrecognized vertebral fracture is through proactive imaging. This can be performed using a lateral thoracic and lumber spine x-ray or a lateral vertebral fracture assessment (VFA) on a DXA machine. Lewiecki and Laster examined the utility of VFA and found it to be beneficial and cost effective for a certain population of patients. The only patients that will derive benefit are those with BMD scores that do not warrant treatment, but still have risk factors for vertebral fracture. The criteria indicated by the 2013 NOF guidelines are designed to target such patients.

Summary

Osteoporosis can cause significant morbidity, mortality, and economic burden. Fracture prevention through increasing BMD is of prime importance, as the risk of fractures increases dramatically after the initial fracture. The NOF guidelines serve to highlight the standard of care, helping practitioners better manage patients with osteoporosis. In 2013, the 2010 guidelines were updated to reflect new literature and strengthened evidence. Main differences between the guidelines are recommended daily calcium intake, recommendations for treatment of low vitamin D, and inclusion of denosumab as an approved osteoporosis medication. New recommendations for duration of bisphosphonate treatment and indications for vertebral fracture screening were also given. The goal of the updated NOF guidelines is to serve as a comprehensive summary of the current literature and further improve osteoporosis related care.

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Calcium Perspective

Calcium supplements have long been used to help maintain bone health, the benefit of this being more clear in patients with previous fracture or at high risk for one. Newer data has related calcium supplementation to potential increase in risk for adverse cardiovascular events. The data is not clear, but patients that do not take adequate vitamin D or take excessive amounts of calcium supplements may be at higher risk.

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