Management of Postmenopausal Osteoporosis

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Annu. Rev. Med. 2015. 66:329–42

First published online as a Review in Advance on October 29, 2014

The *Annual Review of Medicine* is online at med.annualreviews.org

This article's doi: 10.1146/annurev-med-070313-022841

Keywords

bone microarchitecture, fracture risk, combination therapy

Abstract

A hallmark of menopause, which follows the decline in the ovarian production of estrogen, is the aggressive and persistent loss of bone mineral and structural elements leading to loss of bone strength and increased fracture risk. This review focuses on newer methods of diagnosing osteoporosis and assessing fracture risk, as well as on novel management strategies for prevention and treatment. Fracture-risk prediction has been significantly enhanced by the development of methods such as the trabecular bone score, which helps assess bone microarchitecture and adds value to standard bone densitometry, and the Fracture Risk Assessment Tool (FRAX) algorithm techniques. The treatment of osteoporosis, which has the goals of fracture prevention and risk reduction, is moving beyond traditional monotherapies with antiresorptives and anabolic agents into new combination regimens.

INTRODUCTION

Genetically determined low bone mass along with the loss of bone associated with estrogen deficiency probably account for the majority of patients with postmenopausal osteoporosis. Nevertheless, all postmenopausal patients with osteoporosis should be evaluated for secondary causes of bone loss, such as long-term (more than three months) administration of systemic glucocorticoids, including high doses of inhaled steroids and endogenous hypercortisolism; rheumatoid arthritis; chronic liver disease; alcoholism; untreated hypogonadism following bilateral oophorectomy; anorexia nervosa or other severe eating disorders; administration of chemotherapy or aromatase inhibitors; hypopituitarism; prolonged immobility associated with spinal cord injury, Parkinson's disease, stroke, muscular dystrophy or ankylosing spondylitis; immunosuppression in organ transplantation patients; diabetes mellitus type 1 or type 2; untreated hyperthyroidism and overreplacement in hypothyroidism; inflammatory bowel disease; and chronic obstructive pulmonary disease. However, this review focuses on newer issues in postmenopausal osteoporosis that are not attributable to secondary conditions.

IDENTIFYING PATIENTS AT RISK

Bone mineral density (BMD) is an assessment of the mineral content in key skeletal regions. The World Health Organization (WHO) has defined osteoporosis using a BMD score derived from dual-energy X-ray absorptiometry (DXA), that is, 2.5 (T-score) standard deviations below the mean for healthy young adults at the spine, femoral neck or total hip (1). T-scores between −1.0 and −2.5 are consistent with low bone mass, and those above −1.0 are considered normal. A consensus report by the US National Institutes of Health emphasized the structural basis by defining osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing to increased risk of fracture" (2). Hence, surrogate measurements of bone strength have proven extremely helpful in better assessing fracture risk.

Dual X-Ray Absorptiometry

Central DXA is used for measurement of BMD of the spine and hip. It has proven utility for the diagnosis of osteoporosis, assessment of fracture risk, and monitoring of response to treatment. This method is widely available with readily interpretable results (3, 4). The risk of fracture exponentially increases as BMD decreases at the spine, hip, forearm, humerus, and pelvis (3). Nearly all randomized clinical trials have utilized BMD changes as a surrogate endpoint for assessing the efficacy of agents used for osteoporosis prevention and treatment (5). Additionally, DXA may include an assessment of lower thoracic and lumbar (T4–L4) vertebral fracture (6).

Areal BMD measurements, however, are affected by bone size and shape, soft tissue composition, severe degenerative disc disease, vertebral fractures, prior spinal surgery, bilateral hip replacement, and obesity. Most importantly, it is not possible to differentiate between undermineralized bone (osteomalacia) and osteoporosis.

Peripheral DXA measurements of the BMD of the forearm, heel or hand correlate less well with central DXA measurements (7), and they have little utility as serial measurements to assess treatment efficacy.

Fracture Risk Assessment Tool

The WHO's Fracture Risk Assessment Tool (FRAX) is a fracture risk prediction model that utilizes the femoral neck BMD as measured by DXA and incorporates clinical risk factors for bone loss

in order to better estimate the 10-year probability of hip and other major osteoporotic fractures (spine, humerus, forearm). The clinical risk factors include the country or geographic region and the patient's ethnic origin, age, sex, weight, height, prior fragility fracture, parental history of hip fracture, current smoking, excess alcohol intake, long-term use of oral glucocorticoids, rheumatoid arthritis, and secondary osteoporosis (8). The FRAX algorithm was based on data derived from population cohorts in Europe, North America, Asia, and Australia (9–11). FRAX is becoming part of standard DXA reports and may be accessed online at **https://www.shef.ac.uk/FRAX/**. FRAX models are available for 52 countries, and there are additional ethnic-specific models for the United States, because fracture probability varies significantly among different regions and ethnic groups (12).

In the United States, the National Osteoporosis Foundation recommends treatment of patients with a FRAX-calculated 10-year fracture probability of >3% for hip fracture and >20% for major osteoporotic fracture. FRAX, however, has not been evaluated in patients who have already received treatment (13). It is impossible to incorporate every possible clinical scenario into the FRAX algorithm, such as the number or sites of prior fractures, the dose and duration of glucocorticoids, or use of tobacco and alcohol. Currently, only the femoral neck BMD can be entered into the FRAX algorithm despite the frequent discordance between BMD of the hip and spine, although corrective calculations have been proposed (14). Finally, DXA and FRAX do not take into account information on the microstructural integrity of bone.

Assessments of Bone Microarchitecture

Although diagnosis and treatment decisions often rely on DXA measurements (4), when one closely reviews fracture incidence, the majority of low-trauma fractures occur in individuals with low or normal bone density measurements (15). Therefore, assessment of other major determinants of bone strength—such as trabecular structure, cortical thickness, focal defects, material properties, and geometry, as well as personal clinical and family history and propensity for falls—must be considered for a more complete risk assessment.

Extensive progress has been made in assessing microstructure and bone strength utilizing high-resolution peripheral quantitative computed tomography (QCT) (16), advanced CT imaging (17), and high-field magnetic resonance imaging (MRI) (18). Detailed plain CT analyses of the femoral neck, for example, have revealed focal sites of cortical thinning with a much higher frequency in patients with prior hip fractures (16, 19). Utilization of geometric properties derived from DXA (20) coupled with computational modeling (21) provide increased understanding of fracture susceptibility. Unfortunately, the use of these methods is limited to centers with well-established expertise in the particular technique.

Trabecular Bone Score

Newly developed advances in DXA methods have greatly expanded their functionality (22). New software (TBSiNsight®, Medimaps Group, Plan-les-Ouates, Switzerland) enables estimation of trabecular bone texture, which can be correlated to bone microarchitecture (23). A relationship between 3D bone characteristics, mechanical parameters, and the trabecular bone score (TBS) has been established (23, 24).

Many studies have demonstrated that TBS predicts current and future fragility fractures in osteoporosis beyond those predicted by BMD and clinical risk factors and has value in monitoring response to treatment (25). TBS may have additional value in secondary osteoporosis when abnormal trabecular microarchitecture may help explain the paradox of increased fractures at a higher BMD in specific diseases or conditions (e.g., diabetes, rheumatoid arthritis, glucocorticoid-induced

Table 1 Proposed trabecular bone score (TBS) ranges for postmenopausal women (28)

TBS	Microarchitecture
<1.2	Degraded = higher risk of fracture
1.2–1.35	Partially degraded = medium risk of fracture
>1.35	Normal = lower risk of fracture

osteoporosis). The precision error for TBS is equivalent to areal BMD (26, 27). One way of interpreting TBS would be to provide clinically relevant ranges (28) (**Table 1**).

Because TBS data are generated automatically in the regular DXA scan of the lumbar spine, huge databases are available for analysis (25). A summary of findings from clinical studies is given in **Table 2** (26, 27, 29–36). Degenerative disc disease and periarticular spinal disease have little effect on TBS, in contrast to their impact on bone density measurements (37). BMD has shown a positive correlation with body mass index (BMI) (38). By contrast, TBS has shown a negative but mild correlation with BMI. Both BMD and TBS predict fracture risk but are consistently found to be independent predictors (38), and both show a strong positive association with many risk factors that can predict osteoporotic fracture risk. Furthermore, TBS significantly enhances the ability of FRAX to classify fracture risk (9, 39). The WHO is considering possible inclusion of TBS in the FRAX calculation.

There are limits to TBS. Older densitometers can impair the quality of the variogram and may not be compatible with TBS software. The effect of abdominal soft tissue in attenuating photon absorption has not been fully elucidated, and BMI has not proven helpful in correcting for artifacts due to body type or composition. Appropriate phantom measurements to enable inter- and intrascan calibration have been used by the manufacturer when installing the software. The current TBS algorithm is used only in women; however, an international prospective meta-analysis is under way that should provide risk thresholds for both sexes and for different ethnicities.

Nevertheless, the easy availability of tools to assess bone microarchitecture has enormous potential to identify skeletal deterioration and fragility as these tools are integrated into physicians' workflow without consuming extra time.

INTERVENTIONAL STRATEGIES

A strategic approach to postmenopausal osteoporosis would embrace early detection and staged interventions. Bone mass is largely genetically determined. More than one-third of women reach

Table 2 Clinical studies using the trabecular bone score (TBS)

Goal	Study type	Outcome	References
Fracture risk assessment	Retrospective	Low TBS associated with ~2 × greater risk in women and men	29–33
Fracture risk assessment	Prospective	1 SD decline in TBS associated with 35% increase in fracture risk after adjustment for spine BMD and clinical risk factors TBS better predictor than BMD Lower TBS in patients with fractures	26, 27, 34
Treatment response: antiresorptives	Prospective	Change in TBS < BMD TBS and BMD changes not correlated	35
Treatment response: teriparatide	Prospective	No correlation between changes in TBS and BMD, both slightly increased	36

Abbreviations: BMD, bone mineral density; SD, standard deviation.

menopause with low bone density, which is frequently worsened by years of inadequate calcium and/or vitamin D intake. This can lead to regions of undermineralized bone and loss of structural elements, resulting in increased skeletal fragility that is often undetected by bone density measurements alone.

Therefore, a starting point for proper risk assessment includes a detailed medical, activity, and nutritional history. Bone density measurement by DXA provides an excellent surrogate measure of fracture risk. In addition, an appreciation of the geometry of the bones from the DXA printouts can be informative. A narrow femoral neck or radial shaft resulting in a low moment of inertia can be a predictor of low bone strength. Assessing trabecular bone structure by calculating TBS may provide insights into the structural integrity.

Starting early to prevent osteoporosis means ensuring adequate calcium, vitamin D, and exercise during the formative years to build bone mass to its genetically programmed ideal level. Deficiencies in calcium and vitamin D intake during the perimenopausal years can accelerate the rate of bone loss, as can diets high in phosphate or acid content. Therefore, initiating and maintaining a healthy bone program as early as possible is one starting point.

Calcium

Bone is a living and dynamic tissue, which allows for continued growth and remodeling throughout life. Thousands of milligrams of calcium passively diffuse into and out of bone daily and are bioactively moved into and out of the bone matrix during cell-mediated bone remodeling. As much as 10,000 mg of calcium are filtered by the kidneys daily, and more than 98% of that is reabsorbed. Minor increments in the renal filtered load over a prolonged period of time can lead to chronic deficits in calcium balance. Inadequate dietary calcium can result in a compensatory loss of calcium from bone—a negative spending—that can have detrimental consequences for skeletal integrity. During normal bone homeostasis, there are obligatory losses of calcium by the kidneys, gastrointestinal tract, and skin; replenishment via dietary intake is necessary to maintain a positive calcium balance. Beyond calcium homeostasis, several studies suggest additional bone benefits from calcium supplementation.

Evidence that calcium supplementation reduces fracture incidence would be the most convincing proof of skeletal benefit. Post hoc analyses have shown a positive effect of calcium supplementation on fractures in compliant patients; however, intent-to-treat analyses have not shown an effect. In a meta-analysis of 17 trials with 52,625 participants, there was a 12% risk reduction. In the subgroup that had calcium supplementation alone, an analysis of only 6,517 participants, the reduction in fracture risk was even greater (24%) when compliance was high (greater than 80%) and when calcium supplementation was equal to or greater than 1,200 mg per day (40).

Recently, controversy has raged over the incidence of myocardial infarction in patients receiving calcium supplements. Randomized controlled trials and meta-analyses have not resolved the controversy (41–43), and the disagreement persists (44). In 2013, a study in patients with osteoporosis who were followed for 10 years reported that calcium supplements, up to 1,000 mg per day, along with increased dietary intake of calcium may be associated with a reduced risk of mortality in women (45).

Vitamin D

Based on data from randomized placebo-controlled clinical trials evaluating falls and fractures, the US Institute of Medicine recently recommended that a circulating level of 25-hydroxy vitamin D (25OHD) at 20 ng/ml is sufficient for 97.5% of the population, although up to 50 ng/mL is safe (46). Adults up to 70 years old need 600 IU vitamin D daily to meet the goal of 20 ng 25OHD,

although up to 4,000 IU daily is considered safe (47). However, several experts consider these recommendations to be too strict, given data from other relevant studies. Parathyroid hormone levels increase at 25OHD levels less than 30 ng/mL, and intestinal calcium transport increases at 25OHD levels greater than 32 ng/mL. Epidemiological studies have shown that both BMD and muscle function (e.g., walking speed) positively correlate with 25OHD levels. BMD improves in elderly individuals receiving a combination of Vitamin D and calcium supplements. Supplementation with at least 800 IU of Vitamin D daily is associated with improved lower extremity function, greater balance, and reduced falls, as well as fracture prevention (48, 49).

THERAPEUTIC INTERVENTIONS

The average bone loss in the five years around menopause (perimenopause) can reach 15%, which puts women who come to menopause with low bone density at significant risk for future fracture. These women need to be identified early so that appropriate measures can be implemented to preserve and protect their skeletal mass. In the early perimenopausal period, simple antiresorptive agents can preserve and protect skeletal mass. Late in the perimenopausal period, only prolonged therapy with costly anabolic agents can partially repair the skeletal loss. Premenopausal women at increased risk for osteoporosis, such as those with a strong family history of osteoporosis; history of inflammatory vascular, musculoskeletal, or bowel diseases; diabetes; history of disordered eating; and medical treatments such as steroids or aromatase inhibitors merit full evaluation. These women, prior to menopause or in their early perimenopause, should undergo a bone density determination; a biochemical evaluation of bone turnover, urinary calcium loss, and vitamin D levels; and a detailed history of lifestyle factors that might contribute to bone loss.

Antiresorptives

The use of estrogen replacement therapy to prevent or treat postmenopausal osteoporosis is limited due to its adverse effects in the uterus, breast, and cardiovascular system (50). The Women's Health Initiative confirmed that oral estrogen (0.625 mg daily) with progestin in women with an intact uterus, or without progestin after hysterectomy, prevents bone loss and is associated with a reduction in fracture risk (51); however, this diminishes within a year after discontinuation (52). Selective estrogen receptor modulators, such as raloxifene, exert an antiestrogen effect in the uterus and breast, whereas they have an estrogen agonist effect in bone. Raloxifene reduces the incidence of vertebral fractures; however, evidence regarding hip and nonvertebral fractures is lacking (53), and its efficacy is lower than that of other antiresorptives. The increased risk of venous thromboembolic events persists, and it may aggravate menopausal vasomotor effects.

Bisphosphonates (BPs), such as alendronate, risedronate, ibandronate, and zoledronic acid, have unique properties that enable them to decrease bone resorption by inactivating osteoclasts (partly by inducing their apoptosis). This results in the maintenance of bone microarchitecture and mineralization, and leads to a reduced fracture risk. BPs remain embedded in bone and are slowly released from the skeleton over time; this long elimination half-life likely explains the delayed reversal of their antiresorptive effect after discontinuation (54).

As demonstrated by randomized placebo-controlled trials (55–57) and their extensions (6–10 years) (58, 59), BPs significantly reduced vertebral fracture risk by 35–65% within 6 months to 1 year (60–63), reduced nonvertebral fracture risk by 20–30% (62), and reduced hip fracture risk by 53% (alendronate) and 26% (risedronate). After 3 years the annual intravenous infusion of zoledronic acid decreased the incidence of vertebral fractures by 70%, of hip fractures by 41%, and of nonvertebral fractures by 25% (64).

These agents are generally safe with few adverse events, mainly the gastrointestinal reflux symptoms associated with oral BPs and the transient acute phase reaction that may develop after the initial infusion of zoledronic acid. An association between BPs and esophageal cancer has not been confirmed. An increased incidence of atrial fibrillation after infusion of zoledronic acid compared with placebo has been noted but not confirmed (64, 65). Due to BPs' renal clearance, they are contraindicated in severe renal impairment.

Perhaps the greatest safety concerns are with regard to rare adverse events, such as osteonecrosis of the jaw and atypical fractures that may occur with higher frequency during BP therapy lasting longer than 5 years. Osteonecrosis of the jaw has been extensively discussed in recent consensus papers (66).

Atypical low energy or low-trauma fractures of the femoral shaft have been reported as a rare occurrence in BP-treated patients (67). These fractures can occur anywhere in the femoral shaft, from just below the lesser trochanter to above the supracondylar flare, and are transverse or short oblique in orientation, without evidence of comminution. Causality has not been established because these fractures also occur in osteoporotic and non-osteoporotic patients who have not been treated with BPs. Several studies have not (68–70) suggested a higher incidence of these fractures during prolonged therapy with BPs, whereas others have (71–74). Atypical femur fractures most commonly occur with minimal or no trauma to the affected area. They may be bilateral, and many patients report prodromal pain in the affected area, usually presenting as dull, aching thigh pain, weeks to months before a complete fracture occurs. A number of reports have noted that patients were also receiving treatment with glucocorticoids at the time of fracture. Any patient with a history of BP exposure who presents with thigh or groin pain should be evaluated to rule out an incomplete atypical femur fracture. Patients presenting with an atypical fracture should also be assessed for fracture in the contralateral limb. Atypical fractures have been reported in patients treated with denosumab and may represent a rare complication associated with prolonged use of potent antiresorptives in susceptible individuals, who at present cannot be clearly identified.

Therefore, general guidelines for the long-term use of antiresorptives have been suggested (75). Patients with a femoral neck T-score less than −2.5 after 3–5 years of treatment are at the highest risk for vertebral fractures and, therefore, appear to benefit most from continuation of BPs (58). Patients with an existing vertebral fracture who have a somewhat higher T-score (although not greater than −2.0) may also benefit from continued therapy. Patients with a femoral neck T-score greater than −2.0 have a low risk of vertebral fracture and are unlikely to benefit from continued treatment (75).

Reductions in morbidity and mortality have been reported with BP therapy following hip fracture and in frail, elderly women (65, 76, 77). Overall, the reduced fracture risk with BP treatment in the appropriate patient population greatly outweighs the risks of extremely rare adverse events.

Denosumab is a human monoclonal immunoglobulin G (IgG) antibody to RANKL, the receptor activator for NFκB, an essential factor for osteoclast differentiation and activation. A large clinical trial has documented denosumab's efficacy in reducing fracture incidence (78). Concerns about its safety derive from the known requirement for RANKL in activated T and B cells, marrow stromal cells, osteoblasts and osteocytes, and chondrocyte differentiation (79). Denosumab is also known to affect other members of the tumor necrosis factor (TNF) family (80). However, drug safety has been confirmed (81). BMD continued to increase with prolonged denosumab therapy, by 10.1% and 6.7% at the spine and hip, respectively, after 36 months of therapy (82) and in extension trials (82), whereas other potent antiresorptives did not show the same improving outcome with therapy beyond three years. However, with cessation of denosumab therapy, the gains were lost after one year (83). Fracture risk remained reduced with continued denosumab therapy (84).

Anabolics

Only one anabolic agent, teriparatide (TPTD), has been approved by the US Food and Drug Administration as a treatment for severe osteoporosis. TPTD, a 34-amino-acid peptide, is the biologically active N-terminal portion of recombinant human parathyroid hormone. When injected subcutaneously daily at 20 μg, a brief spike in active hormone levels lasting only minutes results in an anabolic response in bone. Bone morphometric studies show increased osteoblast activation and new bone formation within a few months of initiating therapy. However, the newly formed matrix mineralizes slowly, as changes in BMD at the spine, with its high trabecular bone content, start to be seen only after 10 or 12 months of treatment. At the hip, which has a much higher cortical, or dense, bone content, increasing BMD is more likely to be seen after 18 months of treatment. Following TPTD therapy, the increase in BMD is slowly lost unless the newly formed and probably undermineralized bone is protected by administration of an effective antiresorptive agent. Thus, successful anabolic treatment with TPTD requires combination therapy.

In patients with severe senile osteoporosis who are at very high risk for fracture, the reduction in fracture risk is greater than that seen in subjects treated with the antiresorptive agents alone (85). Importantly, the change in BMD with TPTD has a better correlation with the reduction in fracture incidence than that seen with any of the other treatments (86). Therefore, change in BMD has proven to be an excellent surrogate measure for predicting outcome with TPTD treatment. Given the cost and duration of treatment, it is disappointing that a favorable response to TPTD occurs in less than 50–70% of patients (87).

Combined Therapy

In an effort to improve outcomes with TPTD, a number of studies have varied the doses, agents and regimens of combined therapy. Early studies examining concurrent use (often starting with BP before TPTD) reported attenuation of the BMD response when compared with the anabolic agent alone (88–90). Treatment with one year of TPTD alone followed by BP alone resulted in improved bone density and mass at year two (91). Denosumab combined with TPTD increased BMD at the lumbar spine and hip more than either denosumab alone or TPTD alone after one (92) and two years (93), and it produced favorable structural changes in cortical parameters (94).

Altering the sequence of anabolic and antiresorptive BP therapy has improved BMD outcomes, particularly in year two of combined therapy. In a randomized open-label design Muschitz et al. (95) treated severely osteoporotic patients for nine months with TPTD alone. The patients were then randomized to receive an additional nine months of therapy: TPTD with alendronate, TPTD with raloxifene, or TPTD alone. After 18 months, areal BMD at the lumbar spine had nearly doubled in the combined treatment groups compared with the group receiving TPTD alone for 18 months. The TPTD plus BP group increased areal BMD at the hip by more than 40% above that seen with TPTD alone or in combination with raloxifene. Volumetric BMD changes in the spine measured by QCT were similar to the changes in areal BMD. QCT at the total hip showed that the TPTD plus alendronate combination increased bone content at both the trabecular and cortical regions. The critical time during which TPTD induces increased bone formation, which is presumed to precede bone resorption, the so-called anabolic window, was not defined. When bone markers were tracked during the first 4–8 months of TPTD treatment, patients with an early rise in bone resorption, reflecting early closure of the anabolic window, showed a poor response to TPTD in terms of BMD change at 2 years (96). The early closure of the anabolic window helps explain data showing that the initial anabolic stimulus was augmented by the delayed administration of an antiresorptive agent (95). However, neither study provided

insights on how to identify those patients receiving anabolic therapy who are most likely to benefit from appropriately timed combination therapy.

Newer anabolic therapies that are not constrained by an anabolic window are in clinical trials or are being developed. These agents act more directly on bone-forming pathways to enhance bone formation without provoking an osteoclast-mediated bone-resorptive response. One such agent is a humanized monoclonal antibody directed against sclerostin, an inhibitor of the bone-forming Wnt pathway. The earlier human trials have reported an excellent safety and efficacy response (97). Intermittent therapy with a pure anabolic could achieve treatment to goal, with a significant reduction in fracture risk.

CONCLUSION: TREATMENT TO GOAL IN OSTEOPOROSIS

The approach to osteoporosis should in principle follow a treatment-to-goal strategy. A therapeutic regimen to lower fracture risk should be individually applied, reassessed, and then changed to meet endpoints that best predict outcome. For example, treatment with raloxifene usually results in little or no significant increase in BMD. Therefore, there is little benefit to monitoring BMD to assess the reduction in fracture risk. However, a significant decline in BMD could indicate increasing fracture risk. By contrast, anabolic therapy with TPTD typically results in a significant increase in BMD, and this change is strongly correlated with a reduction in fracture risk.

Regrettably, specific treatment goals have yet to be defined. Therefore, a pragmatic approach to treatment is advised. This starts with making the best assessment of fracture risk based on BMD, microstructure as determined either by CT or TBS analysis, and clinical evidence of prior skeletal fragility.

Those at highest fracture risk are likely to require parenteral antiresorptives (98, 99) or anabolic therapy (85, 86). In these high-risk patients, it is often appropriate to monitor the increase in BMD, and perhaps to set a goal that would be associated with a significantly lowered fracture risk.

For low-risk patients with a BMD T-score at or near −2.5 and evidence of normal bone structure, normal geometry, and normal bone turnover, along with a negative history of skeletal fragility, a less intense regimen may be sufficient—for example, ensuring adequate calcium and vitamin intake and sufficient exercise. In all cases, periodic reassessment of BMD, skeletal and general health, and new medication use, is necessary because all of these may affect risk status and may require treatment modification.

DISCLOSURE STATEMENT

The authors are not aware of any affiliations, memberships, funding, or financial holdings that might be perceived as affecting the objectivity of this review.

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