Osteoporosis, actualizaciones en diagnóstico

Dr. José Alfredo Álvarez López

La **osteoporosis** se define como una enfermedad esquelética sistémica caracterizada por una **baja masa ósea mineral y un deterioro de la microarquitectura del tejido óseo**, más específicamente una disminución en el número de trabéculas junto con un adelgazamiento trabecular y pérdida de conectividad, así como una disminución del grosor cortical y un aumento de la su porosidad, que tiene como consecuencia una **fractura** o incremento del riesgo de sufrir la misma.

Se considera en algunos países como un **problema de salud pública**, por su alta prevalencia, y se estima que cada 3 segundos se sufre una factura secundaria a osteoporosis en todo el mundo; por eso la importancia de realizar el diagnóstico de forma temprana para establecer el tratamiento adecuado y evitar fracturas.

El **diagnóstico de osteoporosis** está vigente desde el año 1994, cuando el grupo del Dr. Kanis propuso esta definición basado en la **medición de la densidad mineral ósea por medio de DXA (absorciometría de rayos X dual)**, en los sitios de: **cadera total, cuello femoral, columna lumbar y después se incluyo antebrazo no dominante**, todo esto fue aceptado por las OMS y sigue vigente hasta la fecha.

En el año 2010, surge el **software FRAX** (Herramienta de Evaluación de Riesgo de Fractura, por sus siglas en inglés), que nos ayuda a determinar el riesgo de factura para cada paciente, estimado a 10 años, conociendo los factores de riesgo de nuestro paciente, contestando preguntas y colocando las respuestas en esta herramienta como lo son: peso, talla, edad, sexo, si padres padecieron fractura de cadera, tabaquismo, alcoholismo, consumo de esteroides, antecedente de fractura previa, causa secundaria de osteoporosis, artritis reumatoide y valorar de DMO (densidad mineral ósea). Al final nos da dos resultados que son el riesgo de fractura a 10 años para fractura de cadera (si su valorar es igual o mayor al 3%, requiere tratamiento), y el riesgo de fractrua osteoporótica mayor (si el resultado es igual o mayor al 20%, requiere tratamiento); cabe mencionar que esta herramienta también fue desarrollada por el grupo de trabajo del Dr. Kanis, de la Universidas de Shifield en Reino Unido.

Actualmente han surgido **nuevas guías sobre osteoporosis** y en el 2014 la IOF (Fundación Internacional de Osteoporosis, por sus siglas en inglés) emitió una guía haciendo alusión a la determinación del riesgo de fractura con la herramienta FRAX y en el año 2019 la Endocrine Society en su guía hace hincapié en la utilización del FRAX y en 2020 la AACE (Asociación Americana de Endocrinólogos Clínicos, por sus siglas en inglés), recomienda lo mismo y emiten algoritmos para diagnóstico y tratamiento de osteoporosis.

Durante la plática se dara un ejemplo de FRAX y su uso, así como la nueva actualización de esta herramienta que se llama FRAX Plus, la cual al parecer ya tendrá un costo adicional al utilizarla.

Al final se hablará sobre las generalidades del tratamiento, haciendo enfasis de que el grupo más amplio: el de los **antirresortivos** y, dentro de estos, los **bifosfonatos**; se presentarán una parte de los **algoritmos de las guías** comentadas y una línea del tiempo sobre la historia de los criterios diagnósticos y las probables consecuencias.

Pharmacological Management of Osteoporosis in Postmenopausal Women: An Endocrine Society* Clinical Practice Guideline

Richard Eastell,[1] Clifford J. Rosen,[2] Dennis M. Black,[3] Angela M. Cheung,[4] M. Hassan Murad,[5] and Dolores Shoback[6,7]

[1]University of Sheffield, Sheffield S10 2TN, United Kingdom; [2]Maine Medical Center Research Institute, Scarborough, Maine 04074; [3]University of California San Francisco, San Francisco, California 94107; [4]University of Toronto, Toronto, Ontario M5S 1A1, Canada; [5]Mayo Clinic Evidence-Based Practice Center, Rochester, Minnesota 55905; [6]Endocrine Research Unit, San Francisco Veterans Affairs Medical Center, San Francisco, California 94121; and [7]Department of Medicine, University of California San Francisco, San Francisco, California 94143

ORCiD numbers: 0000-0003-3436-8199 (C. J. Rosen).

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Objective: The objective is to formulate clinical practice guidelines for the pharmacological management of osteoporosis in postmenopausal women.

Conclusions: Evidence from clinical trials and insights from clinical experience with pharmacologic therapies for osteoporosis were critically evaluated in formulating this guideline for the management of postmenopausal osteoporosis. Patient preferences, data on adherence and persistence, and risks and benefits from the patient and provider perspectives were also considered in writing committee deliberations. A consensus by the Writing Committee members was achieved for four management principles: (i) The risk of future fractures in postmenopausal women should be determined using country-specific assessment tools to guide decision-making. (ii) Patient preferences should be incorporated into treatment planning. (iii) Nutritional and lifestyle interventions and fall prevention should accompany all pharmacologic regimens to reduce fracture risk. (iv) Multiple pharmacologic therapies are capable of reducing fracture rates in postmenopausal women at risk with acceptable risk-benefit and safety profiles. (***J Clin Endocrinol Metab*** **104: 1–28, 2019)**

List of Recommendations

Who to treat

1.1 We recommend treating postmenopausal women at high risk of fractures, especially those who have experienced a recent fracture, with pharmacological therapies, as the benefits outweigh the risks. (1|⊕⊕⊕⊕)

Bisphosphonates

2.1 In postmenopausal women at high risk of fractures, we recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) to reduce fracture risk.(1|⊕⊕⊕⊕)
Technical remark: Ibandronate is not recommended to reduce nonvertebral or hip fracture risk.

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Abbreviations: ACP, American College of Physicians; AFF, atypical femoral fracture; ASBMR, American Society for Bone and Mineral Research; BMD, bone mineral density; BTM, bone turnover marker; CKD, chronic kidney disease; CTX, C-terminal crosslinking telopeptide; DVT, deep venous thrombosis; eGFR, estimated glomerular filtration rate; FLEX, Fracture Intervention Trial Long-term Extension; FRAX, Fracture Risk Assessment Tool; FREEDOM, Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months; HR, hazard ratio; HT, hormone therapy; ONJ, osteonecrosis of the jaw; P1NP, procollagen type 1 N-terminal propeptide; RCT, randomized control trial; SmPC, summary of product characteristics.

2.2 In postmenopausal women with osteoporosis who are taking bisphosphonates, we recommend that fracture risk be reassessed after 3 to 5 years, and women who remain at high risk of fractures should continue therapy, whereas those who are at low-to-moderate risk of fractures should be considered for a "bisphosphonate holiday." (1|⊕⊕OO)

Technical remark: A bisphosphonate holiday is operationally defined as a temporary discontinuation of bisphosphonate for up to 5 years. This period may be longer depending on the bone mineral density and clinical circumstances of the individual patient. The evidence is stronger for retention of benefits during a holiday for alendronate and zoledronic acid where there are randomized extension trials. A shorter reassessment period of 3 years is more appropriate for annual intravenous zoledronic acid (5 mg) based on evidence from research control trials showing residual effects after 3 years of annual use. Once a bisphosphonate holiday is initiated, reassess fracture risk at 2- to 4-year intervals and consider reinitiating osteoporosis therapy earlier than the 5-year suggested maximum if there is a significant decline in bone mineral density, an intervening fracture, or other factors that alter the clinical risk status.

Denosumab

3.1 In postmenopausal women with osteoporosis who are at high risk for osteoporotic fractures, we recommend using denosumab as an alternative initial treatment. (1|⊕⊕⊕⊕)

Technical remark: The recommended dosage is 60 mg subcutaneously every 6 months. The effects of denosumab on bone remodeling, reflected in bone turnover markers, reverse after 6 months if the drug is not taken on schedule. Thus, a drug holiday or treatment interruption is not recommended with this agent.

3.2 In postmenopausal women with osteoporosis who are taking denosumab, we suggest that the fracture risk be reassessed after 5 to 10 years and that women who remain at high risk of fractures should either continue denosumab or be treated with other osteoporosis therapies. (2|⊕OOO)

3.3 In postmenopausal women with osteoporosis taking denosumab, administration of denosumab should not be delayed or stopped without subsequent antiresorptive [*e.g.*, bisphosphonates, hormone therapy, or selective estrogen receptor modulator] or other therapy administered to prevent a rebound in bone turnover and to decrease the risk of rapid bone mineral density loss and an increased risk of fracture. (Ungraded Good Practice Statement)

Teriparatide and abaloparatide (parathyroid hormone and parathyroid hormone–related protein analogs)

4.1 In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe or multiple vertebral fractures, we recommend teriparatide or abaloparatide treatment for up to 2 years for the reduction of vertebral and nonvertebral fractures. (1|⊕⊕⊕O)

4.2 In postmenopausal women with osteoporosis who have completed a course of teriparatide or abaloparatide, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone density gains. (1|⊕⊕OO)

Selective estrogen receptor modulators

5.1. In postmenopausal women with osteoporosis at high risk of fracture and with the patient characteristics below, we recommend raloxifene or bazedoxifene to reduce the risk of vertebral fractures. (1|⊕⊕⊕⊕)

Patient characteristics: With a low risk of deep vein thrombosis and for whom bisphosphonates or denosumab are not appropriate, or with a high risk of breast cancer.

Menopausal hormone therapy and tibolone

6.1 In postmenopausal women at high risk of fracture and with the patient characteristics below, we suggest menopausal hormone therapy, using estrogen only in women with hysterectomy, to prevent all types of fractures. (2|⊕⊕⊕O)

Patient characteristics: Under 60 years of age or <10 years past menopause; at low risk of deep vein thrombosis; those in whom bisphosphonates or denosumab are not appropriate; with bothersome vasomotor symptoms; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke; without breast cancer; willing to take menopausal hormone therapy.

6.2 In postmenopausal women with osteoporosis at high risk of fracture and with the patient

characteristics below, we suggest tibolone to prevent vertebral and nonvertebral fractures. (2|⊕⊕⊕O)

Patient characteristics: Under 60 years of age or <10 years past menopause; with a low risk of deep vein thrombosis; those in whom bisphosphonates or denosumab are not appropriate; with bothersome vasomotor symptoms; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke or high risk for cardiovascular disease; without breast cancer; willing to take tibolone.

Technical remark: Tibolone is not available in the United States or Canada.

Calcitonin

7.1 In postmenopausal women at high risk of fracture with osteoporosis, we suggest that nasal spray calcitonin be prescribed only in women who cannot tolerate raloxifene, bisphosphonates, estrogen, denosumab, tibolone, abaloparatide, or teriparatide or for whom these therapies are not considered appropriate. (2|⊕OOO)

Calcium and vitamin D

8.1 In postmenopausal women with low bone mineral density and at high risk of fractures with osteoporosis, we suggest that calcium and vitamin D be used as an adjunct to osteoporosis therapies. (2|⊕⊕OO)

8.2 In postmenopausal women at high risk of fracture with osteoporosis who cannot tolerate bisphosphonates, estrogen, selective estrogen response modulators, denosumab, tibolone, teriparatide, and abaloparatide, we recommend daily calcium and vitamin D supplementation to prevent hip fractures. (1|⊕⊕⊕O)

Monitoring

11.1 In postmenopausal women with a low bone mineral density and at high risk of fractures who are being treated for osteoporosis, we suggest monitoring the bone mineral density by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment. (2|⊕OOO)

Technical remark: Monitoring bone turnover markers (serum C-terminal crosslinking telopeptide for antiresorptive therapy or procollagen type 1 N-terminal propeptide for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy.

Introduction

Postmenopausal osteoporosis is common, and fractures are injurious to patients and costly to the health care system; however, effective treatments are available. One in two postmenopausal women will have an osteoporotic fracture in her lifetime (1). Those who have had a fracture are at high risk of subsequent fractures (2). Fractures can cause pain, decreased mobility and function, and fear of falling and are associated with decreased quality of life and increased mortality (3–6). However, many postmenopausal women at highest risk do not receive treatment to prevent major osteoporotic fractures and their associated morbidity and mortality (7). With ongoing reports of atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ), there is uncertainty among postmenopausal women and their health care providers regarding the benefits and risks of different management strategies for osteoporosis, who to treat, when to monitor and what tests to do for monitoring, the appropriate duration of therapy, and when to consider a bisphosphonate holiday. In fact, there has been a decline in the use of bisphosphonates (8), and the recent hip fracture incidence among postmenopausal women is higher than projected in the United States, suggesting a leveling off and possible reversal in what had been a decade-and-a-half-long decline (9, 10). Recently, the American College of Physicians (ACP) published their guidelines for the treatment of low bone mineral density (BMD) or osteoporosis to prevent fractures in women and men (11), but certain recommendations in those guidelines have raised new questions and generated much discussion, especially with regard to the duration of therapy and monitoring. The ACP recommends that physicians should treat women with osteoporosis with drug therapy for 5 years and recommends against monitoring the BMD during that period. No differentiation between bisphosphonates and denosumab was made for duration of therapy even though the pharmacokinetics of the two classes of drugs are quite different. The ACP guidelines also do not include recommendations regarding the use of abaloparatide, a new bone-formation therapy, which was approved by the Food and Drug Administration just prior to the release of the guidelines. The ACP guidelines recommend against using menopausal hormone therapy (HT) or raloxifene, a selective estrogen receptor modulator, for osteoporosis

treatment and do not consider teriparatide a potential treatment option for patients severely affected by the disease. The Endocrine Society's international guideline Writing Committee has reviewed current evidence and has different recommendations regarding pharmacotherapies to treat osteoporosis in postmenopausal women.

Systematic Review and Meta-Analyses

The guideline Writing Committee commissioned two systematic reviews to support this guideline. The first review synthesized the evidence derived from randomized controlled trials (RCTs) enrolling postmenopausal women with primary osteoporosis (12). The review included 107 trials (193,987 postmenopausal women; mean age of 66 years; 55% white; median follow-up of 28 months). The maximum duration for most trials was 4 years. The meta-analyses were done in two ways: a direct comparison with placebo and a combination of direct and indirect comparisons, or network approach. We have focused on the results of the direct approach in this guideline except when there was a clear discrepancy. In that case, we took into account the quality of the trials of comparison with placebo and consistency within the class.

Significant reduction in vertebral fractures was observed with alendronate, risedronate, ibandronate, zoledronic acid, denosumab, teriparatide, abaloparatide, raloxifene, bazedoxifene, HT, tibolone, calcitonin, PTH (1-84), romosozumab, strontium ranelate, and lasofoxifene (Fig. 1). A significant reduction in hip fractures was observed with alendronate, risedronate, zoledronic acid, denosumab, menopausal HT (estrogen with or without progestogen), and a calcium with vitamin D combination (Fig. 1). A significant reduction in nonvertebral fractures was observed with alendronate, risedronate, zoledronic acid, denosumab, teriparatide, abaloparatide, HT, tibolone, calcium or vitamin D, romosozumab, and lasofoxifene (Fig. 1).

The second review was aimed at evaluating values and preferences relevant to the management of osteoporosis in women and followed a qualitative approach (13). Women in general seemed to consider effectiveness and adverse events equally, followed by the convenience of taking the drug and the impact on daily routines (less frequent dosing was preferred, an oral route was preferred, but an injectable route was preferred over oral if given less frequently). Cost and duration of treatment were less important factors for decision-making. Fear of breast cancer and refusal to resume uterine bleeding were common reasons for not choosing menopausal HT. Calcium and vitamin D were viewed as safe and

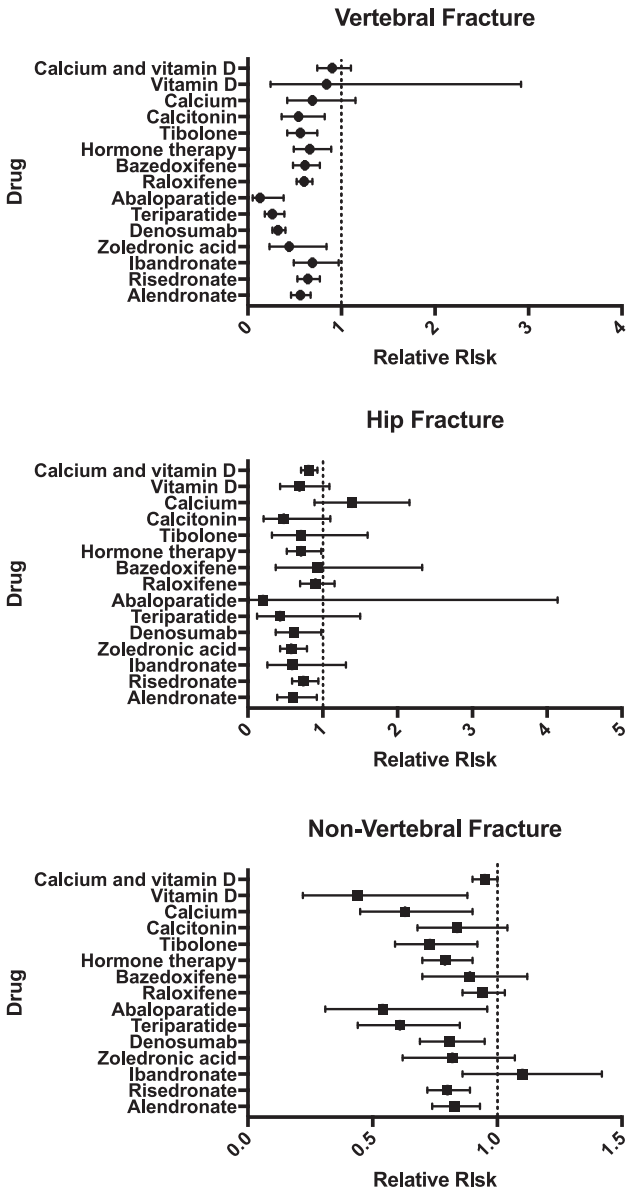

Figure 1. Relative risks of vertebral, hip, and nonvertebral fractures (and 95% CIs) in response to the treatments for postmenopausal osteoporosis, calculated directly and compared with placebo. Note that the evidence is based on a direct meta-analysis of 107 trials of drugs in postmenopausal women with primary osteoporosis in which the trial duration lasted for 3 to 120 mo. In this analysis, each agent was compared with placebo and so direct comparisons should not be made between treatments based on this figure. (12). [Adapted with permission from data presented in Moreno PB, Kapoor E, Asi N, et al. Efficacy of pharmacological therapies for the prevention of fractures in postmenopausal women: a network meta-analysis. J Clin Endocrinol Metab. 2019;104(5):XXX-XXX].

"natural." Across studies, preference was not affected by age, previous drug exposure, or employment.

1. Who to Treat

1.1 We recommend treating postmenopausal women at high risk of fractures, especially those who have experienced a recent fracture, with pharmacological

therapies, as the benefits outweigh the risks. (1|⊕⊕⊕⊕)

Evidence

The goal of using pharmacological therapies to treat low BMD or osteoporosis in postmenopausal women is to decrease the burden of major osteoporotic fractures. Various scientific bodies from different countries have determined treatment thresholds based on either a BMD T-score or various risk assessment tools such as the Fracture Risk Assessment Tool (FRAX), Canadian Association of Radiologists and Osteoporosis Canada calculator, Osteoporosis Self-Assessment Tool, and Garvan Institute fracture risk calculator, as well as the values, preferences, and costs for their populations. Currently there are 52 national guidelines in 36 countries. Some guidelines use fracture-risk thresholds, such as those used in the United States, Canada, and the United Kingdom (14–16), whereas other guidelines use T-score–based thresholds, such as those used in Austria, Belgium, India, and Brazil (17–22). Of the 52 guidelines, 30 include the FRAX-based 10-year absolute fracture risk in their treatment threshold (23). Some of these guidelines (such as those in the United States and Canada) have fixed fracture-risk thresholds across ages, whereas other guidelines, such as the United Kingdom National Osteoporosis Guideline Group guideline, the Lebanon osteoporosis guideline, and the Chilean guideline (14, 23, 24), are hybrid models, using age-dependent intervention thresholds for certain age groups and fracture-risk thresholds for other age groups (25). In the United States, pharmacological therapy is recommended for postmenopausal women with hip or vertebral fractures; those with T-scores of -2.5 or less in the femoral neck, total hip, or lumbar spine; and those with T-scores of -1 to -2.5 and a 10-year probability of $\geq 20\%$ for major osteoporotic fractures or $\geq 3\%$ for hip fractures based on the US-adapted FRAX tool (15). BMD T-score is defined as the number of SDs from the mean BMD of white females age 20 to 29 years in the Third National Health and Nutrition Examination Survey database. For the treatment of osteoporosis, only lumbar spine, total hip, and femoral neck BMD T-scores are usually considered.

Data suggest that a recent fracture (within the past 2 years) is a better predictor of imminent fracture risk (*i.e.*, risk of fracture within the next 2 years) than is a distant fracture history (>5 years ago) (26, 27). This is true for recent vertebral fractures (28, 29) as well as nonvertebral fractures such as wrist and humerus fractures (30–33). Pharmacological therapies should be initiated without delay in patients with recent fractures to prevent more fractures, based on their fracture risk. Data on optimal timing of initiation of therapy after a fracture are scant. Based on the Horizon trial (34), we would suggest initiating therapy 2 weeks or more after a hip fracture. Women should also be counseled regarding adequate calcium and vitamin D intake, fall prevention strategies, smoking cessation, avoidance of excessive alcohol intake, and weight-bearing, muscle-strengthening exercises as well as balance training. Once osteoporosis is diagnosed, strategies to prevent subsequent fractures (pharmacologic and otherwise) need to be reinforced indefinitely, much like the management strategies for hypertension and hypercholesterolemia.

Patient values and preferences

When making decisions regarding who to treat, patient preferences and patient-specific clinical factors should be taken into account. Values and costs vary across countries depending on the needs and resources of the specific country. The Writing Committee is recommending pharmacologic therapies for postmenopausal women at high risk of fractures based on country-specific risk assessment guidelines, especially for women who have had a recent fracture.

2. Bisphosphonates

2.1 In postmenopausal women at high risk of fractures, we recommend initial treatment with bisphosphonates (alendronate, risedronate, zoledronic acid, and ibandronate) to reduce fracture risk. (1|⊕⊕⊕⊕)

Technical remark: Ibandronate is not recommended to reduce nonvertebral or hip fracture risk.

2.2 In postmenopausal women with osteoporosis who are taking bisphosphonates, we recommend that fracture risk be reassessed after 3 to 5 years, and women who remain at high risk of fractures should continue therapy, whereas those who are at low-to-moderate risk of fractures should be considered for a "bisphosphonate holiday." (1|⊕⊕OO)

Technical remark: A bisphosphonate holiday is operationally defined as a temporary discontinuation of bisphosphonate for up to 5 years. This period may be longer depending on the BMD and clinical circumstances of the individual patient. The evidence is stronger for retention of benefits during a holiday for alendronate and zoledronic acid where there are randomized extension trials. A shorter reassessment period of 3 years is more appropriate for annual IV zoledronic acid (5 mg) based on evidence from RCTs showing residual effects after 3 years of annual use. Once a bisphosphonate holiday is initiated, reassess fracture risk at 2- to 4-year intervals and consider

reinitiating osteoporosis therapy earlier than the 5-year suggested maximum if there is a significant decline in BMD, an intervening fracture, or other factors that alter the clinical risk status.

Evidence

Bisphosphonate treatment up to 5 years

Three oral bisphosphonates available in the United States and internationally include alendronate (weekly), ibandronate (monthly), and risedronate (weekly or monthly). Additionally, there are two IV agents: zoledronic acid, given annually, and ibandronate, given quarterly. Note that all results below are taken from the "direct" meta-analysis comparing each drug with placebo [see appendix in Moreno *et al.* (12)] unless otherwise specified.

Most of the evidence included in the meta-analysis reflects RCTs in older women (most >65 years of age) with high fracture risk, as defined by varying combinations of low BMD, prevalent vertebral fracture, or presence of other risk factors. The meta-analysis comparison of alendronate with placebo (Fig. 1) showed a 44% reduction in vertebral fracture risk [hazard ratio (HR), 0.56; 95% CI, 0.46 to 0.67], a 40% reduction in hip fracture risk (HR, 0.60; 95% CI, 0.39 to 0.92), and a 17% reduction in nonvertebral fracture risk (HR, 0.83; 95% CI, 0.74 to 0.93). The meta-analysis comparison of risedronate with placebo (Fig. 1) showed a 36% reduction in vertebral fracture risk (HR, 0.64; 95% CI, 0.53 to 0.77), a 26% reduction in hip fracture risk (HR, 0.74; 95% CI, 0.59 to 0.94), and a 20% reduction in nonvertebral fracture risk (HR, 0.80; 95% CI, 0.72 to 0.89). The meta-analysis comparison of ibandronate with placebo (Fig. 1) showed a 31% reduction in the vertebral fracture risk (HR, 0.69; 95% CI, 0.49 to 0.97). There was no evidence for a reduction in hip or nonvertebral fracture risk. The meta-analysis comparing zoledronic acid with placebo (Fig. 1) showed a 56% reduction in vertebral fracture risk (HR, 0.44; 95% CI, 0.23 to 0.84), a 42% reduction in hip fracture risk (HR, 0.58; 95% CI, 0.43 to 0.79), and an 18% reduction in nonvertebral fracture risk (HR, 0.82; 95% CI, 0.62 to 1.07). The absence of significance for the last result in the direct meta-analysis was one of the few that was inconsistent with the network meta-analysis, which showed a 21% (significant) reduction in nonvertebral fracture risk (HR, 0.79; 95% CI, 0.67 to 0.94) (12).

One large trial of zoledronic acid conducted among women and men after hip fracture found a 35% (significant) reduction (HR, 0.65; 95% CI, 0.50 to 0.84) in all clinical fractures, supporting the value of bisphosphonate treatment after a hip fracture (34). In this trial, there was also evidence of 28% (significant) reduction (HR, 0.72; 95% CI, 0.56 to 0.93) in mortality (34), although a reduction in mortality has not been shown in other trials with zoledronic acid.

Long-term bisphosphonate treatment beyond 5 years

Bisphosphonates are distinct from other osteoporosis therapies in that their positive effects persist for several years after discontinuation. For alendronate and zoledronic acid, two moderate-sized randomized, placebo-controlled trials (1099 and 1233 women, respectively) of long-term use (10 years vs 5 years for alendronate and 6 vs 3 years for zoledronic acid) (35, 36) form the primary evidence base. For the Fracture Intervention Trial Long-term Extension (FLEX) trial with alendronate, during the 5 years of the study, BMD (the primary endpoint) decreased gradually in the placebo compared with the continued alendronate group. Thus, at the end of 5 years, ~50% to 75% of the BMD gains during the initial treatment period were lost in those who discontinued alendronate. Similarly, bone turnover gradually increased. Among those who continued alendronate compared with those who discontinued its use, vertebral fracture risk was significantly lower, but there were no significant reductions in nonvertebral or hip fractures. However, the CIs for nonvertebral and hip fracture rates were wide. In the extension study with zoledronic acid, BMD fell more slowly after discontinuation compared with the study with alendronate, and levels of bone turnover markers (BTMs) rose more slowly. Fracture results in this study were similar to the FLEX study with a reduction in vertebral fractures but no significant effects on nonvertebral fractures.

There are more limited data regarding discontinuation of risedronate and ibandronate. In the Tablets, Rings, and Injectables as Options for Women (TRIO) study, osteoporotic women were randomized to receive alendronate, risedronate, or ibandronate (37, 38). The effect of 2 years of use followed by 2 years of discontinuation was compared between the three groups (n = 57 women). Results showed no difference between groups in BTMs or change in BMD after discontinuation. These preliminary data did not show that the rate of offset of action after stopping ibandronate and risedronate on both BMD and BTMs differs from alendronate. A larger study with treatment longer than 2 years, however, is needed to obtain a more definitive comparison (39).

Bisphosphonate treatment holidays

The risk of AFFs and ONJ, particularly with long-term bisphosphonate use beyond 5 years, has prompted concerns about defining the treatment course (see "Optimal Duration of Treatment and Drug Holidays"). The American Society for Bone and Mineral Research (ASBMR) Task Force on Long-Term Bisphosphonates has

proposed that AFF risk might be reduced, with little compromise in reduction in osteoporotic fractures, by taking a temporary holiday from oral bisphosphonates after 5 years and after 3 years of IV bisphosphonates, in patients who are not at high risk of fracture (40). That fracture efficacy might be maintained during a holiday is supported by several studies. First, results from the two long-term randomized trials with alendronate and zoledronic acid discussed above suggest that after stopping either of these treatments, BMD gains remain but are slowly lost during 3 to 5 years. Levels of BTMs remain decreased initially, but slowly increase, and the risk of nonvertebral fractures is not increased over 5 years after discontinuation. Second, a recent large observational study also showed no increase in nonvertebral or hip fracture risks for those discontinuing bisphosphonates compared with persistent users (41).

An important assumption about the value of a bisphosphonate holiday is that AFF risk would be reduced. There is limited evidence that AFF risk will be reduced during a bisphosphonate holiday: one large observational study showed that AFF is reduced by >80% in the 3 years after stopping bisphosphonates (42). Preliminary results from a study in Kaiser Permanente Southern California showed a similar reduction in AFF risk after stopping bisphosphonates (41).

The ASBMR Task Force suggests that those at low to moderate fracture risk can initiate a bisphosphonate holiday, whereas those at high risk should continue the bisphosphonate or switch to another therapy (Fig. 2) (40). An algorithm based on the FLEX trial for identifying candidates for a drug holiday, based on vertebral fracture status and femoral neck BMD at the time of potential discontinuation, has been proposed (43).

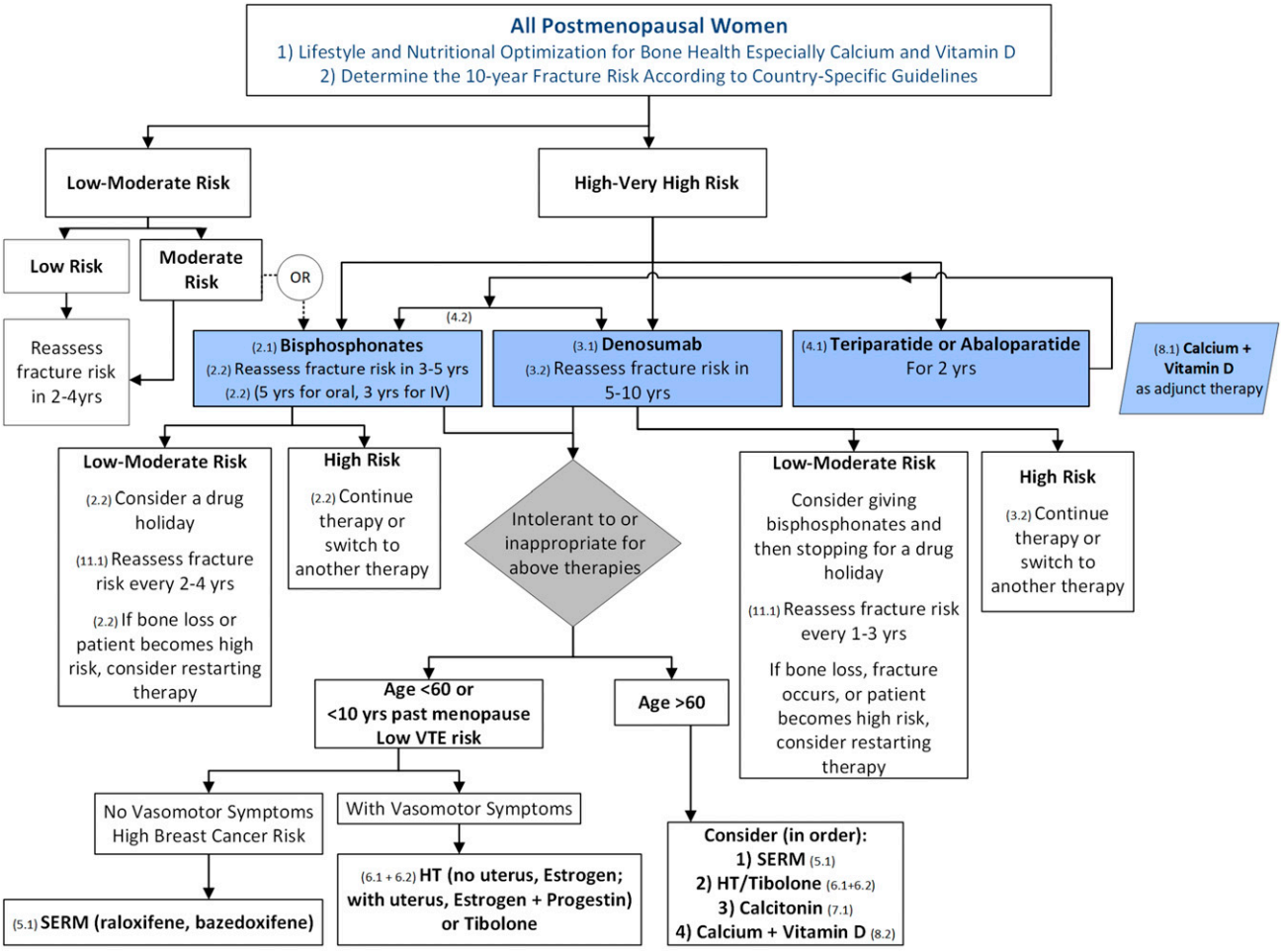

Figure 2. Algorithm for the management of postmenopausal osteoporosis. Note that in this algorithm, we considered that a determination of fracture risk would include measurement of lumbar spine and hip BMD and inserting the total hip or femoral neck BMD value into the FRAX tool. Using that FRAX algorithm, we define the following risk categories: "low risk" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −1.0, and 10-year hip fracture risk <3% and 10-year risk of major osteoporotic fractures <20%; "moderate risk" includes no prior hip or spine fractures, a BMD T-score at the hip and spine both above −2.5, or 10-year hip fracture risk <3% or risk of major osteoporotic fractures <20%; "high risk" includes a prior spine or hip fracture, or a BMD T-score at the hip or spine of −2.5 or below, or 10-year hip fracture risk ≥3%, or risk of major osteoporotic fracture risk ≥20%; and "very high risk" includes multiple spine fractures and a BMD T-score at the hip or spine of −2.5 or below.

Once a holiday has begun, fracture risk and BMD should be re-evaluated every 2 to 4 years after discontinuation (Fig. 2). A significant drop in BMD (or a large increase in BTMs) may lead to reinitiation of osteoporosis therapy, depending on the individual's fracture risk before the 5-year maximum holiday is completed.

Although there are some data suggesting that a lower dose of alendronate (5 mg/d) begun after 5 years of alendronate is equally effective in maintaining BMD and levels of BTMs, as is continuing the full dose (10 mg/d) (36), we do not know whether a dose reduction decreases AFF risk. Further study of this question might establish whether lowering the dose after 5 years might be an alternative to a bisphosphonate holiday.

Balance of benefits and harms

Original safety concerns for oral bisphosphonates focused on upper gastrointestinal irritation. However, in practice, these adverse effects can be minimized by careful adherence to correct dosing procedures even in patients with esophageal disease (12, 44). For IV zoledronic acid, an acute-phase reaction (flu-like symptoms, *e.g.*, pyrexia and myalgia) is common (occurring in approximately one in four patients), but usually only after the first infusion, and lasts for 1 to 7 days. The frequency and severity can be reduced by pretreatment with agents such as acetaminophen or ibuprofen. Due to concerns about renal toxicity, bisphosphonates are indicated only for patients with estimated glomerular filtration rate (eGFR) >30 mL/min for risedronate and ibandronate and >35 mL/min for alendronate and zoledronic acid. Although there have been particular concerns about IV zoledronic acid and renal damage, as long as a minimum of a 15-minute infusion time is maintained and the patient is well hydrated, there has been no evidence of any loss of renal function with zoledronic acid treatment in randomized clinical trials (45) when only patients with an eGFR >35 mL/min are given the drug. A meta-analysis of the effect of bisphosphonate treatment on atrial fibrillation concluded that zoledronic acid may modestly increase the risk, but not the other bisphosphonates (46).

ONJ and AFFs (discussed in detail in "Optimal Duration of Treatment and Drug Holidays") were first reported in case studies in 2003 and both are extremely rare (47). Epidemiologic studies suggest an association with long-term bisphosphonate use, and these complications have also been observed with other osteoporosis treatments (48). Despite these concerns, the benefits of bisphosphonate therapy for up to 5 years strongly outweigh any AFF risks in postmenopausal women at high risk for fracture. One analysis showed that treating 1000 osteoporotic women with bisphosphonates for 3 years was associated with 0.08 AFF while preventing 100 fractures, including 11 hip fractures (49). However, there are no comparable benefit/risk analyses for longer-term bisphosphonate treatment.

Patient values and preferences

Compliance with oral bisphosphonates, as with other medications used to lower chronic disease risks, is low (~30% still continuing at 1 year) (50). In patients who may have difficulties with adherence to oral medications or who fail to respond, the use of zoledronic acid (given annually as an IV infusion) or denosumab (given by subcutaneous injection every 6 months, see "Denosumab") may be advantageous for effectively lowering the fracture risk. Concerns of patients about risk of AFFs or ONJ should be taken into account when considering bisphosphonate holidays.

3. Denosumab

3.1 In postmenopausal women with osteoporosis who are at high risk for osteoporotic fractures, we recommend using denosumab as an alternative initial treatment. (1|⊕⊕⊕⊕)
Technical remark: The recommended dosage is 60 mg subcutaneously every 6 months. The effects of denosumab on bone remodeling, reflected in BTMs, reverse after 6 months if the drug is not taken on schedule. Thus, drug holiday or treatment interruption are not recommended with this agent.

3.2 In postmenopausal women with osteoporosis who are taking denosumab, we suggest that the fracture risk be reassessed after 5 to 10 years and that women who remain at high risk of fractures should either continue denosumab or be treated with other osteoporosis therapies. (2|⊕OOO)

3.3 In postmenopausal women with osteoporosis taking denosumab, administration of denosumab should not be delayed or stopped without subsequent antiresorptive (*e.g.*, bisphosphonate, HT, or selective estrogen receptor modulator) or other therapy administered to prevent a rebound in bone turnover and to decrease the risk of rapid BMD loss and an increased risk of fracture. (Ungraded Good Practice Statement)

Evidence

A meta-analysis that compared denosumab with placebo (Fig. 1) showed a 68% reduction in the risk of vertebral fractures (HR, 0.32; 95% CI, 0.26 to 0.40), a 39% reduction in the risk of hip fractures (HR, 0.61; 95% CI, 0.37 to 0.98), and a 19% reduction in the risk of

nonvertebral fractures (HR, 0.81; 95% CI, 0.69 to 0.95) (12).

The duration of the double-blind, placebo-controlled phase of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial was 3 years. In the FREEDOM Extension study, all patients received denosumab during the 7-year extension. There was no control group during this extension. Continuing low rates of new radiographic vertebral fractures (0.9% to 1.86% per year), nonvertebral fractures (0.84% to 2.55% per year), and hip fractures (0% to 0.61% per year) were noted in years 4 to 10. These rates were comparable to those in the initial phase 3 study in subjects taking denosumab, supporting a stable level of fracture reduction up to 10 years (51). There are no published data on the use of denosumab beyond 10 years of treatment. Shorter courses of therapy with this agent may be considered depending on the BMD response and the ongoing fracture risk assessment done by the treating clinician. However, BMD gains are rapidly lost with cessation of denosumab and another therapy such as a bisphosphonate should be given after a course of denosumab is ended to maintain the BMD gains of the treatment course.

Balance of benefits and harms

One limitation in the use of denosumab is the risk of hypocalcemia due to concomitant medical conditions such as malabsorption or chronic kidney disease (CKD). In contrast to the bisphosphonates, denosumab may be administered to patients with CKD and those with eGFRs of $\leq$35 mL/min/1.73 m^2. Denosumab has been shown to be effective at reducing fracture rates and increasing the BMD at all sites and (to a similar extent) in patients with CKD stage 1 (eGFR $\geq$90 mL/min), 2 (eGFR of 60 to 89 mL/min), or 3 (eGFR of 30 to 59 mL/min). In stage 4 CKD (eGFR of 15 to 29 mL/min), compared with placebo, denosumab increased the BMD at hip sites ($P <$ 0.0002) but had no significant effects on fracture rates (52). No subjects with stage 5 CKD were enrolled in the FREEDOM trial. Denosumab should be administered with caution in patients with CKD, however, because the drug lowers bone turnover rapidly and substantially and blocks calcium mobilization from bone in defense of hypocalcemia. Two groups studied individuals with varying degrees of renal impairment, including those defined as severe (eGFR $<$30 mL/min/1.73 m^2) or requiring dialysis (53, 54), and found that such individuals were at greater risk of posttreatment hypocalcemia than were those with normal renal function. The prescribing information approved by the US Food and Drug Administration states that clinical monitoring of the serum levels of calcium, magnesium, and phosphorus should be considered in patients predisposed to hypocalcemia and disturbances of mineral balance within 14 days of denosumab injection, as does the summary of product characteristics (SmPC) of the European Medicines Agency (55). Further recommendations from the SmPC emphasize the importance of identifying patients at risk for hypocalcemia and addressing this risk by assuring an adequate intake of calcium and vitamin D before initiating therapy. Serum calcium levels may be checked prior to each dose of denosumab. Individuals at risk for hypocalcemia should be educated about the signs and symptoms of hypocalcemia before administration of the agent.

Adverse events

Adverse events assessed in the phase 3 FREEDOM trial included infections, inflammatory disorders, and malignancies, as well as ONJ, AFFs, and hypocalcemia. In the first 3 years of the FREEDOM trial, there were no statistically greater risks of cancer, infection, delayed fracture union, hypocalcemia, or ONJ (56). In the FREEDOM Extension during 10 years, adverse events and serious adverse events did not increase with time (57, 58). There were seven and six cases, respectively, of ONJ in the long-term (10-year) vs crossover (7-year) denosumab treatment groups and two AFFs occurred during the 7-year extension study (one per treatment group) (51).

In a meta-analysis of safety incorporating data from 11 trials, compared with placebo, denosumab increased the risk of serious adverse events related to infection in postmenopausal women (relative risk, 1.23; 95% CI, 1.00 to 1.52; P = 0.05) (59). No increased risk of malignancy or of skeletal fragility (reflected by a greater rate of nonvertebral fractures) was noted. Infections reported as serious adverse events in the FREEDOM trial included several body sites, and the gastrointestinal and urinary tracts, heart, skin, and ear were numerically greater in the denosumab-treated group vs the placebo-treated group, but the differences were not statistically significant (60). Serious opportunistic and/or fatal infections were few in number and were not significantly different between the denosumab-treated and placebo-treated subjects (60). Serious adverse events involving the skin (among them, erysipelas and cellulitis) occurred in 1 placebo-treated subject ($<$0.1%) but in 15 denosumab-treated subjects (0.4%) (60). The eczema incidence was also higher (118 cases in denosumab-treated subjects vs 65 cases in placebo-treated subjects during 3 years) (56).

Several case reports and series of patients have emphasized that the cessation of denosumab treatment may be associated with a risk of multiple and/or severe vertebral fractures (61). In the FREEDOM and the

FREEDOM Extension trials (62), there was an excess occurrence of multiple new vertebral fractures in patients who discontinued denosumab vs placebo, but those rates did not exceed the baseline fracture rate. BTM data (63, 64) show that the levels of serum C-terminal crosslinking telopeptide (CTX) and procollagen type 1 N-terminal propeptide (P1NP) increase above baseline values within 3 to 6 month of denosumab discontinuation. Concomitantly, levels of BMD at the spine and hip decline to pretreatment levels within 24 months. The vertebral fractures occurring after drug cessation have been ascribed to the rapid rebound in bone turnover as the medication effect quickly wears off. This situation has led to a cautionary note that doses of denosumab should not be delayed and should be administered on an every-6-month basis. The risk of hypocalcemia (decline in serum calcium to <1.88 mmol/L or 7.6 mg/dL) due to denosumab is estimated to be ~0.05% in data compiled from two large clinical trials (2 of 4050 patients) (55) and in the range of 14% to 25% of subjects in small studies of subjects at risk for hypocalcemia (53, 65, 66). The key risk factor for that complication is underlying CKD, as noted above. Vitamin D deficiency at baseline and higher rates of baseline bone turnover, as assessed by turnover markers, may increase the risk of hypocalcemia (66).

Overall, the rates of these adverse events in patients with normal renal function are low, and there are significant antifracture benefits with the use of denosumab therapy. The agent acts rapidly, is straightforward to administer, and produces marked suppression of bone turnover (reduction in serum CTX levels) within the first week of administration (67). The weight of evidence supports the use of this agent for its strong antifracture efficacy.

Patient values and preferences

Studies have compared adherence (combination of persistence and compliance) and patient preference for denosumab injections every 6 months to oral bisphosphonates (weekly or monthly) (68). The Denosumab Adherence Preference Satisfaction (DAPS) study reported that regardless of the treatment sequence during 24 months (alendronate for 12 months, followed by denosumab for 12 months or vice versa), trial participants significantly preferred denosumab to alendronate based on questionnaires (69, 70). Subject scores for denosumab showed greater preference and satisfaction than with alendronate (69). In an observational study of routine clinical practice, persistence with treatment was estimated at ~87% to 95% and adherence at ~83% to 89% after 12 months (71). High rates of persistence and adherence help to ensure that the fracture reduction benefits reported in clinical trials are attained in clinical practice.

Remarks

At the doses used to treat osteoporosis and with the lack of incorporation of this monoclonal antibody into bone, the drug's actions reverse after 6 months. Injections should be given every 6 (±1) months. If longer intervals between doses occur, then the drug's effect wears off and bone resorption rates rise promptly. Bone turnover increases to pretreatment levels or higher, and eventually BMD declines by 18 to 24 months after treatment discontinuation (62, 63). In the period after treatment discontinuation, patients may be more vulnerable to sustaining vertebral fractures, and this vulnerability may underlie the "rebound" vertebral fractures that have been reported with denosumab discontinuation or missed dosing, which is to be strictly avoided (see "Impact of Stopping Non-Bisphosphonate Therapies").

4. Teriparatide and Abaloparatide (PTH and PTH-Related Protein Analogs)

4.1 In postmenopausal women with osteoporosis at very high risk of fracture, such as those with severe or multiple vertebral fractures, we recommend teriparatide or abaloparatide treatment of up to 2 years for the reduction of vertebral and nonvertebral fractures. (1|⊕⊕⊕O)

4.2 In postmenopausal women with osteoporosis who have completed a course of teriparatide or abaloparatide, we recommend treatment with antiresorptive osteoporosis therapies to maintain bone density gains. (1|⊕⊕OO)

Evidence

Anabolic agents increase BMD by increasing bone formation when administered intermittently (*i.e.*, daily). There are now two licensed peptides that are anabolic for bone: PTH(1–34) (teriparatide) and a PTH-related protein analog (abaloparatide). Compared with other agents, the evidence base for teriparatide and abaloparatide fracture reduction is more limited both in terms of number of trials and number of patients who have participated in the trials.

The meta-analysis comparison of teriparatide with placebo (Fig. 1) showed a 74% reduction in the risk of vertebral fractures (HR, 0.26; 95% CI, 0.18 to 0.39) and a 39% reduction in the risk of nonvertebral fractures (HR, 0.61; 95% CI, 0.44 to 0.85) (12). There is evidence that teriparatide reduces fractures more than risedronate based on the VERtebral Fracture Treatment Comparisons in Osteoporotic Women (VERO) trial. In this study of women at very

high risk of fracture, teriparatide reduced vertebral and clinical (nonvertebral plus clinical vertebral) fractures compared with risedronate (72).

The meta-analysis comparison of abaloparatide with placebo (Fig. 1) showed an 87% reduction in the risk of vertebral fractures (HR, 0.13; 95% CI, 0.05 to 0.38) and a 46% reduction in the risk of nonvertebral fractures (HR, 0.54; 95% CI, 0.31 to 0.96) (12). In the meta-analysis, hip fracture reductions for both agents were not statistically significant, despite trends toward reductions for both. However, the numbers of hip fractures in these studies were small and the studies were inadequately powered for this endpoint.

A significant increase in osteosarcoma in rats given lifelong treatment with teriparatide or abaloparatide led to black box warnings for both of these agents with limits for lifetime therapy to a maximum of 24 months. However, since the introduction of teriparatide in 2002, with >1 million human users, the rate of osteosarcoma has not been greater than expected, with only one case reported as of 2016 (49). Side-effects of teriparatide (20 mg dose) vs placebo included greater rates of dizziness and leg cramps (73), while side-effects of abaloparatide that led to study discontinuation were nausea, postural hypotension, dizziness, headache, and palpitations (74). Teriparatide and abaloparatide have been shown to increase serum calcium slightly and can result in cases of hypercalcemia. Therefore, it is recommended that serum calcium should be assessed prior to use and that neither agent be used in patients with elevated serum calcium.

The durability of the effect of anabolic drugs after they are stopped has been tested for several anabolic agents. For example, a randomized trial compared 1 year of PTH (1–84) followed by a second year of placebo vs a second year of alendronate. As assessed by decreases in dual-energy X-ray absorptiometry BMD and trabecular BMD by quantitative CT as well as finite element modeling of bone strength, most of the effect of the drug had worn off within 1 year of stopping use (75, 76). Studies of antiresorptive agents used after anabolic drugs are stopped have shown that antiresorptive agents can maintain and possibly slightly enhance their anabolic effects (74, 75, 77–79). Since the benefits of anabolic therapy are quickly lost after discontinuation, we concur with most clinical guidelines, which recommend that a course of teriparatide or abaloparatide (up to 2 years) be followed by a bisphosphonate, raloxifene, denosumab, or menopausal HT.

Bisphosphonates are generally the initial therapy for osteoporosis for most women. However, in cases where a patient on bisphosphonates continues to lose bone mass or sustains a fracture, a clinician may want to consider switching to an anabolic treatment. Since bisphosphonate effects as measured by BTMs and BMD persist after stopping, there has been some controversy about the efficacy of anabolic agents following bisphosphonate therapy. Several studies have examined the effects of teriparatide on BTMs and BMD following bisphosphonates. Those studies have suggested that teriparatide retains its anabolic effect, although the timing of onset may be somewhat delayed and the magnitude of the effect somewhat blunted (80). A randomized trial of 24 months of teriparatide vs risedronate (VERO trial) recently published a subgroup analysis comparing fracture efficacy in those with and without bisphosphonate use prior to study entry (81). This analysis suggested similar fracture reductions for vertebral and clinical fractures in prior bisphosphonate users compared to treatment-naive patients. There was a suggestion (not significant) that fracture reductions were slightly delayed for prior bisphosphonate users compared with treatment-naive patients. These results provide support that anabolic therapy remains efficacious in reducing fracture risk even after a prior course of bisphosphonates.

Teriparatide and abaloparatide are the only anabolic agents currently approved for osteoporosis. However, other anabolic agents (*e.g.*, romosozumab) have been or are being tested and may be available in the future. PTH (1–84) (82) was approved and used for several years in Europe but is no longer available for this indication.

Patient values and preferences

The BMD increases with either teriparatide or abaloparatide are substantial, as are reductions in vertebral fracture. However, there are two important limitations of these medications. First, they require a daily injection, which some patients may not be willing to do or to which many patients may find adherence challenging. Second, both teriparatide and abaloparatide are much more expensive than other therapies, and this may be an important barrier for many patients, particularly when insurance coverage may be limited.

5. Selective Estrogen Receptor Modulators

5.1. In postmenopausal women with osteoporosis at high risk of fracture and with the patient characteristics below, we recommend raloxifene or bazedoxifene to reduce the risk of vertebral fractures. (1|⊕⊕⊕⊕)

Patient characteristics: With a low risk of deep vein thrombosis (DVT) and for whom bisphosphonates or denosumab are not appropriate, or with a high risk of breast cancer.

Evidence

The meta-analysis that compared raloxifene with placebo (Fig. 1) showed a 40% reduction in the risk of vertebral fractures (HR, 0.60; 95% CI, 0.52 to 0.69), but no significant effect on reduction in the risk of hip or nonvertebral fractures (12). Several side effects limit use, including venous thromboembolism, hot flushes, and leg cramps (83).

The effect of raloxifene (60 mg daily) on vertebral fractures was present in women with osteoporosis (BMD T-score of −2.5 or less) with or without a prior vertebral fracture (84). This effect was also present in women not selected on the basis of fracture risk (85). The effect of raloxifene on BMD is less than that of menopausal HT (86), but there are no comparative fracture data.

The meta-analysis that compared bazedoxifene with placebo (Fig. 1) showed a 39% reduction in the risk of vertebral fractures (HR, 0.61; 95% CI, 0.48 to 0.77), but no significant effect on the reduction in the risk of hip or nonvertebral fractures (12). Several side effects limit use, including venous thromboembolism, hot flushes, and leg cramps (87). There is no evidence regarding the effects on breast cancer. The effects of 3 years of treatment with bazedoxifene (20 mg or 40 mg daily) on the risk of vertebral fracture are similar to those of raloxifene (60 mg daily) (87). The effect of bazedoxifene on vertebral fracture risk after 5 years of treatment is similar to that after 3 years of treatment (88).

Bazedoxifene is licensed in Germany, Lithuania, Sweden, Croatia, Japan, and Israel for the prevention of osteoporosis, but not in the United States or Canada (89). Bazedoxifene is only licensed in the United States and Canada as a combination with conjugated estrogens for the treatment of hot flushes or prevention of osteoporosis in patients for whom other treatments for osteoporosis are not suitable. The combination of conjugated estrogens and bazedoxifene results in less increase in spinal BMD at 1 year compared with conjugated estrogens and a progestin, but less breast tenderness and more amenorrhea (90). Conjugated estrogens/bazedoxifene have not been shown to reduce the risk of fracture (11).

Balance of benefits and harms

Raloxifene has the added benefit of a reduced incidence of invasive estrogen receptor–positive breast cancer both during treatment and for at least 5 years after completion (91). This benefit of treatment should be taken into account when counseling patients.

Raloxifene may be well suited to younger women with osteoporosis and no vasomotor symptoms, as we have insufficient data to link this drug to long-term harm such as AFFs. Furthermore, it may be particularly suitable in women who are at increased risk of breast cancer. The more minor adverse events (hot flushes, leg cramps) tend to be worse in the first 6 months of administration. Therefore, it is common practice to encourage perseverance with the drug during the first few months of treatment.

The risk of thromboembolic events is similar to that with the current use of HT. The SmPC (92) recommends the following: "The risk-benefit balance should be considered in patients at risk of venous thromboembolic events of any etiology. Raloxifene should be discontinued in the event of an illness or a condition leading to a prolonged period of immobilization. Discontinuation should happen as soon as possible in case of illness, or from 3 days before the immobilization occurs. Therapy should not be restarted until the initiating condition has resolved and the patient is fully mobile."

6. Menopausal Hormone Therapy and Tibolone

6.1 In postmenopausal women at high risk of fracture and with the patient characteristics below, we suggest menopausal HT, using estrogen only in women with hysterectomy, to prevent all types of fractures. (2|⊕⊕⊕O)
Patient characteristics: Under 60 years of age or <10 years past menopause; at low risk of DVT; those in whom bisphosphonates or denosumab are not appropriate; with bothersome vasomotor symptoms; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke; without breast cancer; willing to take menopausal HT.

6.2 In postmenopausal women with osteoporosis at high risk of fracture and with the patient characteristics below, we suggest tibolone to prevent vertebral and nonvertebral fractures. (2|⊕⊕⊕O)
Patient characteristics: Under 60 years of age or <10 years past menopause; with a low risk of DVT; those in whom bisphosphonates or denosumab are not appropriate; with bothersome vasomotor symptoms; with additional climacteric symptoms; without contraindications; without prior myocardial infarction or stroke or high risk for cardiovascular disease; without breast cancer; willing to take tibolone.
Technical remark: Tibolone is not available in the United States or Canada.

Evidence

The meta-analysis that compared menopausal HT (estrogen with or without progestogen) with placebo (Fig. 1) showed a 34% reduction in the risk of vertebral

fractures (HR, 0.66; 95% CI, 0.49 to 0.89), a 29% reduction in the risk of hip fractures (HR, 0.71; 95% CI, 0.52 to 0.98), and a 21% reduction in the risk of nonvertebral fractures (HR, 0.79; 95% CI, 0.70 to 0.90) (12). The fracture benefits are present in women at lower risk of fractures (93–95) and at high risk of fractures (96, 97) and with oral conjugated equine estrogen (0.625 mg daily) or with estradiol (100-mg patch or 2 mg daily oral) use. However, the evidence of fracture benefit in women is based mainly on clinical trials in women not at high risk of fracture.

Several potential side effects limit use, including venous thromboembolism, stroke, myocardial infarction, cancer (breast, endometrial, ovary), dementia, gallbladder disease, and urinary incontinence (98). Recent data from the Women's Health Initiative Study covering 13 years showed reversal of most of these risks after stopping therapy; furthermore, the risks with estrogen alone (*e.g.*, breast cancer) are less than those with the combination (99). Benefits include relief of menopausal symptoms (*e.g.*, hot flushes), less diabetes, and a lower risk of colon cancer.

The meta-analysis that compared tibolone with placebo (Fig. 1) showed a 44% reduction in the risk of vertebral fractures (HR, 0.56; 95% CI, 0.42 to 0.74), no significant effect on reduction in the risk of hip fractures, and a 27% reduction in the risk of nonvertebral fractures (HR, 0.73; 95% CI, 0.59 to 0.92) (12). Several side effects limit use, including stroke (HR, 2.19; 95% CI, 1.14 to 4.23), vaginal discharge, and bleeding. There are benefits for menopausal symptoms such as hot flushes and for the risks of breast cancer (HR, 0.32; 95% CI, 0.13 to 0.80) and colon cancer (HR, 0.31; 95% CI, 0.10 to 0.96), and patients taking tibolone have fewer falls (100). Even though the risk of breast cancer was reduced in the Long-Term Intervention on Fractures with Tibolone (LIFT) study, there was an increased recurrence of breast cancer in women with previous breast cancer in the Livial Intervention Following Breast Cancer: Efficacy, Recurrence and Tolerability Endpoints (LIBERATE) study (101).

Balance of benefits and harms

The Writing Committee has no preference between estrogen and tibolone; most of the evidence for HT is based on women at low risk of fracture, whereas the evidence for tibolone is based on women at high risk of fracture. The benefits and risks of estrogen and tibolone need to be evaluated on an individual basis (102). These risks depend on the duration of treatment, the woman's age, and her underlying health and are lower in healthy younger women, hence the recommendation to select women <60 years of age or within 10 years of menopause (102). The risk of venous thromboembolic disease may be lower with transdermal rather than oral estrogen (103). The balance of risks and benefits differs between individual women according to their needs for treatment. If menopausal HT is prescribed for osteoporosis and it is stopped, then alternative treatments for osteoporosis should be given.

7. Calcitonin

7.1 In postmenopausal women at high risk of fracture with osteoporosis, we suggest that nasal spray calcitonin be prescribed only in women who cannot tolerate raloxifene, bisphosphonates, estrogen, denosumab, tibolone, abaloparatide, or teriparatide or for whom these therapies are not considered appropriate. (2|⊕OOO)

Evidence

The meta-analysis that compared calcitonin with placebo (Fig. 1) showed a 46% reduction in the risk of vertebral fractures (HR, 0.54; 95% CI, 0.36 to 0.82), but no significant effect on reduction in the risk of hip or nonvertebral fractures (12). The trials with nasal spray calcitonin were never powered to show fracture risk reduction; however, the Prevent Recurrence of Osteoporotic Fractures (PROOF) trial did show efficacy for vertebral fracture reduction (at the dose of 200 IU but not 100 or 400 IU of nasal spray calcitonin per day) (104). Similarly, there is weak evidence for vertebral fracture pain relief from calcitonin, with one randomized, placebo-controlled trial of 68 postmenopausal women showing efficacy (105).

Patient values and preferences

In patients who cannot tolerate denosumab, bisphosphonates, hormone-based therapies, selective estrogen response modulators, tibolone, or anabolic treatments, nasal spray calcitonin may be used and is well tolerated. However, there is considerable doubt about its benefit in reducing fractures, particularly nonvertebral fractures.

Balance of benefits and harms

Recent studies have raised doubt about the long-term safety of nasal spray calcitonin due to an increased risk (from cross-sectional and cohort studies and a meta-analysis) of prostate and liver cancer and other malignancies, although the pathophysiologic basis is unclear (106, 107). The European Medicines Agency and Health Canada have both withdrawn nasal spray calcitonin from the market.

8. Calcium and Vitamin D

8.1 In postmenopausal women with low BMD and at high risk of fractures with osteoporosis, we suggest that calcium and vitamin D be used as an adjunct to osteoporosis therapies. (2|⊕⊕OO)

8.2 In postmenopausal women at high risk of fracture with osteoporosis who cannot tolerate bisphosphonates, estrogen, selective estrogen response modulators, denosumab, tibolone, teriparatide, and abaloparatide, we recommend daily calcium and vitamin D supplementation to prevent hip fractures. (1|⊕⊕⊕O)

Evidence

The meta-analysis that compared calcium with placebo (Fig. 1) showed no significant effect on reduction in the risk of vertebral or hip fractures, but a 37% reduction in the risk of nonvertebral fractures (HR, 0.63; 95% CI, 0.45 to 0.90). The meta-analysis that compared vitamin D with placebo (Fig. 1) showed no significant effect on reduction in the risk of vertebral or hip fractures, but a 56% reduction in the risk of nonvertebral fractures (HR, 0.44; 95% CI, 0.22 to 0.88). The meta-analysis that compared the combination of calcium and vitamin D with placebo (Fig. 1) showed no significant effect on reduction in the risk of vertebral fractures, but a 19% reduction in the risk of hip fractures (HR, 0.81; 95% CI, 0.71 to 0.93), and a 5% reduction in the risk of nonvertebral fractures (HR, 0.95; 95% CI, 0.90 to 1.00) (12).

The level of evidence for hip fracture prevention with the combination of calcium and vitamin D supplementation is strong but only in selected circumstances, and with the following caveats. First, the greatest risk reduction (33%) from calcium and vitamin D supplementation is in elderly individuals living in residential care (108). (The data are based on studies predominantly of women 70 years and older in residential care.) Second, the largest trial to date in postmenopausal women, the Women's Health Initiative, demonstrated risk reduction, but the original analysis was per protocol and was not an intention-to-treat analysis (109). Third, women in that trial were also randomized to either HT or placebo. Only those receiving calcium and vitamin D plus HT showed significant hip fracture reduction. For the prevention of vertebral fractures, calcium and vitamin D have no impact on risk, but the level of evidence is weak. Expert opinion suggests that increasing dietary calcium intake is the most appropriate and safest way to enhance bone mineralization.

As mentioned above, the strength of the evidence for hip fracture risk reduction with calcium and vitamin D is driven principally by one large randomized, placebo-controlled trial in elderly women who were nursing home residents in which there was a significant (*i.e.*, 33%) risk reduction in hip fractures (108). However, the mean 25-hydroxyvitamin D levels in that cohort were low (<16 ng/mL). In addition to fracture risk reduction, with adequate vitamin D repletion, the mean PTH levels decreased, almost certainly as a result of vitamin D and calcium supplementation (108, 110, 111). No other studies have shown this degree of hip fracture risk reduction. It has also been thought that calcium and vitamin D could prevent falls, and that in turn could result in a reduction in hip fractures (112). This led to the use of high-dose supplementation with vitamin D administered less frequently. However, a recent trial showed the opposite effect, with an increased risk of fracture (113). Additionally, a new meta-analysis revealed inconsistent or no effects from vitamin D supplementation on falls, fractures, or BMD (114).

Note that virtually all the recent trials of drugs to treat osteoporosis use a study design of drug plus calcium and vitamin D supplementation vs calcium and vitamin D alone. Hence, the proven antifracture efficacy for all osteoporosis drugs includes the addition of calcium and vitamin D supplementation. For example, in the Women's Health Initiative trial of calcium and vitamin D, there was a 2×2 design in which some women who received calcium (1000 mg/d) plus vitamin D supplementation (400 IU/d) were also randomized to HT (estrogen or estrogen plus progesterone) or no treatment. In that arm, women who received both active treatments (calcium plus vitamin D plus HT) had a 42% reduction in hip fractures (0.37 to 0.93) vs calcium plus vitamin D alone. Similar results have been noted with other antiresorptive therapies (34, 36, 56).

The amount of calcium supplementation in randomized trials ranges from 500 to 1500 mg/d. Expert opinion currently recommends ≤1000 mg/d in the form of supplements, whereas the overall recommendation from the National Osteoporosis Foundation and Institute of Medicine (for women >50 years and men >70 years of age) is a total calcium intake of 1200 mg/d. The total calcium intake per day should include both dietary and supplemental calcium. We prefer that this be achieved through dietary intake, but this is often difficult, especially in older individuals. In the largest randomized, placebo-controlled trial for calcium and vitamin D in postmenopausal women, the Women's Health Initiative, the daily dietary intake in the active arm was ~1100 mg/d in addition to the 1000 mg of calcium supplementation, resulting in a total intake of ~2100 mg/d (109). This intake led to a 17% increase in the development of renal stones (109).

In the current meta-analysis, calcium plus vitamin D supplementation reduced the risk of hip fractures but not vertebral or nonhip fractures. The magnitude of risk reduction is consistent with that reported by a previous meta-analysis (115), although not the most recent meta-analysis (116), and is driven principally by trials in older individuals (108). The highest absolute risk of hip fracture occurs in the frail elderly, owing to both low bone mass and a higher rate of falls. Notwithstanding, among all women in the Women's Health Initiative trial (mean age, 61 years) who were randomized to calcium (1000 mg/d) and vitamin D (400 IU/d), and who were adherent after 6 months, there was a 29% reduction in hip fractures, but no effect on other fractures. As noted, however, those subjects included women who were also randomized to HT (116). Although there are no clinical trial data, most experts would agree that dietary intake with calcium is the safest and most appropriate approach for postmenopausal women undergoing treatment for osteoporosis.

Balance of benefits and harms

With respect to cardiovascular safety, some meta-analyses analyzing the effects of calcium supplementation alone (without vitamin D) on cardiovascular events show a weak association with increased risk of myocardial infarction and stroke, whereas others show no association (117–119).

There is no evidence that supplementation with vitamin D of up to 4000 IU/d (*i.e.*, the tolerable upper limit set by the Institute of Medicine) is associated with any safety issues beyond hypercalciuria (118). However, when combined with high amounts of supplemental calcium, there is the potential for a greater risk of kidney stones (109). Additionally, there is evidence from two randomized trials that high-dose intermittent vitamin D (500,000 IU/y or 20,000 IU/wk) can lead to a greater risk of falls and fractures (113, 120).

Thus, most postmenopausal women in the United States now consume close to 1000 mg of calcium per day from their diet, which is an increase of >200 mg/d from the late 1990s (109, 121). The Institute of Medicine recommends 1000 to 1200 mg of calcium per day in diet and/or supplements (121). Writing Committee members prefer encouraging women to increase their dietary intake of calcium and to keep calcium supplement intake <1000 mg/d because of potential safety concerns with supplements, particularly renal calculi. There is no consensus concerning a threshold level of vitamin D that should be reached when supplementing postmenopausal women. However, all postmenopausal women with a confirmed diagnosis of osteoporosis should be screened with a serum level of 25-hydroxyvitamin D. The preference of the Writing Committee is that adequate serum 25-hydroxyvitamin D levels in women with osteoporosis should be at least 20 ng/mL (50 nmol/L) as noted by European guidelines, although Endocrine Society guideline recommends a threshold of 30 ng/mL (75nmol/L), either of which can often be met by ingesting 1000 IU of vitamin D per day.

Patient values and preferences

There is consensus that calcium and vitamin D should be added to all osteoporosis treatment regimens to enhance mineralization and maintenance of bone mass in high-risk postmenopausal women, many of whom also consume diets low in calcium. There is no direct evidence that the calcium and vitamin D added to other treatments for osteoporosis contribute to the reduction in fracture risk from clinical trials testing those agents, because calcium and vitamin D supplements are the standard baseline intervention at randomization. There may be a small additional BMD benefit of calcium plus vitamin D for individuals in addition to a prescribed osteoporosis medication, particularly because calcium plus vitamin D are thought to be important for mineralization (122). Supplemental intake of calcium and vitamin D has increased during the last two decades, but dietary calcium intake, with the advent of more supplemented food choices, has also increased.

9. Approach to Treatment or Choosing Among Approved Therapies

The goal of treatment is to decrease fractures associated with osteoporosis; thus, the overall approach is to recommend good bone health maintenance efforts. These include adequate calcium and vitamin D intake, resistance and balance exercises, smoking cessation, limited alcohol use, decreased use of drugs, and optimization of comorbid conditions that can harm bone for all postmenopausal women. For those at high fracture risk, we recommend treatment with approved medications. For those at low-to-moderate fracture risk, we recommend following the country-specific guidelines for treatment, as the fracture risks, values, and costs of therapies vary across populations.

Decisions regarding the choice of therapies must take into account the country-specific availability of various drugs, local guidelines, values, and preferences of the patient, costs, and drug coverage (*e.g.*, insurance, government coverage). Because of the lower costs and longer experience with bisphosphonates, they are often used as initial therapies for postmenopausal osteoporosis in most countries. However, it is important to weigh risks, benefits, and preferences on an individual basis, and there may be individual patient characteristics that help to

determine which drug is optimal. For example, a woman in her late 50s with osteoporosis and at high risk of breast cancer may consider raloxifene as an initial therapy, whereas another woman with gastroesophageal reflux disease at high risk of fracture may prefer to start with denosumab or zoledronic acid. Theoretically, one may want to use bone formation therapy as the initial therapy, if the patient has sustained recent vertebral fractures. In general, calcium and vitamin D aside, we recommend using one drug therapy at a time, and not combining them.

The decision to switch therapy from one agent to another is often based on availability, tolerability, costs, and preferences. Health care providers may also want to consider switching therapy because of adherence issues or "failure" of therapy. As osteoporosis drug therapies do not totally eliminate fracture risk, it is often unclear whether sustaining a fracture while on therapy is considered a failure of therapy. In general, we consider loss of BMD greater than the least significant change (usually 5% in the lumbar spine, 4% in the total hip, and 5% in the femoral neck) over 2 years and BTM decrease on antiresorptive drugs less than the least significant change as "failure" of therapy. We would consider having two or more fractures while on therapy as treatment failure, especially vertebral fractures (123). In clinical practice, the occurrence of one fracture while on effective therapy and in a compliant patient will raise the consideration for changing therapy. In such cases, we suggest switching to one of the alternative therapies discussed in this guideline. It is important to rule out secondary osteoporosis when a patient "fails" therapy, as intervening medical conditions (such as multiple myeloma) or medications (such as tenofovir or oversupplementation of thyroid hormone in hypothyroidism) may be the root cause of BMD loss or fracture, rather than failure of osteoporosis drug therapy. What is less clear is when to switch from an antiresorptive therapy to a bone formation therapy. Again, there is a lack of evidence to guide such decisions. Patients for whom we would consider switching from an antiresorptive to a bone formation therapy include the following: a woman with recurrent vertebral fractures due to osteoporosis, a woman at high fracture risk who has been on long-term potent antiresorptive therapy and is sustaining fractures, and a woman with ONJ or an AFF on antiresorptive therapy.

There is an alternative to decision-making about the choice of treatment and when to stop treatment, namely "treat to target" BMD (124, 125). The idea of "treat to target" is to choose therapy that will most likely achieve the target BMD, change to a more potent agent if the initial therapy is not achieving the BMD goal, and stop when fracture risk is at an acceptable low level. Existing therapies, however, may not be potent enough to achieve the target or maintain the target BMD once it is stopped.

We propose that the algorithm in Fig. 2 be applied to an individual postmenopausal woman when considering the management of her osteoporosis. We considered those women at high risk as being eligible for drug therapy and defined this high-risk group as having a prior spine or hip fracture, or a BMD T-score of -2.5 or below at either the hip or spine, or a 10-year hip fracture risk $\geq 3\%$, or a risk of major osteoporotic fracture $\geq 20\%$ (Fig. 2).

10. Optimal Duration of Treatment and Drug Holidays

There is an abundance of evidence that treatment of 3 to 5 years with osteoporosis therapies described in earlier sections is highly beneficial with only minimal risk. However, recent concerns about AFFs and ONJ have led to reconsideration of the optimal length of therapy. Considerations for longer-term treatment are more complex and depend on the individual woman's fracture risk, risk factors for AFF, ONJ, and vertebral, nonvertebral, and hip fractures, as well as the type of therapy being used. The ASBMR established a task force that reviewed the current evidence and published guidelines for long-term treatment in 2016 (40). These recommendations are incorporated into Fig. 2. However, there are important evidence gaps that, when filled, may help to establish more precise and stronger evidence-based guidelines.

Considerations for continuation of therapy depend strongly on the type of medication being used. The evidence on which to base long-term therapy decisions is most robust for bisphosphonates, which represent the vast majority of treatment in the United States and internationally. This evidence is described in detail in the "Bisphosphonate" section and includes two randomized trials (one of alendronate and one of zoledronic acid) that inform decisions about long-term continuation or temporary discontinuations for this class of drugs (see "Long-term bisphosphonate treatment beyond 5 years"). These studies support a residual effect of bisphosphonates after stopping, which support bisphosphonate holidays. However, for all other therapies, as described below, after discontinuation, benefits are quickly lost. Thus, these therapies must be continued indefinitely or followed with bisphosphonates or another type of therapy to retain the gains achieved.

In terms of continued efficacy for fracture reduction with long-term continued therapy, there are some data for bisphosphonates, denosumab, and HT that are described in the respective earlier sections of this report for each of those types of medications.

Impact of stopping nonbisphosphonate therapies

There are data showing that the effects of all nonbisphosphonate therapies (denosumab, abaloparatide,

teriparatide, selective estrogen response modulator, HT, tibolone, and calcitonin) disappear with the discontinuation of therapy. When these therapies are discontinued, the gains in BMD observed with these therapies are lost rapidly. Discontinuation of denosumab is associated with a BMD decrease of 6.6% in the lumbar spine and 5.3% in the total hip within the first 12 months of treatment discontinuation (126, 127). In fact, there are data to suggest that the discontinuation of denosumab, a potent antiresorptive therapy, can result in increased vertebral fractures (128–131). Whether this increased risk is the return to the baseline risk of the individual if that individual were not on therapy or whether there is a "rebound" effect (an increased risk beyond the individual's baseline risk) is unclear. Recent data from the FREEDOM trial suggest that the increase in risk is likely secondary to the absence of drug protection, rather than to a rebound phenomenon (132). One study of alendronate following 1 year of denosumab showed retention of BMD gains for at least 12 months (133). Two small case series examining zoledronic acid after denosumab suggested that it was most effective in BMD retention when administered 8 months, rather than 6 months, after the last dose of denosumab (134, 135). The second study (134, 135) also suggested that a second annual infusion was needed to continue retention of benefits. This study also showed only a partial retention of benefits for risedronate after denosumab. Several studies have shown that use of alendronate after anabolic treatment will retain and perhaps increase BMD gains (36, 136), and thus alendronate after anabolic therapy is usually given.

Osteonecrosis of the jaw

ONJ is a nonhealing wound in the oral mucosa with exposed bone that lasts >8 weeks, usually associated with an invasive dental procedure such as dental extraction or implantation but can occur *de novo* as well (47). An international task force on ONJ reported on the association of bisphosphonate therapy and ONJ; the absolute risk of ONJ in osteoporosis patients was estimated to range from 1 in 10,000 to 1 in 100,000 (or 0.001% to 0.01%) (137). Higher doses and more frequent use of bisphosphonate and denosumab have been associated with greater ONJ risks in the oncology setting (138), but these patients have other risk factors such as cancer, chemotherapy, radiation therapy, and antiangiogenic therapies. In osteoporosis patients on long-term oral bisphosphonate therapy, the risk of ONJ has been reported to be as high as 21 in 10,000 (or 0.21%) for patients on >4 years of therapy (139). Tooth extraction in a patient exposed to bisphosphonate therapy carries a 0.5% risk of developing ONJ (140). Currently, the American Dental Association does not recommend stopping bisphosphonates for dental procedures; however, if a tooth extraction or implant is planned or ongoing, initiation of potent antiresorptive therapy could be deferred until the area healed (141). In contrast, the American Association of Oral and Maxillofacial Surgeons recommends a 2-month drug holiday for those who have taken >4 years of bisphosphonates (140). Routine dental care is also important for the prevention of ONJ in patients treated with potent antiresorptive therapy (142, 143).

Conservative management such as antibacterial mouth rinse is recommended as initial therapy for stage 0 to 2 ONJ, whereas surgical debridement and resection is recommended for stage 3 ONJ (140). Although there have been case reports of using teriparatide as well as other therapies (such as platelet-rich plasma, low-level laser irradiation, and bone morphogenic protein) in the successful treatment of ONJ, controlled studies are needed to establish efficacy of these therapies (140).

Atypical femoral fractures

AFFs are insufficiency stress fractures of the femoral shaft first noted in case reports in about 2007 (144, 145) that suggested a possible association with bisphosphonate use. These fractures have specific radiological characteristics that have been formalized in a case definition by the ASBMR (146, 147) based on radiographic criteria and low trauma. AFFs have been most studied in relationship to bisphosphonate use but have been noted with other osteoporosis medications including denosumab, odanacatib, and romosozumab (48). Patients often present with pain or aching in the thigh or groin with or after weight-bearing activities. The pathogenesis of these fractures is not understood, although a number of hypotheses including factors related to femur shape, genetics, and ethnicity have been advanced (48).

A large number of epidemiologic studies focusing on bisphosphonate usage and duration have been published. However, many have not had assessments of individual radiographs and instead relied on femoral shaft fractures as defined by ICD codes from population registries [*e.g.*, see Refs (148) and (149)]. Unfortunately, this endpoint is problematic because <5% of these femoral shaft fractures would have met AFF criteria if radiographs had been evaluated (42, 150). This nonspecific endpoint could have masked AFF increases in these studies, as well as in a meta-analysis of AFFs published in 2013 (151), which included many such studies.

Calculation of AFF incidence restricted to studies with radiographic evaluation shows incidence to be very low. For example, a study in Sweden using national data for women and men >55 years of age for 2008 to 2010 showed that among a total of 50,325 femur (hip or

femoral shaft) fractures, only 172 (about 3 AFFs per 1000 hip fractures) met ASBMR criteria. A similarly low ratio of AFFs to hip fractures was shown in a study performed in Kaiser Permanente Northwest (152). This study showed very low AFF incidence in their population (about 5 per 100,000 person-years) compared with an almost 100-fold higher incidence of hip fractures (300 to 400 per 100,000 person-years). Despite low incidence rates, studies with radiographic assessment have shown strong increases in AFFs with longer duration of bisphosphonate use. For example, one widely cited study from a large health maintenance organization in California of people >45 years of age (~1.8 million) showed AFF risk (unadjusted) for 2 years of use to be ~3 per 100,000 person-years, increasing to ~20 per 100,000 person-years with 5 years of use and ~50 per 100,000 with >8 years of use (153). Despite this increase, risks of hip and other osteoporotic fractures that can be prevented by treatment are much higher, suggesting a positive benefit-risk ratio even for long-term treatment, particularly in older women at highest risk of hip and other osteoporotic fractures. Whereas one analysis of benefit vs risk for bisphosphonate treatment of 3 years showed that treating 1000 osteoporotic women would prevent 100 fractures, including 11 hip fractures, while causing about 0.1 AFF (49), similar data for longer-term treatment are not available, and the consistent increase shown for treatment beyond 5 years suggests consideration of AFF risk in treating patients for >5 years. As discussed in section 2, the ASBMR long-term has proposed that the risk could be reduced by taking a "holiday" from oral bisphosphonates after 5 years and from IV bisphosphonates after 3 years in patients who are at low to moderate fracture risk (40). Specific recommendations for bisphosphonate holidays are discussed in "Bisphosphonates". There are insufficient data about the relationship of long-term denosumab to AFF risk to make a recommendation about duration of use.

11. Monitoring

11.1 In postmenopausal women with a low BMD and at high risk of fractures who are being treated for osteoporosis, we suggest monitoring the BMD by dual-energy X-ray absorptiometry at the spine and hip every 1 to 3 years to assess the response to treatment. (2⊕OOO)

Technical remark: Monitoring BTMs (serum CTX for antiresorptive therapy or P1NP for bone anabolic therapy) is an alternative way of identifying poor response or nonadherence to therapy.

Evidence

Treatments for osteoporosis increase the BMD, but only modestly. The usual time point for monitoring is after 2 years of treatment. The expected (mean) changes in lumbar spine BMD after alendronate at 70 mg weekly, risedronate at 35 mg weekly, ibandronate at 150 mg monthly, zoledronate at 5 mg annually, denosumab at 60 mg 6-monthly, and raloxifene at 60 mg daily are 7%, 3%, 7%, 7%, 8%, and 3%, respectively (37, 56, 84, 154). The expected (mean) changes in total hip BMD after alendronate at 70 mg weekly, risedronate at 35 mg weekly, ibandronate at 150 mg monthly, zoledronate at 5 mg annually, denosumab at 60 mg 6-monthly, and raloxifene at 60 mg daily are 5%, 2%, 3%, 4%, 5%, and 1%, respectively (37, 56, 84, 154). Teriparatide (20 μg/d) increased the BMD of the spine and total hip by ~13% and 4%, respectively, after 24 months (73). Evidence to support the use of BMD for monitoring the treatment response is weak but suggests that BMD can be used for this purpose (155). It has been suggested that serial BMD measurements in treated subjects may identify patients who are not adhering to treatment or patients who have a secondary cause for bone loss. Although there is evidence that total hip BMD changes reflect medication compliance (156), use of serial BMD measurements to identify subjects with secondary osteoporosis is anecdotal. It has also been suggested that serial BMD measurements may identify subjects who fail therapy. A retrospective study showed that BMD monitoring was associated with improved compliance (157, 158).

There is uncertainty over what constitutes an adequate BMD response to treatment. Stable or increasing BMD appears to indicate a good response (155). One approach is to consider whether any BMD change exceeds that expected due to normal intermeasurement variation (the least significant change approach); this requires information about the variability of BMD measurements. In women with osteopenia, estimates of the least significant changes at the spine and hip made in research settings are between 4% and 5% in the short term (123). In all of the studies mentioned above, the changes in the spine BMD were greater than the least significant change in most women treated for 2 years, whereas the changes in the hip BMD were generally within the expected reproducibility error. It has been estimated that the BMD response to treatment accounts for a substantial proportion of the fracture risk reduction with treatments for osteoporosis (159). The least significant change approach can also be used to identify significant bone loss in women who are untreated or to identify the offset of effects after stopping treatment of osteoporosis. Because the expected rate of bone loss is slower in these situations than the rate of gain during treatment, it may be better to wait longer between measurements (*e.g.*, 2 to 4 years) in untreated women. Assessing changes in BMD on serial measurements

requires careful attention to detail. Using the same machine and a trained technologist aware of the pitfalls of bone densitometry can mitigate these problems. The provider responsible for reporting the results also needs to be aware of these limitations. Degenerative changes in the spine or a new fracture in the region of the scan may falsely give the impression of a gain in BMD.

Treatments for osteoporosis in women produce significant changes in BTMs. In postmenopausal women, alendronate reduces serum CTX and serum P1NP by 80% and 60%, respectively (38). Reductions in BTMs become maximal within several months and remain stable throughout therapy. Bone formation and resorption markers increase dramatically during the first 6 to 12 months of teriparatide therapy in women, after which they gradually decline toward baseline levels (160).

There is uncertainty over what constitutes an optimal BTM response to treatment. Decreasing bone resorption markers (for antiresorptive agents) or increasing bone formation markers (for anabolic agents) indicates a good response to treatment. There is evidence that an inadequate response may be due to the presence of secondary osteoporosis or noncompliance with treatment (161). A change in BTMs relates to fracture risk reduction with antiresorptive treatments (162, 163).

Monitoring treatment with BTMs requires attention to detail. Because of diurnal variations (a higher turnover in the morning) and the effects of food (bone resorption markers decrease after eating), samples for bone resorption markers (urinary N-terminal telopeptide and serum CTX) should be collected with the patient in the fasting state, in the morning. Because manual and automated assays give different results for the same analysis, changes can be compared only if the laboratory continues to use the same assay (164).

As with changes in BMD, changes in BTMs can be compared with the least significant change to determine whether the observed changes exceed those likely to occur as a result of normal variation. Least significant change estimates are ~56% for serum CTX and 38% for serum P1NP. With oral bisphosphonates, by 12 weeks on treatment, between 70% and 90% of women are expected to respond (38). The BTM response to treatment may account for 30% to 75% of the fracture risk reduction with standard treatments for osteoporosis (163). Additionally, the magnitude of the BTM response has been shown to be associated with the level of compliance (156).

Some experts recommend measuring BTMs before and 3 to 6 months after starting treatment (165). If the change in markers exceeds the least significant change (~40%), then one goal has been met. In women, a low risk of fractures while on treatment is associated with BTMs that are below the median of the reference interval for young women (166). If the markers do not change, there are several options, including questioning the patient about her compliance with medication, considering causes of secondary osteoporosis, or changing the medication or the route of administration.

Method of Development of Evidence-Based Clinical Practice Guidelines

Participants

The Writing Committee consisted of five content experts representing endocrinology and epidemiology. Two of the committee members brought an international perspective to this guideline topic. The Writing Committee also included a clinical practice guideline methodologist who led the team of comparative effectiveness researchers that conducted the systematic reviews and meta-analyses. The methodologist also supervised application of the GRADE methodological framework for each recommendation, including quality of evidence assessments and strength of recommendation designations.

Guideline development process

The Endocrine Society's guideline development process combines elements of the GRADE framework (167) with, when relevant, an approach thought to be appropriate for rare endocrine diseases where scientific evidence is limited or nonexistent. The Society applies the steps in the GRADE framework to research questions for which there is an ample body of knowledge of low quality or higher (see Table 1). In these situations, GRADE provides the methodological and statistical rigor that results in robust recommendations that are classified using quality of evidence and strength of recommendation as described by Guyatt *et al.* (168) and also represented graphically in Table 1.

Where evidence is extremely limited and/or not systematically analyzed, we provide recommendations based on an expert review of the limited data. This process is less systematic than the GRADE methodological framework; however, these recommendations are also clearly classified using the GRADE classification system.

Some of the Society's clinical practice guidelines also include ungraded good practice statements (169). This unclassified clinical guidance can include expert opinion statements on good practice, references to recommendations made in other guidelines, and observations on preventive care and shared decision-making.

Guideline recommendations include the relevant population, intervention, comparator, and outcome. When further clarification on implementation is needed, we include technical remarks. These provide supplemental information such as timing, setting, dosing regimens, and

Table 1. GRADE Classification of Guideline Recommendations

QUALITY OF EVIDENCE		High Quality	Moderate Quality	Low Quality	Very Low Quality
Description of Evidence		• *Well-performed RCTs* • *Very strong evidence from unbiased observational studies*	• *RCTs with some limitations* • *Strong evidence from unbiased observational studies*	• *RCTs with serious flaws* • *Some evidence from observational studies*	• *Unsystematic clinical observations* • *Very indirect evidence from observational studies*
STRENGTH OF RECOMMENDATION	**Strong (1): "We recommend…"** *Benefits clearly outweigh harms and burdens, or vice versa*	**1|⊕⊕⊕⊕**	**1|⊕⊕⊕O**	**1|⊕⊕OO**	**1|⊕OOO**
	Conditional (2): "We suggest…" *Benefits closely balanced with harms and burdens*	**2|⊕⊕⊕⊕**	**2|⊕⊕⊕O**	**2|⊕⊕OO**	**2|⊕OOO**

necessary expertise. All recommendations are followed by a synopsis of the evidence on which they are based. Authors may also include short statements on patients' values and preferences, the balance of benefits and harms, and minority opinions, where relevant.

Internal and external review

Approximately 18 months into the development process, Endocrine Society clinical practice guidelines undergo a comment review period of 1 month when there is an opportunity for internal and external stakeholders to review the guideline draft and provide comments. These stakeholders include Endocrine Society members, the Society's Clinical Guidelines Subcommittee, representatives of any cosponsoring organizations, a representative of Council, and an expert reviewer. Following revisions to the guideline manuscript in response to comment review period comments, it is returned to Clinical Guidelines Subcommittee, the Council reviewer, and the expert reviewer for a second review and ballot. Finally, the guideline manuscript is subject to the *Journal of Clinical Endocrinology & Metabolism* publisher's review prior to publication. This review is undertaken by an individual with expertise in the topic, without relevant conflicts of interest, and external to the guideline Writing Committee, Clinical Guidelines Subcommittee, and Council.

Conflict of interest

The Endocrine Society's conflict of interest (COI) policy and procedures for the development of clinical practice guidelines can be found on the Endocrine Society Web site. In summary, the rules are as follows:

1. To be considered for membership of a Writing Committee, nominees are required to disclose all relationships with industry for the 12-month period prior to guideline Writing Committee initiation. This is consistent with the reporting timeframe for the National Institutes of Health and the Food and Drug Administration.
2. Potential COIs that should be declared include all relationships with commercial, noncommercial, institutional, and patient/public organizations that are (or may be) pertinent to the scope of the guideline.
3. The Chair of the Clinical Guidelines Subcommittee reviews all disclosed relationships and determines whether they are relevant to the topic of the guideline and present a potentially relevant COI.

Appendix Relevant COIs of the Osteoporosis Guideline Writing Committee

Writing Committee Member	Employment	Uncompensated Memberships	Uncompensated Leadership	Personal Financial	Organizational Financial	Spousal/ Family Info.
Clifford Rosen, Chair	Senior Scientist, Director, Maine Medical Center Research Institute	None	None	None	None	None
Dennis Black	Professor in Residence, Division of Clinical Trials and Multicenter Studies, University of California San Francisco	None	None	• Asahi-Kasei, consultant • EffRx, consultant • Merck, CME presentations • Zuellig, speaker	None	None
Angela Cheung	Director, Osteoporosis Program, University of Toronto Professor of Medicine, University of Toronto Director of Osteoporosis Program, University Health Network/Sinai Health System	• International Osteoporosis Foundation Committee of Scientific Advisors, member • International Society for Clinical Densitometry Position Development Conference Monitoring Task Force member • Osteoporosis Canada, Guidelines Committee member • 2019 Osteoporosis Canada Clinical Practice Guidelines Fracture Risk Assessment Task Force member	• International Society for Clinical Densitometry Canadian, Panel Chair • International Society for Clinical Densitometry, Board Member • Quantitative Musculoskeletal Imaging, 2019 Meeting Co-Chair	• Amgen, consultant and speaker for accredited CME programs • Eli Lilly, consultant and speaker for accredited CME programs	• Amgen, educational grant awardee	None
Richard Eastell	Professor and Head of the Academic Unit of Bone Metabolism, University of Sheffield–Sheffield Teaching Hospitals NHS Trust Director of the Mellanby Centre for Bone Research	• International Osteoporosis Foundation Committee of Scientific Advisors, member • National Institute for Health Research, Senior Investigator Emeritus	• European Calcified Tissue Society, Program Co-Chair • American Society for Bone and Mineral Research, grant review • IBMS, Treasurer • *Endocrine Reviews*, IAB • *Lancet Diabetes and Endocrinology*, IAB	• Immunodiagnostic Systems, Nittobo, and Roche Diagnostics, consultant • D-Star, consultant • GlaxoSmithKline Nutrition, consultant • Foundation for the National Institutes of Health, consultant • *Bone*, Senior Editor • Sandoz, consultant	• Amgen, grant awardee • Alexion, grant awardee • Immunodiagnostic Systems, Nittobo, and Roche Diagnostics, grant awardee • D-Star, consultant • GlaxoSmithKline Nutrition, consultant • Medical Research Council, grant awardee • National Osteoporosis Society, grant awardee • Arthritis Research UK, grant awardee	None
M. Hassan Murad	Professor of Medicine, Mayo Clinic	None	None	None	None	None
Dolores Shoback	Professor, University of California San Francisco	None	None	None	None	None

4. The Chair of the Clinical Guidelines Subcommittee selects Writing Committee Chairs and Co-Chairs based on COI information, as well as the individuals' clinical expertise and other skills. The Endocrine Society Council reviews and endorses the nominees or makes appropriate changes. The three Chairs then select and appoint Writing Committee members.
5. The Chair and Co-Chair of the Writing Committee must be free of any COI or other biases that could undermine the integrity or credibility of the work.

6. A majority (≥50%) of the Writing Committee members must be free of relevant COIs.
7. Writing Committee members with relevant COIs are required to declare the situation and recuse themselves from any relevant discussions, votes, and from drafting recommendations.
8. All Writing Committee members must refrain from adding new relevant industry relationships throughout the guideline development process.
9. If a member is aware of another person who might have a conflict and has not declared it for some reason, they are obliged to bring this to the Writing Committee Chair's attention.
10. Staff, Writing Committee Chairs, and members must be alert for situations that might present a potential or perceived COI.

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Correspondence: Clifford J. Rosen, MD, Maine Medical Research Institute, 81 Research Drive, Scarborough, Maine 04074. E-mail: cjrofen@gmail.com.

Disclosure Summary: See Appendix.

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AMERICAN ASSOCIATION OF CLINICAL ENDOCRINOLOGISTS/ AMERICAN COLLEGE OF ENDOCRINOLOGY CLINICAL PRACTICE GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS— 2020 UPDATE

Pauline M. Camacho, MD, FACE[1]; Steven M. Petak, MD, JD, FACP, FCLM, MACE, CCD[2]; Neil Binkley, MD[3]; Dima L. Diab, MD, FACE, FACP, CCD[4]; Leslie S. Eldeiry, MD[5]; Azeez Farooki, MD[6]; Steven T. Harris, MD, FACP, FASBMR[7]; Daniel L. Hurley, MD, FACE[8]; Jennifer Kelly, DO, FACE[9]; E. Michael Lewiecki, MD, FACE, FACP, CCD[10]; Rachel Pessah-Pollack, MD, FACE[11]; Michael McClung, MD, FACP, FACE[12]; Sunil J. Wimalawansa, MD, PhD, MBA, FCCP, FACP, FRCP, DSc, FACE[13]; Nelson B. Watts, MD, FACP, CCD, FASBMR, MACE[14]

The American Association of Clinical Endocrinologists' Medical Guidelines for Practice are systematically developed statements to assist health-care professionals in medical decision-making for specific clinical conditions. Most of the content herein is based on literature reviews. In areas of uncertainty, professional judgment was applied. These guidelines are a working document that reflect the state of the field at the time of publication. Because rapid changes in this area are expected, periodic revisions are inevitable. We encourage medical professionals to use this information in conjunction with their best clinical judgment. The presented recommendations may not be appropriate in all situations. Any decision by practitioners to apply these guidelines must be made considering local resources and individual patient circumstances.

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From the [1]Guideline Task Force Co-Chair, Professor of Medicine, Director, Loyola University Osteoporosis and Metabolic Bone Disease Center, Maywood, Illinois, [2]Guideline Task Force Co-Chair, Associate Clinical Professor, Weill-Cornell Medical College, Division Head and Service Chief, Endocrinology, Houston Methodist Hospital, Charles and Anne Duncan Centennial Clinical Academic Scholar in Endocrinology, Houston, Texas, [3]Professor of Medicine, Divisions of Endocrinology and Geriatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, [4]Associate Professor of Clinical Medicine, Fellowship Associate Program Director, Director of UC Bone Health and Osteoporosis Center, Division of Endocrinology, Diabetes and Metabolism, University of Cincinnati College of Medicine, VA Interim Endocrinology Section Chief, Veterans Affairs Medical Center, Cincinnati, Ohio, [5]Assistant Professor of Medicine, Harvard Medical School, Staff, Department of Endocrinology, Harvard Vanguard Medical Associates/Atrius Health, Boston, Massachusetts, [6]Associate Attending Physician, Memorial Sloan Kettering Cancer Center, Endocrinology Service, Associate Clinical Professor, Weill Cornell Medical College, Key Clinical Faculty, MSKCC-WCMC Endocrinology Fellowship Program, New York, New York, [7]Clinical Professor of Medicine, University of California, San Francisco, California, [8]Consultant, Division of Endocrinology, Diabetes, Metabolism and Nutrition, Mayo Clinic, Rochester, Minnesota, Immediate Past President, American Association of Clinical Endocrinologists, [9]Associate Professor of Medicine, Division of Endocrinology and Diabetes, Director, Metabolic Bone Program, University of Vermont Medical Center, Burlington, Vermont, [10]Director, Bone Health TeleECHO, University of New Mexico Health Sciences Center, Albuquerque, New Mexico, [11]Assistant Clinical Professor, Division of Endocrinology, Diabetes, and Bone Disease, Icahn School of Medicine at Mount Sinai, New York, New York, [12]Founding Director, Oregon Osteoporosis Center, Portland Oregon, Professional Fellow, Mary MacKillop Institute for Health Research, Australian Catholic University, Melbourne, Victoria, Australia, [13]Division of Endocrinology, Metabolism and Lipids, Department of Medicine, Emory University School of Medicine and the Atlanta VA Medical Center, Atlanta, Georgia, and [14]Director, Mercy Health Osteoporosis and Bone Health Services, Cincinnati, Ohio.
Address correspondence to Dr. Pauline M. Camacho, Loyola University Medical Center, 2160 South First Avenue, Fahey Center, Suite 137, Maywood, IL 60153.
E-mail: PCAMACH@lumc.edu.
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Abbreviations:
25(OH)D = 25-hydroxyvitamin D; **AACE** = American Association of Clinical Endocrinologists; **ACE** = American College of Endocrinology; **AFF** = atypical femoral fracture; **ASBMR** = American Society for Bone and Mineral Research; **BEL** = best evidence level; **BMD** = bone mineral density; **BTM** = bone turnover marker; **CI** = confidence interval; **CPG** = clinical practice guideline; **CTX** = C-terminal telopeptide type-I collagen; **DXA** = dual-energy X-ray absorptiometry; **EL** = evidence level; **FDA** = U.S. Food and Drug Administration; **FRAX®** = Fracture Risk Assessment Tool; **GI** = gastrointestinal; **HORIZON** = Health Outcomes and Reduced Incidence with Zoledronic acid ONce yearly Pivotal Fracture Trial (zoledronic acid and zoledronate are equivalent terms); **ISCD** = International Society for Clinical Densitometry; **IU** = international units; **IV** = intravenous; **LSC** = least significant change; **NOF** = National Osteoporosis Foundation; **ONJ** = osteonecrosis of the jaw; **PINP** = serum amino-terminal propeptide of type-I collagen; **PTH** = parathyroid hormone; **R** = recommendation; **ROI** = region of interest; **RR** = relative risk; **SD** = standard deviation; **TBS** = trabecular bone score; **VFA** = vertebral fracture assessment; **WHO** = World Health Organization

ABSTRACT

Objective: The development of these guidelines is sponsored by the American Association of Clinical Endocrinologists (AACE) Board of Directors and American College of Endocrinology (ACE) Board of Trustees and adheres with published AACE protocols for the standardized production of clinical practice guidelines (CPGs).

Methods: Recommendations are based on diligent reviews of the clinical evidence with transparent incorporation of subjective factors, according to established AACE/ACE guidelines for guidelines protocols.

Results: The Executive Summary of this 2020 updated guideline contains 52 recommendations: 21 Grade A (40%), 24 Grade B (46%), 7 Grade C (14%), and no Grade D (0%). These detailed, evidence-based recommendations allow for nuance-based clinical decision-making that addresses multiple aspects of real-world care of patients. The evidence base presented in the subsequent Appendix provides relevant supporting information for the Executive Summary recommendations. This update contains 368 citations: 123 (33.5%) evidence level (EL) 1 (highest), 132 (36%) EL 2 (intermediate), 20 (5.5%) EL 3 (weak), and 93 (25%) EL 4 (lowest). New or updated topics in this CPG include: clarification of the diagnosis of osteoporosis, stratification of the patient according to high-risk and very-high-risk features, a new dual-action therapy option, and transitions from therapeutic options.

Conclusion: This guideline is a practical tool for endocrinologists, physicians in general, regulatory bodies, health-related organizations, and interested laypersons regarding the diagnosis, evaluation, and treatment of postmenopausal osteoporosis. **(Endocr Pract. 2020;26 (Suppl 1):1-44)**

INTRODUCTION

Osteoporosis is a growing major public health problem, with an impact on quality and quantity of life that crosses medical, social, and economic lines. These guidelines have been developed by the American Association of Clinical Endocrinologists (AACE) with hopes of reducing the risk of osteoporosis-related fractures and thereby maintaining the quality of life for people with osteoporosis. The guidelines use the best evidence, taking into consideration the economic impact of the disease and the need for efficient and effective evaluation and treatment of postmenopausal women with osteoporosis. The intent is to provide evidence-based information about the diagnosis, evaluation, and treatment of postmenopausal osteoporosis for endocrinologists, physicians in general, regulatory bodies, health-related organizations, and interested laypersons.

METHODS

The AACE Board of Directors approved this 2020 update of the 2016 AACE/American College of Endocrinology (ACE) Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis. Selection of the co-chairs, primary writers, and expert reviewers as well as the logistics for creating this guideline update were conducted in adherence with the AACE Protocol for Standardized Production of Clinical Practice Guidelines, Algorithms, and Checklists–2017 Update (2017 Guidelines for Guidelines; 2017 G4G) (Tables 1 through 4) (1). Methods established by AACE in 2004 and clarified in 2010, 2014, and 2017 more clearly delineate the mapping of recommendation grades for transparency and allow for more interpretative flexibility (Tables 1 through 4) (1-4). This updated methodology provides for patient-first language, greater detail regarding ratings for evidence, and general oversight of the entire clinical practice guideline (CPG) production process.

All members of the appointed task force and reviewers made disclosures regarding multiplicities of interests and attested that they are not employed by industry. Primary writers submitted contributions to specific clinical questions, which were subsequently reviewed, discussed, and integrated into the final document. This input provides the basis for the recommendations herein. This CPG was

approved by all primary writers, invited expert reviewers, the AACE CPG Oversight Committee, and the AACE Board of Directors before submission to *Endocrine Practice* for peer review.

Evidence was obtained through literature searches using the MEDLINE® database through PubMed® and other designated reference sources. Based on the 2017 AACE protocols for standardized production of CPGs (1), the appointed task force of medical experts evaluated available literature and graded references with numerical descriptors (evidence level [EL] 1 [highest] to 4 [lowest]) according to semantic descriptors of study type (Table 1), analyzed the graded evidence in consideration of subjective factors related to interpretation of the quality of each individual study's design and data analysis (Table 2), and then assessed recommendation qualifiers (such as risks and benefits, gaps in evidence, and cost-effectiveness when available) for the aggregate evidence base of an individual recommendation (Tables 3) (1). Based on identified subjective factors and qualifiers, the task force assigned recommendations with grades A through D (strong, intermediate, weak, no conclusive evidence/expert opinion) by expert consensus, mapping to the best evidence level (BEL), or highest quality rating, of supporting literature (Table 4). The process leading to a final recommendation and grade is not rigid but incorporates expert integration of objective and subjective factors meant to reflect optimal real-life clinical decision-making, options, and individualization of care. This document is a guideline; since individual circumstances and clinical presentations differ from patient to patient, ultimate clinical management is based on what is in the best interest of the patient that would also involve the patient's input ("patient-centered care") and reasonable clinical judgment by the treating clinician.

The Executive Summary lists 12 clinical questions related to postmenopausal osteoporosis and 52 recommendations, organized by corresponding question; some recommendations include multiple statements. Recommendation grade and BEL are provided after each recommendation (labeled R and numbered) in the Executive Summary. The relevant evidence base with discussion to support each recommendation as well as tables and figures for the updated recommendations follow the Executive Summary in an Appendix.

KEY UPDATES FOR 2020

The following key updates highlight the most important new recommendations in this CPG. See also the updated AACE/ACE Postmenopausal Osteoporosis Treatment Algorithm included at the end of the Executive Summary.

- Postmenopausal women with osteoporosis can be stratified according to high-risk and very-high-risk features, which includes prior fractures. Stratification of the patient drives the choice of the initial agent as well as the duration of therapy.
- The new anabolic agent romosozumab is included in the treatment algorithm.
- Transitions from therapeutic agents, including denosumab, are further elucidated.

EXECUTIVE SUMMARY

To guide readers, recommendations (R) are organized into the following questions:

- Q1. How is fracture risk assessed and osteoporosis diagnosed?
- Q2. When osteoporosis is diagnosed, what is an appropriate evaluation?
- Q3. What are the fundamental measures for bone health?
- Q4. Who needs pharmacologic therapy?
- Q5. What medication should be used to treat osteoporosis?
- Q6. How is treatment monitored?
- Q7. What is successful treatment of osteoporosis?
- Q8. How long should patients be treated?
- Q9. What is the role of concomitant use of therapeutic agents?
- Q10. What is the role of sequential use of therapeutic agents?
- Q11. What is the role of vertebral augmentation for compression fractures?
- Q12. When should referral to a clinical endocrinologist or other osteoporosis specialist be considered?

Q1. How Is Fracture Risk Assessed and Osteoporosis Diagnosed?

R1. Evaluate all postmenopausal women aged ≥50 years for osteoporosis risk **(Grade B; BEL 1, downgraded due to gaps in evidence)**.

R2. A detailed history, physical exam, and clinical fracture risk assessment with fracture risk assessment tool (FRAX®) or other fracture risk assessment tool should be included in the initial evaluation for osteoporosis **(Grade B; BEL 1)**.

R3. Consider bone mineral density testing based on clinical fracture risk profile **(Grade B; BEL 2)**.

R4. When bone mineral density is measured, axial dual-energy X-ray absorptiometry (DXA) measurement (lumbar spine and hip; 1/3 radius if indicated) should be used **(Grade B; BEL 2)**.

R5. Osteoporosis is diagnosed based on presence of fragility fractures in the absence of other metabolic bone disorders and even with a normal bone mineral density (T-score)

Table 1
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised Logical Ranking of Scientific Methodologies (Step I: Evidence Rating)

Numerical Descriptor	Semantic Descriptor	Methodology Descriptor
STRONG EVIDENCE		
1 (1)	RCT	Randomized controlled trial
1 (1)	MRCT	Meta-analysis of only randomized controlled trials
INTERMEDIATE EVIDENCE		
2 (2)	MNRCT	Meta-analysis including nonrandomized prospective or case-controlled trials
2 (new)	NMA	Network meta-analysis
2(2)	NRCT	Nonrandomized controlled trial (or unconfirmed randomization)
2 (2)	PCS	Prospective cohort study (does not include open-label extension study)
2 (2)	RCCS	Retrospective case-control study
2 (new)	NCCS	Nested case-control study
2 (3; reassigned)	ES	Epidemiological study (hypothesis driven; includes survey, registry, data-mining, with or without retrospective uni-multivariate analyses or propensity matching)
2 (new)	OLES	Open-label extension study
2 (new)	PHAS	Post hoc analysis study
WEAK EVIDENCE		
3 (new)	DS	Discovery science (explorative/inductive; includes -omics, "big data," network analysis, systems biology, Bayesian inference, modeling) (48)
3 (new)	ECON	Economic study (includes Markov models, pharmacoeconomics) (49-53)
3 (3)	CCS	Consecutive case series (N > 1)
3 (3)	SCR	Single case report (N = 1)
3 (new)	PRECLIN	Preclinical study (e.g., feasibility, safety)
3 (new)	BR	Basic research (must be high impact and relevant)
NO EVIDENCE		
4 (4)	NE	No evidence (theory, opinion, consensus, review, position, policy, guideline)
4 (new)	O	Other (e.g., lower impact/relevant basic research; any highly flawed study)

Abbreviations: EBM = evidence-based methodology; EL = evidence level.
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Table 2
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised Evaluation of Studies (Step II: Scientific Analysis and Subjective Factors)

Study design	Data analysis	Interpretation
Allocation concealment (randomization)	Intent-to-treat	Generalizability
Blinding	Modeling (e.g., Markov)	Incompleteness
Comparator group	Network analysis	Logical
Endpoints (real clinical vs. surrogate)	Statistics	Overstated
Hypothesis	Appropriate follow-up	Validity
Power analysis (too small sample size)	Appropriate trial termination	
Premise		
Type 1 error (e.g., adjusted for PHAS)		

Abbreviations: AACE = American Association of Clinical Endocrinologists; PHAS = post hoc analysis study.
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Table 3 2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised Evaluation of Recommendations (Step III: Recommendation Qualifiers)
Cascades (are there other recommendation versions based on ethnocultural factors?)
Dissenting opinions (based on health-care professional and patient preferences)
Economic (e.g., cost-effectiveness, cost-benefit, value)
Evidence base (are there significant gaps or is there overwhelming evidence?)
Relevance (patient-oriented evidence that matters vs. disease-oriented evidence; social acceptability)
Resource availability (limited or sufficient)
Risk to benefit
Abbreviation: AACE = American Association of Clinical Endocrinologists. Reprinted with permission from Mechanick et al. *Endocr Pract*. 2017;23:1006-1021 (1).

Table 4
2017 AACE Protocol for Production of Clinical Practice Guidelines
Revised and Detail Mapping Protocol (Step IV: Creating Initial Recommendation Grades)[a]

Best Evidence Level	Predominantly Negative SF and/or RQ	Predominantly Positive SF and/or RQ	Consensus for Recommendation and for Grade	EL to Grade Mapping	Map to Final Recommendation Grade
1	No	No	>66%	Direct	1 → A
Any[b]	No	No	100%	Rule	Any → A (new)
2	No	Yes	>66%	Adjust up	2 → A
2	No	No	>66%	Direct	2 → B
1	Yes	No	>66%	Adjust down	1 → B
3	No	Yes	>66%	Adjust up	3 → B
3	No	No	>66%	Direct	3 → C
2	Yes	No	>66%	Adjust down	2 → C
4	No	Yes	>66%	Adjust up	4 → C
4	No	No	>66%	Direct	4 → D
3	Yes	No	>66%	Adjust down	3 → D
Any[b]	Yes/no	Yes/no	>66%	Rule	Any → AD (new)

Abbreviations: AACE = American Association of Clinical Endocrinologists; BEL = best evidence level; EL = evidence level; RQ = recommendation qualifiers; SF = subjective factors.
[a]Recommendation Grade A = "Very Strong"; B = "Strong"; C = "Not Strong"; D = "Primarily Based on Expert Opinion." Mappings are provided in online supplementary material from (1).
[b]Rule-based adjustment wherein any recommendation can be a "Very Strong" Grade A if there is 100% consensus to use this designation. Similarly, if >66% consensus is not reached, even with some degree of scientific substantiation, a "Primarily Based on Expert Opinion" Grade D designation is assigned. The reasons for downgrading to D may be an inconclusive or inconsistent evidence base or simply failure of the expert writing committee to sufficiently agree. Note that any formulated recommendation is omitted from the document if sufficiently flawed, so any Grade D recommendation in the final document must be deemed sufficiently important. Rule-based adjustments are provided in online supplementary material from (1).
Reprinted with permission from Mechanick JI, et al. *Endocr Prac*t. 2017;23:1006-1021 (1).

(Grade B; BEL 2). Osteoporosis is also diagnosed based on a T-score of –2.5 or lower in the lumbar spine (anteroposterior), femoral neck, total hip, or 1/3 radius (33% radius), even in the absence of a prevalent fracture **(Grade B; BEL 4, upgraded by consensus)**. When the initial diagnosis of osteoporosis is made according to a T-score of –2.5 or below, the diagnosis persists even when a subsequent dual-energy X-ray absorptiometry (DXA) measurement shows a T-score better than –2.5 **(Grade B; BEL 4, upgraded by consensus**).

R6. Osteoporosis may also be diagnosed in patients with a T-score between –1.0 and –2.5 and increased fracture risk using FRAX® (fracture risk assessment tool) country-specific thresholds **(Grade B; BEL 2)**.

Q2. When Osteoporosis Is Diagnosed, What Is an Appropriate Evaluation?

R7. Evaluate for causes of secondary osteoporosis **(Grade B; BEL 1, downgraded due to limited evidence)**.

R8. Evaluate for prevalent vertebral fractures **(Grade B; BEL 2)**.

R9. Consider using bone turnover markers in the initial evaluation and follow-up of osteoporosis patients. Elevated levels can predict more rapid rates of bone loss and higher fracture risk **(Grade A; BEL 1)**.

Q3. What Are the Fundamental Measures for Bone Health?

R10. Measure serum 25-hydroxyvitamin D (25[OH]D) in patients who are at risk for vitamin D insufficiency, particularly those with osteoporosis **(Grade B; BEL 2)**.

R11. Maintain serum 25-hydroxyvitamin D (25[OH]D) ≥30 ng/mL in patients with osteoporosis (preferable range, 30 to 50 ng/mL) **(Grade A; BEL 1)**.

R12. Supplement with vitamin D3 if needed, with a daily dose of 1,000 to 2,000 international units (IU) typically required to maintain an optimal serum 25(OH)D level **(Grade A; BEL 1)**.

R13. Higher doses of vitamin D3 may be necessary in patients with present factors such as obesity, malabsorption, and older age **(Grade A; BEL 1)**.

R14. Counsel patients to maintain adequate dietary intake of calcium, to a total intake (including diet plus supplement, if needed) of 1,200 mg/day for women age ≥50 years **(Grade B; BEL 1, downgraded due to limited evidence)**.

R15. Counsel patients to limit alcohol intake to no more than 2 units per day **(Grade B; BEL 2)**.

R16. Counsel patients to avoid or stop smoking **(Grade B; BEL 1, downgraded due to limited evidence)**.

R17. Counsel patients to maintain an active lifestyle, including weight-bearing, balance, and resistance exercises **(Grade A; BEL 1)**.

R18. Provide counseling on reducing risk of falls, particularly among the elderly **(Grade B; BEL 1, downgraded due to limited evidence)**.

R19. Consider referral for physical therapy, which may reduce discomfort, prevent falls, and improve quality of life **(Grade A; BEL 1)**.

Q4. Who Needs Pharmacologic Therapy?

R20. Pharmacologic therapy is strongly recommended for patients with osteopenia or low bone mass and a history of fragility fracture of the hip or spine **(Grade A; BEL 1)**.

R21. Pharmacologic therapy is strongly recommended for patients with a T-score of –2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius **(Grade A; BEL 1)**.

R22. Pharmacologic therapy is strongly recommended for patients with a T-score between –1.0 and –2.5 if the FRAX® (fracture risk assessment tool) (or if available, trabecular bone score [TBS]-adjusted FRAX®) 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% in the U.S. or above the country-specific threshold in other countries or regions **(Grade A; BEL 1)**.

R23. Consider patients with a recent fracture (e.g., within the past 12 months), fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), very low T-score (e.g., less than –3.0), high risk for falls or history of injurious falls, and very high fracture probability by FRAX® (fracture risk assessment tool) (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm to be at very high fracture risk. Consider patients who have been diagnosed with osteoporosis but are not at very high fracture risk, as defined above, to be high risk **(Grade B; BEL 1; downgraded due to limited evidence)**.

Q5. What Medication Should Be Used to Treat Osteoporosis?

R24. Approved agents with efficacy to reduce hip, nonvertebral, and spine fractures including alendronate, denosumab, risedronate, and zoledronate are appropriate as initial therapy for most osteoporotic patients with high fracture risk, as defined in R23 **(Grade A; BEL 1)**.

R25. Abaloparatide, denosumab, romosozumab, teriparatide, and zoledronate should be considered for patients unable to use oral therapy and as initial therapy for patients at very high fracture risk, as defined in R23 **(Grade A; BEL 1)**.

R26. Ibandronate or raloxifene may be appropriate initial therapy in some cases for patients requiring drugs with spine-specific efficacy **(Grade B; BEL 1, downgraded due to limited evidence)**.

Q6. How Is Treatment Monitored?

R27. Obtain a baseline axial (lumbar spine and hip; 1/3 radius if indicated) dual-energy X-ray absorptiometry (DXA) and repeat DXA every 1 to 2 years until findings are stable. The 1/3 radius may be considered as an alternate site when the lumbar spine/hip are not evaluable or as an additional site in patients with primary hyperparathyroidism. Continue with follow-up DXA every 1 to 2 years or at a less frequent interval, depending on clinical circumstances **(Grade B; BEL 2)**.

R28. Monitor serial changes in lumbar spine, total hip, or femoral neck bone mineral density; if lumbar spine, hip, or both are not evaluable, monitoring with 1/3 radius site may be acceptable but is limited by a small area and a very large least significant change (LSC) **(Grade B; BEL 1, downgraded due to limited evidence)**.

R29. Follow-up of patients should ideally be conducted in the same facility with the same dual-energy X-ray absorptiometry (DXA) system, provided the acquisition, analysis, and interpretation adhere to International Society for Clinical Densitometry DXA best practices **(Grade C; BEL 2, downgraded due to limited evidence)**.

R30. Consider using bone turnover markers (BTMs) for assessment of patient compliance and efficacy of therapy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction, and significant increases indicate good response to anabolic therapy **(Grade B; BEL 1, adjusted down due to limited evidence)**.

Q7. What Is Successful Treatment of Osteoporosis?

R31. Consider stable or increasing bone mineral density, with no evidence of new fractures or vertebral fracture progression as a response to therapy for osteoporosis **(Grade A; BEL 1)**.

R32. Consider bone turnover markers at or below the median value for premenopausal women as a target for response to therapy for patients taking antiresorptive agents. Consider significant increases in bone formation markers as a pharmacologic response to anabolic therapy **(Grade B; BEL 1, adjusted down due to limited evidence)**.

R33. Consider alternative therapy or reassessment for causes of secondary osteoporosis in patients who have recurrent fractures or significant bone loss while on therapy. Although a single fracture while on therapy is not necessarily evidence of treatment failure, consider two or more fragility fractures are evidence of treatment failure **(Grade B; BEL 1, downgraded due to limited evidence)**.

Q8. How Long Should Patients Be Treated?

R34. Limit treatment with abaloparatide and teriparatide to 2 years and follow abaloparatide or teriparatide therapy with a bisphosphonate or denosumab **(Grade A; BEL 1)**.

R35. Limit treatment with romosozumab to 1 year and follow with a drug intended for long-term use, such as a bisphosphonate or denosumab **(Grade B; BEL 1, downgraded due to limited evidence)**.

R36. For oral bisphosphonates, consider a bisphosphonate holiday after 5 years of treatment if fracture risk is no longer high (such as when the T score is greater than -2.5, or the patient has remained fracture free), but continue treatment up to an additional 5 years if fracture risk remains high **(Grade B; BEL 2)**.

R37. For oral bisphosphonates, consider a bisphosphonate holiday after 6 to 10 years of stability in patients with very high fracture risk **(Grade B; BEL 2)**.

R38. For zoledronate, consider a bisphosphonate holiday after 3 years in high-risk patients or until fracture risk is no longer high, and continue for up to 6 years in very-high-risk patients **(Grade A; BEL 1)**.

R39. The ending of a bisphosphonate holiday should be based on individual patient circumstances such as an increase in fracture risk, a decrease in bone mineral density beyond the least significant change (LSC) of the dual-energy X-ray absorptiometry (DXA) machine, or an increase in bone turnover markers **(Grade A; BEL 1)**.

R40. A holiday is not recommended for non-bisphosphonate antiresorptive drugs **(Grade A; BEL 1)**, and treatment with such agents should be continued for as long as clinically appropriate **(Grade A; BEL 1)**.

R41. If denosumab therapy is discontinued, patients should be transitioned to another antiresorptive **(Grade A; BEL 1)**.

Q9. What Is the Role of Concomitant Use of Therapeutic Agents?

R42. Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use of these agents for prevention or treatment of postmenopausal osteoporosis **(Grade A; BEL 1)**.

Q10. What Is the Role of Sequential Use of Therapeutic Agents?

R43. Follow treatment with an anabolic agent (e.g., abaloparatide, romosozumab, teriparatide) with a bisphosphonate or denosumab to prevent bone density decline and loss of fracture efficacy **(Grade A; BEL 1)**.

Q11. What Is the Role of Vertebral Augmentation for Compression Fractures?

R44. Vertebroplasty and kyphoplasty are not recommended as first-line treatment of vertebral fractures, given an unclear benefit on overall pain and a potential increased risk of vertebral fractures in adjacent vertebrae **(Grade A, BEL 1)**.

Q12. When Should Referral to a Clinical Endocrinologist or Other Osteoporosis Specialist Be Considered?

R45. Patients who experience fragility fractures should be evaluated and treated. Referral to an osteoporosis specialist or a fracture liaison team, if available, should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R46. When a patient with normal bone mineral density sustains a fracture without major trauma, referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R47. When recurrent fractures or continued bone loss occur(s) in a patient receiving therapy without obvious treatable causes of bone loss, referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R48. When bone mineral density is unexpectedly low or when osteoporosis has unusual features such as young age, unexplained artifacts on bone density, and unexplained laboratory studies, including high or low alkaline phosphatase and/or low phosphorus, referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

R49. When a patient has a condition that complicates management (e.g., decreased kidney function, hyperparathyroidism, or malabsorption), referral to a clinical endocrinologist or other osteoporosis specialist should be considered **(Grade C; BEL 2, downgraded due to limited evidence)**.

UPDATED EVIDENCE BASE FOR 2020

In this update, there are 368 reference citations, of which 125 (33.5%) are EL 1 (strong), 133 (36%) are EL 2 (intermediate), 20 (5.5%) are EL 3 (weak), and 95 (25%) are EL 4 (no clinical evidence). The evidence base presented here provides relevant information for the recommendations in the Executive Summary.

Public Health Impact of Osteoporosis

Osteoporosis is a major public health problem. The National Osteoporosis Foundation (NOF) estimates that 10.2 million Americans have osteoporosis and that an additional 43.4 million have low bone mass. More than 2 million osteoporosis-related fractures occur annually in the U.S.; more than 70% of these occur in women (Fig. 1) (5,6). In the U.S., Medicare currently pays for most of these costs; with an aging population, the costs of these fractures are estimated to be more than $25 billion by 2025. Despite these significant costs, less than 1 in 4 women aged 67 years or older with an osteoporosis-related fracture gets their bone density measured or begins osteoporosis treatment (7). A recent retrospective analysis demonstrated that the annual cost of caring for osteoporotic fractures exceeds the annual costs of caring for breast cancer, myocardial infarction, or stroke in women aged 55 years and older (8).

Osteoporosis is preventable and treatable, but only a small proportion of those at increased risk for fracture are evaluated and treated. Age is an important risk factor for bone loss; by age 60 years, half of white women have low bone mass (osteopenia) or osteoporosis (9). The average femoral neck T-score by dual-energy X-ray absorptiometry (DXA) for 75-year-old women is –2.5, meaning that more than half of women age 75 and older meet the criterion for osteoporosis (10). More than 20% of postmenopausal women have prevalent vertebral fractures (11). Although these guidelines focus only on the evaluation and treatment of osteoporosis in postmenopausal women, osteoporosis may affect men as well as women before and after menopause.

Q1. How Is Fracture Risk Assessed and Osteoporosis Diagnosed?

Q1.1. What Is the Definition of Postmenopausal Osteoporosis?

Osteoporosis is defined as "a [silent] skeletal disorder characterized by compromised bone strength predisposing

to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density and bone quality" (12).

In 1994, a Working Group of the World Health Organization (WHO) established an operational definition of postmenopausal osteoporosis (Table 5) (7). The T-score is defined as the standard deviation of an individual's bone mineral density (BMD) from the mean value for young normal white women. Although the WHO diagnostic criteria were not intended to serve as thresholds for treatment decisions, they are often used for this purpose. In addition, the WHO criteria are useful for making decisions about public health and health policy and are commonly accepted as standards for inclusion in clinical trials for research purposes.

Q1.2. What Are the Diagnostic Criteria?

Clinically, osteoporosis can be diagnosed if there is a low-trauma (i.e., fragility) fracture in the absence of other metabolic bone disease, independent of the BMD (T-score) value. A fragility fracture is usually a fracture sustained from force similar to a fall from a standing position or less that would not have occurred in healthy bone, excepting fractures of the skull, face, fingers, and toes. Thus, patients with low bone mass (osteopenia) or low bone mass defined as T-score between –1.0 and –2.5 based on BMD testing, but with a low-trauma (fragility) fracture of the spine, hip, proximal humerus, pelvis, or possibly distal forearm, are also at an increased risk for future fractures and should be diagnosed with osteoporosis and considered for pharmacologic therapy (see **R20–R22**) (Table 6) (12-16). While osteoporosis has traditionally been diagnosed based on low bone density in the absence of fracture (7), AACE agrees that osteoporosis may also be diagnosed in patients with osteopenia and increased fracture risk using FRAX® (Fracture Risk Assessment Tool) country-specific thresholds (14-17). Patients diagnosed with osteoporosis should be treated. Indications for pharmacologic therapy are low T-score, increased fracture risk based on FRAX®, or fragility fracture. Once the diagnosis of osteoporosis is made, the diagnosis remains even if treatment results in a T-score better than –2.5.

All postmenopausal women age ≥50 years of age should undergo clinical assessment for osteoporosis and

Table 5
World Health Organization Criteria for Classification of Osteopenia and Osteoporosis

Category	T-score
Normal	–1.0 or above
Low bone mass (osteopenia)[a]	Between –1.0 and –2.5
Osteoporosis	–2.5 or below
Severe or established osteoporosis	–2.5 or below with fragility fracture

[a]Fracture rates within this category vary widely. The category of "osteopenia" is useful for epidemiology studies and clinical research but is problematic when applied to individual patients and must be combined with clinical information to make treatment decisions.

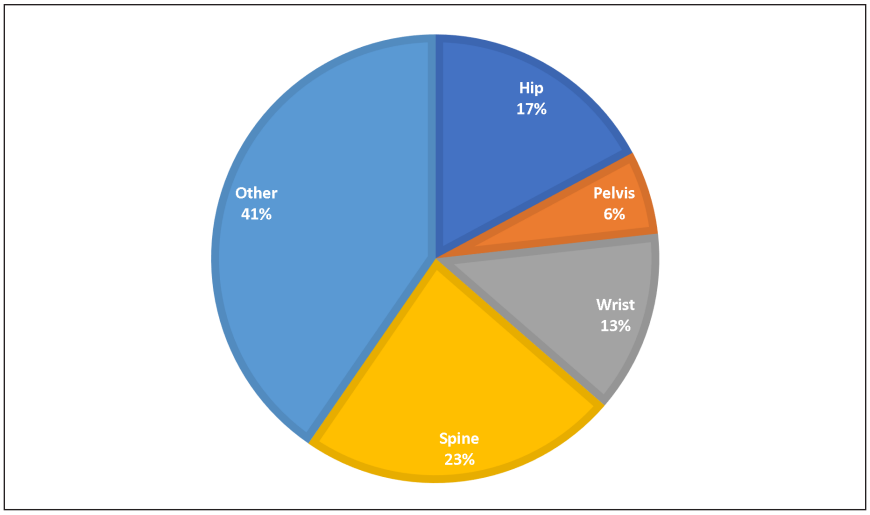

Fig. 1. Incidence of new osteoporotic fractures among Medicare beneficiaries by fracture type in 2015. Over 1.6 million new osteoporotic fractures were diagnosed in Medicare beneficiaries in 2015. Estimates of fracture incidence were based on diagnosis codes on medical claims for Medicare beneficiaries. Adapted with permission from Hansen D, Bazell C, Pelizzari P, Pyenson B. Medicare cost of osteoporotic fractures: The clinical and cost burden of an important consequence of osteoporosis.

Table 6
2020 AACE Diagnosis of Osteoporosis in Postmenopausal Women

1.	T-score –2.5 or below in the lumbar spine, femoral neck, total proximal femur, or 1/3 radius
2.	Low-trauma spine or hip fracture (*regardless of bone mineral density*)
3.	T-score between –1.0 and –2.5 **and** a fragility fracture of proximal humerus, pelvis, or distal forearm
4.	T-score between –1.0 and –2.5 **and** high FRAX® (or if available, TBS-adjusted FRAX®) fracture probability based on country-specific thresholds

Abbreviations: AACE = American Association of Clinical Endocrinologists; FRAX® = fracture risk assessment tool; TBS = trabecular bone score.

fracture risk, including a detailed history and physical examination (Table 7) (18-25). Tools such as FRAX® should be utilized when available (26). The U.S. Preventive Services Task Force recommends BMD testing for all women aged 65 years or older and younger women whose fracture risk is equal to or greater than that of a 65-year-old white woman who has no additional risk factors (20,21).

Q1.3. What Are the Clinical Features and Complications of Postmenopausal Osteoporosis?

Q1.3.1 Low BMD

Low BMD, as noted above, can be used to define postmenopausal osteoporosis. A strong inverse relationship between BMD and risk of fracture exists. Therefore, low BMD is a major indicator of fracture risk, although it is important to realize that individual patients may sustain fractures at different BMD levels, and factors other than bone density influence fracture risk (see **Q1.4 What Are the Risk Factors for Osteoporosis-related Fractures?**). Low BMD and/or bone loss are not associated with symptoms prior to fracture.

Q1.3.2. Fracture

Fracture is the single most important manifestation of postmenopausal osteoporosis. Osteoporotic fractures are usually precipitated by low-energy injuries, such as a fall from standing height. Osteoporosis can also be diagnosed in patients with or without fragility fractures. Vertebral fractures, however, may occur during routine daily activities, without a specific fall or injury. In clinical practice, it may be difficult or impossible to reconstruct the mechanical force applied to bone in a fall.

Osteoporosis-related fractures often lead to pain, disability, and deformity and reduce quality and quantity of life. Hip fractures are the most serious consequences of osteoporosis. Women have an increased mortality of 12 to 20% during the 2 years following hip fracture. More than 50% of survivors of hip fractures are unable to return to independent living; many require long-term nursing-home care (27). Other low-trauma fractures that are considered related to osteoporosis include those of the proximal humerus and pelvis and some cases of distal forearm.

Q1.4 What Are the Risk Factors for Osteoporosis-Related Fractures?

BMD testing is a powerful tool, but clinical risk factors also significantly influence fracture risk in individual patients. The FRAX® tool is readily available (www.shef.ac.uk/FRAX) and incorporates multiple clinical risk factors that predict fracture risk, largely independent of BMD (28-36). Clinical risk factors in FRAX® include age, sex, body mass index (BMI), smoking, alcohol use, prior fracture, parental history of hip fracture, use of glucocorticoids, rheumatoid arthritis, secondary osteoporosis, and femoral neck BMD, when available. FRAX® predicts the 10-year probability of hip fracture and major osteoporotic fracture (hip, clinical spine, humerus, or forearm). Postmenopausal women aged 50 years or older with osteopenia (T-score between –1.0 and –2.5 with a 10-year probability ≥3% for hip fracture or ≥20% for major osteoporotic fracture in the U.S. or above country-specific threshold) are recommended to consider osteoporosis treatment (Table 8).

It is important to note that FRAX® underestimates future fracture risk, as it reports risk for only hip fracture and major fractures, which comprise approximately half of all fragility fractures. Additionally, FRAX® underestimates risk in patients with multiple osteoporosis-related fractures, recent fractures, lumbar spine BMD much lower than femoral neck BMD, those with secondary osteoporosis, and in those at increased risk of falling (37-44). Fall events are not directly captured in the FRAX® tool. Falls magnify the risk due to other factors and are the proximate cause of most fractures in older adults (45). For individuals with a history of falls, the Garvan fracture risk calculator, though based on much less data than FRAX®, can be utilized to gain insight into fracture risk. Table 9 shows factors that increase the risk of falls and fractures.

Q1.5. Bone Densitometry

Q1.5.1. Bone Density Scores

Bone density results are reported as grams of mineral per square centimeter of projected bone area and are converted to T- and Z-scores. The T-score represents the number of standard deviations (SDs) from the normal

Table 7
Assessment for Fracture Risk and Osteoporosis in Postmenopausal Women

- Medical history and physical examination to identify:
  Prior fracture without major trauma (other than fingers, toes, skull) after age 50 years
  Clinical risk factors for osteoporosis
    Age ≥65 years
    Low body weight (<57.6 kg [127 lb])
    Smoking
    Early menopause
    Excessive alcohol intake (more than 3 drinks daily)
  Secondary osteoporosis
  Height loss of kyphosis
  Risk factors for falling (see Table 9)
  Patient's reliability, understanding, and willingness to accept interventions
- Lateral spine imaging with standard radiography or vertebral fracture assessment in patients with unexplained height loss, self-reported but undocumented prior spine fractures, or glucocorticoid therapy equivalent to ≥5 mg of prednisone per day for 3 months or more
- Bone mineral density measurements in those at increased risk for osteoporosis and fractures and willing to consider pharmacologic treatment if low bone mass is documented:
  All women 65 years of age or older
  Younger postmenopausal women
    With a history of fracture(s) without major trauma
    Starting or taking long-term systemic glucocorticoid therapy
    With radiographic osteopenia
    With clinical risk factors for osteoporosis (low body weight, cigarette smoking, family history of spine or hip fractures, early menopause, or secondary osteoporosis)
- In women who are candidates for pharmacologic therapy, laboratory evaluation to identify coexisting conditions that may contribute to bone loss or interfere with therapy (or both).

Table 8
Risk Factors Included in FRAX®

Country of residence
Ethnicity (U.S. models only—white, black, Hispanic, and Asian)
Age (accepts ages between 40 and 90 years)
Sex
Weight (kg) and height (cm) used to calculate body mass index; a converter from English to metric units is provided within the FRAX® tool
Family history (either parent with a hip fracture)
Personal history of fragility fracture, including radiographic vertebral fracture
Glucocorticoid use (prednisolone 5 mg daily or more for 3 months or longer, current or past)
Rheumatoid arthritis (confirmed diagnosis)
Smoking (current)
Alcohol use (2 or more units daily)
Secondary osteoporosis[a] (specifically mentioned are type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause, chronic malnutrition or malabsorption, and chronic liver disease)
BMD. Femoral neck BMD should be entered. The model also works without BMD.

Abbreviations: BMD = bone mineral density; FRAX® = fracture risk assessment tool.
[a]Because the effects of causes of secondary osteoporosis on fracture risk are assumed to be mediated through changes in BMD, a "yes" answer to this question does not change fracture risk if BMD is entered into the risk tool.
Reproduced with permission from Watts NB, et al. *J Bone Miner R*es. 2009;24:975-979 (274).

young-adult mean values, whereas the Z-score represents the number of SDs from the normal mean value for age-, race- or ethnicity-, and sex-matched control subjects. T-scores are used for diagnostic classification in postmenopausal women. Z-scores are recommended for premenopausal women, with a Z-score –2.0 or lower defined as "below the expected range for age" and greater than –2.0 defined as "within the expected range for age." Postmenopausal women with very low Z-scores often have secondary osteoporosis and should undergo comprehensive evaluation for these causes.

Q1.5.2. Indications for BMD measurement

Testing of BMD is useful for screening and monitoring therapy in people at high risk for osteoporosis (e.g., postmenopausal women, patients with hyperparathyroidism or other bone disorders, or those being treated with medications associated with bone loss [e.g., glucocorticoids]), if evidence of bone loss would result in modification of therapy. A list of indications for BMD testing is shown in Table 10.

Testing of BMD is the gold standard in diagnosing osteoporosis; however, not everyone has access to BMD

Table 9
Factors that Increase Risk of Falling and Fracture

Neurologic disorders
Parkinson disease
Seizure disorder
Peripheral neuropathy
Prior stroke
Dementia
Impaired gait or balance (or both)
Autonomic dysfunction with orthostatic hypotension
Impaired vision
Impaired hearing
Frailty and deconditioning
Proximal myopathy
Sarcopenia
Medications
Sedatives and hypnotics
Antihypertensive agents
Narcotic analgesics
Environmental factors
Poor lighting
Stairs
Slippery floors
Wet, icy, or uneven pavement
Uneven roadways
Electric or telephone cords
Walking large dogs, being tripped up by small dogs
Throw rugs
Positioning in a wet or dry bathtub

testing. Therefore, the decision to measure BMD should be based on an individual's clinical fracture risk profile and skeletal health assessment (46). AACE recommends BMD testing for women aged 65 years and older and younger postmenopausal women at increased risk for bone loss and fracture, based on analysis of fracture risk. Measurement of BMD is not recommended in children, adolescents, or healthy young men or premenopausal women, unless there is a significant fracture history or there are specific risk factors for bone loss, such as long-term glucocorticoid therapy.

In addition to its role in diagnosis, BMD measurement is useful in monitoring response to therapy, as shown in Table 11.

Q1.5.3. BMD Measurement Sites and Techniques

DXA of the lumbar spine and proximal femur (hip) provides accurate and reproducible BMD measurements at important sites of osteoporosis-associated fracture. Optimally, both hips should be initially measured to prevent misclassification and to have a baseline for both hips in case a fracture or replacement occurs in one hip. These axial sites are preferred over peripheral sites for both baseline and serial measurements. The most reliable comparative results are obtained when the same instrument and, ideally, the same technologist are used for serial measurements at a high-quality DXA facility (47).

Diagnostic criteria, therapeutic studies, and cost-effectiveness data have been based primarily on DXA measurements of the total hip, femoral neck, and/or lumbar spine (L1 to L4) and are the preferred measurement sites (36,48,49). The 1/3 radius can also be used as a diagnostic site, particularly when other preferred sites are not available (50). Use of other subregions within the proximal femur (i.e., Ward's triangle or trochanter) or of an individual vertebra has not been validated and is not recommended. For BMD measurement, several other techniques are available, including quantitative computed tomography for measurement of both central and peripheral sites, quantitative ultrasonometry, radiographic absorptiometry, and single-energy X-ray absorptiometry. Peripheral bone density measurements can identify patients at increased risk for fracture; however, the diagnostic DXA criteria established by the WHO and recommended by AACE apply only to the axial measurements (i.e., lumbar spine, femoral neck, and total hip) and distal 1/3 of the radius. Thus, other technologies should not be used to diagnose osteoporosis but may be used to assess fracture risk.

Q1.5.4. Role of BMD in Diagnosis and Clinical Decision-Making

For women without prior fragility fractures, BMD is the single best predictor of osteoporotic fracture risk (for every 1–standard deviation [SD] decrease in age-adjusted BMD, the relative risk [RR] of fracture increases 1.6- to 2.6-fold) (51). The relationship between bone density and fracture risk, however, is a continuum, without a clear "fracture threshold." The WHO has defined T-score criteria

Table 10
Indications for Bone Mineral Density Testing

All women 65 years of age or older
All postmenopausal women
With a history of fracture(s) without major trauma
With osteopenia identified radiographically
Starting or taking long-term systemic glucocorticoid therapy (≥3 months)
Other perimenopausal or postmenopausal women with risk factors for osteoporosis if willing to consider pharmacologic interventions
Low body weight (<127 lb or body mass index <20 kg/m^2)
Long-term systemic glucocorticoid therapy (≥3 months)
Family history of osteoporotic fracture
Early menopause
Current smoking
Excessive consumption of alcohol
Secondary osteoporosis

Table 11
Bone Mineral Density Measurements: Potential Uses in Postmenopausal Women

Screening for osteoporosis
Establishing the severity of osteoporosis or bone loss in patients with suspected osteoporosis (for example, patients with fractures or radiographic evidence of osteopenia)
Determining fracture risk—especially when combined with other risk factors for fractures
Identifying candidates for pharmacologic intervention
Assessing changes in bone density over time in treated and untreated patients
Enhancing acceptance of, and perhaps adherence with, treatment
Assessing skeletal consequences of diseases, conditions, or medications known to cause bone loss

for the classification of osteoporosis (T-score at or below –2.5) and low BMD (i.e., low bone mass or "osteopenia"; T-score between –1.0 and –2.5) (Table 5) based on DXA measurements. Evidence supporting the association of BMD by DXA and fracture risk is well established, and a relationship between BMD change with therapy and reduction of fracture risk has also been shown (52). These criteria are useful for classification and risk stratification in individual patients, epidemiologic studies, and therapeutic trial design, but they are not intended as treatment thresholds. Although there is good evidence that the risk for fractures is sufficiently high in most postmenopausal women with osteoporosis to merit pharmacologic intervention, cost-effective management of women with low bone mass (osteopenia) is less clear. While their overall rate of fractures is lower than that of patients with osteoporosis, more than 80% of fragility fractures occur in women with BMD in the "osteopenia" range. It is now recommended that treatment decisions include consideration of fracture probability. Thus, BMD results should be combined with other clinical risk factors for fractures for accurate assessment of fracture risk and to guide treatment decisions. FRAX® integrates the contribution of BMD and other clinical risk factors and calculates an individual's probability of fracture over 10 years. Other fracture tools of varying complexity have been proposed, but FRAX® is the most widely used.

Role of Trabecular Bone Score in Adjusting FRAX® Risk

Trabecular bone score (TBS) is a textural index that measures pixel gray-level variations in the lumbar-spine DXA image, providing an indirect index of trabecular microarchitecture. Variability in the 2-dimensional projected DXA image is presumed to correlate with absorption parameters in 3-dimensional bone according to a mathematical relationship (53). TBS is obtained using commercially available U.S. Food and Drug Administration (FDA)-approved software that is installed in compatible DXA systems. High TBS values (note that TBS is unitless) correlate with homogeneous (i.e., normal) bone texture, while low values are indicative of more variable (i.e., weaker) bone texture. Numerous studies have shown that TBS predicts fracture risk independent of BMD (54) and that it enhances fracture risk prediction capabilities of FRAX® (55,56). Low TBS values increase FRAX® estimated risk, while high TBS values reduce it. TBS adjustment of FRAX® has been validated in 14 prospective international cohorts (56).

Age substantially alters the impact of TBS on FRAX® estimated risk, with the effect of TBS on fracture risk being much greater for younger women. Why TBS has less of an impact on FRAX® risk in older women is unclear, but a logical hypothesis is that falls become more common with advancing age and play a greater role in fracture risk. It is likely that bone strength is more important for fracture

risk in younger women while falls play a greater role with advancing age. Adjustment of TBS in FRAX® may have greatest clinical utility in patients whose fracture risk is close to the therapeutic intervention threshold. In patients with low bone mass (osteopenia), TBS-adjusted FRAX®, which can be included with the DXA printout, can sometimes be the deciding factor in making treatment decisions. TBS may be especially useful in clinical situations, such as type 2 diabetes and primary hyperparathyroidism, where FRAX® without TBS may underestimate fracture risk.

Q1.5.5. Inaccuracies in Bone Density Reports

Inaccuracies in BMD readings can result from a variety of factors. These include the following: inadequate training in DXA testing and interpretation; positioning errors (of the patient as well as of the region of interest), inadequate knowledge of how to eliminate fractured vertebrae or vertebrae with more severe osteoarthritis and extra-articular calcification from the field, nonadherence to the guideline published by the International Society for Clinical Densitometry (ISCD) recommending measurement of at least two consecutive vertebrae, inclusion of artifacts in the analysis, errors in use of ethnic- or gender-specific databases, faulty data input to the FRAX® calculator, failure to exclude extraskeletal calcifications, inaccurate reporting of results (e.g., "patient has lost 30% of BMD" or "bones are equivalent to an 80-year-old"), and failure to compare results or comparing results from different machines or following major software changes without appropriate adjustment or recalibration. Clinicians need to be aware of these potential pitfalls in the interpretation of DXA reports, which are described in the "Consensus Statement by the AACE/ACE on the Quality of DXA Scans and Reports" (57). Best Practices for high-quality technical performance and interpretation of DXA scans have been published by the ISCD (58).

Q2. When Osteoporosis Is Diagnosed, What Is an Appropriate Evaluation?

Q2.1. What Laboratory Testing Is Recommended to Assess for Causes of Secondary Osteoporosis?

An appropriate medical evaluation is indicated in all women with postmenopausal osteoporosis and at high fracture risk to identify coexisting medical conditions that cause or contribute to bone loss. Some of these disorders may be asymptomatic and require laboratory testing for detection. Some causes of secondary osteoporosis in adults are summarized in Table 12

Because of the high prevalence of causes of secondary osteoporosis even in apparently healthy, postmenopausal women, laboratory testing should be considered for all women with osteoporosis (59). This is reasonable, as a few simple laboratory tests provided useful information in 40 to 85% of women who did not have clinical evidence of secondary osteoporosis in several studies (60-64). If medical history, physical findings, or laboratory test results suggest causes of secondary osteoporosis, additional laboratory evaluation is warranted and may include, but is not limited to, the tests listed in Table 13.

Laboratory evaluation should include a complete blood count, comprehensive metabolic panel, 25-hydroxyvitamin D (25[OH]D), intact parathyroid hormone (PTH), phosphate, and a 24-hour urine collection for calcium, sodium, and creatinine. The 24-hour urine calcium collection must occur after the patient is replete of vitamin D and has been on a reasonable calcium intake (1,000 to 1,200 mg/d) for at least 2 weeks. If the patient is receiving thyroid hormone or there is a suspicion for hyperthyroidism, thyroid-stimulating hormone should also be obtained. Celiac antibodies or serum/urine protein electrophoresis could also be obtained.

Q2.2. Vertebral Fracture Detection

Vertebral fracture is the most common osteoporotic fracture and indicates a high risk for future fractures, even when the T-score does not meet the threshold for osteoporosis. Prevalent fractures, therefore, may change an individual's diagnostic classification, estimated risk of future fractures, and clinical management. Most vertebral fractures, however, remain undetected unless specifically sought by imaging techniques (spine X-ray or vertebral fracture assessment [VFA]) (65). VFA, a technique to assess vertebral fractures with DXA technology, can often be done at the same time with DXA (66-68). Both historical and prospective height loss have been associated with a new vertebral fracture (69,70). Lateral spine imaging with standard radiography or VFA with DXA is indicated when T-score is less than −1.0 and one or more of the following is present:

- Women aged ≥70 years or men aged ≥80 years
- Historical height loss >4 cm (>1.5 inches)
- Self-reported but undocumented prior vertebral fracture
- Glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months (https://iscd.app.box.com/OP-ISCD-2015-Adult)

In patients with unexplained height loss or back pain, thoracic and lumbar spine radiography or VFA by DXA is indicated if prevalent vertebral fractures would alter clinical management. Although these thresholds for height loss have >90% specificity, the sensitivity for detecting prevalent vertebral fractures is low. Other indications for vertebral radiographs include kyphosis and systemic glucocorticoid therapy, both of which are associated with increased risk of vertebral fracture. The sensitivity and reliability of standard radiography to assess BMD are poor, and in the absence of vertebral fractures, this technique should not be used to diagnose osteoporosis. If fracture is diagnosed by VFA, then additional imaging should be done to confirm the impression of fracture.

Table 12
Causes of Secondary Osteoporosis in Adults[a]

Endocrine or metabolic causes	Nutritional/ GI conditions	Drugs	Disorders of collagen metabolism	Other
Acromegaly Diabetes mellitus Type 1 Type 2 Growth hormone deficiency Hypercortisolism Hyperparathyroidism Hyperthyroidism Hypogonadism Hypophosphatasia Porphyria Pregnancy	Alcoholism Anorexia nervosa Calcium deficiency Chronic liver disease Malabsorption syndromes/ malnutrition (including celiac disease, cystic fibrosis, Crohn disease, and gastric resection or bypass) Total parenteral nutrition Vitamin D deficiency	Anti-epileptic drugs[b] Aromatase inhibitors Chemotherapy/ immunosuppressants Medroxyprogesterone acetate Glucocorticoids Gonadotropin-releasing hormone agents Heparin Lithium Proton pump inhibitors Selective serotonin- reuptake inhibitors SGLT2-inhibitors Thiazolidinediones Thyroid hormone (in supraphysiologic doses)	Ehlers-Danlos syndrome Homocystinuria due to cystathionine deficiency Marfan syndrome Osteogenesis imperfecta	AIDS/HIV Ankylosing spondylitis Chronic obstructive pulmonary disease Gaucher disease Hemophilia Hypercalciuria Immobilization Major depression Myeloma and some cancers Organ transplantation Renal insufficiency/ failure Renal tubular acidosis Rheumatoid arthritis Systemic mastocytosis Thalassemia

AIDS = acquired immunodeficiency syndrome; GI = gastrointestinal; HIV = human immunodeficiency virus; SGLT2 = sodium-glucose cotransporter 2.
[a]Not meant to be a complete list.
[b]Phenobarbital, phenytoin, primidone, valproate, and carbamazepine have been associated with low bone mass.

Table 13
Laboratory Tests to Consider in Detecting Secondary Osteoporosis

Complete blood cell count
Serum chemistry, including calcium, phosphate, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes
24-hour collection for calcium, sodium, and creatinine excretion (to identify calcium malabsorption or hypercalciuria)
Serum 25-hydroxyvitamin D

Additional tests if clinically indicated might include (but not limited to):
- Serum intact parathyroid hormone concentration for possible primary or secondary hyperparathyroidism
- Serum thyrotropin
- Tissue transglutaminase antibodies for suspected celiac disease
- Serum protein electrophoresis and free kappa and lambda light chains for suspected myeloma
- Urinary free cortisol or other tests for suspected adrenal hypersecretion
- Serum tryptase, urine N-methylhistidine, or other tests for mastocytosis
- Bone marrow aspiration and biopsy to look for marrow-based diseases
- Undecalcified iliac crest bone biopsy with double tetracycline labeling

  Recommended for patients with bone disease and renal failure to establish the correct diagnosis and direct management
  May be helpful in the assessment of patients with the following:
  Suspected osteomalacia or mastocytosis when laboratory test results are inconclusive
  Fracture without major trauma despite normal or high bone density
  Vitamin D–resistant osteomalacia and similar disorders to assess response to treatment

Genetic testing for unusual features that suggest rare metabolic bone diseases

Q2.3. How Are Bone Turnover Markers Used in the Initial Evaluation and Follow-up of Postmenopausal Osteoporosis?

Bone turnover markers (BTMs) provide a dynamic assessment of skeletal activity and are useful modalities for skeletal assessment. Although they cannot be used to diagnose osteoporosis, elevated levels can predict more rapid rates of bone loss (71-73) and are associated with increased fracture risk independent of BMD in some studies (74-76). One recent study without data for BMD failed to verify prediction of hip fractures with BTMs (77). Automated immunoassays have improved reproducibility of BTMs. In addition, these markers respond quickly to therapeutic intervention; changes in markers have been associated with bone response to therapy and reduction of fracture risk (78-83). In 2010, the International Osteoporosis Foundation proposed that serum C-terminal telopeptide type-1 collagen (CTX) and serum carboxy-terminal propeptide of type-I collagen (PINP) be used as reference analytes for BTMs in clinical and observational studies (76). The National Bone Health Alliance, working in association with the American Association for Clinical Chemistry, established that the preferred resorption marker is CTX and the preferred formation marker is PINP and defined the steps necessary to enhance the science and clinical utility of BTMs (84). Serum CTX must be drawn in the fasting state and ideally at the same time in the morning every time. Recommendations to reduce pre-analytical variability of BTMs have been published (85). Problems with the use of BTMs include their high cost (and variable insurance coverage), lack of appropriate reference ranges reported by commercial labs, and the influence of renal insufficiency on all markers except bone-specific alkaline phosphatase. Some experts routinely utilize BTMs in clinical practice, while others do not.

The most useful BTMs include the bone-formation osteoblast-derived products and the bone-resorption products of collagen degradation. Clinical trials have shown that early changes in BTMs are associated with long-term BMD changes in women taking antiresorptive (86) or anabolic (87) drugs. Thus, clinicians might use the results of BTMs obtained after 3 to 6 months of oral bisphosphonate therapy to counsel patients that the therapy is effective and to maintain their compliance, rather than waiting 2 years for a DXA result. Significant reductions in BTMs for up to several months have also been shown to explain more of the fracture reductions associated with antiresorptive therapy than do increases in BMD (82,88,89). The preferred BTMs for monitoring are PINP for bone formation and CTX for bone resorption, except in the setting of renal insufficiency or if there are insurance issues, then bone-specific alkaline phosphatase may be used. Use of a bone resorption marker, such as a fasting-morning CTX, may be helpful in determining the reason for bone loss despite antiresorptive therapy. For example, an elevated CTX level is associated with high bone turnover and could represent malabsorption of medication or poor compliance and the need for further evaluation for causes of secondary osteoporosis and/or the need to change to parenteral osteoporosis therapy. It must be noted, however, that a recent fracture will transiently raise BTMs, and thus, such elevations after an acute fracture should not be interpreted as treatment failure. Conversely, loss of BMD in the face of well-suppressed BTMs (greater than the least significant change [LSC] of the BTMs) and stable body weight might raise concern for factors that may confound DXA interpretation and prompt further scrutiny of DXA images (see section **Q6**). An additional potential use of BTMs is in the setting of a bisphosphonate drug holiday, where highly suppressed bone turnover (as compared with a baseline value) indicates continued antiresorptive effect and, theoretically, continued antifracture benefit. However, presently, there are no peer-reviewed trials supporting or refuting this approach. In summary, BTMs are useful in certain situations, such as assessment of fracture risk and to provide early feedback to patients that their drug is or is not working, which leads to discussions pertaining to medication compliance, drug absorption, and/or therapeutic efficacy. BTMs do not need to be assessed in all osteoporosis patients.

Q3. What Are the Fundamental Measures for Bone Health?

Q3.1. How Can Bone Loss and Fractures Be Prevented?

Several lifestyle modifications may improve musculoskeletal integrity and balance, preserve bone strength, and prevent future fractures. These include an adequate intake of calcium and vitamin D; lifelong participation in regular, weight-bearing, resistance, and balance-improving exercises to minimize falls; avoiding use of tobacco and excessive use of alcohol; and elimination of potential risk factors for falling. This "bone healthy" lifestyle is important for everyone, not only patients with osteopenia and osteoporosis.

Patients with osteoporosis may benefit from physical therapy or other activities and other nonpharmacologic measures to improve strength and reduce the risk of falls and fractures. Goals include the following:

- Optimize skeletal development and maximize peak bone mass at skeletal maturity
- Maintain skeletal mass and prevent age-related bone loss
- Preserve the structural integrity of the skeleton
- Prevent falls and fractures

Q3.2. Vitamin D

Vitamin D plays a major role in calcium absorption and bone health and may be important in muscle performance, balance, and risk of falling. Moreover, optimal

vitamin D status may increase response to bisphosphonate therapy (90), increase BMD, and prevent fractures (91). Many scientific organizations recommend intake of at least 1,000 IU of vitamin D per day for adults aged 50 years and older. The Institute of Medicine (IOM) (now the National Academy of Medicine [NAM]) suggest 4,000 IU of vitamin D per day as the safe upper limit in the general population (92,93).

Vitamin D deficiency is common in patients with osteoporosis (94) and hip fracture (95). It is advisable to measure serum 25(OH)D levels in patients at risk of deficiency, especially in those with osteoporosis. The effectiveness of anti-osteoporosis treatment may be hindered by vitamin D deficiency. The dose of vitamin D needed to correct vitamin D deficiency varies among individuals (96,97), with recent data suggesting daily vitamin D doses greater than 1,000 IU or even 4,000 IU may be needed (98,99). In addition, patient factors, including obesity and history of malabsorption, may influence vitamin D status and increase the vitamin D dose necessary to achieve adequate levels (100-105).

An individual's vitamin D status is assessed by measurement of serum 25(OH)D—not by measurement of 1,25-dihydroxyvitamin D. The optimal 25(OH)D level is controversial; AACE and the Endocrine Society recommend serum 25(OH)D ≥30 ng/mL to define vitamin D sufficiency based on evidence that secondary hyperparathyroidism is increasingly common as 25(OH)D levels fall below 30 ng/mL (93,106-108). Other groups recommend that 25(OH)D values ≥20 ng/mL be considered adequate (109,110). Controversy about the optimal upper limit for serum 25(OH)D remains, and evidence of the safety of higher levels in different populations is not conclusive. A reasonable upper limit, based on levels in sun-exposed healthy young adults, is 50 ng/mL until further evidence is available. Evidence from one randomized trial suggested no benefit to exceeding serum levels of 30 ng/mL (111). However, in patients with stage 3 or 4 chronic kidney disease, treatment with the calcifediol form of vitamin D (25[OH]D) to levels of 50 ng/mL has been shown to improve secondary hyperparathyroidism (112).

A meta-analysis of randomized studies in postmenopausal women found a significant reduction in hip and nonvertebral fractures with vitamin D supplementation at doses of 700 to 800 IU/day or more (113). The Women's Health Initiative (WHI) study showed a small but significant increase in hip BMD (1%) in the group that received 1,000 mg of calcium and 400 IU of vitamin D per day (114). In addition to the skeletal effects of vitamin D, some studies have also shown improvement in muscle strength, balance and fall risk (113,115,116), and survival (117). However, a randomized trial in frail elderly patients with baseline mean 25(OH)D levels of 18.4 to 20.9 ng/mL comparing three different *monthly* doses of vitamin D (a low-dose control group receiving 24,000 IU of vitamin D_3, a group receiving 60,000 IU of vitamin D_3, and a group receiving 24,000 IU of vitamin D_3 plus 300 μg of calcifediol) showed an increase in falls with the two more-aggressive doses of vitamin D, demonstrating that caution should be used with bolus dosing in this patient population until the optimal dose and schedule are known (118). Single, larger annual bolus doses of vitamin D are also not recommended based on a placebo-controlled randomized trial in women with risk factors for hip fracture (median age of 76 years and baseline median 25[OH]D level of 21 ng/mL), where 500,000 IU of vitamin D_3 was given annually (119). Daily dosing has been hypothesized to more closely replicate serum vitamin D_3 (cholecalciferol) levels achieved by cutaneous production (120). Additionally, the high vitamin D_3 (cholecalciferol) concentrations obtained with bolus dosing may induce 24-hydroxylation, resulting in inactive vitamin D (121)—a concept supported by work finding that a single vitamin D_3 dose of 150,000 IU led to greater 24,25-dihydroxyvitamin D_3 than daily dosing of 5,000 IU for 1 month (122). The possibility that daily and intermittent bolus dosing might have different effects on vitamin D metabolism raises the question whether these supplementation approaches should be considered equivalent in randomized controlled trials.

Adults who are vitamin D insufficient or deficient (serum 25[OH]D 20 to 29 or <20 ng/mL, respectively) may be treated with 5,000 IU vitamin D_3 daily for 8 to 12 weeks to achieve a 25(OH)D blood level >30 ng/mL (93,96). Vitamin D_3 (cholecalciferol) rather than vitamin D_2 should be used for replacement (123). Not every 25(OH)D assay measures 25(OH)D_2. Moreover, due to unequal cross-reactivity for 25(OH)D_2, many current assays are inaccurate if there is a significant amount of 25(OH)D_2 (124,125). As such, when substantial amounts of 25(OH)D_2 are present, a spuriously low total 25(OH)D level will be reported. It should be noted that vegetarians may refuse to take vitamin D_3 given its animal source. In such individuals, and in those receiving high-dose ergocalciferol, use of an appropriate assay, generally one performed using liquid chromatography–tandem mass spectrometry that accurately quantifies both 25(OH)D_2 and 25(OH)D_3 with the sum of these defining the individual's vitamin D status, is essential.

The above-noted repletion regimen should be followed by maintenance therapy of 1,000 to 2,000 IU of vitamin D_3 daily (or an appropriate dose to maintain an adequate target 25[OH]D blood level). A higher dose may be required in patients with obesity or malabsorption and those on medications affecting metabolism of vitamin D, as well as other individuals. Only in uncommon clinical situations is there a need to prescribe high-dose (e.g., 50,000 IU) treatment with vitamin D.

In patients with active granulomatous disease, repletion of vitamin D must be undertaken with caution due to risk for hypercalciuria and/or hypercalcemia (96).

Q3.3. Calcium

Adequate calcium intake is a fundamental aspect of any osteoporosis prevention or treatment program and part of a lifestyle for healthy bones at any age. The recommended daily calcium intake for various populations is outlined in Table 14 (92). For adults aged 50 years and older, the recommended calcium intake (including diet, plus calcium supplements if necessary when dietary intake is insufficient) is 1,200 mg/day. Calcium supplementation has been shown to increase BMD slightly. A recent meta-analysis from the NOF showed a 15% reduced risk of total fractures (summary relative risk estimate [SRRE], 0.85; 95% confidence interval [CI], 0.73 to 0.98) and a 30% reduced risk of hip fractures (SRRE, 0.70; 95% CI, 0.56 to 0.87) (126). Other studies have shown mixed results as far as calcium and fracture efficacy. This is likely due, in part, to problems with study design and patient compliance (114,127-129).

The optimal intake and utility of calcium supplements are controversial. In a Swedish prospective longitudinal cohort, calcium intake (both dietary and supplemental) of more than 1,500 mg/day was associated with a hazard ratio of 1.40 (95% CI, 1.17 to 1.67) for all-cause mortality (130). Three prospective cohort studies and a meta-analysis, all from one group, suggested increased risk of cardiovascular disease and stroke among calcium supplement users (131-134). The meta-analysis involved trials that did not collect cardiovascular outcomes as primary or secondary study endpoints, and thus, these events were not adjudicated. In contrast, low dietary calcium intake (<700 mg/day compared with 1,400 mg/day) has been associated with increased cardiovascular risks (135). Other studies found no effect of calcium supplements on cardiovascular risk (136,137). A study of more than 9,000 participants followed for 10 years found that postmenopausal women taking 500 to 1,000 mg of supplemental calcium had a significant survival advantage over women not taking supplements (138). Moreover, there was no increase or decrease in mortality in women taking more than 1,000 mg of supplemental calcium. A large study raised concerns about the risk of nephrolithiasis from calcium supplementation (114); however, hypercalciuria may worsen with calcium supplementation, and participants in the study were not evaluated for renal calcium wasting. Also, the absolute risk of kidney stones was small (2.5% in the calcium-supplemented group versus 2.1% in the control group). In addition, in these subjects, the mean total calcium intake from diet and supplements was much higher (~2,100 mg) than currently recommended. Patients with a history of nephrolithiasis should be evaluated for the etiology of renal stone formation or hypercalciuria prior to deciding about calcium supplementation. Patients who are found to have idiopathic hypercalciuria may be treated with thiazide diuretics. Patients with kidney stones that have hyperoxaluria should be treated with calcium citrate. In summary, studies to date suggest that dietary calcium may be preferred over supplemental calcium and that total calcium intake should not exceed 1,500 mg/day (139). Increasing calcium intake beyond the recommended levels has not been shown to be useful and may be harmful (140-144). AACE, NOF, the IOM (now NAM), and the Endocrine Society recommend that women aged 51 years or older consume 1,200 mg per day of calcium from all sources (93,108,109,139).

A dietary history to assess calcium intake prior to recommending calcium supplements is important. The average daily calcium intake among American adults is about half of what is recommended, with a median of approximately 600 mg/day (145). Patients with low dietary intake may increase their daily intake by consuming extra calcium-rich foods, including dairy products, nuts, and seeds. For individuals who are unable to increase dietary calcium due to lactose intolerance or lack of access to calcium-rich foods, use of calcium supplements is an option.

Numerous calcium supplements are available. Calcium carbonate is generally the least expensive and requires the smallest number of tablets, due to a generous calcium content (40%). Calcium carbonate, however, may cause gastrointestinal (GI) complaints (e.g., constipation and bloating). In addition, it requires gastric acid for absorption and is best absorbed when taken with meals. Calcium citrate is often more expensive than calcium carbonate and requires more tablets to achieve the desired dose due to a lower calcium content (21%), but its absorption is not dependent on gastric acid, and it may be less likely to cause GI complaints. In addition to tablets, which can be large and difficult for some patients to swallow, calcium supplements are available as soft chews and gummy preparations. For optimal absorption, calcium supplementation should not exceed 500 to 600 mg per dose, irrespective of the preparation. For patients requiring more than 600 mg calcium supplement daily, the dose should be divided.

It is advisable to assess adequacy of calcium and vitamin D through laboratory evaluation prior to initiation of pharmacologic therapy for osteoporosis. It should be noted that a 24-hour urine calcium collection is the best commercially available method of evaluating adequacy of calcium intake and absorption. Urinary creatinine excretion may be assessed in the same 24-hour urine collection as a gauge of the completeness of the collection. Urinary sodium excretion may be measured as well if hypercalciuria is suspected. High sodium intake may increase urine calcium.

Q3.3.1. Other Supplements and Nutrition Considerations

Magnesium: Patients frequently question whether supplementation of magnesium is needed, but no randomized controlled study has evaluated the effect of magnesium intake on fracture risk or BMD. Most people have adequate dietary intake of magnesium. Individuals who are at risk for hypomagnesemia (e.g., those with GI malabsorption, chronic liver disease [including alcoholics], or renal tubu-

Table 14
Recommended Dietary Allowance for Calcium

Age	Sex	Recommended dietary allowance (mg/day)
0-6 months	M + F	200
6-12 months	M + F	260
1-3 years	M + F	700
4-8 years	M + F	1,000
9-18 years	M + F	1,300
19-50 years	M + F	1,000
51-70 years	M	1,000
51-70 years	F	1,200
71+ years	M + F	1,200

Reproduced with permission from Ross AC, et al. *J Clin Endocrinol Metab*. 2011;96:53-58 (109).

lar loss or those using proton-pump inhibitors or diuretics long term), however, may benefit from supplementation of magnesium. Magnesium may also help counteract constipation associated with calcium supplementation.

Although magnesium is required for adequate calcium absorption, if body stores are adequate, magnesium supplementation does not increase BMD (146). In fact, there is no evidence that adding magnesium to calcium tablets increases the absorption of calcium. One study showed that adding 789 to 826 mg of magnesium per day did not increase rates of calcium absorption (147).

Vitamins A and K and Phytoestrogens: Excessive chronic intake of vitamin A (i.e., more than 10,000 IU daily) should be avoided, as this has been shown to have detrimental effects on bone (148). Some data suggest that vitamin K (1 mg/day) may reduce bone turnover and bone loss in postmenopausal women (149). However, not all studies replicate this finding, and further studies are needed before vitamin K can be considered a part of the standard recommendation for osteoporosis prevention. "Natural" estrogen-receptor agonists, isoflavones, are promoted to prevent bone loss, but there are no conclusive data to support the use of these agents for increasing bone density or decreasing fracture risk (150-152).

Caffeine: Patients should be advised to limit caffeine intake to less than 1 to 2 servings (8 to 12 ounces/serving) of caffeinated drinks per day. Several observational studies have shown an association between consumption of caffeinated beverages and fractures (153-155). Caffeine intake leads to a slight decrease in intestinal calcium absorption and increase in urinary calcium excretion.

Protein: Adequate protein intake (U.S. recommended daily allowance, 0.8 g/kg) helps minimize bone loss among patients who have suffered hip fractures (156,157). In one study, patients who received supplemental protein after hip fracture had shorter hospital stays and better functional recovery (157).

Q3.4. Alcohol

Excessive intake of alcohol is associated with increased fracture risk (158). The mechanisms of increased fractures from alcohol are multifactorial and include a negative effect on bone formation, a predisposition to falls, calcium deficiency, and chronic liver disease. Chronic liver disease, in turn, predisposes to vitamin D deficiency. Postmenopausal women at risk for osteoporosis should be advised against consuming more than 2 drinks daily, with 1 drink equivalent to 120 mL of wine, 30 mL of liquor, or 260 mL of beer (158) (http://www.shef.ac.uk/FRAX/).

Q3.5. Smoking

Cigarette smoking has been validated by multiple studies to increase osteoporotic fracture risk and thus should be avoided (159,160). The exact mechanism is unclear but may relate to increased metabolism of endogenous estrogen or direct effects of cadmium on bone metabolism. No prospective studies have been done to determine whether smoking cessation reduces fracture risk, but a meta-analysis showed a higher risk of fractures in current smokers compared with previous smokers (161). All smokers should be counseled on smoking cessation. The use of tobacco products is detrimental to the skeleton, as well as to overall health.

Q3.6. Exercise

Regular weight-bearing exercise (e.g., walking 30 to 40 minutes per session, plus back and posture exercises for a few minutes, 3 to 4 days per week) should be advocated throughout life. Studies on early postmenopausal women have shown that strength training leads to small yet significant changes in BMD; a meta-analysis of 16 trials including 699 subjects showed a 2% improvement in lumbar spine BMD in the group that exercised compared with the group that did not (162). Among the elderly, these exercises help slow bone loss attributable to disuse, improve balance and muscle strength, and, ultimately, help reduce the risk of falls (163-167).

BMD effects of exercise are modest, but a meta-analysis concluded that the exercise-induced improvement in lumbar spine and femoral neck BMD would reduce osteoporosis fracture risk by approximately 10% (168). The reduction in fall risk is likely more important than the effects of exercise on BMD, as approximately 95% of hip fractures are due to a fall (169). Both home and group exercise programs reduce falls (170); exercises that challenge balance and improve trunk muscle strength produce a greater reduction in risk of falls (167,171).

Individuals with severe osteoporosis should use caution when engaging in activities that involve forward spine flexion and rotation, lifting heavy weights, or even

side bending of the trunk, because these maneuvers exert compressive forces on the spine that may lead to fracture.

Q3.7. Fall Prevention

Falls are the precipitating cause of most fractures, and an effective osteoporosis treatment regimen must include a program for fall prevention. All patients should be counseled on fall prevention. Particularly predisposed are individuals who are older or frail, have a stroke history, or are on medications that decrease mental alertness. Although several interventions have been shown to reduce the risk of falling, none have been shown to reduce the risk of fractures, though it seems logical that they would.

Approximately one-third of people aged 65 years or older and roughly half of those aged 80 years or older fall each year (172,173). Twenty to 30% of persons who fall suffer moderate-to-severe injury (174,175). A higher percentage of women with osteoporosis have a history of falling within the prior year than women without osteoporosis (176). This association has been ascribed to shared risk factors, such as age, muscle weakness, and sedentary lifestyle (177). Indeed, a French guideline supported BMD measurement in individuals at high risk of falling (177,178).

Table 15 lists measures that can be taken to avoid falls at home. Individuals who are older or frail, have recently been hospitalized, have suffered a prior stroke, are receiving medications that decrease mental alertness, or have cognitive impairment are particularly vulnerable (179). In addition to minimizing the use of medications that impair balance, appropriate correction of visual impairment may improve mobility and reduce risk of falls. Several interventions reduce risk of falls (166,170,180); a meta-analysis found decreased fracture risk with exercise, but fracture numbers were small and the possibility of publication bias was raised (181). The relationship of vitamin D with falls is unclear; some, but not all, meta-analyses found vitamin D supplementation reduced fall risk (182,183), and a randomized controlled trial failed to find a decrease in falls with vitamin D (184). Annual high-dose vitamin D, however, was associated with an increased risk of falls (119). Rigorous prospective studies are needed to clarify the role of vitamin D deficiency in risk of falls. In the interim, assurance of a normal 25(OH)D status in patients with osteoporosis is appropriate.

Q3.8. Exercises and Proper Body Mechanics

Weight-bearing and resistance exercise can improve agility, strength, posture, and balance, which may reduce the risk of falls. In addition, exercise may modestly increase bone density. AACE strongly endorses lifelong physical activity for cardiovascular health, osteoporosis prevention, and overall health. Weight-bearing exercise includes walking, jogging, Tai Chi, stair climbing, and dancing, among other activities. Muscle-strengthening exercise includes weight training and other resistive exercises. Before initiating an exercise program in an individual with osteoporosis, a clinician's evaluation is recommended. Physical therapy plays an important role in the effort to mitigate sarcopenia and reduce risk of falls.

Q3.9. Physical Therapy

Elderly patients with significant kyphosis, back discomfort, and gait instability may benefit from referral for physical therapy. A treatment plan that focuses on weight-bearing exercises, back strengthening, and balance training with selective use of orthotics may help reduce discomfort, prevent falls and fractures, and improve quality of life (185). Table 16 summarizes the recommendations for lifestyle modifications.

Q4. Who Needs Pharmacologic Therapy?

AACE strongly recommends pharmacologic therapy for the following patients:

a. Those with a T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or 1/3 radius and a history of fragility fracture of the hip or spine (186-195).
b. Those with a T-score of −2.5 or lower in the spine, femoral neck, total hip, or 1/3 radius (189,193,194,196-205).
c. Those with a T-score between −1.0 and −2.5 in the spine, femoral neck, total hip, or 1/3 radius, if the FRAX® (or if available, TBS-adjusted FRAX®) 10-year probability for major osteoporotic fracture is ≥20% or the 10-year probability of hip fracture is ≥3% (in the U.S.) or above the country-specific threshold in other countries or regions (206-208).

Table 15
Measures for Prevention of Falls

Anchor rugs
Minimize clutter
Remove loose wires
Use nonskid mats
Install handrails in bathrooms, halls, and long stairways
Light hallways, stairwells, and entrances
Encourage patient to wear sturdy, low-heeled shoes

Table 16
Recommendations Regarding Lifestyle Issues

Ensure adequate intake of calcium
Ensure adequacy of vitamin D intake
Consume a balanced diet
Regularly perform weight-bearing and balance exercises
Avoid use of tobacco
Limit alcohol consumption
Take measures to avoid falls

Q4.1. Decision-Making on Pharmacologic Therapy

Therapeutic intervention thresholds vary from country to country based on the cost of treatments, the approach taken to setting the intervention threshold, and available therapeutic modalities and resources (206,209). To be most effective, clinical experience of the treating physician is incorporated with best practices in a given country and locally available resources. Potential risks and benefits of available osteoporosis interventions should be reviewed and incorporated into local guidelines, while allowing physicians to individualize treatment decisions for patient preferences and circumstances.

Q4.2. Stratification of Fracture-Risk Categories

Pharmacologic therapy to reduce fracture risk is indicated when fracture risk is high based on T-scores between −1.0 and −2.5 and a history of fragility fracture of the hip or spine, and T-scores between −1.0 and −2.5 and a FRAX® 10-year probability of major osteoporotic fracture ≥20% or 10-year probability of hip fracture ≥3% in the U.S. or above country-specific threshold in other countries or regions. It is important to note that these criteria were based on a pharmacoeconomic analysis from a decade ago. Were the same quality-adjusted life year criterion applied today, the treatment thresholds would be notably lower.

When starting treatment, it is appropriate to stratify patients by level of fracture risk, since this may influence selection of initial treatment. Most patients are started on treatment because of high fracture risk. Some who are at very high fracture risk may require more aggressive treatment to achieve an acceptable level of fracture risk. There is evidence supporting superiority of anabolic agents over antiresorptive agents in reducing vertebral fracture risk in very high fracture risk patients (210-213). Patients at very high fracture risk include those with a recent fracture (e.g., within the past 12 months), those that have fractures while on approved osteoporosis therapy, multiple fractures, fractures while on drugs causing skeletal harm (e.g., long-term glucocorticoids), those with a very low T-score (e.g., less than −3.0), high risk of falls or history of injurious falls, and those with a very high fracture probability by FRAX® (e.g., major osteoporosis fracture >30%, hip fracture >4.5%) or other validated fracture risk algorithm (214-217).

Q4.3. Assessment of Fracture Risk in Special Populations

FRAX® underestimates fracture risk among patients with diabetes mellitus (218). Analyses from three prospective cohort studies (Study of Osteoporotic Fractures, Osteoporotic Fractures in Men Study, and the Health, Aging, and Body Composition study) found that for the same T-score, age, and FRAX® score, those with diabetes had higher fracture risks than those without. Conversely, for similar fracture risks, individuals with diabetes had higher T-scores than those without diabetes (219). This could be due to several pathophysiologic processes that occur in diabetes and could even be medication induced (thiazolidinediones, canagliflozin).

Significantly lower TBS and higher TBS-adjusted FRAX® scores are found in patients with type 2 diabetes mellitus with prevalent vertebral fractures compared with patients with type 2 diabetes mellitus without vertebral fractures; however, no BMD differences were found between these two groups (220).

Rheumatoid arthritis may be entered into the FRAX® algorithm as a surrogate for fracture risk associated with type 2 diabetes mellitus (221). Additionally, adjusting FRAX® scores using TBS could be a useful tool for this population.

Q4.4. Review of Evidence or Expert Opinion to Support Recommendations for Medication Based on Category of Fracture Risk

Many large randomized trials have documented the efficacy of various pharmaceutical agents in reducing fracture risk (186-189,192-194,201,202,222-224). It is intuitive that agents which stimulate bone formation (anabolic treatment) and restore degraded bone microarchitecture could be expected to have greater effects on BMD and fracture reduction than those that inhibit bone breakdown (antiresorptive therapies). Consistent with this, an increasing body of evidence documents superiority of anabolic agents. For example, from results among patients treated with glucocorticoids, teriparatide produced a greater lumbar spine BMD increase (7%) than did alendronate (3.4%) and a greater reduction in vertebral fracture incidence (6.1% vs. 0.6%) (210). Similarly, in high-risk patients, teriparatide produced greater increase in BMD and greater reduction in incidence of vertebral fracture than risedronate (211,212). Providing further support for the superiority of anabolic therapy, patients who received 1 year of an anti-sclerostin agent (romosozumab) experienced substantially reduced vertebral fracture and incidence of clinical fracture than alendronate (213). Moreover, in the setting of prior antiresorptive therapy, initiation of teriparatide is followed by a reduction in hip BMD, causing some experts to advocate anabolic therapy as initial osteoporosis treatment for high-risk patients or any patient with a T-score of −2.5 or worse, followed by antiresorptive therapy (225).

Q5. What Medication Should Be Used to Treat Osteoporosis?

Several agents are approved by the FDA for prevention and/or treatment of postmenopausal osteoporosis, as shown in Table 17. Full prescribing information should be reviewed before recommending any specific agent.

Head-to-head trial data are limited (212). Four agents (alendronate, risedronate, zoledronate, and denosumab)

have evidence for "broad-spectrum" antifracture efficacy (spine, hip, and nonvertebral fracture risk reduction) and should, in the absence of contraindications, be considered as initial options for most patients who are candidates for treatment (Table 18) (52,188,189,202,212,223,226). Those who have "high fracture risk" (for example, postmenopausal women with no prior fractures and moderately low T-scores) can be started on oral agents. Injectable agents such as abaloparatide, denosumab, romosozumab, teriparatide, or zoledronate can be considered as initial therapy for those who are at very high fracture risk (for example, older women who have had multiple vertebral fractures or hip fractures, or who have very low T-scores), those who have GI problems and might not tolerate or absorb oral medication, and for patients who have trouble remembering to take oral medications or coordinating an oral bisphosphonate with other oral medications or daily routine. Importantly, patients taking the anabolic agents or denosumab are advised to transition to an oral bisphosphonate when the course of therapy is complete to avoid bone loss after stopping those drugs. Anabolic and dual-action agents may be preferable for patients at very high risk of fracture as initial therapy. For patients at high risk of spine fracture but not at risk for hip or nonvertebral fractures, raloxifene may be appropriate and has a "side benefit" of reducing the risk of breast cancer.

Denosumab is not contraindicated in patients with renal insufficiency, and no dose adjustment is required in these patients. However, the risk of hypocalcemia upon starting denosumab appears to be greater in patients with significantly impaired renal function. There is minimal experience with the use of denosumab in dialysis patients.

Q5.1. How Are Bisphosphonates Used?

Bisphosphonates, first introduced in the 1990s, have been the most widely used drugs for treatment of osteoporosis. Bisphosphonates bind to hydroxyapatite in bone, particularly at sites of active bone remodeling, and reduce the activity of bone-resorbing osteoclasts. In the U.S., four bisphosphonates are available (alendronate, ibandronate, risedronate, and zoledronate) (187-189,202,223,227); three of the four (alendronate, risedronate, and zoledronate) have evidence for broad-spectrum antifracture efficacy (188,189,202,223). All of these agents are available as generic preparations.

Orally administered bisphosphonates (most commonly used are alendronate 70 mg weekly and risedronate 35 mg weekly or 150 mg monthly) must be taken after a prolonged fast (usually fasting overnight and taken in the morning soon after arising) and swallowed with a full glass of water (with at least a 30-minute wait after ingestion before other medications, food, or beverages other than water). Orally administered bisphosphonates should be used with caution in patients with active esophageal disease. Other contraindications to oral bisphosphonate administration include the inability to follow the dosing regimen for oral use (i.e., inability to remain upright for 30 to 60 minutes), the presence of anatomic or functional esophageal abnormalities that might delay transit of the tablet (e.g., achalasia, stricture, or dysmotility), and the presence of documented or potential GI malabsorption (e.g., gastric bypass procedures, celiac disease, Crohn's disease, infiltrative disorders, etc.) (228). A special formulation of risedronate (Atelvia) can be taken with or after food and, because the delayed-release coating does not dissolve until after exiting the stomach, may be considered for patients with upper-GI problems. The incidence of upper-GI adverse events, however, is not lower with the coated preparation compared with the conventional preparation (229).

Contraindications to oral or intravenous (IV) bisphosphonate therapy include drug hypersensitivity or hypocalcemia. Bisphosphonates should be used with caution, if at all, in patients with reduced kidney function (glomerular filtration rate [GFR] <30 mL/min for risedronate and ibandronate or <35 mL/min for alendronate). Prior to the administration of zoledronate, a creatinine clearance should be calculated based on the serum creatinine and actual body weight using the Cockcroft-Gault formula before each dose. For most patients, there is little difference between estimated GFR and Cockcroft-Gault, but it can be significant. The prescribing information says not to give to "patients with creatinine clearance less than 35 mL/min and in those with evidence of acute renal impairment" (230). Rapid IV administration of nitrogen-containing bisphosphonates may cause transient or permanent decreases in kidney function, especially in older patients, with dehydration or those using diuretics or potentially nephrotoxic drugs (231,232).

IV or high-dose oral administration of nitrogen-containing bisphosphonates may cause acute-phase reactions in up to 30% of patients receiving their first dose (233). These reactions are characterized by fever and muscle aches—a flu-like illness—lasting several days. Acetaminophen, given 1 to 2 hours before treatment, may reduce the likelihood of these reactions and can also be given to treat the symptoms.

Although not seen in clinical trials, there are postmarketing reports of patients treated with an oral or IV bisphosphonate who experienced bone, joint, or muscle complaints that may be severe (234) but usually resolve on discontinuation. The possible association between orally administered bisphosphonates and esophageal cancer has been explored. One study suggested no increased risk (235), and one suggested that risk was increased with long-term use but small in absolute terms—from 1 case per 1,000 in untreated subjects to 2 cases per 1,000 with bisphosphonate use of 5 years or more (236). The FDA concluded that there is no definite association between bisphosphonate use and esophageal cancer (237). Atrial fibrillation as a serious adverse event was noted in the Health Outcomes

and Reduced Incidence with Zoledronic acid (zoledronate) ONce yearly (HORIZON) Pivotal Fracture Trial (202), but was not seen in other trials of zoledronate or other bisphosphonates and is thought by the FDA to be a chance finding.

Osteonecrosis of the jaw (ONJ) and atypical femoral fractures (AFFs) are safety concerns not only with bisphosphonates but with other agents as well and will be discussed elsewhere.

Q5.2. How Is Denosumab Used?

Denosumab is a fully humanized monoclonal antibody that prevents receptor activator of nuclear factor kappa-B ligand from binding to its receptor, receptor activator of nuclear factor kappa-B, thereby reducing the differentiation of precursor cells into mature osteoclasts and decreasing the function and survival of activated osteoclasts. For treatment of osteoporosis, the dose is 60 mg by subcutaneous injection every 6 months. In a 3-year, pivotal placebo-controlled clinical trial of 7,808 women with postmenopausal osteoporosis (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months [FREEDOM] Trial), denosumab showed "broad-spectrum" antifracture efficacy as early as 12 months after starting therapy. Studies of denosumab treatment with duration of up to 10 years indicate persistent fracture protection and a good safety profile (238). Switching from bisphosphonates to denosumab results in additional gains in BMD (239). Denosumab is contraindicated in patients with hypocalcemia, who often have hypoparathyroidism or osteomalacia (240). Intakes of calcium and vitamin D should be adequate upon starting denosumab treatment to minimize the risk of hypocalcemia (193,226,240-242). In the FREEDOM study, there was an imbalance in some low-frequency events (skin rash and cellulitis, serious adverse events related to infection) that did not seem causally related to denosumab treatment (243), did not increase in frequency with long-term therapy (238), and have not been reported with higher-dose denosumab (Xgeva) used to treat patients with advanced cancer.

When treatment with denosumab was stopped after 2 or 8 years, BMD decreased rapidly, and BTMs increased to values above baseline by 12 months after discontinuation (237,240). Protection from vertebral fractures is quickly lost, but the risk does not usually exceed that in untreated patients (244). Case reports of multiple vertebral fractures upon stopping denosumab therapy have been reported (245,246). Drug holidays from denosumab are

Table 17
Drugs Approved by the U.S. Food and Drug Administration for Prevention and Treatment of Postmenopausal Osteoporosis[a]

	Postmenopausal Osteoporosis	
Drug	**Prevention**	**Treatment**
Abaloparatide (Tymlos)	—	80 μg SQ daily
Alendronate (Fosamax)	5 mg PO daily 35 mg PO weekly	10 mg PO daily 70 mg PO weekly[b] 70 mg + D[c]
Calcitonin (Miacalcin, Fortical)	—	200 IU intranasally once daily, or 100 IU SQ qod
Denosumab (Prolia)	—	60 mg SQ every 6 months
Estrogen (multiple formulations; estrogen-bazodoxifene)	Multiple regimens	—
Ibandronate (Boniva, generic form)	2.5 mg PO daily 150 mg PO monthly	2.5 mg PO daily 150 mg PO monthly 3 mg IV every 3 months
Raloxifene (Evista)	60 mg PO daily	60 mg PO daily
Risedronate (Actonel, Atelvia, generic form)[d]	5 mg PO daily 35 mg PO weekly 150 mg PO monthly	5 mg PO daily 35 mg PO weekly 150 mg PO monthly
Romosozumab (Evenity) Teriparatide (Forteo)	— —	20 μg SQ daily 210 mg SQ monthly
Zoledronate (Reclast, generic infusion form)	5 mg IV every 2nd year	5 mg IV once yearly

Abbreviations: IV = intravenously; PO = orally; qod = every other day; SQ = subcutaneously.
[a]Please review the package inserts for specific prescribing information.
[b]Fosamax 70 mg is available as both a tablet and a unit dose liquid. Alendronate (generic Fosamax) is available.
[c]Fosamax Plus D is a tablet containing 70 mg of alendronate and 2,800 IU or 5,600 IU of vitamin D for weekly administration.
[d]Risedronate 150 mg once monthly tablet is available.

Table 18
Summary of Evidence for Reduction of Fracture Risk with Pharmacologic Agents

	Reduction of Fracture Risk		
Drug	**Vertebral**	**Nonvertebral**	**Hip**
Abaloparatide (Tymlos) (273, 282)	Yes	Yes	No effect demonstrated[a]
Alendronate (Fosamax) (223)	Yes	Yes	Yes
Calcitonin (Miacalcin, Fortical) (191)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Denosumab (Prolia) (193, 242)	Yes	Yes	Yes
Ibandronate (Boniva) (187, 227)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Raloxifene (Evista) (192)	Yes	No effect demonstrated[a]	No effect demonstrated[a]
Risedronate (Actonel, Atelvia) (188, 189)	Yes	Yes	Yes
Romosozumab (Evenity) (213, 283)	Yes	[b]	[b]
Teriparatide (Forteo) (194, 306)	Yes	Yes	No effect demonstrated[a]
Zoledronate (Reclast) (202)	Yes	Yes	Yes

[a]The lack of demonstrable effect at these sites should be considered in the context that the studies may not have been adequately powered.
[b]Clinical fracture reduction was shown in both trials. Nonvertebral and hip fracture reductions were shown at month 24 for patients receiving 12 months of romosozumab followed by 12 months of alendronate compared with patients receiving 24 months of alendronate (213).

not recommended due to this potential increased fracture risk. However, it should be noted that it is uncertain how commonly multiple vertebral fractures occur and how best to optimally prevent this phenomenon.

Although much more data are needed to determine the clinical magnitude of this issue, patients should be informed about the importance of not missing a dose of denosumab. If treatment is discontinued, patients should be transitioned to an alternative antiresporptive therapy. There is concern that using an IV antiresorptive may not be effective if it is given before the inhibitory effect of the denosumab has worn off.

Q5.3. How Is Calcitonin Used?

Injectable and nasal spray recombinant salmon calcitonin are approved by the FDA for treatment of postmenopausal osteoporosis (247,248). The approved dosage of injectable calcitonin for treatment of postmenopausal osteoporosis is 100 IU daily given subcutaneously or intramuscularly. The approved dose of nasal spray calcitonin is 200 IU (1 spray) daily. Injectable calcitonin is available in a sterile solution. The main contraindication to use of calcitonin is drug hypersensitivity (247,248). For patients with suspected sensitivity to the drug, skin testing is recommended before treatment.

There are no published studies with injectable calcitonin that show antifracture efficacy. Nasal spray calcitonin (200 IU daily) has been shown to reduce the risk of new vertebral fractures in women with postmenopausal osteoporosis, but neither a lower dose (100 IU daily) nor a higher dose (400 IU daily) was effective in reducing vertebral fractures, and the approved dose was not shown to reduce hip or nonvertebral fracture risk (191). Calcitonin produces a minimal increase in BMD in the spine in women >5 years after onset of menopause but does not increase BMD at sites other than the spine (191,249).

A clinical study of 5 years' duration indicated a good safety profile (191). Common side effects of parenterally administered calcitonin include nausea, local inflammatory reactions at the injection site, and vasomotor symptoms, including sweating and flushing. The most common side effect of nasally administered calcitonin is nasal discomfort, including rhinitis, irritation of the nasal mucosa, and occasional epistaxis. Use of calcitonin with either route of administration is well tolerated (247,248).

Safety and efficacy data are available through 5 years (191). When use of calcitonin is stopped, the skeletal benefits are lost relatively quickly during the subsequent 1 or 2 years.

Primarily because more effective agents are available to increase bone density and reduce fracture risk, we recommend limiting the use of calcitonin as long-term treatment for osteoporosis. Because of a suggestive analgesic effect (250-254), short-term prescriptions are often given to patients with acute painful vertebral fractures with hopes of an analgesic effect.

A meta-analysis of 21 randomized clinical trials of nasal spray calcitonin and an investigational oral calcitonin formulation showed a higher incidence of malignancy in the calcitonin-treated patients (255,256). The FDA did not find sufficient evidence to establish a causal relationship between calcitonin administration and cancer risk but urged that the risks and benefits of the various osteoporosis treatment options be weighed for individual patients.

Q5.4. How Is Raloxifene Used?

Raloxifene is approved by the FDA for prevention and treatment of postmenopausal osteoporosis as well as

for the reduction of risk of breast cancer in women with postmenopausal osteoporosis or at high risk of breast cancer (257) and is available in a generic formulation. The approved dose is 60 mg daily. Raloxifene is contraindicated in women of childbearing potential, those who have had venous thromboembolic disease, and those who are known to be hypersensitive to any component of raloxifene tablets (257). Raloxifene has been shown to reduce the risk of fractures of the spine (192), but neither nonvertebral nor hip fracture efficacy has been demonstrated (238).

In an osteoporosis trial with raloxifene, a significant reduction in breast cancer was seen (258). This finding was confirmed in a larger trial of women at high risk of breast cancer (259). Of note, raloxifene is not indicated for the treatment of invasive breast cancer, for reduction of the risk of recurrence of breast cancer, or for reduction of the risk of noninvasive breast cancer.

Because raloxifene has not been shown to reduce hip or nonvertebral fracture, it may not be the best treatment option in many patients with osteoporosis. For patients with low BMD in the spine but not in the hip (discordance), however, it may be an acceptable initial choice, and it may be particularly attractive in these patients who are also at high risk of breast cancer. Although we recommend against the use of two antiresorptive drugs in combination for treatment of osteoporosis, patients at high risk of hip fracture who are taking raloxifene with the main goal of reducing their risk of breast cancer can reasonably have a bisphosphonate or denosumab added for hip fracture risk reduction. The risk-benefit ratio of combined treatment with raloxifene and bisphosphonate or denosumab is unclear, as data on fracture risk reduction and adverse events, such as ONJ and AFF, are lacking.

Raloxifene is associated with an approximately 3-fold increase in occurrence of venous thromboembolic diseases (similar to estrogen), although the absolute risk is low (259). Other side effects include menopausal symptoms (e.g., hot flashes and night sweats) and leg cramps (260).

When use of raloxifene is stopped, the skeletal benefits appear to be lost relatively quickly during the following 1 or 2 years.

Q5.5. Selective Estrogen-Receptor Modulators/ Conjugated Equine Estrogens

The selective estrogen-receptor modulator, bazedoxifene, has been studied and is FDA approved in a combination pill with conjugated equine estrogen. The rationale was that such a combination would improve BMD and reduce hot flashes, but without some of the other adverse effects on the endometrium and breast associated with estrogen therapy alone (261,262). In a study by Lindsey et al (263), the combination of bazedoxifene and estrogen in 3,997 postmenopausal women showed a statistically significant increase in BMD at multiple sites over 2 years compared with placebo, along with a decrease in BTMs. In addition to the favorable effects on bone, bazedoxifene-conjugated estrogen therapy significantly reduced the frequency and severity of hot flushes and improved vulvar-vaginal atrophy and its symptoms compared with placebo, with a good tolerability profile (264).

A 3-year, randomized, double-blind study performed in 7,492 postmenopausal women with osteoporosis showed a reduction in new vertebral fractures with bazedoxifene but not in nonvertebral fractures (265). An extension of this study demonstrated the efficacy and safety of bazedoxifene over 7 years in this group with similar fracture data (266). The bazedoxifene-conjugated estrogen combination comes as a once-a-day tablet. It carries a boxed warning that there is an increased risk for endometrial cancer in women with a uterus who take unopposed estrogens. There are data that this medication reduces the risk of endometrial hyperplasia, which may be a precursor to endometrial cancer. Other warnings that come with estrogen therapy alone also apply, including that this medication should be given for the shortest duration necessary consistent with the goals and risks for the individual patient. Unlike raloxifene, the effect of treatment with this combination medication on the risk of breast cancer is unknown. A recent review of this formulation concluded that there was a significant reduction in vasomotor symptoms, improved sleep, protection of bone tissue, and improvement in vaginal atrophy with no stimulation of breast tissue, endometrial tissue, or increase in cardiovascular risk (267). This medication has not been studied in patients over 75 years of age.

Indications for bazedoxifene-conjugated estrogens are for women with a uterus with moderate-to-severe vasomotor symptoms associated with menopause and the prevention of postmenopausal osteoporosis. The package insert states that when this medication is prescribed solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis, and non-estrogen medication should be carefully considered (268). Based on its data and mechanism of action, this medication serves a very limited use in the prevention or treatment of postmenopausal osteoporosis and likely would not be selected except for in very specific situations and ideally in conjunction with a gynecologist.

Q5.6. What Is the Role of Estrogen and Menopausal Hormone Therapy in Treatment of Postmenopausal Osteoporosis?

Although once considered the treatment of choice for postmenopausal osteoporosis, estrogen was never specifically approved for this use. Estrogen is approved by the FDA for prevention of postmenopausal osteoporosis with the added caveat, "when prescribing solely for the prevention of postmenopausal osteoporosis, therapy should only be considered for women at significant risk of osteoporosis and for whom non-estrogen medications are not considered to be appropriate" (268).

When estrogen is prescribed for a patient with an intact uterus, a progestin should also be used, either daily or cyclically, to protect against endometrial stimulation. In the WHI, conjugated equine estrogen (0.625 mg daily), with or without medroxyprogesterone acetate, was shown to reduce the risk of fractures of the spine, hip, and nonvertebral sites in postmenopausal women (269,270). The extraskeletal effects of estrogen have generated considerable controversy, particularly regarding cardiovascular disease and breast cancer. Current recommendations are to use estrogen for the relief of menopausal symptoms in the lowest dose necessary and for the shortest time possible.

Q5.7. How Are Anabolic Agents (Abaloparatide and Teriparatide) Used?

Abaloparatide (modified PTH-related peptide 1-34) (271) and teriparatide (recombinant human PTH1-34) are considered "anabolic" agents (by contrast, the medications discussed above work by reducing bone resorption). Both are approved by the FDA for initial treatment of women with postmenopausal osteoporosis who are at high risk of fracture or have failed or been intolerant of previous osteoporosis therapy (271,272). Teriparatide is also approved for treatment of glucocorticoid-induced osteoporosis and treatment of osteoporosis in men. Both are injected subcutaneously. Abaloparatide does not require refrigeration after use. The dose of abaloparatide is 80 μg daily, while teriparatide is given at 20 μg daily. It is prudent to measure serum calcium, PTH, and 25(OH)D levels, and alkaline phosphatase (to rule out Paget disease) before treatment with either medication.

Both abaloparatide and teriparatide have been shown to increase BMD and reduce the risk of vertebral and nonvertebral fractures in women with postmenopausal osteoporosis in randomized controlled trials (194,273), but the incidence of hip fracture was low in these trials; whether anabolic agents protect against hip fracture is not known. In a head-to-head trial, gains in BMD were greater with abaloparatide compared with teriparatide, especially in the femoral neck, total hip, and 1/3 radius. Fracture reduction was numerically greater with abaloparatide than with teriparatide, although the difference between active arms was only significant for major osteoporosis-related fractures. Patients who lose BMD in the hip with teriparatide treatment are still protected against vertebral fracture compared with placebo related to improvements in bone geometry and microarchitecture (274).

Side effects of both abaloparatide and teriparatide have been mild and transient and include nausea, orthostatic hypotension (which usually does not necessitate discontinuation of the drug, occurs in association with the first few doses, and responds to assumption of a recumbent posture), and leg cramps. Hypercalcemia, usually mild, asymptomatic, and transient, has been observed but is not common (271,272) and less likely with abaloparatide than with teriparatide. If serum calcium is measured, the blood should be drawn at least 16 hours after drug administration.

Both abaloparatide and teriparatide have boxed warnings because of the occurrence of osteosarcomas in rats treated with very high doses (275). Subsequent studies in the same strain of rats showed no development of malignant bone tumors with doses of teriparatide up to 3 times higher than the human equivalent dose (276). Because of the increased incidence of osteosarcomas in rats, abaloparatide and teriparatide should not be used in patients at increased risk of osteosarcoma (those with Paget disease of bone, open epiphyses, a history of irradiation involving the skeleton, or an unexplained elevation of alkaline phosphatase level of skeletal origin) (271,272). The annual incidence of osteosarcoma in women aged 50 years or older in the general population is approximately 1 in 250,000. The actual incidence of osteosarcoma in users of teriparatide is unknown; there are rare reports, consistent with the background incidence (277,278). Abaloparatide and teriparatide also should not be administered to patients with primary or any form of secondary untreated or unresolved hyperparathyroidism (271,272). Both abaloparatide and teriparatide are limited to no longer than 2 years in total duration (271,272).

When treatment with teriparatide is stopped, bone density declines quickly during the following year, although fracture reduction may persist for 1 or 2 years (279). Use of bisphosphonates or denosumab after teriparatide therapy prevents this loss and may result in a further increase in BMD (272,280,281). Alendronate has also been studied after abaloparatide, with similar results (282). Available data demonstrate that treatment with either teriparatide or abaloparatide should routinely be followed by antiresorptive therapy, typically with either a bisphosphonate or denosumab followed by an oral bisphosphonate. There is no apparent rationale for a "washout period" or "drug holiday" between the end of anabolic therapy and the initiation of antiresorptive treatment.

There are several studies in which teriparatide was used in patients treated with oral bisphosphonates, either previously or concurrently. None were large enough to assess fracture risk reduction, but BMD and BTM changes appeared to be "blunted" because of the previous bisphosphonate therapy. In a small study in which patients first received 2 years of denosumab, BMD decreased for 6 to 12 months after they were changed to teriparatide (281). It is probably not advisable to use teriparatide (or abaloparatide) if denosumab is stopped, but teriparatide (and probably abaloparatide) may be added to ongoing denosumab therapy.

Q5.8. What Is Romosozumab and What Is Its Role?

Romosozumab is a monoclonal antibody directed against sclerostin. Sclerostin binds with the Wnt receptor and inhibits the differentiation of precursor cells into

mature bone-forming osteoblasts. Blocking sclerostin binding to osteoblasts allows osteoblast activity to increase. BTMs suggest an early anabolic effect, bone density increases are dramatic, and biopsies indicate an anabolic effect through both modeling (increase in cross-sectional area) and remodeling (bone repair). Approval of romosozumab for postmenopausal women at high risk of fracture was based on two large trials. In the larger of the two trials (N = 7,180) (283), patients received either subcutaneous romosozumab 210 mg monthly or placebo for 12 months; then, all patients received denosumab. In the other trial (N = 4,093) (213), patients received monthly romosozumab or oral alendronate (double-blind, double-dummy) for 12 months; then, all received open-label alendronate. Both trials showed significant reductions in radiographic vertebral fractures at 12 months (73% reduction vs. placebo, 34% reduction vs. alendronate) and 24 months (75% for romosozumab followed by denosumab compared with placebo followed by denosumab, 48% for denosumab followed by alendronate compared with alendronate for 2 years). Clinical fractures were also significantly reduced in both trials at 12 and 24 months by 27 to 33%. Nonvertebral fracture reduction (19%) and hip fracture reduction (38%) were significant only in the smaller trial at 24 months (213). In a 12-month study of romosozumab versus teriparatide versus placebo (N = 367), Genant et al (284) found changes in total spine (17.7%, 12.9%, –0.8%, respectively) and total hip (4.1%, 1.2%, and 0.3%, respectively) with QCT (high-resolution computed tomography scan). Langdahl et al (285) enrolled 436 patients with at least 3 years of oral bisphosphonate therapy (mean, 6.2 years) who were then assigned to 12 months of either romosozumab or teriparatide. Greater gains in BMD were seen with romosozumab in the lumbar spine (9.8% vs. 5.4%), femoral neck (3.2% vs. –0.2%), and total hip (2.9% vs. –0.5%).

Romosozumab will likely be viewed as a "rescue drug" for patients at very high fracture risk" in the near term. It is an option for patients previously treated with teriparatide or abaloparatide, and future retreatment with romosozumab may be possible. Romosozumab can be used in patients with prior radiation exposure. In the smaller of the phase 3 trials (N = 4,093), serious cardiovascular events were significantly more common with romosozumab compared with the alendronate control group (213), but the increased risk did not persist and was small. Because of this, the black-box warning for romosozumab states that it should not be used in patients at high risk for cardiovascular events or who have had recent myocardial infarction or stroke.

Romosozumab has also been studied in men (286) but is not currently approved for male osteoporosis.

Q6. How Is Treatment Monitored?

Serial BMD testing may be done to determine if or when to initiate treatment and to monitor the response to treatment. In untreated patients, the frequency of testing depends on the results of the initial test (e.g., how close the patient is to an intervention threshold) and the likelihood of significant future bone loss. Age-related bone loss, which begins in the fifth decade of life, occurs at an average rate of 0.5 to 1.0% per year (287). Menopause-related bone loss, which begins 3 to 5 years before the last menstrual period and continues for 3 to 5 years after the cessation of menses, occurs at an average rate of 1 to 2% per year (288). More rapid bone loss (3 to 5% in a year) may occur in some women after natural menopause, after stopping postmenopausal estrogen therapy, or after initiation of glucocorticoid or aromatase inhibitor therapy (64,289,290). A bone-loss calculator can be found on the ISCD website (www.iscd.org). One SD is about a 10% deviation from the young-adult mean. Thus, a 10% bone loss (which typically occurs over 10 to 20 years of age-related bone loss or 5 to 10 years of menopause-related bone loss) will result in a decrease of about 1.0 T-score units. Serial monitoring is based on absolute BMD and not T-scores.

For patients on treatment or with a baseline evaluation near a fracture intervention threshold, BMD testing every 1 to 2 years is often appropriate. This frequency of BMD testing may be appropriate in recently postmenopausal women, for whom rates of bone loss are increased, and in women of any age with other disorders or medications that adversely affect bone. The frequency of testing is individualized, depending on the patient's clinical state (291).

The goal of monitoring osteoporosis therapy is to identify those who have significant bone loss. In patients on treatment, stable or increasing BMD at the spine and hip indicates a satisfactory response (292). In treated patients, if BMD decreases significantly, patients should be evaluated for noncompliance, secondary causes of osteoporosis, or use of medications that might cause bone loss (293).

Differences between BMD results may simply reflect the inherent variability of the test measurement; thus, testing facilities must calculate the LSC for relevant measurement sites to determine the magnitude of difference that represents a real change. This is determined using a facility's regular technologist(s), patients, and device (294,295). The ISCD has established guidelines for determining the number of patients and repetitive scans needed to determine the LSC (30 patients in duplicate or 15 patients in triplicate) (294,295). The LSC is usually set at the 95% confidence limit for change. The manufacturer's LSC should not be used, because it does not account for differences in patients who will be tested and the performance and skill of the technologist. If serial studies show a difference that exceeds the LSC, the probability that the difference is real is greater than 95%.

In addition to knowing the LSC, it is important to note that differences in regions of interest (ROIs), local structural change, or skeletal artifacts may result in an apparent "change" in BMD that does not reflect true progression of bone loss or gain. Before accepting a report of significant

loss, images and numeric results of the studies should be viewed to assess comparability.

Ideally, BMD monitoring should occur at the same facility, using the same DXA machine and, if possible, the same technologist as the previous DXA and should involve the same ROIs for both the spine and hip (58,296). The 1/3 radius site is also acceptable, when spine and hip sites are not evaluable (7,297,298). It must be noted that two of the three manufacturers of DXA instruments calibrate their spine BMD for the same ROI (spine), so that, for the same patient, GE's Lunar DXA gives a BMD 20% higher than Hologic's DXA. Other peripheral sites (e.g., heel, finger, and tibia) should not be used for monitoring. Most third-party payers and some Medicare carriers financially support yearly BMD testing in appropriate circumstances (e.g., with a diagnosis of osteoporosis or high risk for rapid bone loss); all Medicare carriers financially support testing every 2 years. AACE recommends a repeat DXA 1 to 2 years after initiation of therapy until bone density is stable, and longer intervals between testing with evidence of continued BMD stability, based on expert opinion. Because sites rich in trabecular bone, such as the posteroanterior spine, are more metabolically active, a significant change is likely to occur earlier at the spine than at the hip.

Skeletal status also can be examined by assessing the development or progression of asymptomatic vertebral fractures, using lateral X-rays of the thoracic and lumbar spine or VFA (66-70,299,300).

BTMs are useful for assessing patient compliance and efficacy of therapy. Significant reductions in BTMs are seen with antiresorptive therapy and have been associated with fracture reduction, and significant increases indicate good response to anabolic therapy (292).

Q7. What Is Successful Treatment of Osteoporosis?

Pharmacologic and nonpharmacologic treatments for osteoporosis aim to prevent fractures by improving bone strength, preventing falls, and reducing the impact force of falls. Randomized trials have demonstrated a reduction in fracture risk in patients with stable or increasing BMD receiving pharmacologic therapy, in particular, use of bisphosphonates for osteoporosis treatment compared with those receiving placebo (188,189,202,223). In addition, larger increases in BMD may result in increased reduction of fracture risk; however, this association has not been consistently shown (301-303).

The goal of treatment is prevention of fractures, but no treatment can eliminate risk of fracture. A fracture during therapy is not necessarily a treatment failure but should trigger reconsideration of risk factors for fracture and possibly a change in treatment strategies. The risk of fracture is highest after a recent fracture and diminishes over time (40,304). The number, severity, and recency of vertebral fractures are directly correlated with the risk of future fractures (305,306).

The concept that response to therapy is not necessarily the same as achieving an acceptable level of fracture risk has led to proposals for the development of treat-to-target goals (307,308), as are used in the management of some other chronic silent diseases, such as hypertension and diabetes. Consequently, an American Society for Bone and Mineral Research (ASBMR)/NOF task force was formed to review the medical evidence, determine the feasibility of developing treat-to-target goals, propose targets (if possible), and recommend an agenda for further study. At this time, treatment targets have not been identified.

The definition of a "nonresponder" to therapy is complex, and the proportion of nonresponders for different therapies varies. Treatment failure may be defined by a significant decrease in BMD or recurrent fractures in a patient who is compliant to therapy. In clinical trials, some patients experienced bone loss and/or fractures; however, these patients may still have benefited from treatment by preventing even greater bone loss or postponing the occurrence of fractures (292). Nevertheless, it is reasonable that a patient with significant bone loss or one or more new fragility fractures be evaluated for compliance with medication, secondary causes of bone loss, and new medications or diseases that can cause bone loss. Furthermore, the change in BMD accounts for <20% of the fracture risk reduction following antiresorptive therapy (88, 309). Finally, although it has been suggested that BMD monitoring might improve patient compliance, nonadherence to therapy usually occurs early (after 6 to 7 months), before the second BMD would be performed (310).

When treatment is initiated due to a low DXA T-score (such as –2.5 or lower), it is intuitive that the treatment target be a higher T-score. When treatment is started due to high fracture probability with an algorithm such as FRAX®, it is also intuitive that fracture probability should be reduced to a level that is less than the threshold for starting treatment, perhaps to a level that is similar to an age-matched person with normal BMD by WHO criteria and no clinical risk factors for fracture. A change in BTMs is also a possible treatment target. There are strengths and weaknesses to each of these strategies, which have been described in detail elsewhere (307). There are many challenges to identifying one or more treatment targets, including limited data on comparative effectiveness of therapeutic agents in reducing fracture risk, lack of consensus on what an acceptable level of fracture risk should be, and limited effectiveness of current therapeutic agents to reduce risk of fracture, particularly nonvertebral fractures. Treat-to-target goals may achieve greater clinical utility as more data comparing fracture risk with different agents

become available and drugs with a more robust antifracture effect are developed.

Q8. How Long Should Patients Be Treated?

Q8.1. What Are the Safety Concerns of Antiresorptive Therapy?

ONJ was first reported in patients with advanced cancer receiving high-dose bisphosphonate therapy. Head-to-head trials in advanced cancer patients showed an incidence of 1 to 2% per year with zoledronate (at an annual dose 10 times higher than that used to treat osteoporosis) and denosumab (at an annual dose 12 times higher than that used to treat osteoporosis in patients who do not have cancer). The incidence of ONJ is much lower with oral or IV bisphosphonate therapy for osteoporosis, on the order of 1/10,000 to 1/100,000 patients per year (311-314) and appears to be low with denosumab therapy for osteoporosis, with 5.2 cases per 10,000 patient-years (193,315). Risk factors include dental pathologic conditions, invasive dental procedures, and poor dental hygiene. An oral examination should be done in patients being considered for treatment with these agents. If significant dental issues are present, delaying the initiation of bisphosphonate or denosumab therapy until the dental issues have been corrected should be considered. For patients already receiving bisphosphonates or denosumab who require invasive dental procedures, there is no evidence that discontinuing or interrupting treatment will change the outcome or reduce the risk of ONJ. Nonetheless, stopping should at least be considered for patients undergoing extensive invasive dental procedures such as extraction of several teeth (316).

AFF of the subtrochanteric region is another rare event that seems to be increased with long-term bisphosphonate therapy (>5 years duration) and is also rarely seen with the higher dosing frequencies used in advanced cancer treatment (317-320). It is estimated that treatment of 1,000 women with osteoporosis for up to 3 years would be associated with fewer than 1 AFF per 100 osteoporotic fractures prevented (321). Such fractures are sometimes described as "chalk stick" because of their radiologic appearance. They occur after little or no trauma. A literature review of AFF cases by the ASBMR reported a history of prodromal groin or thigh pain in approximately 70% of patients with AFF, bilateral fractures, and bilateral radiographic abnormalities in 28%, and delayed healing in 26% (322). Any patient with a history of bisphosphonate therapy who presents with persistent thigh or groin pain should interrupt bisphosphonate treatment while appropriate imaging studies are obtained. In the early stages, a lateral periosteal stress reaction may be seen radiologically. It has been hypothesized that these patients may have very low bone turnover, although this point has not been rigorously substantiated. Whether a direct etiologic relationship exists between ONJ or AFFs and the use of bisphosphonates is not clear. Evidence for AFFs has been reviewed by a task force of the ASBMR (318,322). Subtrochanteric femur fractures are also seen in patients with low BMD not on bisphosphonates and with other therapies for osteoporosis, such as denosumab. A causal relationship has not been established (323). Because these fractures can occur in patients not on any treatment, unless a new drug for osteoporosis prevents this type of fracture, "atypical" fractures will be seen eventually with any agent. Interestingly, a recent cohort study suggested that these fractures are not associated with excess mortality (324). There is evidence that using anabolic therapy when AFF is diagnosed accelerates fracture healing (325-327).

Definitions and diagnostic criteria for ONJ and AFF are given in Table 19. It is important to remember that the number of fractures that are prevented with osteoporosis treatment far outweighs the risk of ONJ or AFFs (see section on risk communication, Fig. 2 (328).

Q8.2. Bisphosphonate Holidays

Because bisphosphonates accumulate and may have a prolonged residence time in bone (and residual therapeutic effect after stopping), "bisphosphonate holidays" may be considered. A post hoc analysis of results from Fracture Intervention Trial (FIT) Long-Term Extension (FLEX) Trial of 10 versus 5 years of alendronate assessed the influence of fracture status and T-score on treatment effect. Higher-risk women (those with a T-score –2.5 or lower) who stopped treatment had nearly twice as many nonvertebral fractures: 21 (28%) versus 16 (15%) with continued treatment (329), suggesting that longer treatment is better for higher-risk patients. In the first 2 years, the Kaplan-Meier curve for clinical vertebral fractures, however, showed no difference between those who stopped and those who continued, indicating a residual benefit. A 3-year extension study of the zoledronate arms of the HORIZON study showed significantly fewer morphometric spine fractures in patients who continued yearly zoledronate for 6 years versus those who switched to placebo after 3 years of treatment. No differences in clinical vertebral fractures or nonvertebral fractures, however, were noted (330). In the second extension of the HORIZON trial, postmenopausal women previously treated with zoledronate for 6 years were randomized to continue treatment or switched to placebo for an additional 3 years. Three morphometric vertebral fractures were reported with 9 years of treatment compared with 5 reported with 6 years of treatment. Clinical fractures were similar between the two groups, reported in 10 of the patients who continued treatment for 9 years and in 9 patients who received 6 years of therapy (331).

AACE agrees with the ASBMR algorithm for management of patients on long-term bisphosphonate treatment that recommends that patients who are initially at very high

risk and remain at high risk receive a treatment duration of 10 years for an oral bisphosphonate (328,329) or 6 years for IV zoledronate (330-332). The risk-benefit ratio for treatment beyond 10 years has not been investigated and remains unknown. For patients at "high fracture risk," a drug holiday can be considered after 5 years of stability on oral bisphosphonates or 3 years of IV zoledronate. For patients at very high fracture risk, a non-bisphosphonate treatment (teriparatide) may be offered during the holiday from the bisphosphonate.

The optimal duration of a bisphosphonate holiday has not been established. Two recent retrospective studies have suggested that the risk of new clinical fractures is higher in patients on a bisphosphonate holiday (333,334), especially if their T-scores equal or are worse than –2.5 (283). Patient selection and monitoring during bisphosphonate holidays are important. The rank order for binding affinity for bone is zoledronate > alendronate > risedronate; logic suggests that the holiday might be longest after treatment with zoledronate, shortest after treatment with risedronate, and intermediate after treatment with alendronate (335). In addition, consider resuming therapy in patients who experience fracture or show significant BMD loss. Some experts feel that a rise in bone resorption markers (e.g., CTX or N-terminal telopeptide type-I collagen) to pretreatment levels might be a signal that the holiday should be over, but this is debatable and may not apply to patients with osteoporosis who had low bone resorption markers before treatment was started.

Q9. What Is the Role of Concomitant Use of Therapeutic Agents?

There are no studies showing that combination treatment with two or more osteoporosis drugs has a greater effect on fracture reduction than treatment with a single agent (336). Modest additive effects on BMD and bone turnover have been observed with combinations of two antiresorptive agents. The combined use of an antiresorptive drug and teriparatide or PTH may alter the BMD and bone turnover response, depending on which antiresorptive agent is used (337).

There is evidence that some combinations may enhance the rapidity of BMD changes. For example, while teriparatide increases lumbar spine BMD more than zoledronate and zoledronate increases hip BMD more than teriparatide, a single dose of IV zoledronate given at the same time as starting teriparatide results in the most rapid increase in BMD at both the lumbar spine and hip (222). The most robust additive BMD effect is seen with the combination of teriparatide and denosumab, which results in a larger increase in BMD than either agent alone (338). However, in contrast to the effects of teriparatide monotherapy, markers of bone formation are reduced with combination therapy, and no fracture data are available.

Combination therapy substantially increases the cost and probably increases the potential for side effects. Until the effect of combination therapy on fracture risk is better understood, AACE does not recommend concomitant use

Table 19
ONJ and AFF: Definitions and Diagnostic Criteria (313, 318, 369)

Osteonecrosis of the jaw (ONJ)	The presence of exposed bone in the maxillofacial region that did not heal within 8 weeks after identification by a health-care professional.
Atypical femoral fracture (AFF)	The fracture must be located along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare.
	Major features (at least 4 of 5) • The fracture is associated with minimal or no trauma, as in a fall from a standing height or less. • The fracture line originates at the lateral cortex and is substantially transverse in its orientation, although it may become oblique as it progresses medially across the femur. • Complete fractures extend through both cortices and may be associated with a medial spike; incomplete fractures involve only the lateral cortex. • The fracture is noncomminuted or minimally comminuted. • Localized periosteal or endosteal thickening of the lateral cortex is present at the fracture site ("beaking" or "flaring").
	Minor features (none required) • Generalized increase in cortical thickness of the femoral diaphysis. • Unilateral or bilateral prodromal symptoms such as dull or aching pain in the groin or thigh. • Bilateral incomplete or complete femoral diaphysis fractures. • Delayed fracture healing.

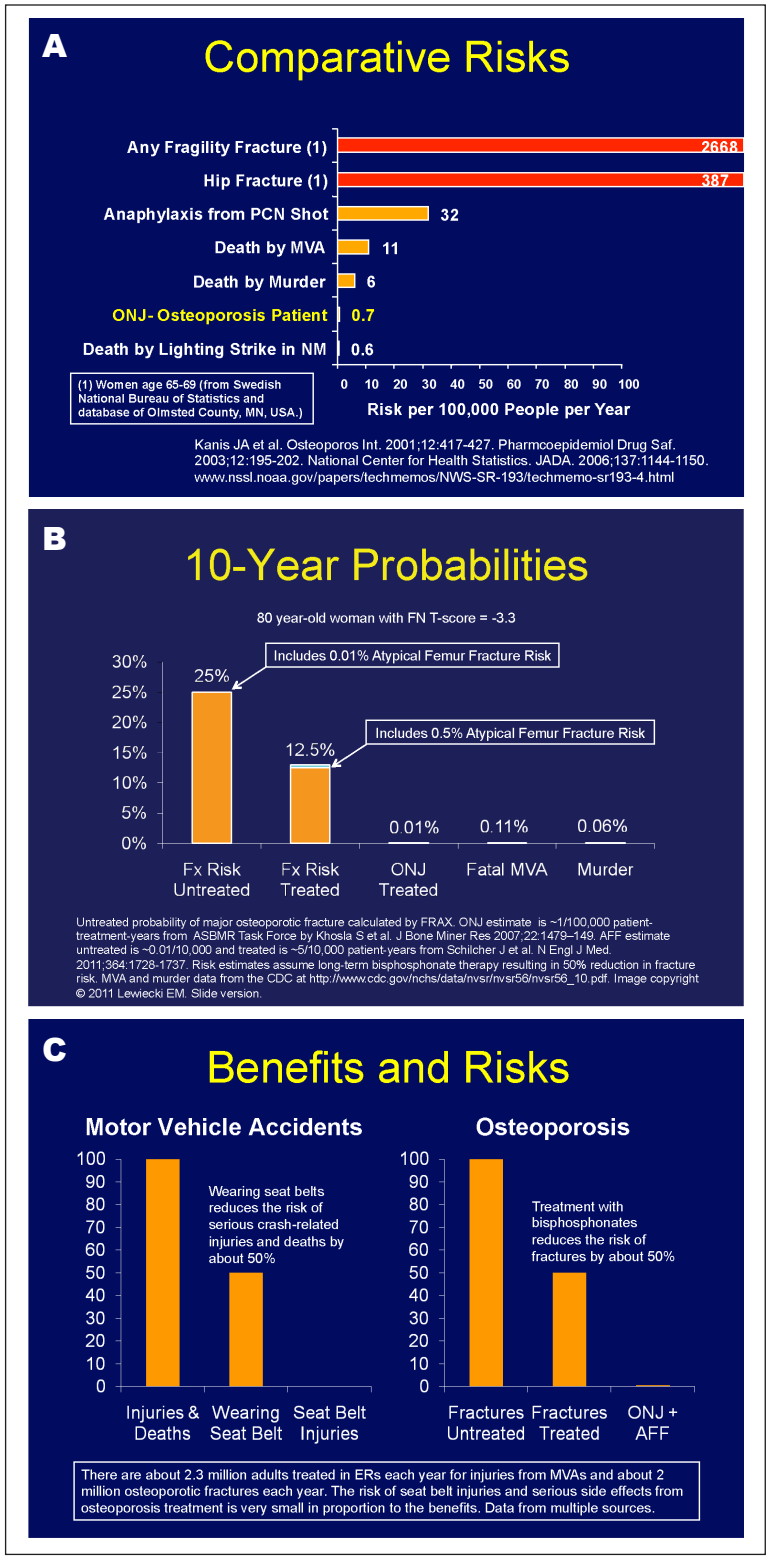

Fig. 2. Comparative risk of fracture, osteonecrosis of the jaw (ONJ), and other events in women age 65 to 69 years (*A*) (371-373); 10-year probability of fracture in treated and untreated patients, ONJ in treated patients, and other events in an 80-year-old woman (*B*) (313, 369); and benefits and risks of treatment in osteoporosis compared with seat-belt intervention in motor vehicle accidents (*C*). *AFF* = atypical femoral fracture; *ERs* = emergency rooms; *FN* = femoral neck; *Fx* = fracture; *MVA* = motor vehicle accident; *NM* = New Mexico; *PCN* = penicillin.

of these agents for prevention or treatment of postmenopausal osteoporosis. However, in certain situations when the patient needs a stronger agent because fracture risk is especially high or there is demonstrated suboptimal effect from raloxifene or hormone replacement therapy (i.e., recurrent fractures, high bone resorption markers, or progression of BMD loss), yet the patient has specific non-bone reasons, such as breast protection with raloxifene, to continue with these agents, another antiresorptive agent or anabolic therapy could be added to the therapy.

Q10. What Is the Role of Sequential Use of Therapeutic Agents?

Upon discontinuation of an anabolic agent (i.e., abaloparatide, romosozumab, teriparatide), therapy with an antiresorptive agent, such as denosumab, bisphosphonates, or raloxifene, is recommended to prevent loss of BMD and fracture efficacy (222,224,337,339-345). Switching from a bisphosphonate to an anabolic agent can be done, but switching from denosumab to a currently available anabolic agent is associated with loss of hip BMD and is not recommended (281,346).

Q11. What Is the Role of Vertebral Augmentation for Compression Fractures?

Vertebral fractures can be associated with pain and limit mobility. Surgical procedures, including vertebroplasty and kyphoplasty, have been considered for relief of vertebral fracture pain. Initial data on two randomized, controlled studies comparing vertebroplasty versus a control procedure on a primary outcome of overall pain showed no significant benefit from vertebroplasty up to 1 month (347) and up to 6 months (348). A meta-analysis of individual patient data from two blinded trials of vertebroplasty failed to show an advantage of vertebroplasty over placebo for participants with acute fractures (<6 weeks) or severe pain (349). A study with 2-year follow-up data of patients with acute osteoporotic vertebral fractures found no beneficial effects of vertebroplasty over a sham procedure at 12 or 24 months (350).

Both vertebroplasty and kyphoplasty have been suggested to increase the risk of vertebral fractures in the adjacent vertebrae. Despite a potential benefit with faster pain relief, a significantly increased incidence of additional vertebral fractures in patients undergoing vertebroplasty compared with placebo was noted in a randomized, controlled trial of 125 patients with vertebral fractures at 12 months' follow-up (351). By contrast, another study found no difference in new fractures in patients receiving vertebroplasty versus usual care at a mean of 11.4 months, with decreased severity of further height loss in treated vertebrae (352). In a meta-analysis assessing the safety of balloon kyphoplasty in patients with symptomatic osteoporotic vertebral fractures, new vertebral fractures were detected in 20.7% of treated patients, and more than half of the cases had fractures adjacent to the treated level (353). Given the limitations to these published studies, the role for surgical procedures in treatment of vertebral fractures remains uncertain.

Q12. When Should Referral to a Clinical Endocrinologist or Other Osteoporosis Specialist Be Considered?

Referral to a clinical endocrinologist or other osteoporosis specialist may be important in patients with normal BMD and fracture without major trauma, those with recurrent fractures or continued bone loss while receiving therapy without obvious treatable causes of bone loss, those with less common secondary conditions (e.g., hyperthyroidism, hyperparathyroidism, hypercalciuria, or elevated prolactin), those with osteoporosis with unexpectedly severe or unusual features such as young age or abnormal laboratory testing (e.g., low phosphorus, high or low alkaline phosphatase), artifacts on DXA that are unexplained, and those with a condition that complicates management (e.g., decreased kidney function, hyperparathyroidism, or malabsorption). Patients who experience fragility fractures should be evaluated and treated. Referral to an osteoporosis specialist or a fracture liaison team, if available, should be considered (354,355).

COMMUNICATING RISK TO PATIENTS

Risk communication has been defined in general terms as "the study and practice of collectively and effectively understanding risks" (356). When applied to health-care interactions, including those concerned with the management of osteoporosis, it can be characterized as "one-to-one communication in which the intervention includes a stimulus to patients to weigh the risks and benefits of a treatment choice or behavioral (risk reducing) change" (357). In addition to understanding the potential risk and expected benefits of osteoporosis treatments, patients must fully appreciate the risk of fractures and their consequences (e.g., pain, disability, loss of independence, and death) when no treatment is given (358). It is incumbent on the clinician to provide this information to each patient in a manner that is fully understood, and it is equally important to learn from the patient about cultural beliefs, previous treatment experiences, fears, and concerns. Estimation of fracture risk should consider that T-score must be combined with clinical risk factors, especially advanced age and previous fracture, and recognize that absolute fracture risk is more useful than RR in developing treatment plans. Treatment recommendations may be quite different; an early postmenopausal woman with a T-score of –2.5 has osteoporosis, although fracture risk is much lower than an

80-year-old woman with the same T-score. Effective risk communication imparts to the patient a good understanding of fracture risk with no treatment compared with the balance of benefits and risks with treatment.

With effective risk communication, the clinician and the patient are both privy to the same information. This is the first step toward shared decision-making (358-360), a process by which a plan of management is developed with active participation of the patient. Shared decision-making often begins with a recommendation from the clinician followed by a response, perhaps with an alternative plan, from the patient. In the end, the desired result is a treatment plan that is medically reasonable and acceptable to the patient, often involving compromises from both participants.

There are many obstacles to risk communication (361). The medical evidence on efficacy and safety of treatment options may be complex, incomplete, and uncertain. Patients often distrust medical experts and pharmaceutical companies. Statistical illiteracy is common in both clinicians and patients. The risk of fracture and its consequences may not be fully appreciated. Clinicians may lack the necessary skills or time needed to explain the balance of benefits and risks. Competing health-care priorities may detract from attention paid to osteoporosis. Patients may be reluctant to reveal their fears and concerns. Risks that may seem trivial or nonexistent to the clinician may nevertheless be frightening for the patient. News media reports of rare possible adverse effects of osteoporosis treatment and questionable overuse of diagnostic procedures sometimes generate concern that osteoporosis treatment is dangerous or overused. Postmarketing case reports of undesirable medical occurrences in patients treated for osteoporosis do not necessarily represent a causal relationship with the medication being used. For a variety of reasons, patients may fail to fill a prescription when it is written. When treatment is started, it may not be taken correctly or for a sufficient length of time to achieve the desired reduction in fracture risk.

Strategies to overcome obstacles to effective risk communication include recognition and acceptance of the limitations of medical evidence (361). Treatment decisions for osteoporosis must be individualized with the understanding that many or most patients would not qualify for participation in the clinical trial that demonstrated efficacy and safety of the medications under consideration (362). Patients can be educated on the current state of medical knowledge using credible information sources. Media reports can be put in perspective by describing the benefits of treatment in proportion to the possible risks. Data can be presented in simple language that is understandable for the patient, sometimes with the use of decision aids such as brochures, graphs, videos, and models to enhance what is spoken and facilitate treatment decisions. The concerns of the patient must be considered and validated. Finally, shared decision-making allows the patient to be an active participant in the management of osteoporosis.

Studies to evaluate the effectiveness of communication interventions have been difficult to compare due to the diversity of measured outcomes. Study endpoints have included those that are behavioral (e.g., compliance and persistence), cognitive (e.g., knowledge and risk perception), and affective (e.g., anxiety and satisfaction) (357). A systematic review of randomized controlled trials of communication tools found that most formats (verbal, written, video, provider-delivered, and computer-based) increased patients' understanding of the medical evidence (363). Understanding was enhanced when the methods were individualized and/or interactive, with decision aids such as cartoons or graphs helping, as well. It was concluded that there is increasing evidence supporting the design of evidence-based communication tools, although access to these tools in clinical practice was limited. Attentive listening to patients is an important component of risk communication and shared decision-making, with evidence that this is a skill that can be learned (364). A randomized controlled trial of risk communication for treatment to prevent hip fractures for patients in primary-care practices found that presentation of treatment benefit and harm using absolute risk estimates (expressed by icon array graphs with human figures with hip fracture risk calculated by FRAX®) led to greater treatment acceptance than presentation of the same information as RRs (365). Another randomized controlled trial evaluated postmenopausal women with low BMD receiving a decision aid (a tailored pictograph of 10-year fracture probability, absolute risk reduction with bisphosphonates, side effects, and cost) compared with controls receiving a standard brochure (366). The decision aid improved the quality of clinical decisions (i.e., patient understanding of benefit and risk) and may have improved adherence but did not affect rates of initiating treatment. Regular contact with a health-care professional after starting osteoporosis treatment appears to be one of the few interventions shown to improve adherence (367,368). Examples of decision aids that illustrate risk in a visual, patient-friendly manner are given in Figure 2. Figure 3 *A* through *C* provides comparisons of risk for osteoporosis, fracture, ONJ, and other events.

More study is needed to determine the most effective means of communicating benefit and risk in the management of osteoporosis. The best available evidence at this time suggests that communication skills can be learned, decision aids may be helpful, and that shared decision-making may improve clinical outcomes.

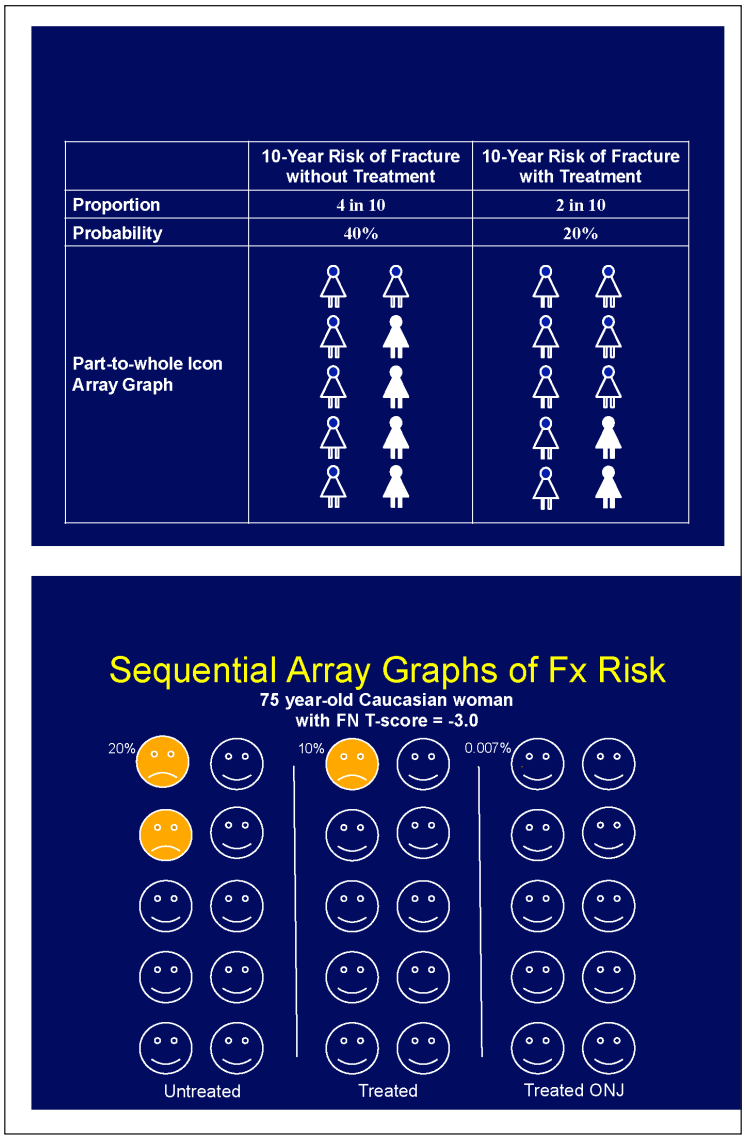

Fig. 3. Examples of visual depictions of fracture risk for use with patients.

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Co-Chairs

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Task Force Members

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Dima L. Diab, MD, FACE, FACP, CCD; Leslie S. Eldeiry, MD; Daniel L. Hurley, MD, FACP; Jennifer Kelly, DO, FACE; and Sunil J. Wimalawansa, MD, PhD, MBA, FCCP, FACP, FRCP, DSc, FACE: The authors have no multiplicity of interest to disclose.

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Rachel Pessah-Pollack, MD, FACE: Boehringer Ingelheim/Eli Lilly, speaker and advisor; Sanofi, consultant; Radius, advisor.

Michael McClung, MD, FACP, FACE: Amgen, Myovant, consultant; Amgen, speaker.

Nelson B. Watts, MD, FACP, CCD, FASBMR, MACE: Amgen, AbbVie, Sanofi, consultant; Amgen, Radius, speaker.

Reviewers

Donald A. Bergman, MD: Clinical Professor of Medicine, Icahn School of Medicine at Mount Sinai, New York, NY. Dr. Bergman has no multiplicity of interest to disclose.

Paul D. Miller, MD: Distinguished Clinical Professor of Medicine, University of Colorado Health Sciences Center, Medical Director, Colorado Center for Bone Research at Panorama Orthopedics and Spine Center, Golden, CO. Dr. Miller has received research grants from Alexion and Radius Health.

AACE/ACE 2020 POSTMENOPAUSAL OSTEOPOROSIS TREATMENT ALGORITHM

Lumbar spine or femoral neck or total hip T-score of ≤ -2.5, a history of fragility fracture, or high FRAX® fracture probability*

Evaluate for causes of secondary osteoporosis

Correct calcium/vitamin D deficiency and address causes of secondary osteoporosis

- Recommend pharmacologic therapy
- Education on lifestyle measures, fall prevention, benefits and risks of medications

High risk/no prior fractures**

- Alendronate, denosumab, risedronate, zoledronate***
- **Alternate therapy:** Ibandronate, raloxifene

Reassess yearly for response to therapy and fracture risk

Increasing or stable BMD and no fractures

Consider a drug holiday after 5 years of oral and 3 years of IV bisphosphonate therapy

Resume therapy when a fracture occurs, BMD declines beyond LSC, BTM's rise to pretreatment values or patient meets initial treatment criteria

Progression of bone loss or recurrent fractures

- Assess compliance
- Re-evaluate for causes of secondary osteoporosis and factors leading to suboptimal response to therapy

- Switch to injectable antiresorptive if on oral agent
- Switch to abaloparatide, romosozumab, or teriparatide if on injectable antiresorptive or at very high risk of fracture
- Factors leading to suboptimal response

ABBREVIATIONS GUIDE

BMD – bone mineral density
LSC – least significant change
BTM – bone turnover marker

Very high risk/prior fractures**

- Abaloparatide, denosumab, romosozumab, teriparatide, zoledronate***
- Alternate therapy: Alendronate, risedronate

Reassess yearly for response to therapy and fracture risk

Denosumab	Romosozumab for 1 year	Abaloparatide or teriparatide for up to 2 years	Zoledronate
Continue therapy until the patient is no longer high risk and ensure transition with another antiresorptive agent.	Sequential therapy with oral or injectable antiresorptive agent	Sequential therapy with oral or injectable antiresorptive agent	• If stable, continue therapy for 6 years**** • If progression of bone loss or recurrent fractures, consider switching to abalopa-ratide, teriparatide or romosozumab

* 10 year major osteoporotic fracture risk ≥ 20% or hip fracture risk ≥ 3%. Non-US countries/regions may have different thresholds.

** Indicators of very high fracture risk in patients with low bone density would include advanced age, frailty, glucocorticoids, very low T scores, or increased fall risk.

*** Medications are listed alphabetically.

**** Consider a drug holiday after 6 years of IV zoledronate. During the holiday, an anabolic agent or a weaker antiresorptive such as raloxifene could be used.

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Review Article

A narrative review of the pharmaceutical management of osteoporosis

Devon Patel[1], Courtney Gorrell[1], Jordan Norris[1], Jiayong Liu[2]^

[1]Department of Medical Education, University of Toledo College of Medicine and Life Sciences, Toledo, OH, USA; [2]Department of Orthopaedic Surgery, University of Toledo Medical Center, Toledo, OH, USA

Contributions: (I) Conception and design: J Liu; (II) Administrative support: J Liu; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: D Patel, C Gorrell, J Norris; (V) Data analysis and interpretation: D Patel, C Gorrell, J Norris; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Jiayong Liu, MD. Associate Professor, Department of Orthopaedic Surgery, University of Toledo Medical Center, 3065 Arlington Avenue, Toledo, OH 43614, USA. Email: jiayong.liu@utoledo.edu.

Background and Objective: Osteoporosis is a skeletal disorder classified by the loss of bone density in older adults leading to compromised bone strength and an increased risk of fracture. It can be divided into categories based on its etiology: senile, post-menopausal, and secondary osteoporosis. Specific prevention measures and treatments exist for targeting bone loss. Here we review and summarize the literature regarding the presentation of osteoporosis and discuss pharmaceutical therapies.

Methods: PubMed and Google Scholar were searched for articles published in English between 1980 and 2021. Search terms combined "senile osteoporosis", "osteoporosis treatment", "osteoporosis", "bisphosphonates", "denosumab", types of hormone therapy, and other relevant keywords used in various combinations.

Key Content and Findings: Osteoporosis affects millions but often goes undiagnosed until a pathologic fracture. Dual-energy X-ray absorptiometry (DEXA) scans evaluate bone mineral density (BMD) and are a diagnostic tool for osteoporosis. Adults over the age of 65, post-menopausal women, and those with risk factors such as previous fractures are recommended to receive DEXA scans every one to two years. Bisphosphonates, denosumab, and hormonal therapies are among the most common pharmacologic treatments for osteoporosis.

Conclusions: Daily, orally administered bisphosphonates are the first-line therapy for osteoporosis given their efficacy in decreasing fracture risk and favorable safety profile. Denosumab is an alternative that is administered subcutaneously every six months and may be given as initial therapy to select patients. Hormonal therapies are used if patients cannot tolerate bisphosphonates or denosumab or are refractory to these medications. Preventative measures for osteoporosis include tailored exercise and sufficient intake of calcium and vitamin D via diet or supplementation.

Keywords: Osteoporosis; pharmacology; bisphosphonates; denosumab

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^ ORCID: 0000-0002-5895-8276.

Introduction

Background

A 2014 study reported a 10.3% prevalence of osteoporosis among Americans 50 years or older, equating to 10.2 million people, with an additional 43.4 million experiencing low bone mass (1). Additionally, the annual healthcare cost of osteoporosis and related fractures was estimated to be $16 billion in 2008 (2). These costs are predicted to increase to $25.3 billion by 2025, with approximately 3 million fractures caused by the disorder (3). Deformities including kyphosis and related height loss often accompany senile osteoporosis (4). These financial and physical burdens are likely to grow along with the aging population in the coming years.

Rationale and knowledge gap

Current treatments for osteoporosis include lifestyle modification, pharmacological management, minimally invasive procedures, and extensive surgical treatments. However, only pharmacological management is recognized as treatment for the cause. There is limited literature that provides the efficacy of various medications for osteoporosis and other relevant pharmacological data in a single compiled manuscript.

Objective

The aim of this review is to focus on the pharmacological management of osteoporosis to provide a succinct source of data for practitioners. This review begins with an overview of osteoporosis and its diagnosis, then we discuss the specific medications that can be used to treat osteoporosis, starting with the first-line treatment of bisphosphonates and denosumab and then hormonal therapy. The efficacy of the various medications will also be discussed, along with comparisons between first- and second-line treatments. Finally, we present lifestyle modifications and nutrient supplementations that can influence the pathogenesis of osteoporosis. We present this article in accordance with the Narrative Review reporting checklist (available at https://aoj.amegroups.org/article/view/10.21037/aoj-23-2/rc).

Methods

A comprehensive search of PubMed and Google Scholar was conducted for articles published between 1980 and 2021 in English (*Table 1* and Table S1). Search terms included “osteoporosis”, “senile osteoporosis”, “osteoporosis pharmacology”, and “treatment”. Other relevant keywords were included in various combinations for searches. Articles were also collected by critically examining the reference lists of publications found in the database search. Exclusion criteria included cadaveric studies.

Discussion

Pathophysiology

Osteoporosis may be of a primary or secondary origin, with primary osteoporosis arising more frequently in post-menopausal women but affecting both sexes in old age as bone density and estrogen levels naturally decline (5). Secondary osteoporosis results when the decreased bone density is due to another conduction, such as hypogonadism or celiac disease, or medications, such as glucocorticoids (6).

Osteoporosis reduces bone volume and integrity, rendering patients vulnerable to fracture and deformity. This can be attributed to an imbalance of osteoblast and osteoclast activity, which results in unequal bone formation and bone reabsorption, respectively (7). Estrogen deficiency may also lead to osteoporosis as estrogen plays an important role in increasing the storage pool of pre-osteoclasts, as well as upregulating transforming growth factor beta (TGF-β), a cytokine that decreases osteoclast activity. Calcium and vitamin D deficiencies also increase the risk of developing osteoporosis because when less calcium is absorbed from the intestinal tract, there is an increased release of stored calcium via osteoclasts in bones to increase serum calcium. The increased osteoclastic activity causes further bone loss and an increased risk of fractures (5).

It is estimated that 1 in 2 women along with up to 1 in 4 men 50 years old and older living with osteoporosis will break a bone due to the disorder. Since osteoporosis weakens bone strength, bone fractures are typically the first sign of the disorder, as one is not able to feel their bones weakening. These fractures are mostly seen in the hip, distal radius, and spine. While these are the frequently seen fractures, there has been an increase in the number of fractures and the types of fractures that should be considered osteoporotic (4). Those who experience a fracture are at an increased risk of subsequent fractures in the future: 10% within one year, 18% within two years, and 31% within 5 years (8). Kyphosis is another sign seen in those with osteoporosis, which can lead to visible height loss (4).

Table 1 The search strategy summary

Items	Specification
Date of search	March 30, 2022
Databases and other sources searched	PubMed, Google Scholar
Search terms used	Osteoporosis, Osteoporosis treatment, Senile osteoporosis, Osteoporosis pharmacology, Osteoporosis medication, Bisphosphonate, Alendronate, Ibandronate, Risedronate, Zoledronate, Denosumab, Raloxifene, Teriparatide, Abaloparatide, Calcitonin
Timeframe	1980–2021
Inclusion and exclusion criteria	Inclusion criteria: (I) written in English; (II) reporting various outcome measurements of different medications; (III) peer-reviewed
	Exclusion criteria: (I) articles not written in English; (II) studies only reporting drug-induced osteoporosis; (III) posters or abstracts at annual meetings; (IV) graduate theses without peer-reviewed publication of an article
Selection process	Three authors independently reviewed the title and abstracts of each article identified in the search. If the articles were appropriate and additional information was necessary, full-text articles were retrieved and data were extracted. If three authors differed on whether to include an article, the fourth author was consulted to achieve consensus

Table 2 National Osteoporosis Foundation DEXA scan recommendations

Women	Men
Age 65 and older	Age 70 and older
Age below 65 and post-menopausal	Age 50–69 with risk factors
Age 50 and older with history of fracture in adulthood	

DEXA, dual-energy X-ray absorptiometry.

Diagnosis

Fractures are typically the first indicator of osteoporosis, as age-related loss of bone density is otherwise difficult to perceive. Estimates of bone mineral density (BMD) can be made using noninvasive dual-energy X-ray absorptiometry (DEXA). The National Osteoporosis Foundation (NOF) recommends BMD testing via DEXA based on age, sex, and risk factors (9) (*Table 2*). After diagnosis and initiation of therapy, BMD testing should be repeated every two years, and more often in the case of recurring fractures (10). The time between scans can also be increased to 15 years in patients with normal BMD or mild osteopenia or five years in patients with moderate osteopenia (11). Osteopenia can be distinguished from osteoporosis by the T-score of BMD testing, with a T-score between –1.01 and –2.49 indicating osteopenia and –2.50 or lower being osteoporosis (11). While it is important to note that BMD test results do not always correlate with fracture probability, early identification of low BMD can inform preventative clinical decision-making (12).

Pharmacological management

First line—bisphosphonates

Mechanism of action and efficacy

Bisphosphonates are Food and Drug Administration (FDA)-approved for the prevention and treatment of osteoporosis. Due to their high affinity for bone mineral and ability to bind to hydroxyapatite crystals, these drugs work well to inhibit osteoclast activation and decrease bone resorption, thereby decreasing bone loss (13-15). The mechanism of action for bisphosphonates varies by generation due to the difference in structure. First-generation non-nitrogen-containing bisphosphonates are incorporated into nonhydrolyzable adenosine triphosphate (ATP) once taken up by osteoclasts on the bone surface. These nonhydrolyzable ATP accumulate, inhibiting numerous ATP-dependent cellular processes, which leads to osteoclast apoptosis. Examples of first-generation bisphosphonates include etidronate, clodronate, and tiludronate. Second- and third-generation bisphosphonates, also called aminobisphosphonates, contain a nitrogen side chain, which allows the drug to inhibit the continuation of the mevalonic acid pathway by binding to and inactivating farnesyl

pyrophosphate synthase. This disruption further causes inhibition of posttranslational modifications of proteins, causing osteoclast apoptosis. Alendronate, risedronate, ibandronate, pamidronate, and zoledronic acid are a few of the second- and third-generation bisphosphonates. Another differentiation between the classes of drugs is what cells they target. Non-nitrogen-containing bisphosphonates can affect mammalian cells expressing farnesyl pyrophosphate synthase, whereas nitrogen-containing-bisphosphonates only cause apoptosis in osteoclasts due to their selective affinity to bone mineral (15). This differentiation could be a contributing factor to why nitrogen-containing bisphosphonates are the favorable choice for the treatment of osteoporosis.

Bisphosphonates can be administered orally after a prolonged fast with water and nothing by mouth for 30–60 minutes after or given intravenously (16). The most common side effects are gastrointestinal, including reflux and esophagitis (17). Some rare adverse complications of bisphosphonates include osteonecrosis of the jaw and atypical fractures (16). The use of bisphosphonates and osteonecrosis of the jaw appear to be more prevalent in patients with cancer, but a causal linkage has not been established due to the small number of cases. Similarly, more conclusive data are needed to associate atypical fractures and bisphosphonates as some reports make it difficult to distinguish if the cause of these fractures is due to the medication use or osteoporosis. Despite having a short plasma half-life, bisphosphonates can remain in bone for years (16,18).

Alendronate, an aminobisphosphonate, is one of the most popular prescribed medications for osteoporosis treatment, with approximately 2.01 million US patients estimated to be taking the drug in 2020, according to the Medical Expenditure Panel Survey (MEPS) administered by the Agency for Healthcare Research and Quality (AHRQ) (19). Specifically, for postmenopausal osteoporosis, alendronate has been the most popular anti-osteoporosis drug since 1996 (20). Alendronate decreases the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women when compared to calcium and vitamin D supplementation (21). Over two years, daily administration of alendronate, 10 mg, increased BMD in the lumbar spine and total hip by 7.4% and 4.3%, respectively (*Table 3*). This was a slightly higher increase when compared to a once-weekly administration of alendronate, 70 mg, with lumbar spine and total hip results of 6.8% and 4.1%, respectively. Because these two administration frequencies are therapeutically equivalent, it is suggested to prescribe the once-weekly regimen as it is more convenient and can enhance compliance (40,41).

In terms of fracture risk for postmenopausal women, daily alendronate for one year provided a 47% risk reduction in nonvertebral fractures relative to a placebo (42). Daily alendronate can be tolerable for an extended period, with some treatments lasting up to 10 years. During a 10-year treatment of 10 mg daily alendronate, an increase in BMD was seen, with the greatest in the lumbar spine (13.7%), followed by the trochanter (10.3%), total proximal femur (6.7%), and femoral neck (5.4%) (22).

In men with osteoporosis, alendronate significantly increases the BMD of the spine, hip, and total body, along with decreasing the incidence of vertebral fractures over nonvertebral fractures (23,24).

Another aminobisphosphonate that can be used in osteoporosis treatment is ibandronate. Ibandronate can significantly increase BMD after 12 months of treatment. Administration of ibandronate in postmenopausal women after a cementless total hip arthroplasty can decrease the amount of bone loss within six months (43). Of note, ibandronate has been shown to only prevent spinal fractures and not hip or non-vertebral fractures, despite increasing BMD (21,44).

Risedronate is a third-generation aminobisphosphonate that is suggested to be one of the first bisphosphonates prescribed when treating osteoporosis. Over three years, risedronate has been shown to reduce the rate of vertebral fractures by 41% and nonvertebral fractures by 39% (25). In terms of BMD, when compared to placebo, risedronate had a greater effect on increasing the BMD of the lumbar spine, femoral neck, femoral trochanter, and midshaft of the radius (25). For women with osteoporosis, between the ages of 70–79, the incidence of hip fractures when treated with risedronate is notably lower than the placebo group, 1.9% and 3.2% respectively (45). Risedronate is more potent than alendronate, but overall leads to less of an increase in BMD; however, it remains a viable treatment, especially when considering patients who cannot tolerate the gastrointestinal side effects of alendronate (21,46,47).

Zoledronate is an intravenous aminobisphosphonate that can be administered once yearly and has the highest potency in its class. In postmenopausal women, it considerably decreased the risk of morphometric vertebral fracture by 70% and hip fractures by 41%. Zoledronate was also shown to decrease the risk of nonvertebral and clinical vertebral fractures by 25% and 77%, respectively. Additionally, it markedly increased the BMD of the total hip (6.02%),

Table 3 Commonly prescribed anti-osteoporosis medications and their clinical outcomes (16,22-39)

Drug	Mean effect on BMD				Mean effect on fracture risk/incidence		
	Lumbar spine	Total hip	Femur	Radius	Vertebral	Nonvertebral	Hip
Bisphosphonate							
Alendronate (Fosamax)	↑ 7.1–7.4% Over 2 years[†a] ↑ 13.7% Over 10 years[†a] ↑ 7.1% Over 2 years[‡a]	↑ 4.3% Over 2 years[†a]	Trochanter: ↑ 2.5% Over 2 years[†a] ↑ 13.7% Over 10 years[†a] Proximal: ↑ 6.7% Over 10 years[†a] Neck: ↑ 5.4% Over 10 years[†a] ↑ 2.5% Over 2 years[‡a]	–	RR =0.41 ↓ 59% RR =0.33[‡]	–	–
Ibandronate (Boniva)	–	–	–	–	RR =0.28 (non-significant)	–	–
Risedronate (Actonel)	↑ 5.4% Over 3 years[†a]	–	Trochanter: ↑ 3.3% Over 3 years[†a] Neck: ↑ 1.6% Over 3 years[†a]	↑ 0.2% Over 3 years[†a]	↓ 41% Over 3 years[†a] ↓ 65% Over 1 year[†a]	↓ 39% Over 3 years[†a]	–
Zoledronate (Reclast)	↑ 6.71% Over 3 years[†b]	↑ 6.02% Over 3 years[†b]	Neck: ↑ 5.06% Over 3 years[†b]	–	Morphometric: ↓ 70% Over 3 years[†b] Clinical: ↓ 77% Over 3 years[†b]	↓ 25% Over 3 years[†b]	↓ 40% Over 3 years[†b]
RANKL inhibitor							
Denosumab (Prolia)	–	–	–	–	Radiographic: ↓ 68% Over 3 years[†c]	↓ 20% Over 3 years[†c]	↓ 40% Over 3 years[†c]

Table 3 (*continued*)

Table 3 (*continued*)

Drug	Mean effect on BMD				Mean effect on fracture risk/incidence		
	Lumbar spine	Total hip	Femur	Radius	Vertebral	Nonvertebral	Hip
Hormones							
Raloxifene (Evista)	60 mg: ↑ 2.5–2.6% Over 4 years[†a] 120 mg: ↑ 2.6–2.7% Over 3 years[†a]	–	60 mg: neck: ↑ 2.1% Over 4 years[†a] 120 mg: neck: ↑ 2.3–2.4% Over 3 years[†a]	–	–	–	–
Teriparatide (Forteo)	20 microg: ↑ 9% Over 21 months (average)[†a] ↑ 7.2% Over 18 months[§a] 40 microg: ↑ 13% Over 21 months (average)[†a] ↑ 17.8% Over 30 months[†a]	20 microg: ↑ 3.8% Over 18 months[§a] 40 microg: ↑ 8.1% Over 30 months[†a]	20 microg: neck: ↑ 3% Over 21 months (average)[†a] 40 microg: neck: ↑ 6% Over 21 months (average)[†a] ↑ 10.8% Over 30 months[†a]	40 microg: ↓ 7.1% Over 30 months[†a]	RR =0.40 (not significant)	RR =0.52 (not significant)	–
Calcitonin (Miacalcin)	–	–	–	–	200 IU: ↓ 33%[a]	RR =0.80 (not significant)	–

[a], indicates daily administration; [b], indicates yearly administration; [c], indicates biannual administration. [†], indicates in postmenopausal women; [‡], indicates in men; [§], indicates in men and women glucocorticoid-induced osteoporosis. ↑, indicates an increase; ↓, indicates a decrease. BMD, bone mineral density; RR, risk ratio.

lumbar spine (6.71%), and femoral neck (5.06%) (26). When comparing three and six years of zoledronate infusions, there were no significant differences in the incidence of clinical fractures; meanwhile, there were increases, albeit non-significant, in serious atrial fibrillation events and stroke in the group receiving six years of treatment, showing zoledronate is preferred in a three-year regimen (48). Interestingly, a single infusion has been shown to have a similar reduction in fracture rate compared to three infusions, 32% and 34%, respectively (49). Further studies are needed to directly compare the efficacy of zoledronate and oral bisphosphonates.

Depending on the patient's risk of fractures, a bisphosphonate drug holiday could be warranted. Because bisphosphonates accumulate in bone and continue to have effects after discontinuation of treatment, it is not necessary for low-risk patients to continue the regimen. For these patients, treatment can be stopped after approximately five years and does not need to continue if bone density is stable and there are no fractures. For higher-risk patients, bisphosphonate therapy can be initiated for 10 years followed by a holiday of one or two years, maximum. Non-bisphosphonate therapy could be indicated for higher-risk patients during their drug holiday (16). The length of the drug holiday depends on the specific bisphosphonate. For example, discontinuation from risedronate would have a

shorter drug holiday (1–2 years) compared to zoledronate (3–6 years) (50). During the drug holiday, the patient's bone density and relevant markers should be monitored (16). For all patients, if there is a fracture or other factors arise that increase fracture risk, then bisphosphonate or other osteoporosis therapy should be initiated.

Second line—denosumab and hormonal therapy

Denosumab: mechanism of action and efficacy

Denosumab is a human monoclonal antibody that decreases bone resorption by inhibiting receptor activator of nuclear factor kappa-B ligand (RANKL), which is involved in the formation and activation of osteoclasts. It is administered every six months subcutaneously by a healthcare professional, benefiting those patients who cannot use oral therapy or are at high risk for fractures (27,51,52). Fatigue and weakness are some adverse effects associated with denosumab (53). It has been shown to decrease hip, vertebral, and non-vertebral fractures when compared to calcium and vitamin D supplementation (52). In postmenopausal women, denosumab reduced the risk of radiographic vertebral fractures by 68%, hip fractures by 40%, and non-vertebral fractures by 20% (28). After discontinuation of denosumab, or other anabolic treatments, patients should transition to oral bisphosphonates to prevent bone loss (51).

Hormonal therapy: mechanism of action and efficacy

Hormonal therapy can also be implemented for the prevention and treatment of postmenopausal osteoporosis. However, the use of hormone replacement therapy has declined due to increasing the risk of cardiovascular complications, including stroke and coronary heart disease, and breast cancer (21,52,54,55). One class of hormone therapy is selective estrogen receptor modulators (SERMs), such as raloxifene. Depending on the target tissue, SERMs act as estrogen receptor agonists or antagonists (56). Raloxifene is the only drug of its class to be approved for the prevention and treatment of osteoporosis (16). It is administered daily by mouth and decreases the risk of vertebral fractures only (29,30). Before prescribing, the benefits of raloxifene should be weighed against the potential adverse effects, such as venous thromboembolism. Combination therapy, such as estrogen-plus-progestin, has been shown to reduce the risk of hip, vertebral, and wrist fractures (54). Even so, the risks of cardiovascular disease and breast cancer do not outweigh the benefits, so it is recommended that these therapies be limited in their usage and not used for long-term treatment (54,57).

Another class of hormones that has been evaluated for the prevention and treatment of osteoporosis is parathyroid hormone analogs, such as teriparatide and abaloparatide. Teriparatide is an anabolic agent that has been shown to increase bone mass by stimulating osteoblasts (31,58). It increases vertebral and hip BMD more than alendronate (32,33,59). Abaloparatide has also been implicated in better reducing the risk of vertebral fracture than alendronate, but additional studies are needed to strengthen this finding (60).

Calcitonin, a thyroid hormone, is indicated for the treatment of osteoporosis in women who have been postmenopausal for at least five years (16). Calcitonin inhibits bone resorption by disrupting the ruffled border of osteoclasts, which causes the cells to move away from bone and thus decreases resorption (61). These morphological changes are observed as soon as 15 minutes after treatment and reach maximal effect within 1 hour (61). Calcitonin is primarily administered intranasally, whereas in the past it was parenterally administered. The efficacy of calcitonin has been variable due to several limitations in multiple studies. However, a meta-analysis by Cranney *et al.* [2002] suggested that calcitonin can increase bone density in postmenopausal women and potentially decrease the risk of vertebral fracture (62). Future studies need to address the potential publication bias surrounding calcitonin's efficacy in treating osteoporosis. An interesting clinical application of calcitonin would be its use as an analgesic to relieve osteoporotic bone pain, but more studies are needed to understand this mechanism since it is independent of calcitonin's metabolic effect (63).

Comparison of first and second line

Even though bisphosphonates are typically the first-line treatment for osteoporosis, denosumab and other effective medications contribute to the controversy around osteoporosis treatment. Multiple meta-analyses have demonstrated denosumab increases BMD of the distal radius, femoral neck, lumbar spine, and total hip, more so than bisphosphonates, but does not decrease the fracture risk relative to bisphosphonates (64-66). Therefore, denosumab and bisphosphonates may be indicated for two different populations: denosumab for patients at low-risk for fracture with low BMD and bisphosphonates for patients at high-risk for fracture regardless of BMD. Additionally, denosumab and other non-oral medications are indicated for patients who cannot take oral medications or who have not responded to bisphosphonates (52). The American College of Physicians (ACP) strongly recommends

treatment with alendronate, risedronate, zoledronate, or denosumab for women with known osteoporosis to reduce the risk for hip and vertebral fractures (67). However, there are fewer studies involving men with osteoporosis, so the ACP weakly recommends bisphosphonates to decrease the risk of vertebral fractures in men with clinically recognized osteoporosis (67). It is also important for practitioners to consider patients' access to healthcare and the feasibility of a medication regimen. For example, elderly patients, who are typically affected by osteoporosis, may have difficulty traveling to receive treatment that needs to be administered by a healthcare professional, such as zoledronate or denosumab. In these instances, an oral pill that could be taken at home would be preferable. However, a medication only administered once a year could be preferred over a pill that needs to be taken daily. Because of the various treatment methods, it is important to discuss the different regimens with the patients to ensure compliance with the regimen.

Lifestyle and supplement prevention methods

Osteoporosis may be prevented by altering modifiable risk factors such as inadequate exercise and nutrition (68). Walking and low-impact aerobic exercise can prevent a decrease in BMD, while high-impact aerobic exercise and weight training can increase BMD in the hips and lumbar spine (69). As BMD naturally declines with age, effective prevention can begin early to ensure healthy development before BMD peaks in the third and fourth decades of life (70). High-impact exercise such as jumping leads to increased bone mass in children that can be maintained for several years (71). However, these benefits are diminished in post-menopausal women, emphasizing the importance of early prevention (72). In cases of senile osteoporosis, exercise regimens must also be designed to diminish the potential for falls and fractures. Although there is no standardized exercise regimen for elderly patients, most focus on improving muscle strength and balance through resistance training, weight-bearing impact exercise, and functionally challenging mobility activities (68,73).

Certain nutrients, such as vitamin D and calcium, are essential for bone strength. However, there have been multiple observations of low vitamin D and calcium intake in the elderly (68,74). The NOF recommends postmenopausal women and men over 65 years old should consume at least 1,200 mg of elemental calcium daily; anyone over the age of 50 should consume at least 800–1,000 IU of vitamin D daily (75,76). Vitamin D-fortified foods have also been shown to significantly increase BMD, but adequate intake is uncommon in geographical areas with lesser annual sun exposure, suggesting many could benefit from supplementation (77,78). A meta-analysis conducted by the NOF found a 30% reduction in the risk of hip fractures and a 15% reduction in the risk of total fractures in adults with calcium plus vitamin D supplementation (79). While dietary modifications or supplementation can be highly beneficial to older adults at risk for osteoporosis, longitudinal optimization of intake beginning as early as childhood is ideal.

Strengths and limitations

This review summarizes the current literature on the pharmacology of osteoporosis and relevant clinical information, including physiology and effectiveness. By compiling this information in a single review, clinicians will have quicker access to relevant information and the original sources for further investigation. Despite these strengths, there are some limitations to this narrative review. There were only two databases searched and they were not exhaustively explored; the search was limited to the most relevant articles using select keywords. The quality of the studies referenced was not assessed using a standardized methodology, although the authors preferentially chose meta-analyses and systematic reviews. Another limitation is the relative lack of literature in certain osteoporotic populations, such as men or drug-induced; much of the studies focus on post-menopausal women. Future studies should address these other populations and include them in comparison studies between different classes of medications for osteoporosis.

Conclusions

Osteoporosis is a highly prevalent condition that is growing along with aging and expanding populations. It carries a large financial burden, and its related fractures can significantly decrease quality of life. Despite the availability of DEXA, many cases of osteoporosis are not diagnosed until a fracture occurs. These often include vertebral compression fractures, hip fractures, and distal radius fractures, which can cause significant pain and functional impairment. First-line treatment for osteoporosis includes bisphosphonates, which can increase lumbar spine BMD between 5.4% (risedronate over three years) and 13.7% (alendronate over 10 years) and femur BMD between

1.6% (femoral neck, risedronate over three years) and 13.7% (femoral trochanter, alendronate over 10 years). Bisphosphonates also decrease the incidence/risk of fracture, ranging from a 25% decrease (nonvertebral fracture, zoledronate over three years) to a 77% decrease (vertebral fracture, zoledronate over three years). Denosumab is a RANKL inhibitor that can decrease the risk of radiographic vertebral fractures by 68% when used over three years. Hormone therapy can also be used to manage osteoporosis if the first-line treatments are not possible or patients are refractory to them. Raloxifene, a SERM, can increase lumbar spine and femoral neck BMD by approximately 2.6% and 2.3%, depending on the dosage. Teriparatide, a parathyroid hormone analog, can increase lumbar spine BMD between 7.2% and 17.8%, depending on time and dosage. Prevention measures include BMD-promoting exercise and dietary adjustment in earlier life, which may also slow BMD decline in older adults. Educating young patients about osteoporosis may prompt them to adopt lifestyle changes that can prevent exacerbation of the condition in old age. Adoption of BMD screening can help identify early cases of osteoporosis that could benefit from medical intervention. Future development of medical devices, surgical techniques, and medications could minimize complications and burdens of living with osteoporosis. Similarly, additional research may identify previously unrecognized preventative measures.

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Footnote

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Supplementary

Table S1 Search strategy

Databases	PubMed, Google Scholar
Search Term (MeSH terms)	Osteoporosis Osteoporosis treatment Senile osteoporosis Osteoporosis pharmacology Osteoporosis medication Bisphosphonate Alendronate Ibandronate Risedronate Zoledronate Denosumab Raloxifene Teriparatide Abaloparatide Calcitonin
Search Query	((((“osteoporosis”[All Fields] OR “senile osteoporosis”[All Fields]) AND “osteoporosis treatment”[All Fields]) OR ((“osteoporosis”[MeSH Terms] OR “osteoporosis”[All Fields] OR “osteoporoses”[All Fields] OR “osteoporosis, postmenopausal”[MeSH Terms] OR (“osteoporosis”[All Fields] AND “postmenopausal”[All Fields]) OR “postmenopausal osteoporosis”[All Fields]) AND (“pharmacology”[MeSH Terms] OR “pharmacology”[All Fields] OR “pharmacologies”[All Fields] OR “pharmacology”[MeSH Subheading])) OR “osteoporosis medication”[All Fields]) AND (“bisphosphonate”[All Fields] OR “alendronate”[All Fields] OR “ibandronate”[All Fields] OR “risedronate”[All Fields] OR “zoledronate”[All Fields] OR “denosumab”[All Fields] OR (“raloxifene”[All Fields] OR “teriparatide”[All Fields] OR “abaloparatide”[All Fields] OR “calcitonin”[All Fields]))) AND ((1980:2021[pdat]) AND (english[Filter]))

Each part was translated for searching other databases.

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REVIEW

Annals of Internal Medicine

Effectiveness and Safety of Treatments to Prevent Fractures in People With Low Bone Mass or Primary Osteoporosis: A Living Systematic Review and Network Meta-analysis for the American College of Physicians

Chelsea Ayers, MPH; Devan Kansagara, MD, MCR; Brittany Lazur, MPH; Rongwei Fu, PhD; Amy Kwon, MD; and Curtis Harrod, PhD, MPH

Background: The prevalence of osteoporosis is increasing in the United States.

Purpose: To evaluate low bone mass and osteoporosis treatments to prevent fractures.

Data Sources: Ovid MEDLINE ALL, Ovid Evidence Based Medicine Reviews: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov from 2014 through February 2022.

Study Selection: Adults receiving eligible interventions for low bone mass or osteoporosis. Randomized controlled trials (RCTs) for fracture outcomes, and RCTs and large observational studies ($n \geq 1000$) for harms.

Data Extraction: Abstracted by 1 reviewer and verified by a second. Independent, dual assessments of risk of bias and certainty of evidence (CoE).

Data Synthesis: We included 34 RCTs (in 100 publications) and 36 observational studies. Bisphosphonates and denosumab reduced hip, clinical and radiographic vertebral, and other clinical fractures in postmenopausal females with osteoporosis (moderate to high CoE). Bisphosphonates for 36 months or more may increase the risk for atypical femoral fractures (AFFs) and osteonecrosis of the jaw (ONJ), but the absolute risks were low. Abaloparatide and teriparatide reduced clinical and radiographic vertebral fractures but increased the risk for withdrawals due to adverse events (WAEs; moderate to high CoE). Raloxifene and bazedoxifene for 36 months or more reduced radiographic vertebral but not clinical fractures (low to moderate CoE). Abaloparatide, teriparatide, and sequential romosozumab, then alendronate, may be more effective than bisphosphonates in reducing clinical fractures for 17 to 24 months in older postmenopausal females at very high fracture risk (low to moderate CoE). Bisphosphonates may reduce clinical fractures in older females with low bone mass (low CoE) and radiographic vertebral fractures in males with osteoporosis (low to moderate CoE).

Limitation: Few studies examined participants with low bone mass, males, or Black-identifying persons, sequential therapy, or treatment beyond 3 years.

Conclusion: Bisphosphonates, denosumab, abaloparatide, teriparatide, and romosozumab, followed by alendronate, reduce clinical fractures in postmenopausal females with osteoporosis. Abaloparatide and teriparatide increased WAEs; longer duration bisphosphonate use may increase AFF and ONJ risk though these events were rare.

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For author, article, and disclosure information, see end of text.
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Osteoporosis is characterized by reduced bone mass, resulting in bone weakness and increased susceptibility to fractures (1, 2). Bone mineral density (BMD) assessment is used to diagnose low bone mass and osteoporosis. The World Health Organization defines low bone mass as a BMD T-score between 1 and 2.5 SDs below average for young healthy females (2) and osteoporosis as 2.5 or fewer SDs below average (2). Some guidelines expand the definition of osteoporosis to include a history of certain low-trauma fractures in the absence of subthreshold T-scores (3). By the standard definition, almost 20% of U.S. females older than age 50 years were estimated to have osteoporosis in 2018, up from 14% a decade earlier, along with more than 4% of males in this age group (4). The aging population is projected to increase these figures. Given the increasing prevalence and effect of osteoporosis, and the availability of newer medications, we conducted a systematic review and network meta-analysis (NMA) to better understand treatments to prevent fractures in those with low bone mass or osteoporosis.

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METHODS

Our review was commissioned by the American College of Physicians (ACP) to inform an update of ACP's clinical practice guideline on treatments for osteoporosis by their Clinical Guidelines Committee (CGC). A protocol describing the review plan was registered to PROSPERO (CRD42021236220). A technical expert panel (TEP) informed our protocol and analyses.

Data Sources and Searches

To identify relevant studies, we searched Ovid MEDLINE ALL, Ovid Evidence Based Medicine (EBM) Reviews: Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, and ClinicalTrials.gov from 2014 through February 2022. We used a prior review (5) to identify studies published before 2014. Search strategies were developed in consultation with a librarian and peer reviewed by another using the Peer Review of Search Strategies guidelines (6) (Search Strategy in the **Supplement**, available at Annals.org).

Study Selection

We included English-language randomized controlled trials (RCTs) in females or males with low bone mass or osteoporosis not due to a secondary cause (for example, glucocorticoid therapy) comparing 1 or more pharmacologic interventions of interest to each other or placebo. Included interventions were bisphosphonates (alendronate, ibandronate, risedronate, and zoledronate), parathyroid hormones (PTHs; abaloparatide and teriparatide), receptor activator of nuclear factor κB ligand inhibitors (denosumab), selective estrogen receptor modulators (SERMs; raloxifene and bazedoxifene), and sclerostin inhibitors (romosozumab). Although our initial protocol included vitamin D and calcium as eligible interventions and comparators, we ultimately relied on a recent, high-quality systematic review to summarize effectiveness and harms (details in the **Supplement**), and combined vitamin D and calcium comparators with other placebo comparisons as all participants received or used these supplements in studies with supplementation.

We included RCTs reporting fractures as efficacy outcomes (rather than safety outcomes) with 12 months or more of follow-up. Adverse events (AEs) of interest included serious AEs (SAEs) and withdrawals due to AEs (WAEs) as reported in trials, osteonecrosis of the jaw (ONJ), atypical femoral fractures (AFFs), and atrial fibrillation (AF). Case–control and cohort studies were eligible if they were large ($n > = 1000$) and evaluated ONJ, AFFs, or AF. We also included studies reporting quality of life (QoL) and functionality, and systematic reviews on cost-effectiveness and patient values and preferences (details in the **Supplement**).

Two independent reviewers screened studies, with disagreements settled by a third.

Data Extraction and Quality Assessment

One reviewer abstracted study characteristics and outcomes data and a second verified accuracy. The primary fracture reduction outcomes of interest were hip, vertebral (clinical or radiological), clinical nonvertebral (symptomatic fractures at sites beyond the vertebrae, which typically excluded minor fractures such as those of the digits), and any clinical fractures (a composite of clinical vertebral and nonvertebral factures).

Two reviewers independently assessed risk of bias (RoB) of included studies using the Cochrane RoB 2.0 tool for RCTs (7) and SIGN (Scottish Intercollegiate Guidelines Network) checklists 3 and 4 for cohort and case–control studies (8, 9), with disagreements settled by a third reviewer.

Data Synthesis and Analysis

When data were sufficient, we conducted quantitative syntheses using pairwise meta-analysis (all outcomes from RCTs and specific harms from observational studies) and NMA (RCTs only). All outcomes were binary, with risk ratios (RRs) and risk differences as the effect measures. We narratively synthesized all other outcomes.

For pairwise meta-analyses, we used a random-effects model based on the profile likelihood method to combine each outcome (10). We stratified analyses by treatment and study duration (12 to <36 or ≥36 months) and evaluated statistical heterogeneity using the Cochran χ^2 test and the I^2 statistic (11). We separately analyzed the following populations: postmenopausal females, males with osteoporosis, and those with low bone mass. We also conducted sensitivity analyses by excluding mixed gender studies that did not stratify their results.

For NMAs, we tested network consistency by comparing direct and indirect estimates, the node-splitting method, and an overall test from an inconsistency model (11). We restricted NMAs to only postmenopausal females with osteoporosis to improve the plausibility of the transitivity assumption. Although limited data were available to form closed loops and test the consistency assumption in the treatment networks, there was no evidence of inconsistency. Therefore, multivariate random-effects NMAs were conducted to combine the direct and indirect evidence using a consistency model (11). All analyses were conducted using Stata/SE 16.1 (StataCorp). In this manuscript, we focused on comparisons with placebo and bisphosphonates and direct head-to-head comparisons if they were statistically significantly different (see the **Supplement** for indirect comparisons).

Through consultation with our TEP and evaluation of statistical heterogeneity, we determined it was appropriate to combine bisphosphonates as a drug class in our meta-analyses and NMAs, which was also done by other reviews (12, 13). Due to a limited number of eligible studies for drugs in other classes, we did not combine those therapies in our analyses.

We assigned fracture and harm outcomes a certainty of evidence (CoE) rating based on the system developed by the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group (14, 15) for pairwise (direct) and NMA estimates. When interpreting effect sizes, we prioritized NMA estimates unless the pairwise estimate was higher CoE. This systematic review will be maintained as a living review with periodic literature searches and updates as new studies emerge. We will consider quantitative and qualitative factors, such as CoE, balance between benefits and harms, and contextual considerations in assessing whether the new evidence may lead to meaningful changes to the recommendations and an update is warranted. The ACP CGC may decide to retire the topic from living status if it is no longer considered a priority for decision making, when there is confidence that conclusions are not likely to change with new evidence, or if it becomes unlikely that new evidence will emerge.

Role of the Funding Source

ACP provided funding, and members served on our TEP and evaluated the protocol, analyses, and manuscript.

RESULTS

We screened 5143 citations and included 136 articles, including 34 RCTs (16–49) in 100 publications (16–115) and 36 observational studies (116–151) (literature flow diagram [**Appendix Figure 145** of the **Supplement**]; study characteristics [**Appendix Table 26** and **Appendix Table 27** of the **Supplement**]). Most studies included postmenopausal females meeting diagnostic criteria for osteoporosis because of low BMD T-scores and/or history of fragility fractures. Our sensitivity analyses excluding mixed gender studies did not reveal differences in direction or significance of effect; thus, we included them in the postmenopausal female analyses (**Appendix Figures 3** to **111** of the **Supplement**). **Table 1** provides an overview of findings for critical outcomes in postmenopausal females with osteoporosis. Meta-analysis and NMA results, including specific bisphosphonates studied by outcome, sample sizes contributing to each, and CoE rating details are in **Appendix Tables 1** to **21** of the **Supplement**. The RoB ratings are in **Appendix Table 29** of the **Supplement**.

Postmenopausal Females With Osteoporosis

Efficacy by Fracture Type

Hip Fractures. Compared with placebo, bisphosphonates reduced hip fracture risk for 24 months (RR, 0.65 [95% CI, 0.43 to 0.97]; moderate CoE) and 36 to 48 months (RR, 0.64 [CI, 0.50 to 0.82]; high CoE). Thirty-six months of denosumab also reduced hip fracture risk (RR, 0.61 [CI, 0.37 to 0.98]; moderate CoE), but teriparatide for 24 months and SERMs for 36 months did not (low CoE; **Appendix Table 1** of the **Supplement**).

In females at very high risk for fracture due to age and fracture history, sequential use of romosozumab then alendronate was more effective than alendronate alone in reducing hip fracture risk for 24 months (RR, 0.62 [CI, 0.42 to 0.91]; moderate CoE) (**Appendix Table 2** of the **Supplement**) (44).

Clinical Vertebral Fractures. We found moderate to high CoE that 12 to 36 months of bisphosphonates and 36 months of denosumab significantly reduced the risk for clinical vertebral fractures by 54% to 68% compared with placebo (**Appendix Table 3** of the **Supplement**). Teriparatide was associated with a 76% reduction in risk at 17 months, but the CoE for this finding was low (31). Romosozumab also reduced the risk for clinical vertebral fractures by 82% at 12 months, but the absolute difference was just 0.3% (112).

The only treatment more effective than bisphosphonates in reducing the risk for clinical vertebral fractures was the sequential use of romosozumab then alendronate for 24 months (moderate CoE; **Appendix Table 4** of the **Supplement**) (44).

Any Clinical Fractures. Between 12 and fewer than 36 months, all treatments except denosumab demonstrated reductions in clinical fracture risk compared with placebo (low to high CoE; **Appendix Table 5** of the **Supplement**). Bisphosphonates (high CoE) and denosumab (moderate CoE) reduced clinical fracture risk for 36 months or more, but bazedoxifene and raloxifene did not (low to moderate CoE; **Appendix Table 5** of the **Supplement**).

In females at very high risk for fracture, sequential romosozumab, then alendronate, was more effective for clinical fracture reduction than alendronate alone (RR, 0.74 [CI, 0.63 to 0.89]; moderate CoE) (44), and teriparatide was more effective than risedronate for 24 months (RR, 0.64 [CI, 0.43 to 0.95]; low CoE) (45). We found moderate CoE that abaloparatide (18 months; RR, 0.35 [CI, 0.15 to 0.81]) and raloxifene (12 months; RR, 0.17 [CI, 0.03 to 0.81]) were more effective than bisphosphonates, though in 36-month studies raloxifene was similarly effective (**Appendix Table 6** of the **Supplement**). In an 18-month, head-to-head RCT (41), abaloparatide reduced clinical fractures more than teriparatide (RR, 0.43 [CI, 0.21 to 0.90]; moderate CoE). Nonvertebral fractures alone are reported in **Appendix Table 9** and **Appendix Table 10** and **Appendix Figures 65** to **78** of the **Supplement**.

Radiographic Vertebral Fractures. We found moderate to high CoE that bisphosphonates reduced radiographic vertebral fracture risk between 12 and 48 months (RR, 0.44 [CI, 0.36 to 0.53]). Abaloparatide, teriparatide, denosumab, and romosozumab all reduced the risk for 12 to more than 36 months (moderate to high CoE), as did SERMs and denosumab for 36 months (moderate CoE; **Appendix Table 7** of the **Supplement**).

We also found moderate CoE that teriparatide and sequential romosozumab, then alendronate, were more effective than bisphosphonates at reducing radiographic vertebral fracture risk at 24 months (**Appendix Table 8** of the **Supplement**).

Adverse Events

Serious Adverse Events and Withdrawals due to Adverse Events. Thirty RCTs provided data on SAEs and WAEs (18–37, 39–47, 49). Regardless of study duration, no included interventions significantly increased the risk for SAEs compared with placebo or active controls (insufficient to high CoE; **Appendix Table 11** and **Appendix Table 12** of the **Supplement**). However, abaloparatide and teriparatide for any duration and raloxifene for 36 months or more significantly increased the risk for WAEs compared with placebo (low to high CoE; **Appendix Table 13** of the **Supplement**). Compared with bisphosphonates, we found significantly increased risk for WAEs with abaloparatide at 18 months (also higher when compared with teriparatide in the same trial) (41) and teriparatide and bazedoxifene at 36 months (**Appendix Table 14** of the **Supplement**). In trials of abaloparatide and teriparatide, WAEs were most commonly due to nausea, dizziness, vomiting, headache, palpitations, and leg cramps, whereas those for SERMs were primarily due to venous thromboembolism (**Appendix Table 18** of the **Supplement**).

Atypical Femoral or Subtrochanteric Fractures. We included 23 studies (in 29 publications) that evaluated an

Table 1. Overview of Findings for Critical Outcomes in Postmenopausal Females With Osteoporosis by Study Duration and Comparison*

Outcome	12 to <36 mo				≥36 mo to ≤60 mo			
	Versus Placebo	CoE	Versus BPs	CoE	Versus Placebo	CoE	Versus BPs	CoE
Bisphosphonates								
Hip fractures	0.65 (0.43–0.97)†	⊕⊕◯	–	–	0.64 (0.50–0.82)†	⊕⊕⊕	–	–
Clinical vertebral fractures	0.46 (0.24–0.89)†	⊕⊕⊕	–	–	0.38 (0.24–0.62)†	⊕⊕⊕	–	–
Any clinical fractures	0.68 (0.51–0.92)†	⊕⊕⊕	–	–	0.79 (0.68–0.91)†	⊕⊕⊕	–	–
Radiographic vertebral fractures	0.44 (0.36–0.53)†	⊕⊕◯	–	–	0.49 (0.40–0.61)†	⊕⊕⊕	–	–
Serious AEs	1.02 (0.85–1.22)	⊕⊕◯	–	–	1.00 (0.89–1.11)	⊕⊕⊕	–	–
Withdrawal due to AEs	1.01 (0.72–1.40)	⊕◯◯	–	–	0.94 (0.86–1.03)	⊕⊕⊕	–	–
	Specific harms from randomized and nonrandomized studies (vs. placebo or unexposed)							
Atypical femoral fractures	Increased risk after 3–5 y of use | Overall CoE: ⊕◯◯							
Osteonecrosis of the jaw	Increased risk after 2–3 y of use | Overall CoE: ⊕◯◯							
Atrial fibrillation	No difference | Overall CoE: ⊕◯◯							
PTH and PTHrP analogs								
Abaloparatide								
Hip fractures	–	–	–	–	–	–	–	–
Clinical vertebral fractures	–	–	–	–	–	–	–	–
Any clinical fractures	0.24 (0.11–0.53)†	⊕⊕◯	0.35 (0.15–0.81)†	⊕⊕◯	–	–	–	–
Radiographic vertebral fractures	0.14 (0.05–0.38)†	⊕⊕◯	0.31 (0.11–0.88)†	⊕◯◯	–	–	–	–
Serious AEs	0.89 (0.67–1.18)‡	⊕⊕◯	0.94 (0.65–1.37)	⊕◯◯	–	–	–	–
Withdrawal due to AEs	1.76 (1.30–2.39)†	⊕◯◯	1.75 (1.17–2.61)†	⊕◯◯	–	–	–	–
Teriparatide								
Hip fractures	0.50 (0.12–1.98)	⊕◯◯	Unclear	◯◯◯	–	–	–	–
Clinical vertebral fractures	0.24 (0.08–0.71)†	⊕◯◯	Unclear	◯◯◯	–	–	–	–
Any clinical fractures	0.44 (0.31–0.62)†	⊕⊕⊕	0.64 (0.43–0.95)†	⊕◯◯	–	–	–	–
Radiographic vertebral fractures	0.19 (0.14–0.26)†	⊕⊕⊕	0.43 (0.32–0.60)†	⊕⊕◯	–	–	–	–
Serious AEs	0.91 (0.69–1.21)‡	⊕⊕◯	1.05 (0.81–1.37)	⊕◯◯	0.77 (0.48–1.22)	⊕◯◯	0.77 (0.48–1.24)	⊕◯◯
Withdrawal due to AEs	1.32 (1.03–1.69)†	⊕⊕◯	1.31 (0.97–1.77)	⊕◯◯	2.93 (1.79–4.80)†	⊕⊕◯	3.11 (1.88–5.13)†	⊕◯◯
RANKL inhibitors								
Denosumab								
Hip fractures	–	–	–	–	0.61 (0.37–0.98)†	⊕⊕◯	0.94 (0.55–1.62)	⊕◯◯
Clinical vertebral fractures	Unclear	◯◯◯	Unclear	◯◯◯	0.32 (0.21–0.48)†‡	⊕⊕⊕	0.82 (0.33–2.06)	⊕◯◯
Any clinical fractures	1.00 (0.48–2.09)	⊕◯◯	Unclear	◯◯◯	0.81 (0.69–0.96)†‡	⊕⊕◯	1.03 (0.74–1.45)	⊕⊕◯
Radiographic vertebral fractures	0.27 (0.14–0.52)†	⊕⊕◯	Unclear	◯◯◯	0.32 (0.20–0.54)†	⊕⊕◯	0.66 (0.38–1.14)	⊕◯◯
Serious AEs	0.98 (0.66–1.46)	⊕⊕◯	Unclear	◯◯◯	1.03 (0.83–1.27)	⊕⊕◯	1.03 (0.82–1.31)	⊕⊕◯
Withdrawal due to AEs	Unclear	◯◯◯	Unclear	◯◯◯	1.15 (0.85–1.54)	⊕⊕◯	1.21 (0.89–1.65)	⊕◯◯
	Specific harms from randomized and nonrandomized studies (vs. placebo or unexposed)							
Atrial fibrillation	No difference | Overall CoE: ⊕◯◯							
Sclerosin inhibitors								
Romosozumab								
Hip fractures	–	–	–	–	–	–	–	–
Clinical vertebral fractures	0.18 (0.05–0.62)†	⊕⊕◯	0.38 (0.09–1.57)	⊕◯◯	–	–	–	–
Any clinical fractures	0.64 (0.47–0.89)†‡	⊕⊕◯	0.94 (0.51–1.76)	⊕◯◯	–	–	–	–
Radiographic vertebral fractures	0.27 (0.16–0.47)†	⊕⊕◯	0.62 (0.35–1.11)	⊕◯◯	–	–	–	–
Serious AEs	1.10 (0.95–1.27)‡	⊕⊕◯	1.08 (0.78–1.52)	⊕◯◯	–	–	–	–
Withdrawal due to AEs	0.88 (0.59–1.31)	⊕◯◯	0.87 (0.52–1.47)	⊕◯◯	–	–	–	–
	Specific harms from randomized and nonrandomized studies (vs. placebo or unexposed)							
Atypical femoral fractures	Unclear ◯◯◯							
Osteonecrosis of the jaw	Unclear ◯◯◯							
SERMs								
Bazedoxifene								
Hip fractures	–	–	–	–	0.93 (0.47–1.81	⊕◯◯	1.44 (0.70–2.95)	⊕◯◯
Clinical vertebral fractures	–	–	–	–	0.68 (0.29–1.60)	⊕⊕◯	1.76 (0.66–4.70)	⊕◯◯
Any clinical fractures	–	–	–	–	0.88 (0.64–1.22)	⊕◯◯	1.12 (0.79–1.59)	⊕◯◯
Radiographic vertebral fractures	–	–	–	–	0.59 (0.43–0.79)†‡	⊕⊕◯	1.20 (0.70–2.06)	⊕◯◯
Serious AEs	–	–	–	–	1.07 (0.85–1.34)	⊕⊕◯	1.07 (0.83–1.38)	⊕⊕◯
Withdrawal due to AEs	–	–	–	–	1.14 (1.01–1.30)†	⊕⊕◯	1.21 (1.04–1.41)†	⊕⊕◯
Raloxifene								
Hip fractures	–	–	–	–	1.12 (0.64–1.94)	⊕◯◯	1.73 (0.95–3.18)	⊕◯◯
Clinical vertebral fractures	0.05 (0.00–0.81)†	⊕◯◯	Unclear	◯◯◯	0.69 (0.38–1.27)	⊕⊕◯	Unclear	◯◯◯
Any clinical fractures	0.11 (0.02–0.54)†	⊕⊕◯	0.17 (0.03–0.81)†	⊕⊕◯	0.92 (0.72–1.16)	⊕⊕◯	1.16 (0.88–1.53)	⊕◯◯
Radiographic vertebral fractures	Unclear	◯◯◯	Unclear	◯◯◯	0.59 (0.48–0.71)†‡	⊕⊕◯	1.18 (0.78–1.81)	⊕◯◯
Serious AEs	Unclear	◯◯◯	Unclear	◯◯◯	0.99 (0.78–1.26)	⊕⊕◯	1.00 (0.77–1.30)	⊕⊕◯
Withdrawal due to AEs	Unclear	◯◯◯	Unclear	◯◯◯	1.14 (1.02–1.27)†	⊕⊕⊕	1.21 (1.05–1.39)†	⊕⊕◯

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Table 1–Continued

Outcome	12 to <36 mo				≥36 mo to ≤60 mo			
	Versus Placebo	CoE	Versus BPs	CoE	Versus Placebo	CoE	Versus BPs	CoE
Sequential therapy of romosozumab to alendronate								
Hip fractures	0.40 (0.23–0.70)†	⊕⊕◯	0.62 (0.42–0.91†	⊕⊕◯	–	–	–	–
Clinical vertebral fractures	0.19 (0.08–0.46)†	⊕⊕◯	0.41 (0.22–0.75)†	⊕⊕◯	–	–	–	–
Any clinical fractures	0.51 (0.29–0.89)†	⊕◯◯	0.74 (0.63–0.89)†‡	⊕⊕◯	–	–	–	–
Radiographic vertebral fractures	0.22 (0.16–0.31)†	⊕⊕◯	0.51 (0.39–0.66)†	⊕⊕◯	–	–	–	–
Serious AEs	0.97 (0.71–1.33	⊕⊕◯	0.96 (0.74–1.24)	⊕⊕◯	–	–	–	–
Withdrawal due to AEs	0.90 (0.61–1.35)	⊕◯◯	0.90 (0.72–1.13)	⊕⊕◯	–	–	–	–
	Specific harms from randomized and nonrandomized studies (vs. placebo or unexposed)							
Atypical femoral fractures				Unclear ◯◯◯				
Osteonecrosis of the jaw				Unclear ◯◯◯				

AE = adverse event; BP = bisphosphonate; CoE = certainty of evidence; Unclear = insufficient evidence from which to draw summary estimates. GRADE Certainty of Evidence: – = no evidence; ◯◯◯ = insufficient; ⊕◯◯ = low; ⊕⊕◯ = moderate; ⊕⊕⊕ = high.
* Shaded rows are harm outcomes. Details of the findings and CoE ratings can be found in Appendix Tables 1 to 138.
† Values are statistically significant.
‡ Estimates are from pairwise rather than network meta-analysis due to higher CoE.

eligible intervention for risk for AFFs; 10 were RCTs (17, 27, 28, 32, 34, 39, 42–44, 48) and 13 were observational studies (117, 120, 122, 125, 127, 129, 134, 135, 138, 139, 145, 146, 150).

Among 15 studies that compared bisphosphonates with placebo or unexposed participants, we found low CoE for an increased risk for AFFs, particularly after 3 to 5 years of treatment though AFF events were infrequent in most studies. The most pertinent data on AFF risk came from observational studies, as RCTs were underpowered or had inadequate follow-up to ascertain risk. Clinical and statistical heterogeneity prevented us from combining observational studies. Of note, 4 studies evaluated duration of bisphosphonate use. Three of these cohorts (117, 129, 150) (all in California) found AFF risk became more pronounced after 3 years of bisphosphonate use and increased with time (**Appendix Table 28** of the **Supplement**). One (117) also observed that females who identified as Asian, compared with non-Hispanic White, had higher risk for AFFs (595 vs. 109 per 100 000 person-years). The fourth study (122), in a Canadian cohort, found a statistically significant difference in AFFs only after 5 or more years of using bisphosphonates. Four other observational studies found a 26- to 55-fold greater risk for an AFF with bisphosphonate use, but these studies were not limited to females with osteoporosis and adjusted for few confounders in their models (120, 139). Several RCTs and observational studies evaluated other treatments and found either no or few AFFs or no significant differences between groups (**Appendix Table 15**) of the **Supplement**).

Osteonecrosis of the Jaw. Overall, we included 22 studies (in 33 publications) that evaluated an eligible intervention for risk for ONJ: 11 RCTs (17, 27, 28, 32–34, 39, 42–44, 48) and 11 observational studies (116, 118, 124, 130, 133, 137, 140, 141, 144, 146, 148).

Among 14 studies that compared bisphosphonates to placebo or unexposed persons, we found low CoE for increased risk for ONJ with bisphosphonate use, particularly after 2 to 3 years of exposure, though, like AFFs, ONJ events were rare (unadjusted incidence, 0.01% to 0.3% of bisphosphonate users). Of note, in our adjusted meta-analysis of 5 observational studies with sufficient data (116, 124, 133, 140, 144), we found a more than 3-fold significantly increased risk for ONJ in those exposed to bisphosphonates versus unexposed (adjusted RR, 3.37 [CI, 1.91 to 5.24]). One additional study of note from South Korea found similarly high odds (adjusted odds ratio, 3.26 [CI, 1.23 to 8.62]) with 2 or more years of bisphosphonate use compared with less than 1 year, but no difference for those exposed 1 to 2 years (148).

Several eligible studies evaluated other treatments and found no or few events of ONJ or no significant difference in risk between groups (see **Appendix Table 16** of the **Supplement**).

Atrial Fibrillation. We included 17 studies (28, 34, 37, 40, 43, 53, 119, 121, 123, 126, 128, 131, 136, 142, 147, 149, 151) (in 24 publications) that evaluated an eligible intervention and, in general, found no significant difference between treatment and placebo or active controls for risk for AF (insufficient to low CoE; **Appendix Table 17** of the **Supplement**).

Other Adverse Events. Bisphosphonates were most associated with nonspecific symptoms, such as pyrexia and myalgia, especially after treatment initiation (**Appendix Table 18** of the **Supplement**). In the HORIZON-PFT (Health Outcomes and Reduced Incidence with Zoledronic acid Once Yearly–Pivotal Fracture Trial) trial and extension study, participants receiving zoledronate, compared with placebo, experienced increased serum creatinine greater than 44.2 μmol/L (0.5 mg/dL) at significantly higher rates, but absolute numbers were low (28).

SERMs were more frequently associated with vasodilatory events such as hot flashes. Several studies noted endometrial cavity fluid collections in participants on SERMs, but no differences in rates of endometrial carcinoma (54). Two trials (29, 55) found a greater risk for deep venous thrombosis among participants taking SERMs than placebo, but

events were rare. Abaloparatide and teriparatide led to more adverse gastrointestinal effects (particularly nausea) compared with placebo, and 2 studies noted hypercalcemia as more common for these medications compared with placebo (41) and bisphosphonate (45), but again, events were relatively rare (**Appendix Table 18** of the **Supplement**). Romosozumab carries a black box warning from the U.S. Food and Drug Administration (FDA) based on a trial showing increased cardiovascular event risk compared with alendronate (HR, 1.87 [CI, 1.11 to 3.14]) (44, 152), though this risk was not observed in a placebo-controlled trial (HR, 1.03 [CI, 0.62 to 1.72) (42).

Participants with Low Bone Mass

We only identified 2 RCTs examining participants with low bone mass and found low CoE that bisphosphonates reduced several fracture outcomes based mostly on a 72-month placebo-controlled trial in females aged 65 years or older. In this trial, zoledronate was associated with a lower risk for clinical (HR, 0.73 [CI, 0.60 to 0.90]; adjusted RR, 6.8%), nonvertebral (HR, 0.66 [CI, 0.51 to 0.85]), and vertebral (HR, 0.45 [CI, 0.27 to 0.73]) fractures (46). The other RCT compared alendronate with placebo in male and female octogenarians but was high RoB, was small (n = 123), and did not substantively contribute to findings (49) (**Appendix Figure 1** and **Appendix Figure 2**, and **Appendix Table 19**, of the **Supplement**). In the limited data, harms were similar between groups.

Males With Osteoporosis

We included 10 studies (16, 20, 35, 36, 43, 50, 53, 138, 139, 143), all of bisphosphonates, that exclusively studied males with osteoporosis or stratified results by sex: 6 placebo-controlled RCTs (**Appendix Table 20** of the **Supplement**) (16, 20, 35, 36, 43, 53) and 4 observational studies in 3 publications (138, 139, 143). We found low to moderate CoE that bisphosphonates reduced radiographic vertebral fractures by 61% at 24 months (3 RCTs; RR, 0.39 [CI, 0.22 to 0.83]) and 58% at 36 months (1 RCT; RR, 0.42 [CI, 0.19 to 0.97]). No trial evaluated hip fractures, and bisphosphonates did not significantly reduce any other fracture outcomes (insufficient to moderate CoE; **Appendix Table 21** and **Appendix Figures 130** to **137** of the **Supplement**).

For SAEs, WAEs, ONJ, and AF, in general, no significant differences were observed between bisphosphonate and placebo or unexposed groups (**Appendix Table 22** and **Appendix Figures 138** to **144** of the **Supplement**). However, findings were mixed in 3 observational studies that evaluated risk for AFFs. One study (138), using Veterans Health Administration data, found that using bisphosphonates 1 to 4 and 4 or more years reduced the risk for AFFs by 51% and 60%, respectively (adjusted HR [aHR], 0.49 [CI, 0.28 to 0.86] and aHR, 0.40 [CI, 0.16 to 0.97]), but use for less than 1 year increased risk (aHR, 1.70 [CI, 1.08 to 2.68]). The other 2 studies from Sweden found large increased AFF risk in bisphosphonate users (19- to 54-fold greater risk); however, estimates were very imprecise, and we previously highlighted limitations of these studies (139). For other harms, zoledronate seemed to increase the likelihood of pyrexia (35, 43, 53), myalgias (35, 53), and arthralgia (35, 43). One RCT (16, 50) found that alendronate significantly decreased the likelihood of hypercalciuria (4.4% vs. 15.1%; P = 0.04; **Appendix Table 18** of the **Supplement**).

Duration and Sequence of Treatment

Three extension studies from 2 RCTs comparing bisphosphonates with placebo provide direct evidence about the comparative effects of continuing or discontinuing bisphosphonates after 3 to 5 years of treatment (56, 77, 84). No studies directly compared durations of other treatments. Continuing alendronate from 5 to 10 years reduced clinical vertebral fractures (RR, 0.45 [CI, 0.24 to 0.85]), but not radiographic vertebral or other clinical fractures (56). Continuing zoledronate from 3 to 6 years reduced radiographic vertebral (odds ratio, 0.51 [CI, 0.26 to 0.95]), but not other, fractures (77). The reduction in vertebral fracture risk was most pronounced in females at higher risk for fracture based on low BMD or prior fracture (82). Furthermore, continuing zoledronate from 6 to 9 years was not associated with additional fracture risk reduction (84).

We found very limited trial evidence examining the effects of sequential therapy on fracture outcomes. The ARCH (Active-Controlled Fracture Study in Postmenopausal Women with Osteoporosis at High Risk of Fracture) study found that romosozumab (12 months) followed by alendronate (12 months) was superior to 24 months of alendronate in reducing all fracture outcomes. The FRAME (Fracture Study in Postmenopausal Women with Osteoporosis) study compared romosozumab with placebo for 1 year followed by an additional 12 months during which both groups received denosumab (42). Although its results suggest that treatment gains from the first year of romosozumab use are likely to be maintained after transitioning to denosumab, it was not designed to test the incremental benefit of this sequence of therapies compared with denosumab use alone for the entire study period. We also identified a study examining teriparatide for 72 weeks followed by alendronate for 48 weeks, compared with 120 weeks of alendronate; however, results of the sequential portion of the study are not yet published (153).

Treatment Effects According to Participant Characteristics

Table 2 illustrates which treatments have similar efficacy across subgroups. Of note, relative treatment effects did not differ by fracture risk, though risk definitions and inclusion criteria varied by study (**Appendix Table 23** of the **Supplement**). Osteoporosis treatment was similarly effective in participants aged 75 years and older (**Appendix Table 24** of the **Supplement**). Most trials excluded participants with the equivalent of chronic kidney disease stage 4 or worse (**Appendix Table 25** of the **Supplement**), but there is evidence that zoledronate, alendronate, and denosumab are effective in persons with mild to moderate chronic kidney disease.

Table 2. Applicability of the Evidence: Treatment Effectiveness Across Subgroups

Treatment	Follow-up Duration, *mo*	Subgroup							
		Prevalent Vertebral Fracture	References	No Prevalent Vertebral Fracture	References	Prior Osteoporosis Treatment	References	Age ≥75 y	References
Versus placebo									
Bisphosphonates	12 to <36	✓ ZOL*	37, 43	Unclear	–	Unclear	–	✓ ZOL ✗ ALN	40 49
	≥36	✓ ZOL ✓ ALN ✓ RIS*	28, 72 27 24	✓ ZOL ✓ RIS*	46, 56, 72 59	✓ ZOL†	72	✓ RIS ✓ ZOL*	75 46, 72
Abaloparatide	12 to <36	✓*	41, 42	✓*	42	Unclear	–	✓*	42, 98, 102
	≥36	Unclear	–	Unclear	–	Unclear	–	Unclear	–
Teriparatide	12 to <36	✓* ✓†	41 26, 31	Unclear	–	Unclear	–	✓*	31, 73, 81
	≥36	Unclear	–	Unclear	–	Unclear	–	Unclear	–
Denosumab	12 to <36	✓†	39	Unclear	–	Unclear	–	Unclear	–
	≥36	✓*	65, 87	✓*	34, 65, 87	✓†	65	✓*	65, 87
Romosozumab	12 to <36	✓†	52	✓*	42, 112	Unclear	–	Unclear	–
	≥36	Unclear	–	Unclear	–	Unclear	–	Unclear	–
Raloxifene	12 to <36	Unclear	–	Unclear	–	Unclear	–	Unclear	–
	≥36	✓†	55	✓†	55	Unclear	–	Unclear	–
Bazedoxifene	12 to <36	Unclear	–	Unclear	–	Unclear	–	Unclear	–
	≥36	✓†	85	Unclear	–	Unclear	–	Unclear	–
Versus bisphosphonate									
Teriparatide versus risedronate	12 to <36	✓*	45, 99	Unclear	–	✓*	45, 99	✓*	45, 99
Romosozumab to alendronate versus alendronate	12 to < 36	✓*	44, 45, 99	Unclear	–	Unclear	–	✓*	44

ALN = alendronate; RIS = risedronate; ZOL = zoledronate; ✓= Effective: To be listed as effective within a given subgroup, the treatment had to be effective in improving 1 or more fracture outcomes in our network meta-analyses of the primary trials (that is, a treatment that was effective in a post hoc subgroup analysis or in a single trial, but not in the overall collection of studies analyzed, would not be listed in this table as effective), and include a population in which most participants have the risk factor in question, and/or be shown to be similarly effective in participants with and without the risk factor in question (usually through post hoc subgroup analyses demonstrating a treatment–risk factor interaction term with $P > 0.10$); Unclear = no studies in which most participants in the parent trial had characteristic of interest, and no subgroup analyses reporting treatment effects according to characteristic of interest; ✗ = not effective for any outcome studied.
* Effective for 1 or more clinical fracture outcomes.
† Effective, but only for radiographic vertebral fractures.

DISCUSSION

In postmenopausal females with osteoporosis, there is moderate to high CoE that, compared with placebo, bisphosphonates and denosumab reduce the risk for hip, clinical and radiographic vertebral, and other clinical fractures; moderate to high CoE that abaloparatide and teriparatide reduce clinical fractures and radiographic vertebral fractures; and low to moderate CoE that SERMs reduce radiographic vertebral, but not clinical, fractures. Bisphosphonates likely reduce radiographic vertebral fractures in males with osteoporosis (low to moderate CoE) but may not reduce the risk for other fractures (insufficient to moderate CoE).

Zoledronate reduced clinical, nonvertebral, and vertebral fractures in postmenopausal females with low bone mass (low CoE). However, the rate of clinical fracture in the control group in the main trial supporting this finding was high, and participants were older (46). Whether bisphosphonates reduce the risk for fracture in younger females with low bone mass at lower risk for fracture is unknown.

Our NMA allowed for direct and indirect comparisons of treatments, though almost all of the identified comparative evidence focused on bisphosphonates. There are only a few head-to-head trials to compare active treatments in the treatment network. Among females at very high risk for fracture, we found moderate CoE that sequential use of romosozumab, then alendronate, was more effective than alendronate alone in reducing hip, clinical and radiographic vertebral, and other clinical fractures, but an FDA black box warning advises against use of romosozumab in those with a myocardial infarction or stroke in the past year given potential concerns for increased cardiovascular events (152). Although abaloparatide (indirect comparison) and teriparatide (direct comparison) may reduce clinical fractures more than bisphosphonates in females at very high risk for fracture, WAEs were higher than with bisphosphonates.

The paucity of evidence examining the effects of sequential treatment on fracture outcomes is an important gap in the literature. Bisphosphonates, SERMs, and denosumab inhibit the resorption of bone; abaloparatide and

teriparatide stimulate bone formation; and romosozumab has both antiresorptive and anabolic properties. In theory, the sequencing of drugs with different mechanisms of action could impact the degree and durability of treatment effect. Findings from ARCH and FRAME suggest that treatment gains observed during the first year of romosozumab treatment are likely to be maintained after transitioning to antiresorptive therapy, but neither trial was designed to assess the incremental value of sequential therapy compared with no follow-on treatment. Outside of the scope of our review, there is evidence that BMD gains from abaloparatide and teriparatide may quickly dissipate after treatment discontinuation (154), and that use of bisphosphonates after an initial course of abaloparatide or teriparatide might help preserve BMD gains (155). The results of a trial reporting sequential therapy with teriparatide then alendronate compared with alendronate alone are expected soon (153). There have also been concerns raised about increased bone turnover after discontinuation of (156)—or delayed treatment with (157)—denosumab, and some experts suggest following a course of denosumab with alternate antiresorptive treatment (156–158). We found no studies examining the fracture-reducing effects of anabolic therapy after antiresorptive therapy, but experts have warned against this sequence of treatment based on data from a study showing that females transitioning from denosumab to teriparatide experienced reduced BMD, bone loss at the hip and radius, and accelerated bone remodeling (154, 159, 160).

The optimal treatment duration is also unclear because most trials lasted 3 to 4 years at most, and, for all treatments other than bisphosphonates, there were no studies directly comparing different treatment durations. Extending bisphosphonate treatment to 6 or 10 years may help reduce vertebral fracture risk in females at high risk for fracture (56, 77). However, this benefit would need to be weighed against the nearly 3-fold increased risk for ONJ after 2 to 3 years of bisphosphonate use and the risk for AFFs, which increased substantially after 3 to 5 years of use. Nevertheless, both harms were rare, and the absolute risk remained low.

Another limitation of this body of evidence is the generalizability of findings. Most studies were of postmenopausal White- or Asian-identifying female populations with osteoporosis; few studies analyzed other racial and ethnic groups, those with low bone mass, and males. Precise application of our findings is further limited because of inconsistent reporting of prior fracture type and frequency, type of prior osteoporosis medication use, and extensive exclusion criteria in some trials.

We took a similar approach to a prior review (5) used to develop the previous ACP clinical practice guideline on treatments for osteoporosis, but there are several differences. We conducted an NMA, set a minimum follow-up period of 12 rather than 6 months, and focused on participants with primary rather than primary and secondary osteoporosis. Although our findings about bisphosphonates, teriparatide, and SERMs were aligned with the prior review, the evidence has also evolved in the interim, including publication of additional observational studies examining harms, additional trials of established treatments, studies of persons with low bone mass, and the emergence of previously investigational drugs—romosozumab and abaloparatide—as therapeutic options. Our findings are consistent with another recent review and NMA, though it only focused on postmenopausal females with osteoporosis (161).

Although we conducted an NMA, we did not provide surface under the cumulative ranking curve ratings and rank-order treatments because we identified few head-to-head studies, which reduced the number of loops in our network and our confidence in the rank-order approach. Of note, we conferred with our expert panel and elected to treat bisphosphonates as a drug class in the NMA due to the comparable mechanisms of action and biological effects of bisphosphonates (162), our finding that RRs were similar across bisphosphonates in pairwise comparisons, and to allow for more robust comparisons in the NMA.

In conclusion, bisphosphonates and denosumab were effective at significantly reducing hip, other clinical, and vertebral fractures in postmenopausal females in studies of 36 months or more (moderate to high CoE). Longer-duration treatment with bisphosphonates may be associated with a significantly increased risk for ONJ and AFF (low CoE), but events were rare. Abaloparatide and teriparatide also significantly reduced clinical fractures and radiographic vertebral fractures up to 24 months (low to moderate CoE), but significantly increased the risk for WAEs (low to moderate CoE). For longer-term fracture outcomes, SERMs reduced radiographic vertebral fractures (moderate CoE), but significantly increased the risk for WAEs (moderate to high CoE). Sequential therapy for romosozumab then alendronate, abaloparatide, and teriparatide may be significantly more effective than bisphosphonates in reducing clinical fractures for 12 to more than 36 months in older postmenopausal females at high fracture risk (low to moderate CoE). More comparative effectiveness, sequential therapy, and longer-duration studies are needed, as well as more research in males, persons with low bone mass, and those identifying as Black or African American.

From Center to Improve Veteran Involvement in Care (CIVIC), VA Portland Health Care System, Portland, Oregon (C.A.); Center to Improve Veteran Involvement in Care (CIVIC), VA Portland Health Care System, Portland, and Division of General Internal Medicine & Geriatrics, Department of Medicine, Oregon Health & Science University, Portland, Oregon (D.K.); Center for Evidence-based Policy, Oregon Health & Science University, Portland, Oregon (B.L.); Oregon Health & Science University-Portland State University School of Public Health, Portland, Oregon (R.F.); Division of General Internal Medicine & Geriatrics, Department of Medicine, Oregon Health & Science University, Portland, Oregon (A.K.); Division of General Internal Medicine & Geriatrics, Department of Medicine, and Center for Evidence-based Policy, Oregon Health & Science University, Portland, Oregon (C.H.)

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Corresponding Author: Devan Kansagara, MD, MCR, VA Portland Health Care System, 3710 SW U.S. Veterans Hospital Road, Portland, OR 97239; e-mail, kansagar@ohsu.edu.

Update Alerts: The authors have specified in the Methods section the interval and stop date for updates to this living review. As *Annals* receives updates, they will appear in the Comments section of the article on Annals.org. Reader inquiries about updates that are not available at approximately the specified intervals should be submitted as comments to the article.

Correction: This article was amended on 16 May 2023 to correct a reporting error in Table 2 and in Appendix Table 26 of the Supplement. None of the revisions substantively changed the results and conclusions of the review. A correction has been published (doi:10.7326/L23-0105).

Author contributions are available at Annals.org.

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Analysis and interpretation of the data: C. Ayers, D. Kansagara, B. Lazur, R. Fu, A. Kwon, C. Harrod.
Drafting of the article: C. Ayers, D. Kansagara, B. Lazur, R. Fu, A. Kwon, C. Harrod.
Critical revision of the article for important intellectual content: C. Ayers, D. Kansagara, B. Lazur, R. Fu, A. Kwon, C. Harrod.
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Review

Current Status of the Diagnosis and Management of Osteoporosis

Agustín Aibar-Almazán [1], Ana Voltes-Martínez [2,3,4], Yolanda Castellote-Caballero [1,*], Diego Fernando Afanador-Restrepo [5], María del Carmen Carcelén-Fraile [1] and Elena López-Ruiz [1,2,3,4]

[1] Department of Health Sciences, Campus de Las Lagunillas SN, University of Jaén, E-23071 Jaén, Spain
[2] Centre for Biomedical Research (CIBM), Biopathology and Regenerative Medicine Institute (IBIMER), University of Granada, E-18011 Granada, Spain
[3] Biosanitary Research Institute of Granada (ibs.GRANADA), University Hospitals of Granada, University of Granada, E-18014 Granada, Spain
[4] BioFab i3D-Biofabrication and 3D (Bio) Printing Laboratory, University of Granada, E-18011 Granada, Spain
[5] ZIPATEFI Research Group, Faculty of Health Sciences and Sports, University Foundation of the Área Andina, Pereira 660001, Colombia
* Correspondence: mycastel@ujaen.es

Abstract: Osteoporosis has been defined as the silent disease of the 21st century, becoming a public health risk due to its severity, chronicity and progression and affecting mainly postmenopausal women and older adults. Osteoporosis is characterized by an imbalance between bone resorption and bone production. It is diagnosed through different methods such as bone densitometry and dual X-rays. The treatment of this pathology focuses on different aspects. On the one hand, pharmacological treatments are characterized by the use of anti-resorptive drugs, as well as emerging regenerative medicine treatments such as cell therapies and the use of bioactive hydrogels. On the other hand, non-pharmacological treatments are associated with lifestyle habits that should be incorporated, such as physical activity, diet and the cessation of harmful habits such as a high consumption of alcohol or smoking. This review seeks to provide an overview of the theoretical basis in relation to bone biology, the existing methods for diagnosis and the treatments of osteoporosis, including the development of new strategies.

Keywords: osteoporosis; regenerative medicine; lifestyle habits

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1. Introduction

In 1993, the WHO defined osteoporosis as a systemic skeletal disease characterized by low bone mass, the deterioration of the microarchitecture of bone tissue, a consequent increase in bone fragility and a susceptibility to fractures [1]. In addition, osteoporosis has been reported to occur when there is an imbalance in bone cell function [2]. This disease has been called "the silent epidemic of the 21st century" because of its public health implications. It is a severe, chronic, progressive and clinically silent disease and the most common of the metabolic bone diseases [3].

Within osteoporosis, there are several types that can be classified into two large groups: primary and secondary osteoporosis. Primary osteoporosis includes idiopathic osteoporosis occurring in children and young adults, with an unknown etiopathogenesis [4], and involutional osteoporosis affects both men and women and is more related to aging [5]. Likewise, involutional osteoporosis is divided into type I or postmenopausal osteoporosis, which mainly affects women between 51 and 75 years of age and is characterized by rapid bone loss [6]. Type II or senile osteoporosis occurs in persons over 75 years of age and is characterized by a loss of trabecular and cortical bone that results from aging [3]. Secondary osteoporosis accounts for less than 5% of all cases of osteoporosis and is a consequence of a disease or the use of medications [7]. Among all of them, the most frequent kind of osteoporosis is postmenopausal osteoporosis, which is linked to two conditions: menopause and aging [6].

Among the metabolic bone diseases known to date, osteoporosis is not only the most frequent but is also a major global public health problem due to its high morbidity, which is caused by osteoporotic fractures in the older population [8]. This process occurs in people of both sexes and in the different types of osteoporosis, and it is also known to affect both pediatric and young patients, either primary or secondary to systemic diseases or medical treatments [9]. The National Institute Health Consensus on Prevention, Diagnosis and Therapy of Osteoporosis concluded that "bone mass acquired early in life may be the major determinant of long-term bone health" [10].

Due to the fact that bone loss is produced by advancing age, the prevalence of osteoporosis increases with it; therefore, as a chronic and prolonged skeletal disorder, it is more common in senile people, occurring in men over 65 years of age and in women over 55 years of age, approximately [11]. However, in women, it is more frequent due to other symptoms produced by menopause. During this stage, the estrogen deficit produces an increase in bone remodeling, which causes the loss of bone density [12]. In fact, in 2010, it was observed that 5.5 million men and 22 million women in the European Union had osteoporosis according to the diagnostic criteria used by the WHO [13], with 80% of the female population being unaware of the risk factors before being diagnosed with the disease [14].

Osteoporosis does not follow pre-established clinical patterns and manifests itself in various ways during its course. Individuals with uncomplicated osteoporosis may remain asymptomatic until a fracture occurs [5]. Although osteoporosis presents a general symptomatology, it also manifests with specific signs and symptoms such as: (i) pain that is secondary to osteoporotic fractures, which can occur in any bone and whose clinical manifestations depend on the location [15]; (ii) deformities and multiple vertebral compression fractures which can produce an increase in thoracic kyphosis and cervical lordosis [16]. The last ribs could contact the iliac crest, causing the relaxation of the diaphragm, which is the cause of digestive (hiatus hernia, meteorism) and respiratory (dyspnea) manifestations [17]. Moreover, there are alterations of the adipose panniculus and the presence of skin folds on the back, pubic region and umbilicus [18]. Likewise, hyperkyphosis causes cervical pain as the patient tries to keep the head upright through cervical hyperextension [19]. Moreover, increased dorsal kyphosis also occurs in osteoporotic males, resulting in shoulder droop, compensatory lumbar, cervical hyperlordosis and a characteristic postural habitus [20]. (iii) A loss of height, as vertebral fractures and hyperkyphosis can result in a decrease in height of about 10–20 cm, approximately [21].

Many factors are involved in the development of osteoporosis. Some of them are modifiable, such as environmental factors and some endocrine factors. Environmental factors include: (a) nutritional factors, such as deficient calcium intake, vitamin D deficiency due to nutritional problems, poor absorption or low sun exposure, excessive protein intake in unbalanced diets, excessive phosphate intake or excessive salt intake that increases urinary calcium loss [22]; (b) sedentary lifestyles, anaerobic exercise and excessive mechanical load, which are three factors that directly cause the risk of osteoporosis [23]; (c) chronic pharmacological treatment such as anti-convulsants, glucocorticoids, sedatives or chemotherapy; (d) the intake of caffeine, alcohol or smoking [24]; (e) body weight, which is responsible for 15% to 30% of the variations in bone mineral density (BMD) at any age and in any measured bone region [25]. Endocrine factors include: (a) late menarche or menstrual cycle alterations, which are conditions that are associated with low bone mass [26]; (b) surgical or non-surgical menopause before the age of 45 years [27]; (c) being a hormonally infertile woman [28]; and (d) estrogen deficiency before menopause as a result of anovulation due to anorexia nervosa, excessive exercise, mental stress, etc. This is the most important risk factor for osteoporosis, at least in Western countries [29]. It is important to look at these modifiable factors because they could be corrected and decrease the risk of developing osteoporosis [30].

In addition, there are non-modifiable risk factors such as genetics, since there are important genetic components in the determination of bone density and mass [31], e.g.,

race, since Caucasians and Asians are at a greater risk than Blacks and Polynesians [32]; sex, since it has been found that the risk is greater in women than in men [33]; and age, since each decade increases the risk by 1.4 to 1.8 times. It is another clear cause of bone density loss, not only because of the drop in hormone levels but also because, histologically, there is a decrease in the average thickness of the bone wall, but bone resorption remains high with aging [34].

Due to the increase in life expectancy produced by the aging of the world population, osteoporosis is becoming an emerging health problem, representing one of the main non-communicable diseases at this time, and it can interfere negatively in the quality of life of people. Therefore, it is essential to know the factors involved in this disease and to establish approaches for its management and treatment [35].

2. Bone Biology

Bone tissue is a dynamic, mineralized connective tissue that serves multiple physiological functions [36]. Bone provides mechanical support for loading and locomotion, offers physical protection to internal soft organs, forms a non-static reservoir of calcium and phosphate ions and provides an environmental niche for bone marrow and hematopoietic cell development.

In bone, there is a hierarchical structure with two separate phases: the organic matrix and the inorganic matrix [37]. The organic matrix is composed mainly of type I collagen, the fibers of which are linked by triple helix cross-links. It is this structure that provides the bone with resistance to longitudinal tensile forces as well as elasticity. On the other hand, the inorganic matrix is mineralized with hydroxyapatite and calcium phosphate crystals, which are located in the free voids of the organic matrix. This matrix is responsible for the stiffness of the bone and its resistance to compressive forces in a way that depends on the amount of mineral, the arrangement of the crystals and the degree of packing [38].

The remaining bone volume is composed of bone cells of two classes: osteoprogenitor cells and osteoclasts. Osteoprogenitor cells are derived from mesenchymal stem cells (MSCs) that subsequently differentiate into osteoblasts and osteocytes. The differentiation of these cells is initiated when they receive migration signals to a certain area, proliferate and, finally, differentiate. Osteoblasts are the cells that line the surfaces of bone and are responsible for the synthesis and secretion of the organic bone matrix. Osteocytes are the majority of bone cells capable of communicating directly with each other [39,40]. All these cells are responsible for maintaining the bone matrix and regulating calcium homeostasis, although they also play an important role in bone resorption. Finally, osteoclasts are the largest cells, have multiple nuclei and are of hematopoietic origin. They are bone resorption cells and act by phagocytosing the matrix through acidification solubilization [41,42].

Furthermore, bone tissue can be differentiated into cortical bone or trabecular bone. Both types of bone are similar in their cellular and molecular composition but different in terms of functionality and mechanical characteristics [43]. Cortical bone is the bone found in the outermost part of the long bones. It is a very compact tissue that circulates the blood vessels, the canaliculi that surround the osteocytes and their connecting cellular processes. On the contrary, trabecular bone, also called cancellous bone, is found in the epiphysis of long bones, in the vertebrae and near the articular surfaces. It consists of a network of thin bony plates and connecting struts surrounded by the bone marrow [44].

Bone remodeling begins in fetal life and continues throughout our lives, adapting the shape of bones by removing and adding bone tissue at different key points [45]. Bone remodeling is crucial for the repair of bone damaged by constant physical loading and the prevention of fractures of various origins. This process is based on the balance of two main phases: bone formation and bone resorption (Figure 1) [46]. Bone is unique in the healing of connective tissue because it is capable of complete healing through cell regeneration and mineral matrix production [47]. As mentioned above, bone tissue is in a constant process of remodeling, which allows the skeleton to renew itself continuously. This remodeling process is directly related to mechanical stresses. This can prevent excessive fatigue dam-

age, ensure the viability of bone cells, repair microfractures or allow for proper calcium homeostasis. The constant changes in bone mass and architecture due to load-bearing are regulated by osteoclasts together with the osteoblast–osteocyte communication system [48]. These bone cells form the main mechanical sensor network of the tissue.

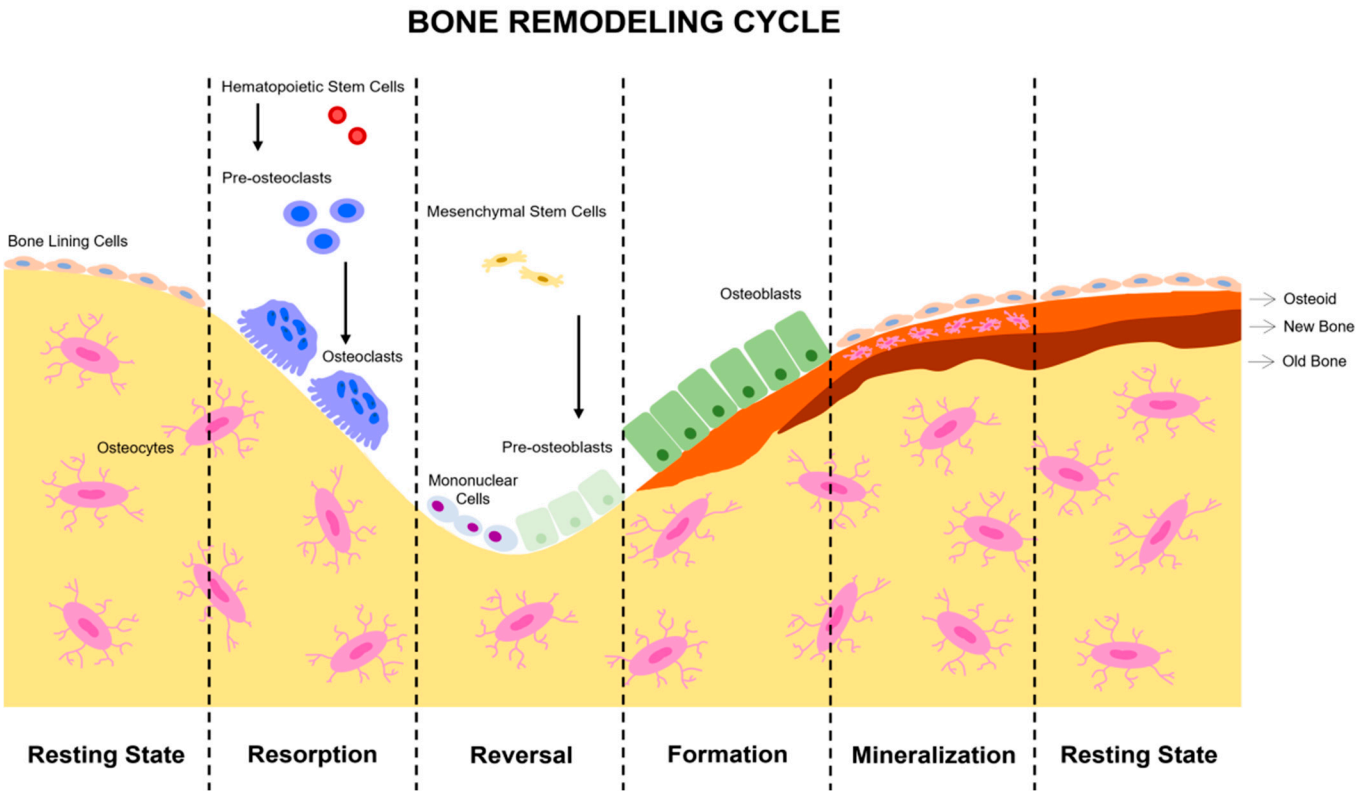

Figure 1. Stages of bone remodeling. In a balanced system, bone remodeling begins with bone resorption and ends with osteoblast formation. The complete cycle is composed of the phases of activation, resorption, reversion, formation and, finally, mineralization. Initially, a signal is detected which activates resorption by attracting osteoclast precursors to the area to be remodeled. This phase is of limited duration and depends on the degree of stimuli received, causing osteoclast differentiation and activity. Then, in the reversion phase, almost all of the osteoclasts disappear, and osteoblast precursors of mesenchymal origin begin to form. In the formation phase, all the osteoclasts are definitively replaced by osteoblasts. Finally, the mineralization of new bone tissue occurs. The new tissue remains at rest until the next cycle of remodeling.

During the remodeling process, there are several markers by which we can identify the existence of bone formation. Some of these markers are indicators of osteoblastic activity and the resulting metabolism after collagen release [49]. Alkaline phosphatase (ALP) is an enzyme associated with the plasma membrane of cells produced by osteoblasts, which play an important role in osteoid formation and mineralization. Its absence can lead to the development of liver disease. Osteopontin (OPN) is another non-collagenous protein with a key role in the structure and mechanics of bone tissue. A charged and phosphorylated protein with a high affinity for calcium, it has been attributed multiple functional roles in bone mineral bioregulation. It acts as a link at the mineral–collagen interface, improving bone hardness [50]. Another useful marker is osteocalcin (OC). OC is the most abundant non-collagenous protein present in the bone matrix. It is a small hydroxyapatite-binding protein synthesized by osteoblasts. It is generated during bone formation and can be released during bone resorption. This protein is rapidly degraded in vivo and ex vivo. Collagen type I is a protein synthesized by the osteoblasts and also serves as a bone formation marker [51].

Disuse can lead to deterioration in bone density and architecture, but physical exercise can slow the progression of these problems [52]. The mechanical forces supported by the cells in this tissue type are complex and multifactorial systems. The response of cells to these forces is regulated by cytoskeletal proteins and transmembrane-bound integrins that link the extracellular microenvironment with the genetic load in the nucleus. The bone marrow is also indirectly involved in bone remodeling. It produces MSCs that are also subjected to these loads, along with dynamic shear forces derived from the bone marrow bone interface. It is precisely these forces that promote osteogenesis and the cell differentiation of MSCs into an osteoblast lineage by dynamically activating the actin structure in the cytoskeleton while inhibiting adipogenesis [53].

Over the years, bones become more fragile and lose their functionality [54]. Factors such as immobilization, hormonal or nutritional deficiencies or chronic diseases can metabolically affect bone remodeling leading to osteopenia [55]. Therefore, the regulation of cellular and molecular processes to maintain the balance between bone resorption and bone formation is fundamental. An imbalance in this process can lead to the loss of bone density and mineral homeostasis, resulting in osteoporosis [56]. Osteoclasts, osteoblasts and osteocytes are bone cells directly involved in bone remodeling and a failure in their molecular mechanism is the possible trigger of the disease [57,58].

Several hormones, primarily estrogens [59], are responsible for regulating bone remodeling by controlling the cytokines and growth factors produced by bone marrow and bone cells. However, bone remodeling is also regulated by other systemic regulators (parathyroid hormone (PTH), vitamin D, calcitonin or glucocorticoids) and local regulators such as cytokines, growth factors mainly transforming growth factor beta (TGF-β), the macrophage colony-stimulating factor (M-CSF), receptor activators of nuclear factor-κB ligand (RANKL) or prostaglandins [58,60].

It is well known that the loss of estrogens increases bone resorption in women and, to some extent, in men. This is only supered by age-related osteoporosis. There are various factors, such as the low absorption of calcium and vitamin D and aging, which cause a decrease in the production of estrogens. The main cause of osteoporosis in women is menopause due to sex hormones reduction. A low production of estrogens causes the prolonged maintenance of osteoclasts. while osteoblastic cells deteriorate, leading to a homeostatic imbalance of the bone [61].

The action of these systemic regulators such as vitamin D and calcium exchange is essential for the physical resistance of bone and is closely related to PTH, one of most prominent regulatory hormones. Vitamin D levels are inversely related to PTH; if existing vitamin D decreases, PTH increases. This leads to a negative calcium balance and, consequently, to the deterioration of bone tissue [62].

Functional PTH receptors are found in osteoblasts, regardless of their maturation state. Problems in PTH regulation, such as ongoing hyperparathyroidism, result in a severe loss of bone mass, even though bone formation by osteoblasts continues. Although it is known that PTH plays a fundamental role in bone remodeling, it is not possible to determine how it is able to promote bone formation, since there is no single mechanism that explains it but rather multiple complementary mechanisms that act in a coordinated manner [63]. PTH anabolic treatments were the first Food and Drug Administration (FDA)-approved osteoporosis medications that could stimulate new bone formation [64].

On the other hand, the main signaling pathways controlling osteoclastic bone resorption and osteoblastic bone formation are the receptor activators of nuclear factor-κB (RANK)/RANKL/osteoprotegerin (OPG) and the canonical Wnt signaling [65,66].

First, for the initiation of the RANKL/RANK/OPG signaling pathway to occur, there must be an adequate concentration of M-CSF, which is expressed by osteocytes and osteoblasts. It stimulates the expression of RANK necessary before the action of RANKL. Subsequently, the binding of RANKL to its receptor on osteoclast precursor cells drives osteoclast differentiation, facilitating their activation and survival. RANKL/RANK binding induces a cascade of protein signaling molecules to enable osteoclast gene expression.

RANKL produced by osteocytes is thought to sense changes in tissue load and initiate the bone remodeling cycle by stimulating osteoclastogenesis. Finally, OPG is a RANK receptor secreted by osteoblasts and osteocytes capable of inhibiting osteoclastic bone resorption by binding to RANKL instead of RANK [56]. The other key signaling pathway, the canonical Wnt pathway, is dependent on β-catenin, an important regulator of osteoblastic bone formation [65]. In the absence of Wnt, the cytoplasmic β-catenin glycoprotein is marked by proteasomal degradation that phosphorylates and ubiquitinates β-catenin. Because of this, the expression of the Wnt target gene is inhibited. If Wnt is present, it binds to a dual receptor complex comprising the Frizzled family of proteins, a seven transmembrane domain receptor and a lipoprotein-related co-receptor (LPL) (5 or 6). This blocks the action of the destruction complex, leading to the accumulation of cytoplasmic β-catenin, which ultimately promotes osteoblast proliferation and differentiation [56].

3. Diagnosis of Osteoporosis and Fracture Risk Assessment

Nowadays. the diagnosis of osteoporosis is mainly based on the evaluation of bone mass by bone densitometry (DEXA) [67]. Although osteoporosis is more than a bone densitometry value, this evaluation allows for the quantification of bone tissue, which is used as a diagnostic criterion and is considered a predictive value for the risk of fracture, which makes it the best method for determining the rate of bone loss and as a reference point for the evolutionary control of the disease [68].

According to the WHO Expert Committee, the classification of BMD values is as follows: (i) normal: BMD > −1 SD t-score; (ii) osteopenia: BMD between −1 SD and −2.5 SD t-score; (iii) osteoporosis: BMD < −2.5 SD t-score; and (iv) established osteoporosis: BMD < −2.5 SD t-score + fragility fracture [69]. The T-score or t-value, which is the number of standard deviations above or below the mean BMD of the normal young population of the same sex, has been taken into account for this classification [70]. However, in the case of premenopausal women, men under 50 years of age and children, the Z-score will be considered (in relation to normal subjects of the same age and sex) such that "normal" will be considered up to −2.0 [71]. This classification is, to date, universally accepted as a diagnostic criterion. Its sensitivity and specificity are close to 90%, and it may be able to increase the detection of patients who would not be classified as osteoporotic. However, limitations exist in this imaging test, especially in the presence of osteomalacia, osteoarthrosis and osteoarthritis [72]. In Europe, the International Osteoporosis Foundation (IOF) has carried out a campaign where diagnostic bone density tests (densitometry) were performed in people at an increased risk of the disease [5]. The results of this campaign in Spain were worrisome: of the 900 citizens in an age group between 50 and 70 years who underwent densitometry tests, about 25% suffered from the disease, and approximately the same percentage had osteopenia, a degree of bone degeneration. In this campaign, it was also found that most of the citizens who underwent densitometry had done for the first time [73]. There are also several diagnostic tests used to monitor the treatment of osteoporosis in clinical practice [74], including dual X-ray absorptiometry, which is the most recommended technique for the diagnosis of osteoporosis since it can predict the risk of fracture, indicate the treatment or monitor its effect [75]. Dual X-ray absorptiometry is based on the quantification of axial bone mineral density (spine and hip) by measuring the transmission of a beam of X-ray photons with two energy peaks in the patient's body, which allows for the assessment of the calcium content of the bone [76]. A study conducted in postmenopausal women showed that BMD and fracture risk were related, thus defining osteoporosis as a t-score value of −2.5 [77].

On the other hand, general blood and urine tests provide information on the general health status and on the existence of elements causing secondary osteoporosis [76]. These markers are really useful tools in identifying metabolic bone diseases, since they provide us with information that is not directly obtained with a bone density measurement or bone histomorphometry [78]. With respect to markers, another commonly used test is bone turnover markers (BMTs), which are capable of measuring peptides of the amino and

carboxy-terminal ends in processes of bone matrix formation or degradation [79]. Among these are formation markers that measure osteoblastic activity, i.e., bone-forming activity, such as ALP and OC. ALP is secreted by different tissues (liver, bone, placenta), and its most frequent isoforms are from hepatic and bone (90%) [80]. The bone isoform does not vary between sexes and is not influenced by the circadian rhythm, which makes it a simple marker, although it has a low sensitivity and specificity in metabolic bone disorders [81]. In situations of increased bone turnover, the half-life of OC decreases, and it is eliminated through urine [82]. On the other hand, the most commonly used resorption markers that measure osteoclast activity are: (i) Pyridinolines (Pir) and deoxypyridinoline (Dpir), which link collagen molecules in the bone matrix through covalent bonds, thus forming fibrils [83]; and (ii) ICTP (C-terminal telopeptide of type I collagen), β-CTX (β-CrossLaps) and NTX (N-terminal telopeptide of type I collagen), which are peptides released during the process of bone resorption. β-CTX and NTX are considered to be the most useful resorption markers in clinical practice for the diagnosis of osteoporosis [78].

In addition, there are other methods, such as ultrasound based on measuring sound velocity and ultrasound attenuation in peripheral skeletal bones. However, it has not been demonstrated that the parameters obtained by this test are clinically useful for monitoring the disease; another assessment technique is quantitative computed tomography, which is based on the measurement of BMD volume in trabecular and cortical bones; however, this is a tool that is not recommended, since its economic cost is very high, and it exposes the patient to greater ionizing radiation than DEXA [84]. Finally, osteoporosis could be diagnosed through a biopsy of bone tissue. This is a very invasive technique in which a tissue sample is extracted, and it is only performed when evidence of tumors is detected [85].

Fragility fractures are the most common consequence of osteoporosis and are particularly common in the vertebrae, hip and forearm. These fractures increase exponentially with age and are a major cause of morbidity and mortality in elderly populations [86]. Moreover, the proximal ends of the femur and humerus, the distal end of the radius and the spine are the most susceptible to osteoporotic fractures in comparison to other parts of the bone [87]. Likewise, hip fracture is considered to be the severe complication that is most associated with high morbidity and mortality [88].

Therefore, it is essential to assess the risk of fracture, which is performed by considering the degree of osteoporosis obtained by densitometry according to the WHO Expert Committee: (i) normal value: the risk of fracture is normal; (ii) osteopenia value: the risk of fracture is double the normal risk; (iii) osteoporosis value: the risk of fracture is quadruple the normal risk; (iv) established osteoporosis value: the risk of fracture for each reduced standard deviation is multiplied by 1.5–2; and (v) severe osteoporosis value: the risk is similar to that of established osteoporosis [89].

4. Treatment of Osteoporosis and Novel Approaches

4.1. Overview of Existing Drug Therapies and New Drug Development

Great advances have been made in the study of the pathogenesis of osteoporosis and in the development of new drugs for its treatment. The primary purpose of a pharmacological treatment is to reduce the risk of fractures and to improve the quality of life of people with osteoporosis [90]. It has been proven that, before beginning pharmacological treatment, it should be ensured that the person has adequate levels of both calcium and vitamin D, since the combination of these two elements has shown great synergy in promoting calcium absorption and in helping to maintain adequate serum calcium concentrations for the proper mineralization of the bone [91]. In the majority of cases, the calcium and vitamin D intake is insufficient in the diet; therefore, a supplement is always prescribed to achieve the recommended levels. Although some authors do not support the use of these supplements because of the adverse effects they could have, such as constipation, this is why their use is mainly recommended in postmenopausal women who do not meet the recommended levels through diet [92].

The drugs used for the treatment of osteoporosis can be divided according to the effect they produce on the bone. On the one hand, there are the antiresorptive drugs classified as "bone resorption inhibitors", and on the other hand, there are the anabolic agents classified as "bone formation accelerators" (Table 1) [93]. Mainly antiresorptive and anabolic drugs approved by the Food and Drug Administration (FDA) [94] are shown at Table 1.

Table 1. Drugs for the treatment of osteoporosis.

	Drug Names	Description	Indication
		Anti-Resorptive	
Selective oestrogen-receptor modulators	Raloxifene Bazedoxifene	They act as estrogen receptor agonists, thereby decreasing bone resorption.	- Postmenopausal OP - Postmenopausal OP with a high fracture risk
Calcitonin		Their main function is to prevent the loss of bone mass due to sudden immobilization.	- Immobilizations
Bisphosphonates	Alendronate Risedronate Ibandronate Zoledronic acid	They are the first choice in postmenopausal osteoporosis. They act by binding to the bone and preventing bone resorption.	- Postmenopausal OP - Postmenopausal OP with a high fracture risk - Advanced neoplasia with bone involvement and tumor-induced hypercalcemia
RANKL antibody	Denosumab	Human IgG2 monoclonal antibody that has a high specificity and affinity for RANKL, which it binds and inhibits.	- Advanced neoplasia with bone involvement - Treatment of giant cell tumors of unresectable bone or when surgical resection involves severe morbidity
		Anabolic Agents	
Parathyroid hormone analogs	Teriparatide Abaloparatide	Increases bone formation with minor increases in bone resorption, resulting in a net anabolic effect.	- Postmenopausal OP and men at a high fracture risk - OP associated with glucocorticoid treatment in women and men at a high fracture risk

OP: Osteoporosis.

These antiresorptive drugs suppress osteoclastogenesis and result in the suppression of bone turnover, thereby increasing mineralization. The function of anti-resorptive drugs is to decrease or prevent bone resorption by trying to balance the bone formation and bone resorption suppressing osteoclast function. Most of the treatments used in osteoporosis fall into this group: bisphosphonates, selective oestrogen receptor modulators (SERMs), calcitonin and denosumab [95]. On the other hand, anabolic agents increase bone turnover, which mostly affects bone formation. However, it has been suggested that the prolonged use of PTH analogs increases the risk of osteosclerosis and osteosarcoma due to their stimulatory effects, and they are not used for the long-term treatment of osteoporosis [93]. Among the most commonly studied anti-resorptive drugs are SERMs, which include raloxifene and azedoxifene. Raloxifene is capable of alleviating climacteric symptoms, preventing bone loss and increasing bone mineral density. Like other SERMs, Raloxifene can bind to the estrogen receptor (ER) in an agonistic or antagonistic manner depending on the target tissue [96]. Bazedoxifene, binds at the cellular level to both ERα and Erβ and inhibits its binding to 17β-estradiol, exerting agonistic activity on the bone [97].

Calcitonin is a thyroid hormone that binds at the calcitonin receptor expressed in the kidney, the hypothalamus and in the membranes of osteoclasts. Calcitonin works by inhibiting osteoclasts and reducing the bone resorption ability. Additionally, it can reduce fracture-related pain, apparently through regulating nociception in the central nervous system. It has a positive impact on reducing vertebral fractures in postmenopausal osteoporotic women. However, the treatment with calcitonin has declined over the years because the use of hormone therapy increases the risk of cardiovascular complications and breast cancer [98].

The most common first-line treatments for osteoporosis are bisphosphonates. Alendronate, or alendronic acid, is a nitrogen-containing bisphosphonate that binds to bone surfaces and inhibits bone resorption by osteoclasts, possibly by inhibiting the mevalonate pathway. It has been shown to be effective in the treatment of women or men with corticosteroid-induced osteoporosis and in the prevention of osteoporosis in postmenopausal women [99]. Risedronate is a pyridinyl bisphosphonate capable of reducing the bone turnover process and decreasing bone resorption by interfering with the activity of osteoclasts and inhibiting their adhesion to the mineralized bone matrix without affecting its porosity [100]. Another nitrogenous bisphosphonate is ibandronate, which has one of the best anti-resorptive capabilities due to the tertiary nitrogenous group on its R2 side chain and the hydroxyl group on its R1 side chain. It reverses the bone loss associated with estrogen depletion and has a strong binding affinity to hydroxyapatite [101]. On the other hand, zoledronic acid, a potent intravenous amino bisphosphonate, is an antiresorptive agent that improves bone mineral density, reduces fracture risk and bone turnover and maintains bone structure. It has a high affinity for mineralized bone and is primarily targeted at sites of increased bone turnover. In addition, it affects the endocytic activity of osteoclasts and inhibits bone resorption by inhibiting farnesyl pyrophosphate synthase (FPPS), which prevents protein prenylation [102].

Another popular medication used for treating osteoporosis is denosumab, a human monoclonal antibody targeting RANKL. RANKL is a protein essential for osteoclast formation, differentiation and survival and is a key mediator of bone resorption. Denosumab is more effective at improving bone density and strength than bisphosphonate drugs, but unlike bisphosphonate drugs, it is not incorporated into bone, so its effect ceases when the treatment is stopped [103].

Anabolic agents such as PTH analogs are also used in the treatment of osteoporosis, although to a lesser extent and generally when antiresorptive treatments are not effective. Currently, only two osteoanabolic drugs are available for the treatment of osteoporosis: Teriparatide and Abaloparatide. Teriparatide, or human PTH (1-34) hormone, is a bone formation promoter derived from the PTH (1-84) chain, the main regulator of calcium formation and bone metabolism in mammals. The primary sequence of Teriparatide is identical to the 34 amino acids of full-length PTH (1-84), which correspond to the active phase of mineral homeostasis. Teriparatide promotes osteoblastogenesis and prevents osteoblastic apoptosis [104,105]. On the other hand, Abaloparatide is a 34-amino acid synthetic analog of PTH that is identical to that of the PTH peptide in the first 20 amino-acids. Abaloparatide promotes bone formation and has similar effects to Teriparatide. Some studies have shown that the use of Abaloparatide reduces the risk of vertebral fractures in postmenopausal women with osteoporosis compared to patients treated using alendronate [106]. Both Abaloparatide and Teriparatide treatments were furthermore able to generate an increase in RANKL and M-CSF mRNA expression in a human osteoblast line [107].

Moreover, new targets are being studied for the treatment of osteoporosis, such as cathepsin K inhibitors, which have been shown to cause a decrease in bone resorption, thus preserving bone, or antisclerostin therapies, products of the SOST gene which bind to the LRP5 or LRP6 receptors in such a way that they inhibit osteoblastic activity, promoting its apoptosis. Additionally, antibodies against sclerostin, an osteocyte-secreted protein that inhibits bone formation by inhibiting the Wnt signaling pathway by binding to the LRP5/6co-receptors, are in clinical development. Romosozumab is a sclerostin inhibitor approved by the FDA for the treatment of osteoporosis in postmenopausal women at a high risk of fracture that can act with both antiresorptive and osteoanabolic functions [108]. However, these novel osteoporosis therapies are still under study [109,110], and the current ones are not fully effective in all patients and also present serious side effects which limit their long-term use.

Therefore, there is an increasing need for the development of new therapies that base their mechanisms on bone biology, have no side effects and promote bone formation and thereby a reduction in the risk of fractures [111].

4.2. The Treatment Gap in Osteoporosis

Despite the epidemiological impact of osteoporosis, not all patients at a high risk of fractures are effectively assessed and treated with osteoporosis drugs [112]. This may be due to most high-risk individuals not being identified, not receiving appropriate treatment or, even when treated, not taking it. Hence, there is the so-called "treatment gap" in bone fragility management, which leads to an increase in the burden of osteoporotic fracture for individuals, societies and healthcare systems [113].

Although some clinical calculators, such as FRAX, are recommended by several guidelines for screening decisions, fracture risk calculation is still underestimated [114]. For example, the FRAX and Garvan risk calculators have demonstrated a low ability to identify the risk of hip fractures, major osteoporotic fractures or any clinical fractures in postmenopausal women aged 50–64 years during 10 years of follow-up [115].

Many studies pointed out that a minority of individuals at a high fracture risk actually receive treatment [116,117]. In this regard, Rodrigues et al. found that only 7.1% of 65-year-old women with fragility fractures were under treatment for osteoporosis, and 13.9% never had treatment [118].

A special need for drug therapy arises in patients who sustain a fragility fracture because of the increased risk of refracture [112]. However, it has been shown that the proportion of patients starting treatment to reduce the risk of future fracture within the year following a diagnosis of fracture is low [119]. In a study developed by the IOF, it was found that the treatment gap for the five largest EU countries (France, Germany, Italy, Spain and the UK), as well as Sweden, is estimated to be 73% for women and 63% for men. Moreover, in France, Sweden and Spain, 85%, 84% and 72% of fracture patients are without any treatment 1 year after fracture, respectively [120].

The treatment gap is particularly marked in the case of hip fracture patients [121,122]. Kim and colleagues studied the use of osteoporosis medications for the secondary prevention of osteoporotic fracture. Among a total of 86,202 patients with hip fracture, only 11 to 39% were treated with osteoporosis medication within 3 months after the fracture. Moreover, the adherence to osteoporosis treatment was also suboptimal [122].

One of the challenges in the treatment of patients with osteoporosis is that, in clinical practice, it is often the case that they show poor compliance with the pharmacotherapy that is prescribed to them. Among the reasons underpinning the low adherence to pharmacotherapy in patients with this pathology is that the asymptomatic nature of the disease maintenance treatment means that the patient sees no manifest benefit from the treatment [112]. Some reports found that the use of telecarers has the potential to be a useful adjunct in the monitoring of osteoporosis treatment and compliance. However, the participation of patients, families, physicians and clinicians is critically important for the success of this tool [123].

Other explanatory factors for the low adherence to pharmacotherapy among osteoporosis patients are: the cost of the drug, concerns regarding the long-term efficacy of the osteoporosis treatment and the fear of rare side effects. Long-term treatment with bisphosphonates is generally well tolerated for the patient and is considered safe and effective. However, the most important reason why patients decide to stop oral forms of bisphosphonates treatment is gastrointestinal irritation. In the most severe cases, reactions in the upper gastrointestinal tract may also include esophageal erosion or esophageal ulcers [124]. Moreover, bisphosphonates treatment has been shown to be associated with the occurrence of rare side effects which include osteonecrosis of the jaw (ONJ), atypical femoral fractures and cardiovascular damage [112].

ONJ is a serious but rare effect of antiresorptive agents or angiogenesis inhibitors. This pathology is characterized by progressive bone destruction in the maxillofacial area of

patients without previous radiation therapy or metastatic disease in the jaws [125]. The risk of bisphosphonate-associated ONJ in patients with long-term therapy has been estimated to be 0.21% over four years of therapy [126]. Recently, it has been reported that the risk of ONJ is higher in patients receiving denosumab therapy compared with those receiving bisphosphonates. In this study, among 9956 registered patients who underwent at least one dual-energy X-ray absorptiometry examination, 17 cases of ONJ were identified. Of these 17 patients, 12 were receiving denosumab at the time of ONJ diagnosis, and 5 of the patients were treated with oral or intravenous bisphosphonate therapy [127]. Interestingly, it has been highlighted that dental management by the screening and treatment of oral diseases during and also after the treatment with ONJ-related drugs can significantly reduce the occurrence of this disease [128].

Atypical femoral fractures are unusual fractures along the femoral diaphyseal and are located in the subtrochanteric region, which occur with little trauma. In a study aimed to evaluate the risk of atypical femur fracture in nearly 200,000 women using bisphosphonates over a ten-year period, the risk of atypical femur fracture increased with longer durations of bisphosphonate use and rapidly decreased after bisphosphonate discontinuation [129]. Although drug holidays decrease the risk of atypical femur fracture, the effect of discontinuation on other osteoporotic fractures must also be considered. The same study also found that, after 3 years of bisphosphonates treatment, 149 hip fractures were prevented, and 2 bisphosphonate-associated atypical fractures occurred in White women. Among Asian women, the balance after 3 years was 8 bisphosphonate-associated atypical fractures compared with 91 hip fractures prevented. By 10 years, bisphosphonates treatment decreased the risk of osteoporotic and hip fractures and outweighed the increased risk of atypical fractures among White women (less so among Asian women) [129].

Additionally, adverse effects have been observed with the use of romosozumab. The treatment with this anti-sclerostin antibody might increase cardiovascular damage and therefore the risk of cardiovascular complications such as cardiac ischemic or cerebrovascular events [130].

In summary, the careful evaluation of patients' previous disorders and the consideration of correct timing, age and comorbidities are necessary to evaluate the risk–benefit ratio of a specific drug therapy. Nevertheless, in the worst scenario, an alternative treatment option is often available. Moreover, for the reduction of the treatment gap, it is suggested that the international development of the Fracture Liaison Services (FLS) should be carried out to better identify patients who are at a high risk of fractures. Moreover, FLS provides an opportunity to improve the adherence to treatment, with a consequent reduction in the risk of refracture [131,132].

4.3. Cell Therapy as a Novel Approach

Osteoporosis is a disease characterized by a change in cell differentiation, with osteogenic differentiation inhibited in favor of adipogenic differentiation [133]. Aging increases the likelihood of osteoporosis, as older patients produce fewer stem cells with self-renewal and immunomodulatory capacities [134]. Clinical therapies for the treatment of osteoporosis have so far focused on bone remodeling and preventing bone loss, although they are not fully effective [57,61].

Cell therapies have attracted great interest in recent years for the treatment of certain chronic diseases including osteoporosis. This type of therapy focuses on the ability of cells to repair damaged tissue [135]. Several preclinical studies have focused on the use of stem cells of different origins [136].

MSCs from bone marrow or adipose tissue are the cells considered optimal for this type of treatment, as they are immunoprivileged and immunomodulatory cells, and their use is approved by the FDA. However, embryonic stem cells or induced pluripotent stem cells have been discarded due to ethical and safety concerns [137].

The results showed that, by using a high number of progenitor stem cells with good proliferation and differentiation capacities, it is possible to control bone resorption, decrease fracture damage and improve tissue mineral density in the treatment of osteoporosis [138].

After transplantation, MSCs may contribute to bone formation through two possible mechanisms of action. On the one hand, MSCs target the damaged site and differentiate into osteogenic cells, and on the other hand, MSCs secrete characteristic growth factors, such as the vascular endothelial growth factor (VEGF), transforming growth factor beta (TGF-β), hepatocyte growth factor (HGF) or insulin-like growth factor-1 (IGF-1), which act by promoting bone remodeling processes and preventing bone loss [139].

Decades ago, clinical studies were already conducted in children, using bone marrow MSCs (BM-MSCs) for the treatment of severe osteogenesis imperfecta [140].

For cell delivery, MSCs can be administered systemically (intravenous or intra-arterial injection) or locally (intracoronary or direct injection into damaged tissue). The cell migration procedure is not yet fully understood, so it is difficult to determine which mode of application is the most beneficial. It would be interesting to monitor the injected cells and their ability to adhere to the damaged tissue to determine this [141].

In a recent study by Lu et al., it was observed that extracellular vesicles (EVs) from MSCs possessed therapeutic potential for the treatment of osteoporosis, similar to that of progenitor cells. To develop this idea, they focused on studying disease models, potential therapeutic targets and the molecular mechanisms of action. The use of EVs in osteoporosis has not yet been studied, but it is being studied in the treatment of cancer, renal and cardiovascular diseases and wound healing. Furthermore, the great advantage of this type of treatment is that it is completely cell-free, eliminating any possibility of rejection in the patient. This would facilitate its application in the clinic [142].

Genetically modified BM-MSCs have also been studied in the treatment of osteoporosis. Sui et al. demonstrated that this cell line showed good homing and osteogenic capacity in glucocorticoid-induced murine osteoporosis (GIOP). The transplantation of allogeneic BM-MSCs reduced the loss of bone tissue mass and hardness and promoted osteoblastogenesis while maintaining bone formation [143].

To regulate osteoblast differentiation, two very important transcription factors, Runx2 and osterix, must be taken into account. The activation or inhibition of these transcription factors controls osteogenic differentiation in MSCs. In addition, miRNA regulators are also important, as they have a suppressive effect on bone cell formation while promoting adipocyte formation. Physical and chemical factors also affect proper bone remodeling and formation and may be of help when it comes to treatment [144].

Even so, it is necessary to continue adapting this type of therapy, as there is the problem of controlling cell migration once the MSCs have been implanted. The cells themselves do not recognize the bone surfaces to be treated, which can trigger cell differentiation to another, non-osteogenic type, and this type of graft is not able to be maintained in the long term [145].

Currently, there are few clinical trials studying the effect of infusion cell therapy for the treatment of osteoporosis. ClinicalTrials.gov was searched for the most recent clinical advances in the field. A search was carried out including the terms “Osteoporosis” and “Cell therapy”. Four clinical trials have been found in which cells were directly applied with therapeutic applications in osteoporosis (Table 2). Among the different cell types used, we can find MSCs (NCT04501354), fucosylated MSCs (NCT02566655), allogeneic adult umbilical cord-derived MSCs (NCT05152381) and autologous osteoblastic cells (NCT02061995). As of yet, no results have been reported for these trials.

Table 2. Clinical trials with cell therapies for osteoporosis.

Cell Type	NTC Number	Title	Phase	Indication
MSC	NCT04501354	Evaluation of Clinical and Bone Density Improvement After Implantation of Allogenic Mesenchymal Stem Cell From Umbilical Cord on Osteoporosis Patients	2	Improvement of bone mass density
Fucosylated MSC	NCT02566655	Clinical Trial of Intravenous Infusion of Fucosylated Bone Marrow Mesenchyme Cells in Patients with Osteoporosis (CSM/OP/2011)	1	Osteoporotic low-impact fractures
Allogeneic adult umbilical cord-derived mesenchymal stem cells	NCT05152381	Safety of Cultured Allogeneic Adult Umbilical Cord Derived Mesenchymal Stem Cell Intravenous Infusion for Osteoporosis	1	OP
Autologous osteoblastic cells	NCT02061995	Phase 2a Study on Intravenous Infusion of Autologous Osteoblastic Cells in Severe Osteoporosis	2	Severe OP

OP: Osteoporosis.

4.4. Hydrogels for Osteoporosis Treatment

In the post-traumatic bone tissue repair process, autologous/allogeneic transplantation has so far been the main path followed by experts, but it presents a major problem of donor limitation. New applications of different biomaterials are presented as a real alternative in bone regeneration. The use of biomaterials in the hydrogel state stands out due to their hydrophilic properties, their good biocompatibility, their porous structure and their adjustable biodegradability mechanical properties. These properties directly influence the cell migration, proliferation and differentiation of MSCs, which favors bone regeneration [146]. Hydrogels have been used as an emerging and promising tool in tissue engineering. They act as a substitute for the conventional materials used in restorative surgery by combining biology and engineering, improving and restoring tissue function [147].

One of the current challenges in tissue engineering for the treatment of osteoporosis is the development of a system for the controlled release of therapeutic substances that can improve their targeting. Injectable hydrogels are presented as a versatile option for different applications in tissue engineering thanks to their adaptability. Despite this, their clinical application is still scarce, and more studies are required to improve the aspects related to the use of polymeric biomaterials, their mechanical properties or their biodegradability [148]. Zheng et al. analyzed different strategies based on hydrogels for the treatment of osteoporosis, concluding that the use of biomaterials based on combined natural and synthetic composites is the best therapeutic strategy. These hydrogels have low cytotoxicity and good biocompatibility and biodegradability, which, together with a physicochemical crosslinking process, improve the mechanical properties of the construct. This makes it possible to control the degradation rate of the hydrogel, generating an excellent vehicle for the controlled release of drugs [149].

Recombinant human BMP-2 was, until a few years ago, the only osteoinductive growth factor approved by the FDA and the European Medicines Agency (EMA) for the treatment of long fractures [150]. However, the direct use of BMPs has been reported to lead to adverse effects, so the use of drug carriers is suggested as an option to reduce the doses applied and improve their cost-effectiveness [151].

Echave et al. developed an osteoconductive hydrogel based on gelatin and calcium sulfate-hydroxyapatite bioceramics that slowed the delivery of the required doses of growth factors such as BMP-2 to promote bone regeneration in an osteoporotic defect model. The resulting hydrogels were biocompatible and had an increased pore size, which favored

mechanical compression properties. In this study, it was demonstrated that the hydrogels promoted the adhesion and proliferation of human bone marrow-derived MSCs and also promoted the osteogenic differentiation of the cells [152].

García-García et al. developed two different scaffolds based on PLGA-Alginate in a hydrogel state (HY) and another in a solid-state as a sponge (SS), which were for the sustained delivery of β-estradiol and BMP-2 for bone regeneration in osteoporosis. In this case, both systems were flexible, adapted well to the shape of the defect and had the same controlled release rate of β-estradiol and BMP-2. According to their trials, both strategies promoted bone regeneration, but in the case of SS, the bone repair was 30% higher than that with HY. This was possible simply due to the shorter degradation time of SS compared to that of HY. This study reflects the importance of modifying the physical properties of hydrogels to optimize regenerative therapies [153]. In another similar study by the same group, a heat-resistant injectable hydrogel was used to encapsulate 17β-estradiol, bone morphogenetic protein-2 (BMP-2) and plasma rich in growth factors (PRGF) microspheres. Here, the loaded hydrogel was applied locally to regenerate a critical calvarial bone defect in rats. PRGF did not increase bone repair, while the addition of BMP-2 increased the response to 17β-estradiol. However, the mineralization of newly formed bone in the osteoporosis groups was markedly lower than that in the non-osteoporosis groups [154].

In the treatment of diseases mainly caused by osteoporosis, such as hypercalcemia, the use of hydrogels may present an advantage for the regulation of calcium formation [155]. Li et al. developed an injectable tetra-PEG-based hydrogel loaded with the drug alendronate (ALN), which allowed for the long-term controlled release of anti-osteoporotic molecules. These hydrogels effectively promoted bone regeneration at the implantation site in a minimally invasive manner [156].

Salmon calcitonin (sCT) is a product currently used in clinical regenerative medicine to regulate calcium metabolism in order to improve the treatment of disorders such as osteoporosis and hypercalcemia. As sCT in serum is rapidly cleared in vivo, Yu et al. designed a hydrogel based on the conjugation of sCT with oxidized calcium alginate (sCT-OCA) and hydroxypropyl chitin (HPCH). These gels were stable for up to 28 days and showed higher biocompatibility when used on pre-osteoblastic cells than sCT alone. In sCT-OCA, the activity of some osteogenic markers such as ALP increased by up to 63%, and calcium deposition increased by 42%, enhancing osteogenic cell differentiation [157].

In osteoporosis, excessive oxidative stress causes osteoblast and osteocyte apoptosis, leading to abnormal bone formation around the damaged area [158]. Melatonin is a hormone that has previously demonstrated its capacity for cell differentiation and bone remodeling and its usefulness in curbing excessive oxidative stress [159]. In a study by Xiao et al., a hydrogel with a dressing function based on methacrylate gelatin (GelMA) doped with melatonin for controlled and targeted release was developed. In a trial with MC3T3-E1 cells, it was shown that melatonin in controlled doses reduced the apoptosis caused by hydrogen peroxide-induced oxidative stress and restored the osteogenic potential of the cells. In addition, it increased the bone mass around the implant in ovariectomized rats treated with this adhesive [160].

On the other hand, Zhao et al. generated a bio-inspired mineralized hydrogel from the supramolecular assembly of nano-hydroxyapatite, sodium carbonate and polyacrylic acid (CHAp-PAA). These hydrogels proved to be able to maintain their morphology and mechanical properties. They were biocompatible, bioactive and osteoconductive in studies carried out using bone marrow mesenchymal stem cells. The results presented in this work demonstrated that these hydrogels enhanced bone growth by accelerating bone formation without the need for additional therapeutic agents [49].

Another study developed a nanoemulsion drug delivery system based on a fluvastatin hydrogel, using carbopol940 as a gelling agent. The drugs were intended to be administered transdermally and were subsequently evaluated for their anti-osteoporotic potential. The in vivo anti-osteoporotic results carried out in this research showed the formation of new

bone in the trabecular region of osteoporotic rat femurs and an increase in load-bearing with respect to the damaged tissue [161].

The encapsulation of alendronate, a bone resorption inhibitor, in different chitosan-based hydrogels crosslinked using genipin (CS/bGP) for the prolonged local delivery of alendronate by injection is an aspect that could be of interest in the treatment of OP. Increasing the concentration of alendronate resulted in hydrogels with a lower porosity and higher density. The CS/bGP hydrogel ensured the controlled release of alendronate for an average of 50 days depending on the initial inhibitor load added, proved to be biocompatible and showed a low immunogenic response. In addition, alendronate-loaded hydrogel was shown to have a lower inflammatory response, higher cell proliferation and faster tissue maturation [162].

Papathanassiou et al. fabricated and characterized silica-based hydrogels for the purpose of releasing bis-phosphonates, which are a synthetic variant of pyrophosphates with advantageous bone remodeling properties. These hydrogels are injectable and thermosensitive and can be reused and refilled. In addition, by altering several factors, such as temperature, the cations present, pH and the structural characteristics of the bis-phosphonates, the release rate can be controlled [163].

Finally, in the literature, we can find studies that combine hydrogels with other types of physical strategies. Chen et al. studied the effect of the application of extracorporeal shock waves (ESW) together with the application of a hydrogel loaded with teriparatide (T-Gel), a drug used in the treatment of osteoporosis, on the activity and cell differentiation of osteoporosis-derived MSCs and their regenerative capacity. Their results showed that the combination of ESW and T-Gel significantly enhanced the viability, proliferation, migration and osteogenic differentiation of MSCs, thus improving the osteogenic activity of the microenvironment in osteoporotic defects [164].

4.5. Lifestyle and Osteoporosis

4.5.1. Nutritional Habits

Calcium and vitamin D were previously considered to be the most important nutrients in preventing osteoporosis; however, there are other factors that can condition BMD and thus bone health [165]. Nutrients can have a direct or indirect influence on osteoporosis; direct influence is understood as being part of the bone structure itself, while indirect influence is related to the process of absorption and the utilization of calcium [166].

Without a doubt, when talking about nutrition and osteoporosis, calcium should be mentioned because it is one of the main constituents of bones and plays an important role in bone stiffness [167]. This nutrient plays an important role in osteogenesis by increasing the concentration of OPNand OC, promoting the formation of new bone and increasing the number of estrogenic markers such as ALP [168]. However, the calcium intake in the general population remains below that recommended by different organizations (<700 mg/day) [126], mainly due to the limited supply of calcium-rich foods [169]. Long periods of calcium deficiency lead to low BMD [170]; hence, the use of calcium supplementation has become very popular, with favorable effects in different populations and age groups [171]. Nevertheless, at present, controversy has arisen over the consumption of calcium supplements since they are associated with cardiovascular disease [172,173] and, when they are not administered with vitamin D, with the risk of myocardial infarction [174]. It is important to emphasize that these risks apparently do not occur when calcium intake comes from dietary sources, making these the best option [167].

Vitamin D is a steroid prohormone essential for the absorption and regulation of calcium in the intestine [170]. Vitamin D levels in the body depend mainly on subcutaneous production following the exposure to sunlight (80–90%) and, to a lesser extent, on diet (10–20%), due to the limited supply of vitamin D-rich foods [175]. This vitamin promotes adequate blood calcium levels, which promote bone growth and remodeling from osteoblasts and osteoclasts, decreasing the risk of osteoporosis [91]. However, some authors state that vitamin D supplementation alone has no effect on fracture risk [176,177] or BMD [178],

attributing these results to the low calcium intake of the general population [179]. In contrast, Weaver et al. [91] conclude in their systematic review with a meta-analysis that joint vitamin D and calcium supplementation significantly decreases the risk of fracture in patients with and without osteoporosis.

Protein intake is an important nutritional factor for bone health, as it provides the amino acids necessary for the construction of the bone matrix and stimulates bone formation from IGF-I [180]. Cadogan et al. conducted a study in which they showed that a high consumption of milk (a protein-rich food) improved BMD and overall bone mineral acquisition. However, the evidence of the effects of protein intake on bone health is still weak [181–183], so further research is needed.

Soy isoflavones are considered to be the most estrogenic compounds found mainly in the legumes of the Fabaceae family [184]. These bioactive compounds have been deeply studied in recent years; it has been found that they have favorable effects on glucose levels [185], breast cancer risk [186] and osteoporosis [187], among others. As for the preventive effects of osteoporosis, these are better in postmenopausal women who have developed the pathology due to hormonal alterations, since they decrease osteoclastic factors such as collagen C-telopeptide and increase osteoblastic factors such as bone alkaline phosphatases [188] in addition to selectively antagonizing the catabolic action on the osteoblasts of parathohormones [189].

Theoretically, folic acid and vitamin B-12 could have important effects on fracture risk due to their action on homocysteine metabolism [170]. The consumption of folic acid and vitamin B-12 is expected to reduce the amount of homocysteine in the blood by a quarter or a third [190], which would slow down its degradative action on the extracellular matrix and decrease BMD [191]. However, the results showed that a chronic intake of folic acid and B-12 has no effect on the risk of fracture [192].

Finally, caloric intake is also an aspect to be considered. Restrictive diets are totally contraindicated in people with osteoporosis, since one of the risk factors for this pathology is thinness (<21 kg/m^2 or <127 pounds). Another related aspect is the number of calories expended at rest at a neutral temperature defined as the Basal Metabolic Rate (BMR) [193]. BMR increases with the amount of cardiovascular exercise practiced and decreases with age. Hsu et al. [194], in their study, found that a BMR above 1182.7 Kcal is associated with better BMD in postmenopausal women, which translates into a lower risk of osteoporosis.

4.5.2. Physical Exercise

It is clear that physical inactivity leads to a decrease in BMD, while physical exercise increases it [170]. BMD depends on the dynamic balance between bone formation and resorption [195], with mechanical loads being the main stimulus for osteoblastic differentiation and mineralization, promoting adequate bone mass and density [196]. In addition, physical exercise has an important hormonal effect by regulating estrogen, PTH and glucocorticoid levels, which are involved in bone metabolism [195]. The constant practice of physical exercise promotes the proliferation of estrogens [197], which are bone protectors since they slow down the production of osteoclastic cytokines, favor the proliferation of osteoblasts and decrease osteocyte apoptosis [198].

Another effect of physical activity related to osteoporosis is related to BMR; cardiovascular and resistance exercise have been shown to increase BMR levels [199]. Several authors have tried to estimate BMD through different methods such as anthropometric measures; however, measures such as the waist hip index are insufficient to achieve a reliable estimate of BMD, while BMR could be positioned as an important predictor of osteoporosis because it has a direct relationship with BMD—the higher the BMR, the better the bone health that is expected [194].

The usual practice of physical exercise has an important effect on body weight, which is closely related to BMD, the most important component of body composition, and lean mass for its effects on BMD in the whole body, while fat mass has only been related to femoral neck BMD [200].

The American College of Sport Medicine recommends, for the prevention or treatment of osteoporosis, that, in addition to the minimum physical activity established by the WHO, weight-bearing exercise should be performed whenever bone loss is mild or is to be prevented; however, when BMD has been compromised, the added stress to the bones may represent an increase in the risk of fracture [201]. There is still no clear consensus on the ideal exercise prescription for this pathology; however, Howe et al. [202], through a systematic review, analyzed 43 RCTs and found that the best exercises to improve BMD in the femoral neck were high strength exercises without weight bearing, while for the spine, combinations of exercises were better. On the other hand, Kemmler et al. [203], through a systematic review with a meta-analysis, concludes that, although positive effects of exercise on fracture risk in old age were found, they were weak. This is mainly due to the wide variety of exercises that can generate different effects.

Some of the most commonly used training modalities in patients with osteoporosis are resistance exercise, aquatic exercise and proprioceptive training [204]. On the one hand, resistance exercise seems to act on the bone from the myotendinous junction, where the increase in tendon tension resulting from muscle contraction stimulates the osteogenic response of the bone, increasing BMD [205]. On the other hand, aquatic exercises, despite not being the best option to increase BMD due to their low or even null impact on bone, do allow for the generation of muscle tension while minimizing any risk of falling, which, for older adults, is a clear advantage [206]. Previously, it was believed that aquatic exercises decreased BMD; however, studies such as that by Su, Chen and Xie [207] show the opposite. Although these types of exercises are not the best for increasing BMD, they do have positive effects on it. Finally, proprioceptive exercises are also one of the main strategies to address the osteoporotic population; the improvement in the perception of the location of their own body in space from exercise has been shown to decrease the risk of falls and increase mobility, in addition to improving functional capacity and dynamic balance, resulting in an improvement in the quality of life of these patients [208].

4.5.3. Alcohol Intake and Smoking

Alcohol consumption has shown heterogeneous effects depending on the dosage. When alcohol is consumed in light or moderate doses, it functions as a protective factor for BMD, while when consumption is high, it is consolidated as a risk factor for fracture [209]. Different studies have shown positive effects of alcohol consumption in low amounts. Berg et al. determined that when a person consumes between 0.5 and 1.0 drinks per day, they have a lower risk of hip fracture [210]. On the other hand, lifestyle habits do not seem to be related to the protective effect of moderate alcohol consumption in women close to menopause [211]. The protective effect of alcohol on bone health could be explained by its acute suppressive effect on bone resorption without the participation of PTH or calcitonin [212], as evidenced by the low levels of CTX associated with ethanol intake [213], while high alcohol consumption interferes with the calcium balance by decreasing its absorption in the intestine, reducing vitamin D production and increasing the risk of falls [210].

On the other hand, in the 1980s, cigarette smoking was identified as a risk factor for osteoporosis [214], which, to date, remains prevalent and increasing, mainly because of the addictive nature of this habit [215]. Different authors have evidenced a negative and independent relationship between cigarette smoking and bone health [216]. In older adults, it has been shown that smoking generates an increase in the loss of bone mass and the risk of fracture [217], which can be explained by the free radicals produced by the consumption of about 150 toxins in cigarettes, leading to an increase in estrogen-destroying enzymes, which, as previously mentioned, are hormones of great importance for the process of bone remodeling [209]. This also explains the early onset of menopause in female smokers, with the consequent effects of this condition on bone health [218]. However, it is unclear which of the toxins found in cigarettes are specifically related to the alteration of bone health [219].

Chronic cigarette smoking suppresses the production of OPG, a protein that works as an inhibitor of osteoclastogenesis, which results in an increase in the number of osteoclasts, thus favoring bone resorption processes [220]. Tang and Lappin, in their articles, studied this phenomenon, finding that individuals who smoked cigarettes presented a lower level of OPG, while the RANKL (receptor activator of nuclear factor κβ ligand), which works as a stimulant of osteoclastic maturation and activity, was higher than those found in non-smoking subjects [221,222]. Smoking also induces inflammatory processes and increases oxidative stress, generating damage to the collagen metabolism, which acts as an important biochemical marker in bone metabolism in addition to inducing toxicity on bone cells by increasing the resistance to calcitonin, which blocks bone angiogenesis [223], preventing the creation of new blood vessels, which would alter the flow of oxygen and nutrients to the bone [224]. In addition to the inverse association between smoking and body weight described in the evidence, it has been shown that cigarette consumption is associated with low weight due to the inhibitory effect of nicotine on appetite [219].

Additionally, it has been observed that the risk of falls increases directly with cigarette smoking. Ampelas, in his systematic review, concludes that the risk of osteoporosis and hip fracture increases due to cigarette smoking because of its negative effect on BMD, regardless of the sex of the subject [225]. Finally, it has been shown that smoking cessation produces an increase in BMD, which reduces the risk of fracture [209]; however, these effects are only appreciable after 10 years of non-consumption [225].

5. Conclusions

Osteoporosis is a severe, chronic, progressive and clinically silent disease which results from an imbalance between bone resorption and bone production. Osteoporosis does not follow pre-established clinical patterns but rather manifests with specific signs and symptoms during its course, including pain, deformities or a loss of height. Fragility fractures are the most common consequence of osteoporosis and are particularly common in the vertebrae, hip and forearm. Despite advances in the diagnosis through different methods such as bone densitometry and dual X-rays, more research is needed.

Current FDA-approved osteoporosis treatments mainly consist of the use of drugs designed to decrease bone resorption. A better understanding of the markers, cellular events and genetic targets of osteoporosis has contributed to the development of novel drug agents. Thus, new targets are being studied for the treatment of osteoporosis, such as cathepsin K inhibitors or anti-sclerostin therapies; however, an ideal osteoporosis therapy has not yet been developed, as they still present considerable adverse effects that limit their long-term use. To overcome these problems, regenerative medicine is now an area of intensive exploration. Among new therapeutic strategies, MSCs are expected to be a promising tool due their immune-privileged potential and their role in bone repair. After transplantation, MSCs may contribute to bone formation through two possible mechanisms of action: by their ability to graft into tissues and differentiate into osteogenic cells, or by secreting characteristic growth factors that promote bone remodeling processes and prevent loss. Moreover, clinical trials using MSCs as the principal treatment are underway. The future evaluation of these studies will provide us with information about the safety, tolerability and efficacy of the transplanted cells and will open the door to establish their therapeutic mechanism in osteoporosis. Meanwhile, other techniques, such as gene modification, the use of EVs and the combination of cells and hydrogels, are under study to improve the activity of stem cells that may represent novel therapeutic approaches in future clinical practice.

In addition, there are non-pharmacological methods for the prevention of further osteoporotic fractures and for the regulation of osteoporosis which are related to lifestyle factors. Critical lifestyle factors include nutritional habits such as maintaining adequate calcium and vitamin D intake, engaging in regular weight-bearing physical activity and avoiding excessive alcohol intake and smoking.

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Abbreviations

MSCs: mesenchymal stem cells; BMD: bone mineral density; ALP: alkaline phosphatase; OPN: osteopontin; OC: osteocalcin; PTH: parathyroid hormone; TGF-β: transforming growth factor beta; M-CSF: macrophage colony-stimulating factor; RANKL: receptor activators of nuclear factor-κβ ligand; OPG: osteoprotegerin; LPL: lipoprotein-related co-receptor; IOF: International Osteoporosis Foundation; BMTs: bone turnover markers; Pir: Pyridinolines; Dpir: deoxypyridinoline; ICPT: C-terminal telopeptide of type I collagen; β-CTX: β-CrossLaps; NTX: N-terminal telopeptide of type I collagen; FDA: Food and Drug Administration; SERMs: selective oestrogen receptor modulators; ER: estrogen receptor; FPPS: farnesyl pyrophosphate synthase; ONJ: osteonecrosis of the jaw; FLS: Fracture Liaison Services; VEGF: vascular endothelial growth factor; TFG- β: transforming growth factor beta; HGF: hepatocyte growth factor; IGF-1: the insulin-like growth factor-1; BM-MSCs: using bone marrow mesenchymal stem cells; EVs: extracellular vesicles; GIOP: glucocorticoid-induced murine osteoporosis; EMA: European Medicines Agency; HY: hydrogel state; SS: solid-state; PRGF: plasma rich in growth factors; ALN: alendronate; sCT: salmon calcitonin; sCT-OCA: salmon calcitonin with oxidized calcium alginate; GelMA: methacrylate gelatin; CHAp-PAA: nano-hydroxyapatite, sodium carbonate and polyacrylic acid; ESW: extracorporeal shock waves; T-Gel: teriparatide; BMR: Basal Metabolic Rate.

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CONSENSUS STATEMENT

The clinician's guide to prevention and treatment of osteoporosis

M. S. LeBoff[1] · S. L. Greenspan[2] · K. L. Insogna[3] · E. M. Lewiecki[4] · K. G. Saag[5] · A. J. Singer[6] · E. S. Siris[7]

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Abstract

Osteoporosis is the most common metabolic bone disease in the USA and the world. It is a subclinical condition until complicated by fracture(s). These fractures place an enormous medical and personal burden on individuals who suffer from them and take a significant economic toll. Any new fracture in an adult aged 50 years or older signifies imminent elevated risk for subsequent fractures, particularly in the year following the initial fracture. What a patient perceives as an unfortunate accident may be seen as a sentinel event indicative of bone fragility and increased future fracture risk even when the result of considerable trauma. Clinical or subclinical vertebral fractures, the most common type of osteoporotic fractures, are associated with a 5-fold increased risk for additional vertebral fractures and a 2- to 3-fold increased risk for fractures at other sites. Untreated osteoporosis can lead to a vicious cycle of recurrent fracture(s), often resulting in disability and premature death. In appropriate patients, treatment with effective antifracture medication prevents fractures and improves outcomes. Primary care providers and medical specialists are critical gatekeepers who can identify fractures and initiate proven osteoporosis interventions. Osteoporosis detection, diagnosis, and treatment should be routine practice in all adult healthcare settings. The Bone Health and Osteoporosis Foundation (BHOF) – formerly the National Osteoporosis Foundation – first published the *Clinician's Guide* in 1999 to provide accurate information on osteoporosis prevention and treatment. Since that time, significant improvements have been made in diagnostic technologies and treatments for osteoporosis. Despite these advances, a disturbing gap persists in patient care. At-risk patients are often *not* screened to establish fracture probability and *not* educated about fracture prevention. Most concerning, the majority of highest risk women and men who have a fracture(s) are *not* diagnosed and *do not* receive effective, FDA-approved therapies. Even those prescribed appropriate therapy are unlikely to take the medication as prescribed. The *Clinician's Guide* offers concise recommendations regarding prevention, risk assessment, diagnosis, and treatment of osteoporosis in postmenopausal women and men aged 50 years and older. It includes indications for bone densitometry as well as fracture risk thresholds for pharmacologic intervention. Current medications build bone and/or decrease bone breakdown and dramatically reduce incident fractures. All antifracture therapeutics treat but do not cure the disease. Skeletal deterioration resumes sooner or later when a medication is discontinued—sooner for nonbisphosphonates and later for bisphosphonates. Even if normal BMD is achieved, osteoporosis and elevated risk for fracture are still present. The diagnosis of osteoporosis persists even if subsequent DXA T-scores

✉ M. S. LeBoff
mleboff@bwh.harvard.edu

S. L. Greenspan
greenspn@pitt.edu

K. L. Insogna
karl.insogna@yale.edu

E. M. Lewiecki
mlewiecki@gmail.com

K. G. Saag
ksaag@uab.edu

A. J. Singer
singeraf@gunet.georgetown.edu

E. S. Siris
es27@cumc.columbia.edu

[1] Brigham and Women's Hospital, Harvard Medical School, 221 Longwood Ave, Boston, MA 02115, USA

[2] University of Pittsburgh Medical Center, 1110 Kaufmann Building, 3471 Fifth Ave, Pittsburgh, PA 15213, USA

[3] Yale School of Medicine, 333 Cedar St, New Haven, CT 06520, USA

[4] University of New Mexico Health Sciences Center, 300 Oak St NE, Albuquerque, NM 87106, USA

[5] University of Alabama at Birmingham, 1720 2nd Avenue South, FOT 820, Birmingham, AL 35294, USA

[6] MedStar Georgetown University Hospital and Georgetown University Medical Center, 3800 Reservoir Road NW, 3rd Floor, Washington, DC 20007, USA

[7] Columbia University Irving Medical Center, 180 Fort Washington Ave, Suite 9-903, New York, NY 10032, USA

are above − 2.5. Ongoing monitoring and strategic interventions will be necessary if fractures are to be avoided. In addition to pharmacotherapy, adequate intake of calcium and vitamin D, avoidance of smoking and excessive alcohol intake, weight-bearing and resistance-training exercise, and fall prevention are included in the fracture prevention armamentarium. Where possible, recommendations in this guide are based on evidence from RCTs; however, relevant published data and guidance from expert clinical experience provides the basis for recommendations in those areas where RCT evidence is currently deficient or not applicable to the many osteoporosis patients not considered for RCT participation due to age and morbidity.

Keywords Fractures · FRAX® · Osteoporosis · Primary care management of osteoporosis · Vertebral imaging · Fracture risk stratification · Bisphosphonate holiday · Novel antifracture therapies (romosozumab, denosumab, abaloparatide)

Synopsis of major recommendations to the clinician

These recommendations apply to postmenopausal women and men aged 50 years and older.

Universal recommendations

- Counsel individual patients on their risk for osteoporosis, fractures, and potential consequences of fractures (functional deterioration, loss of independence, increased mortality).
- Recommend a diet with adequate total calcium intake (1000 mg/day for men aged 50–70 years; 1200 mg/day for women ≥ 51 years and men ≥ 71 years), incorporating calcium supplements if intake is insufficient.
- Monitor serum 25-hydroxyvitamin D levels.
- Maintain serum vitamin D sufficiency (≥ 30 ng/mL but below ≤ 50 ng/mL) [1–3]. Prescribe supplemental vitamin D (800–1000 units/day) as needed for individuals aged 50 years and older to achieve a sufficient vitamin D level. Higher doses may be necessary in some adults, especially those with malabsorption. (Note: in healthy individuals a serum 25(OH) vitamin D level ≥ 20 ng/mL may be sufficient, but in the setting of known or suspected metabolic bone disease ≥ 30 ng/mL is appropriate.)
- Identify and address modifiable risk factors associated with falls, such as sedating medications, polypharmacy, hypotension, gait or vision disorders, and out-of-date prescription glasses.
- Provide guidance for smoking cessation, and avoidance of excessive alcohol intake; refer for care as appropriate.
- Counsel or refer patients for instruction on balance training, muscle-strengthening exercise, and safe movement strategies to prevent fracture(s) in activities of daily life.
- In community-dwelling patients, refer for at-home fall hazard evaluation and remediation.
- In post-fracture patients who are experiencing pain, prescribe over-the-counter analgesia, heat/ice home care, limited bed rest, physical therapy, and alternative non-pharmacologic therapies when appropriate. In cases of intractable or chronic pain, refer to a pain specialist or physiatrist.
- Coordinate post-fracture patient care via fracture liaison service (FLS) and multidisciplinary programs in which patients with recent fractures are referred for osteoporosis evaluation and treatment, rehabilitation, and transition management.

Diagnostic assessment recommendations

- Investigate any broken bone in adulthood as suspicious for osteoporosis, regardless of cause [4, 5].
- Measure height annually, preferably with a wall-mounted stadiometer (without shoes).
- Record history of falls.
- Perform BMD testing in the following:
  - Women aged ≥ 65 years and men aged ≥ 70 years.
  - Postmenopausal women and men aged 50–69 years, based on risk profile.
  - Postmenopausal women and men aged ≥ 50 years with history of adult-age fracture.
  - DXA facilities that employ accepted quality assurance measures.
  - The same facility and on the same densitometry device for each test whenever possible.
- Maintain diagnosis of osteoporosis in patient diagnosed by fracture in adulthood or T-score (− 2.5 or below), even if subsequent DXA T-score is above − 2.5.
- To detect subclinical vertebral fractures, perform vertebral fracture imaging (X-ray or DXA vertebral fracture assessment) in the following:
  - Women aged 65 years and older if T-score is less than or equal to − 1.0 at the femoral neck [6].
  - Women aged 70 years or older and men aged 80 years or older if T-score is less than or equal to − 1.0 at the lumbar spine, total hip, or femoral neck.
  - Men aged 70–79 years if T-score is less than or equal to − 1.5 at the lumbar spine, total hip, or femoral neck.
  - Postmenopausal women and men aged ≥ 50 years with the following specific risk factors:

- Fracture(s) during adulthood (any cause).
- Historical height loss of ≥ 1.5 in. (defined as the difference between the current height and peak height) [7].
- Prospective height loss of ≥ 0.8 in. (defined as the difference between the current height and last documented height measurement) [7].
- Recent or ongoing long-term glucocorticoid treatment.
- Diagnosis of hyperparathyroidism [8].

- Rule out secondary causes of bone loss, osteoporosis, and/or fractures.
- In appropriate untreated postmenopausal women, selectively measure bone turnover markers to help gauge rapidity of bone loss.
- Prior to elective orthopedic procedures, evaluate skeletal health and measure BMD as indicated by risk profile (e.g., inflammatory arthritis, osteoarthritis, chronic kidney disease, or adverse events from surgery or other risk factors) [9–11].

Pharmacologic treatment recommendations

- No uniform recommendation applies to all patients. Management plans must be individualized.
- Current FDA-approved pharmacologic options for osteoporosis are as follows:
  - Bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid)
  - Estrogen-related therapy (ET/HT, raloxifene conjugated estrogens/ bazedoxifene)
  - Parathyroid hormone analogs (teriparatide, abaloparatide)
  - RANK-ligand inhibitor (denosumab)
  - Sclerostin inhibitor (romosozumab)
  - Calcitonin salmon
- Consider initiating pharmacologic treatment in postmenopausal women and men ≥ 50 years of age who have the following:
  - Primary fracture prevention:
    - T-score ≤ − 2.5 at the femoral neck, total hip, lumbar spine, 33% radius (some uncertainty with existing data) by DXA.
    - Low bone mass (osteopenia: T-score between − 1.0 and − 2.5) at the femoral neck or total hip by DXA *with* a 10-year hip fracture risk ≥ 3% or a 10-year major osteoporosis-related fracture risk ≥ 20% (i.e., clinical vertebral, hip, forearm, or proximal humerus) based on the US-adapted FRAX® model.
  - Secondary fracture prevention:
    - Fracture of the hip or vertebra regardless of BMD [4, 5].
    - Fracture of proximal humerus, pelvis, or distal forearm in persons with low bone mass (osteopenia: T-score between − 1.0 and − 2.5). The decision to treat should be individualized in persons with a fracture of the proximal humerus, pelvis, or distal forearm who *do not have osteopenia or low BMD* [12, 13].
- Initiate antiresorptive therapy following discontinuation of denosumab, teriparatide, abaloparatide, or romosozumab.

Monitoring patients and treatment response

- Perform BMD testing 1 to 2 years after initiating or changing medical therapy for osteoporosis and at appropriate intervals thereafter according to clinical circumstances.
  - More frequent BMD testing may be warranted in higher-risk individuals (multiple fractures, older age, very low BMD).
  - Less frequent BMD testing may be warranted as follow-up for patients with initial T-scores in the normal or slightly below normal range (osteopenia) and for patients who have remained fracture free on treatment.
- In patients receiving osteoporosis pharmacologic treatment:
  - Routinely reassess risk for fracture, patient satisfaction and adherence with therapy, and need for continued or modified treatment. The appropriate interval between initiation and reassessment differs with agent prescribed.
  - Serially measure changes in BMD at lumbar spine, total hip, or femoral neck; if lumbar spine, hip, or both are not evaluable or *according to clinical judgment*, consider monitoring at 33% distal radius.
  - Reassess patient and BMD status for consideration of a drug holiday after 5 years of oral and 3 years of intravenous bisphosphonate in patients who are no longer at high risk of fracture (T-score ≥ − 2.5, no new fractures) [14].
  - At each healthcare encounter, ask open-ended questions about treatment to elicit patient feedback on possible side effects and concerns. Communicate risk-benefit trade-offs and confirm understanding: both the risk of adverse events with treatment (usually very low) and risk of fractures and their negative consequences without treatment (usually much higher).

Osteoporosis: impact and overview

Osteoporosis is a disease characterized by low bone density, deterioration of bone tissue, disrupted bone microarchitecture, compromised bone strength, and fracture. According to the World Health Organization (WHO) diagnostic classification, osteoporosis is defined by BMD at the hip or lumbar spine that is less than or equal to 2.5 standard deviations below the mean BMD of a young adult reference population (T-score).

Osteoporosis is a risk factor for fracture, just as hypertension is for stroke and hypercholesterolemia is for heart disease. While risk is highest in individuals with extremely low BMD, the majority of fractures occur in patients with T-scores better than − 2.5. Non-BMD factors contribute to fracture risk, such as falls, frailty, and poor bone quality.

Scope of the problem

Osteoporosis affects an enormous number of people, both men and women, of all races. Among Caucasian adults in the USA aged 50 years and older, about 50% of women and 20% of men will experience an osteoporotic fracture in their remaining lifetime [15]. Rates of fracture differ by ethnic/racial population and skeletal site.

For fracture at any site in women, after adjusting for BMD, weight, and other covariates, non-Hispanic white and Hispanic-American women have the highest risk for fracture, followed by Native Americans, African Americans, and Asian Americans [16, 17]. For hip fracture in men, the age-adjusted incidence was highest for non-Hispanic white men, similar among Hispanic-American and black men, and lowest in Asian men.

In a 2014 cross-sectional analysis of data from five large independent cohorts (in the USA and Asia), prevalence of self-reported non-traumatic fracture in men was non-Hispanic white American 17.1%; Afro-Caribbean, 5.5%; African American, 15.1%; Hispanic-American, 13.7%; Asian American, 10.5%; Hong Kong Chinese, 5.6%, and Korean, 5.1% [18] .

Many factors are thought to contribute to these divergent fracture rates including BMD, cortical thickness, access to healthcare, comorbidities (such as diabetes), and skeletal geometry (e.g., hip axis length) [20]. Fracture rates do not track uniformly with the risk of osteoporosis among different racial/ethnic groups. For example, while fewer African Americans have osteoporosis, those diagnosed with osteoporosis experience fracture rates comparable to Non-Hispanic Whites and experience *worse* overall post-fracture outcomes [19]. Native Americans have BMD similar to Non-Hispanic Whites but higher rates of hip fracture, possibly reflecting challenges with screening, nutrition, lifestyle, and follow-up (Fig. 1).

Based on data from the National Health and Nutrition Examination Survey III (NHANES III), BHOF previously estimated that more than 10.2 million Americans have osteoporosis and an additional 43.4 million have low bone density [21]. Prevalence of fractures continues to increase as the population ages. It is currently projected that 12.3 million Americans have osteoporosis [22]. At present the 2 million new cases of osteoporotic fracture per year *exceeds* the annual number of new cases of myocardial infarction, breast cancer, and prostate cancer combined [23–25]. Annual fracture incidence is expected to increase 68%, to 3.2 million by 2040 [26].

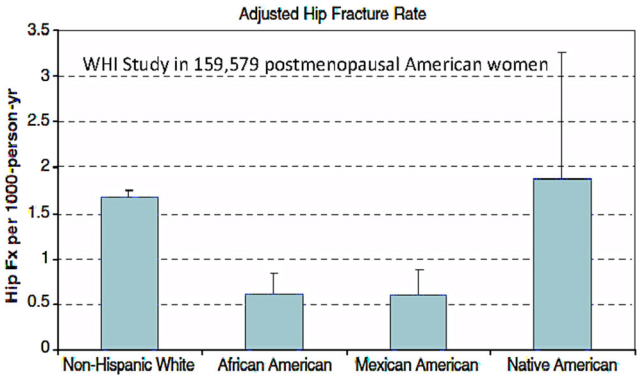


Fig. 1 Hip fracture incidence in postmenopausal women across ethnic/racial populations in WHI data (from Nelson DA et al. *Osteoporos Int.* 2011) [20]

Osteoporosis remains a disease that is *underdiagnosed and undertreated* despite effective antifracture interventions and the potentially lethal consequences of fractures [27]. Hip fractures significantly increase risk of death in the year following fracture and are highly predictive of additional fractures. Nonetheless, as many as 80–95% of patients in some practice settings are discharged following hip fracture repair *with no antifracture treatment or management plan* [28–30].

Crisis in osteoporosis patient care

The benefits of timely diagnosis and treatment have been well documented. Treatment reduces fracture incidence, forestalling injury, disability, and excess mortality. This effect is seen in Medicare claims analyses demonstrating a significant drop in age-adjusted risk for hip fracture in the ten years between 2002 and 2012. This decade-long decline coincided with the advent of bone density testing and application of effective osteoporosis therapies.

However, after declining for decades, incidence rates plateaued between 2013 and 2015 (Fig. 2) [31]. Although more data are needed to draw causal conclusions, it is likely that multiple factors have contributed. In the USA, patient access to osteoporosis care has declined. There are fewer office-based DXA facilities performing smaller numbers of DXA studies. Fewer women and men are diagnosed with

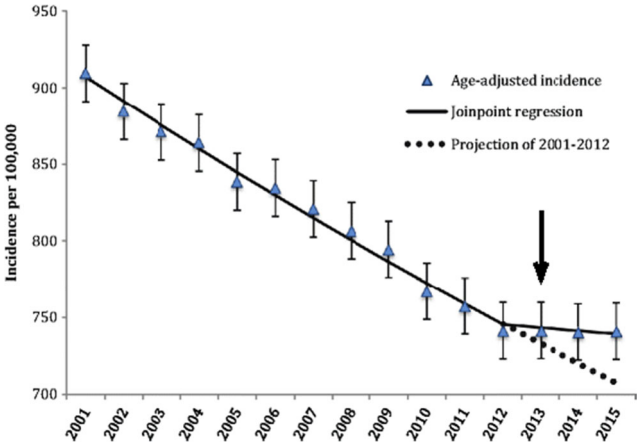


Fig. 2 Incidence of hip fractures (age-adjusted) between 2002 and 2015 according to Medicare claims. Note the decade-long decline in hip fractures and plateau between the years 2013 to 2015. (Lewiecki EM, et al. [2018] *Osteoporos Int.* Reprinted with added arrow by permission of author.) [31]

osteoporosis and/or treated to prevent fractures. Not surprisingly, we have seen an uptick in fractures.

The osteoporosis treatment gap (difference between number meeting treatment indications and number receiving treatment) is recognized globally as a *crisis in patient care* [21, 32, 33]. Since many factors contribute to this crisis, multifactorial approaches should be considered to reverse the trend, including cultivating trust in at-risk patients; generating more data on comparative effectiveness and safety of current osteoporosis drugs; engaging physicians, governmental, and public health organizations; improving insurance coverage for key fracture prevention services, including FLS programs; and adopting quality measures to incentivize clinicians, hospitals, and health systems to routinely screen and treat high-risk patients.

Medical impact

Fractures and their complications are the clinical sequelae of osteoporosis. The most common fractures are those of the vertebrae (lumbar spine), proximal femur (hip), and distal forearm (wrist). *Most fractures in older adults are due at least in part to low bone mass, even when they result from considerable trauma*. All fractures are associated with some degree of low BMD and increased risk of subsequent fracture in older adults [5]. In fact, a large cohort study found high-trauma and low-trauma fractures to be comparably predictive of low BMD and elevated future fracture risk [4].

A recent fracture at any major skeletal site in an adult ≥ 50 years of age should be considered a sentinel event that indicates urgent need for further assessment and treatment. Fractures of fingers, toes, face, and skull are not considered osteoporotic fractures since they are typically traumatic and unrelated to bone fragility.

Fractures may be followed by full recovery or by chronic pain, disability, and premature death. Hip, vertebral, and distal radius fractures lead to a substantial reduction in quality of life, with the greatest hardship among hip fracture patients [34]. Low-energy fractures of the pelvis and/or humerus are common in people with osteoporosis and contribute to increased morbidity and mortality. Psychosocial symptoms, most notably depression and loss of self-esteem, are common consequences of fracture, as patients grapple with pain, physical limitations, and loss of independence.

Hip fractures

Hip fractures are associated with 8.4–36% excess mortality at 1 year, with higher mortality in men than in women [26, 35]. Hip fracture can have devastating impacts on a patient's life. Approximately 20% of hip fracture patients require long-term nursing home care, and *60% do NOT fully regain pre-fracture independence* [27]. In addition, hip fractures are associated with a 2.5-fold increased incidence of secondary fractures [36].

Vertebral fractures

Although the majority of vertebral fractures are subclinical, they can cause pain, disability, deformity, and premature death [37]. Pain and postural changes associated with multiple vertebral compression fractures (kyphosis) can limit mobility and independent function, resulting in significantly diminished quality of life [38]. Multiple thoracic fractures can cause restrictive lung disease. Lumbar fractures can alter abdominal anatomy, leading to constipation, abdominal pain, early satiety, and weight loss. Vertebral fractures, whether clinically apparent or silent, are associated with a 5-fold increased risk for additional vertebral fractures and a 2- to 3-fold increased risk for fractures at other sites.

Wrist fractures

Wrist fractures are five times more common in women than men. They tend to occur earlier in life than other fractures (i.e., between 50 and 60 years of age). When wrist fractures are recognized as evidence of bone fragility and appropriate osteoporosis treatment is prescribed, future fractures could be avoided. While less disabling than hip or vertebral fractures, wrist fractures can be equally detrimental to quality of life, causing pain and limiting activities necessary for independent living.

Wrist fractures are strongly predictive of future fractures, as demonstrated in longitudinal studies of women in the Women's Health Initiative (WHI) and men in the Osteoporotic Fractures in Men Study (MrOs) [39–41]. Among recipients of Medicare, increased risk of other

fractures following a wrist fracture (regardless of BMD) is comparable to risk following hip or spine fracture in the year after the index event [12]. Low BMD at spine, hip, or forearm is a risk factor for wrist fractures in women and men; however, BMD alone is an imperfect predictor of fracture. In women with forearm fractures, advanced imaging with high-resolution peripheral quantitative computed tomography (HR-pQCT) has identified poor bone quality in fracturing women and girls compared with their nonfracturing peers at similar BMDs: lower total and trabecular bone density, decreased trabecular number and thickness, and lower cortical density and thickness. These differences in bone quality remained after adjusting for age and BMD at the hip and 33% radius [42].

Unfortunately, rates of evaluation and treatment for osteoporosis after wrist fractures are low in women and even lower in men [43]. Seventy-nine percent of adult male wrist fracture patients in one prospective, randomized study did not receive a bone density test following fracture repair [44]. This is significant because patients who received BMD measurement were more likely to be prescribed effective antifracture therapy.

As the population ages, it is critical for clinicians to intervene after a sentinel fracture. Appropriate, timely intervention offers the best opportunity to prevent the cycle of recurrent fractures, disability, and premature death in these patients [45].

Economic toll

The personal and economic costs of fractures are enormous. Fractures result in more than 432,000 hospital admissions, almost 2.5 million medical office visits, and about 180,000 nursing home admissions in the US [26]. Annual fracture-related costs are expected to increase from $57 billion to over $95 billion by 2040 [26]. This heavy toll could be significantly reduced with routine use of effective treatments and screenings, including VFA in women aged 65 and older with osteopenia (T-score ≤ − 1.0) [23, 27].

Basic pathophysiology

The human skeleton is comprised of living tissue. Critical to locomotion, skeletal bone houses much of the hematopoietic system and is the major repository for calcium and phosphorus—minerals essential to multiple physiologic systems. Constant serum calcium and adequate cellular calcium and phosphorus are maintained by a complex system of regulatory hormones that act directly on bone and indirectly on other tissues, such as the intestine and kidney. These demands can challenge skeletal equilibrium. When inadequate mineral is present in serum, it is withdrawn from skeletal stores. Over time, continued removal of bone tissue degrades skeletal microarchitecture thereby elevating risk for fractures that occur spontaneously or from minimal trauma.

Skeletal lifecycle

During childhood and adolescence, bones undergo a process called modeling, during which new bone is formed at one site and old bone is removed from another site within the same bone. This process enables individual bones to develop in size, shape, and position. Childhood and adolescence are critical periods of skeletal accrual. This is particularly important for girls, who acquire 40–50% of their total bone mass during early teen years.

During rapid skeletal growth in childhood and adolescence, it takes several months to mineralize the protein scaffolding for new bone, called osteoid. This lag between formation and mineralization produces periods of relatively low bone density and increased propensity to fracture, particularly between ages 10 and 14 years [46]. In the early 20s, fracture rates level off with attainment of peak bone mass. Mineral density stabilizes in most adults by their early 40s, when it begins a gradual decline, which accelerates at menopause in women (~ 2%/year for the 10 years following menopause) [47]. Age-related bone loss thins trabecular bone and increases cortical porosity, creating the preconditions for future fragility and fractures.

Genetic factors appear to account for 60-80% of total adult bone mass [48]. Substantial contributions are made by multiple modifiable factors that include nutrition, physical activity, smoking, chronic illness, and bone-damaging medications. Suboptimal bone acquisition is associated with fracture earlier in adulthood. Conversely, high peak adult bone mass, all other things being equal, protects against osteoporosis later in life.

Bone remodeling

The skeleton responds dynamically to hormonal, mechanical, and pharmacologic stimuli through the resorption and formation processes of bone remodeling, or turnover. After epiphyseal closure, the skeleton repairs damage through bone remodeling, which occurs on bone surfaces throughout the skeleton. The majority of bone surface area resides in trabecular bone, the resilient bony latticework predominantly found inside vertebrae. Remodeling is initiated by bone-resorbing cells, *osteoclasts,* that breakdown and remove damaged bone in a process called resorption. Excavated bone is replaced with new bone produced by *osteoblasts*.

The mechanisms that regulate bone formation involve complex interactions but are mediated, in part, by cells called *osteocytes*. Osteocytes play a role in both bone modeling and remodeling. For example, at sites of specific mechanical strain, osteocytes produce less sclerostin, a

cytokine and powerful inhibitor of bone formation. The result is stimulation of new bone formation. In several RCTs, a fully human neutralizing sclerostin antibody drug called romosozumab has blocked sclerostin, thereby markedly increasing bone formation and decreasing bone resorption [49].

Osteocytes make RANK-ligand (RANKL) a cytokine required for osteoclast formation. The fully human monoclonal antibody to RANKL, denosumab, is a potent antiresorptive drug that directly inhibits osteoclast formation, causes apoptosis of mature osteoclasts, and leads to decreased bone resorption and higher BMD. In addition to these agents, the anabolic PTH analogs (teriparatide and abaloparatide) affect remodeling- and modeling-based bone formation, leading to a net increase in BMD (see US FDA-Approved Drugs for Osteoporosis).

Pathogenesis of osteoporosis

In healthy young adults, the bone turnover cycle is balanced such that resorption is matched by formation. Bone remodeling accelerates in settings of chronic disease, aging, and a variety of mechanical, hormonal, and biochemical exposures such as glucocorticoids. Over time, this process leads to greater and greater deficits in mineralized bone.

Accelerated bone turnover affects cortical and trabecular bone somewhat differently. Bone resorption takes place on the surface of the bone. Because of its higher ratio of surface area to mass, trabecular bone is depleted more rapidly than cortical bone. With each remodeling cycle, there is a net loss of bone tissue. When bone remodeling rates increase—for example, in the setting of estrogen deficiency at menopause—bone loss is seen first at skeletal sites rich in trabecular bone, such as the spine, while sites that have a mix of cortical and trabecular bone, such as the hip, develop clinically apparent loss of bone later (Fig. 3).

Diagnostic considerations

BHOF recommends a multimodal, comprehensive approach to diagnosis of osteoporosis: detailed assessment of individual fracture risk, personal and family history, physical examination, and in patients with suggestive presentations (such as height loss, back pain, and/or fractures), focused studies to rule out secondary causes of bone fragility and vertebral imaging to detect prevalent fractures.

This is a process of screening and evaluation. Fracture risk increases exponentially with age and BMD declines with age. Screening of all older persons on this basis is appropriate. In persons with fractures or conditions associated with elevated fracture risk, more detailed evaluation is needed to monitor and manage their skeletal health. Referral to a metabolic bone specialist may be appropriate [51].

Fracture risk assessment

All postmenopausal women and men aged 50 years and older should be evaluated for osteoporosis risk in order to determine need for BMD testing and/or vertebral imaging. In general, the more risk factors, the more likely a patient will break a bone.

Osteoporotic fractures are preventable. Even after a fracture, osteoporosis is treatable. However, because there are no warning signs, many people with osteoporosis are not diagnosed until a fracture occurs. Factors that have been associated with an increased risk of osteoporosis-related fracture are listed in Table 1. Primary among these is history of broken bones in adulthood, with highest risk in first 1–2 years after the initial fracture [52, 53]. Patients must be evaluated soon after a fracture and receive appropriate treatments to optimize risk reduction.

Most fractures in older adults are associated with a fall. Falls occur in approximately one third of adults aged 65 years and older and this risk increases with age. Fall risk assessment is, therefore, a key component of primary and secondary fracture prevention. Factors associated with falls are shown in Table 2. The most important of these are history of falling,

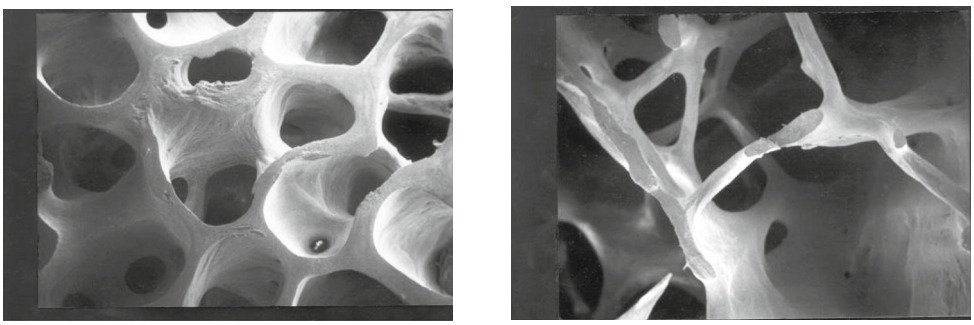


Fig. 3 Micrographs of normal (left) and osteoporotic (right) bone. As trabecular mineral is depleted, individual bony plates and connecting branches are lost, leaving less resilient, weaker bone that is more likely to fail under normally tolerated mechanical loads. Dempster, DW et al. (1986) *J Bone Miner Res* 1:15-27. Reprinted with permission [50]

Dempster, DW et al. (1986) J Bone Miner Res 1:15-27. reprinted with permission.[51]

Table 1 Conditions, diseases, and medications that cause or contribute to osteoporosis and/or fractures [27]

Lifestyle factors
Alcohol abuse
Excessive thinness
Excess vitamin A
Frequent falling
High salt intake
Immobilization
Inadequate physical activity
Low calcium intake
Smoking (active or passive)
Vitamin D insufficiency/deficiency

Genetic diseases
Cystic fibrosis
Ehlers-Danlos
Gaucher's disease
Hemochromatosis
Hypophosphatasia
Hypophosphatemia
Marfan syndrome
Menkes steely hair syndrome
Osteogenesis imperfecta
Parental history of hip fracture
Porphyria
Homocystinuria

Hypogonadal states
Anorexia nervosa
Androgen insensitivity
Female athlete triad
Hyperprolactinemia
Hypogonadism
Panhypopituitarism
Premature menopause (<40 years)
Turner's & Klinefelter's syndromes

Endocrine disorders
Obesity
Cushing's syndrome
Diabetes mellitus (Types 1 & 2)
Hyperparathyroidism
Thyrotoxicosis

Gastrointestinal disorders
Celiac disease
Bariatric surgery
Gastric bypass
Gastrointestinal surgery
Inflammatory bowel disease including Crohn's disease and ulcerative colitis
Malabsorption syndromes
Pancreatic disease
Primary biliary cirrhosis

Hematologic disorders
Hemophilia
Leukemia and lymphomas
Monoclonal gammopathies
Multiple myeloma
Sickle cell disease
Systemic mastocytosis
Thalassemia

Rheumatologic and autoimmune diseases
Ankylosing spondylitis
Other rheumatic and autoimmune diseases
Rheumatoid arthritis
Systemic lupus
Neurological and musculoskeletal risk factors
Epilepsy
Muscular dystrophy
Multiple sclerosis
Parkinson's disease
Spinal cord injury
Stroke

Miscellaneous conditions and diseases
HIV/AIDS
Amyloidosis
Chronic metabolic acidosis
Chronic obstructive lung disease
Congestive heart failure
Depression
Renal disease (CKD III– CKD V/ESRD)
Hypercalciuria
Idiopathic scoliosis
Post-transplant bone disease
Sarcoidosis
Weight loss
Hyponatremia

Medications
Aluminum-containing antacids
Androgen deprivation therapy
Anticoagulants (unfractionated heparin)
Anticonvulsants (e.g. phenobarbital, phenytoin, valproate)
Aromatase inhibitors
Barbiturates
Cancer chemotherapeutic drugs
Cyclosporine A and tacrolimus
Glucocorticoids (≥ 5.0 mg/day prednisone or equivalent for ≥ 3 months)
GnRH (Gonadotropin releasing hormone) agonists and antagonists
Depot medroxyprogesterone acetate (Depo-Provera)
Methotrexate
Parenteral nutrition
Proton pump Inhibitors
Selective serotonin reuptake inhibitors
Tamoxifen (premenopausal use for breast cancer treatment)
Thiazolidinediones (such as pioglitazone and rosiglitazone)
Thyroid replacement hormone (in excess)

muscle weakness, gait and balance disturbances, sedating or hypnotic medications, visual impairment, and any condition associated with dizziness, such as dehydration and orthostatic hypotension [55, 56]. Importantly, multiple studies have demonstrated the safety and efficacy of physical therapy and exercise regimens targeted to fall risk reduction.

Evaluation of patients with fractures

In patients aged 50 years or older, consider hip, vertebral, and/or forearm fractures to be highly suggestive of osteoporosis or other metabolic bone disease, unless excluded by clinical evaluation and imaging. Risk for fracture at all sites rises substantially in the period immediately following an initial fracture. Therefore, any fracture in adulthood should be viewed as a red flag signaling urgent need for focused attention [57].

Secondary skeletal etiologies should be investigated in all patients who present with fractures, low bone mass, or osteoporosis (Table 3). Chronic kidney disease, hyperparathyroidism, osteomalacia, and other diseases can cause skeletal fragility, multiple vertebral fractures, and very low bone density. For some metabolic bone diseases, osteoporosis therapies are not appropriate and may be harmful (e.g., osteomalacia or aplastic bone disease). Relevant blood and urine studies (Table 3) to rule out secondary etiologies should be obtained prior to initiating antifracture therapy. Patients found to have secondary, treatable causes of bone fragility may require no

Table 2 Major risk factors for falls

Medical risk factors
- Advanced age
- Arthritis
- Female gender
- Poor vision
- Urinary urgency or incontinence
- Previous fall
- Orthostatic hypotension
- Impaired transfer and mobility
- Medications that cause dizziness or sedation (narcotic analgesics, anticonvulsants, psychotropics)
- Malnutrition/parenteral nutrition (vitamin D deficiency, insufficient protein)

Neurological and musculoskeletal risk factors
- Poor balance
- Weak muscles/sarcopenia
- Gait disturbances
- Kyphosis (abnormal spinal curvature)
- Reduced proprioception
- Diseases and/or therapies that cause sedation, dizziness, weakness, or lack of coordination
- Alzheimer's/other dementia, delirium, Parkinson disease, and stroke

Environmental risk factors
- Low-level lighting
- Obstacles in the walking path
- Loose throw rugs
- Stairs
- Lack of assistive devices in bathrooms
- Slippery outdoor conditions

Psychological risk factors
- Anxiety and agitation
- Depression
- Diminished cognitive acuity
- Fear of falling

From: NOF Health professional's guide to the rehabilitation of the patient with osteoporosis [54]

Table 3 Diagnostic studies for exclusion of secondary causes of osteoporosis

Blood or serum
- Complete blood count (CBC)
- Albumin
- Chemistry levels (albumin-adjusted calcium, renal function, phosphorus, and magnesium)
- Liver function tests
- 25(OH) vitamin D
- Parathyroid hormone (PTH)
- Total testosterone and gonadotropin (men aged 50–69 years)

Consider in select patients
- Serum protein electrophoresis (SPEP), serum immunofixation, serum free kappa and lambda light chains
- Thyroid-stimulating hormone (TSH) +/− free T_4
- Tissue transglutaminase antibodies (and IgA levels)
- Iron and ferritin levels
- Homocysteine (to evaluate for homocystinuria)
- Prolactin level
- Tryptase
- Biochemical markers of bone turnover

Urine
- 24-h urinary calcium and creatinine

Consider in select patients
- Urinary protein electrophoresis (UPEP)
- Urinary free cortisol level (or salivary cortisol)
- Urinary histamine

additional therapy once the underlying condition is addressed (Table 1).

Osteoporosis affects a significant number of men, yet largely goes undetected and untreated. Some of the laboratory testing to assess secondary etiologies in men differs from that in women. Screening BMD and vertebral imaging recommendations are outlined in Tables 6 and 7. For additional guidance, readers should refer to *Osteoporosis in Men: an Endocrine Society Clinical Practice Guideline*, which provides a detailed approach to evaluation and treatment of osteoporosis in men [58].

Bone mineral density (BMD) measurement and classification

DXA measurement of hip and lumbar spine is the preferred method for establishing and/or confirming a diagnosis of osteoporosis, predicting future fracture risk, and monitoring patients. Areal BMD by DXA is expressed in absolute terms of grams of mineral per square centimeter scanned (g/cm^2) and as a relationship to two BMD norms: an age-, sex-, and ethnicity-matched reference population (Z-score), or a young-adult reference population (T-score). The International Society for Clinical Densitometry (ISCD) recommends using a Caucasian (non-race adjusted) young female normative database for women AND men of ALL ethnic groups. Recommendations may vary with use of sex- and race-adjusted young normal controls for T-scores and these are used by some co-authors of this guide [59].

The difference between a patient's BMD and the mean BMD of the reference population, divided by the standard deviation of the reference population, is used to calculate Z-scores and T-scores. An individual's BMD is reported as the standard deviations above or below the mean BMD, as outlined in Table 4. The BMD diagnosis of normal bone mass, low bone mass (osteopenia), and osteoporosis are based on

Table 4 Diagnostic criteria for osteoporosis: WHO BMD-based classification system and clinical-factor based diagnostic criteria. (Note: These criteria are sufficient for a diagnosis of osteoporosis. However, they should not serve as the sole determinant of fracture risk and/or dictate treatment decisions. Non-BMD risk factors that affect bone quality independently contribute to bone fragility and fractures.)

BMD Criteria for Osteoporosis Diagnosis in Postmenopausal Women and Men Aged ≥ 50 Years		
Normal	BMD within 1.0 SD of the mean for a young-adult reference population	T-score -1.0 and above
Low Bone Mass	BMD between 1.0 and 2.5 SD below for a young-adult reference population	T-score between -1.0 the mean and -2.5
Osteoporosis	BMD 2.5 SD or more below the mean for a young-adult reference population	T-score at or below -2.5
Clinical Criteria for Osteoporosis Diagnosis in Postmenopausal Women and Men Aged ≥ 50 Years		
Incident Fracture	Hip, vertebral, and/or forearm fractures are consistent with osteoporosis (unless excluded by clinical evaluation and imaging)	
FRAX® Score	T-score between -1.0 and -2.5 at the femoral neck or total hip by DXA accompanied by a FRAX-projected 10-year risk of ≥3% for hip fracture and/or >20% for major osteoporosis-related fracture (i.e. clinical vertebral, hip, forearm, or proximal humerus) based on U.S, adapted FRAX® model)	

this World Health Organization (WHO) diagnostic classification [60].

BMD has been shown to correlate well with bone strength. The recent FNIH Bone Quality Study found that improvements in DXA-based BMD predicted reductions in fracture risk. In a meta-regression analysis of 38 placebo-controlled trials of 19 osteoporosis medications, with ~ 111,000 study participants, the FNIH study group found that increased BMD at the total hip and lumbar spine predicted fracture risk reduction at both of these sites [61]. Larger increases in BMD were associated with greater reductions in risk. For example, a 2% increase in total hip BMD could be expected to reduce vertebral fracture risk by 28% and hip fracture risk by 16%, while a 6% increase in hip BMD would result in a 66% reduction in vertebral fracture risk and a 40% reduction in risk factors for hip fractures (Table 5).

Table 5 Increases in BMD and associated estimated fracture risk reduction (FNIH Study)

% Increase in BMD	% Reduction in Vertebral Fracture	% Reduction in Hip Fracture
Total hip	Total hip	Total hip
2%	28%	16%
4%	51%	29%
6%	66%	40%
Femoral neck	Femoral neck	Femoral neck
2%	28%	15%
4%	55%	32%
6%	72%	46%
Lumbar spine	Lumbar spine	Lumbar spine
2%	28%	22%
4%	62%	38%
6%	79%	51%

Note: Larger improvements in DXA-based BMD are associated with greater reductions in fracture risk, particularly for vertebral and hip fractures

DXA scans are associated with exposure to trivial amounts of radiation. These highly sensitive measurements of lumbar spine, hip, and/or forearm must be performed by trained technologists on well-calibrated instruments. For meaningful interpretation, serial scans should be performed on the same densitometry device at the same facility.

In postmenopausal women and men aged 50 years and older, WHO diagnostic T-score criteria (normal, low bone mass, and osteoporosis) are applied to BMD measurement by central DXA at the lumbar spine and femoral neck [62]. BMD measured by DXA at the 33% radius is used for diagnosing osteoporosis when hip or lumbar spine cannot be measured; scans are unusable or cannot be interpreted, in clinical conditions associated with low forearm BMD, or as dictated by clinical judgment [59, 62].

It is important to note that DXA of the lumbar spine can be difficult to accurately interpret. This is in large part due to degenerative changes in the lumbar spine, very common in older adults, that are typically characterized by localized bone proliferation. In this setting, DXA findings can overestimate spinal BMD and underestimate fracture risk. Patients with degenerative spinal changes may benefit from trabecular volumetric BMD (vBMD) measured with quantitative computed tomography (QCT), which is less affected by these changes, although this technology is not widely available [63, 64].

These diagnostic classifications should not be applied to everyone. Premenopausal women, men less than 50 years of age, and children cannot be diagnosed on the basis of densitometric criteria alone. In populations between 20 and 50 years of age, the ISCD recommends that ethnicity- or race-adjusted Z-scores be used instead. Z-scores of − 2.0 or lower are classified as low BMD for chronological age and those above − 2.0 classified as within the expected range

for age [59]. In children, height-for-age Z-score (HAZ) (BMC/BMD_{haz}) has been demonstrated to most effectively offset the effect of short or tall stature on BMC/BMD Z-scores. A calculator for pediatric Z-score adjustment is available at https://zscore.research.chop.edu.

Who should be tested?

The decision to perform initial bone density measurement should be based on an individual's fracture risk profile and skeletal health assessment. Measuring bone density is not indicated unless test results will influence treatment and management decisions. The BHOF recommends screening densitometry in women aged ≥ 65 years and men aged ≥ 70 years, younger postmenopausal women aged 50–64 years, and men aged 50-69 years with risk factors for osteoporosis. The BHOF also recommends BMD testing for women and men with fracture(s). These recommendations are in concert with those of the ISCD and Endocrine Society clinical practice guidelines for osteoporosis in men [58, 59]. BHOF recommendations for BMD testing are listed in Table 6. Routine bone density measurement is not recommended for children or adolescents and is not routinely indicated in healthy young men or premenopausal women unless there is a significant fracture history or specific risk factors for bone loss (such as glucocorticoid use).

Recommended screening densitometry in men

BHOF (formerly NOF) and other societies recommend BMD testing in men to inform clinical decisions regarding treatment (Table 6). This includes men aged 70 years and older regardless of risk factors, men aged 50–69 years with clinical risk factors for fracture, and men who have broken a bone at age 50 years or older. In addition, men with conditions or on treatments associated with bone loss or low bone mass should be considered appropriate candidates for BMD screening (in its 2018 report, the US Preventive Services Task Force [USPSTF] confirmed the utility of BMD by DXA in predicting fracture in both women and men, but they found insufficient evidence at that time to recommend routine testing in men) [22, 65].

Table 6 Indications for BMD testing

Consider BMD testing in the following individuals
Women ≥ 65 years of age and men ≥ 70 years of age, regardless of clinical risk factors
Younger postmenopausal women, women in the menopausal transition, and men aged 50 to 69 years with clinical risk factors for fracture
Adults who have a fracture at age 50 years and older
Adults with a condition (e.g., rheumatoid arthritis, organ transplant) or taking a medication (e.g., glucocorticoids, aromatase inhibitors, androgen deprivation therapy) associated with low bone mass or bone loss

Vertebral fracture assessment

Vertebral fracture in an adult aged 50 years or older is diagnostic of osteoporosis, even in the absence of a bone density diagnosis. The presence of a single vertebral fracture signifies a 5-fold increased risk for additional vertebral fractures and a 2- to 3- fold increased risk for hip or other fractures [66].

Unfortunately, most vertebral fractures are subclinical and/or completely asymptomatic. As a result, they may go undiagnosed for many years. At the same time, a high proportion of women with asymptomatic vertebral fractures have BMD levels that would not warrant treatment based on BMD alone [67]. The finding of a previously unrecognized vertebral fracture may change a patient's diagnostic classification, alter fracture risk calculations, and determine treatment decisions [68]. Proactive investigation is required to detect these fractures so that further bone damage can be prevented.

Traditionally, conventional lateral thoracic/lumbar spine X-ray has been considered the gold standard for identification of vertebral fractures and minor vertebral deformities. However, DXA-assisted vertebral fracture assessment (DXA-VFA) is emerging as an alternative to radiography for its convenience, low cost, and minimal radiation exposure. Recently performed MRI or CT imaging studies done for other purposes can and should also be evaluated for presence of vertebral fractures or evidence of vertebral deformity.

Because subclinical vertebral fractures are so prevalent in older individuals, vertebral fracture assessment is recommended for the high-risk individuals listed in Table 7 [7, 8, 69]. As demonstrated in a recent study, incorporation of

Table 7 Indications for vertebral imaging

Consider vertebral imaging tests for the following individuals***

- All women aged ≥ 65 years and all men aged ≥ 80 years if T-score at the lumbar spine, total hip, or femoral neck is ≤ − 1.0 [6].
- Men aged 70 to 79 years if T-score at the lumbar spine, total hip, or femoral neck is ≤ − 1.5
- Postmenopausal women and men age ≥ 50 years with specific risk factors:
  - Fracture during adulthood (age ≥ 50 years)
  - Historical height loss of 1.5 in. or more*
  - Prospective height loss of 0.8 in. or more**
  - Recent or ongoing long-term glucocorticoid treatment
  - Medical conditions associated with bone loss such as hyperparathyroidism

*Current height compared to peak height during young adulthood

**Cumulative height loss measured during interval medical assessment

***If bone density testing is not available, vertebral imaging may be considered based on age alone

DXA-VFA into routine DXA screening for postmenopausal women with osteopenia or osteoporosis (T-score ≤ − 1, aged ≥ 65 years) has demonstrated cost-effectiveness for predicting increased risk of osteoporotic fractures [6].

Baseline DXA-VFA imaging provides a benchmark for future comparison when DXA-BMD is reassessed or when suggestive symptoms present: such as prospective height loss, new back pain, or postural changes [7]. Follow-up vertebral imaging may also be appropriate for patients being considered for a bisphosphonate holiday (temporary suspension of pharmacotherapy), since discontinuing antifracture therapy would not be advisable in patients who have recent vertebral fractures [70].

Using US-adapted Fracture Risk Assessment Tool (FRAX®)

The Fracture Risk Assessment Tool (FRAX®) was developed to calculate 10-year probabilities of hip fracture and major osteoporotic fracture (defined as clinical vertebral, hip, forearm or proximal humerus fracture). The FRAX® algorithm takes into account the validated clinical risk factors for fractures shown in Table 8. FRAX® is validated for women and men aged 40–90 years. FRAX® was tested in treatment-naïve patients not on osteoporosis medications. It may, however, be useful for assessing risk in previously treated individuals who have discontinued bisphosphonate therapy for 2 years or non-bisphosphonate therapy for 1 year [65, 71].

A country-specific FRAX® score can be calculated with BMD, without BMD, with BMD and body mass index (BMI), or with BMI alone. Studies have demonstrated modest agreement between assessments of FRAX®-with-BMD and FRAX®-with-BMI (correlation coefficient ~ 0.5) [72]. While FRAX®-with-BMI may overestimate probability in older frail adults, it may underestimate fracture risk in younger patients compared to FRAX-with-BMD [73, 74].

FRAX® can be calculated with either femoral neck BMD or total hip BMD (in g/cm^2), but, when available, femoral neck BMD is preferred. The use of BMD from non-hip sites is not recommended. Caution should be taken when using FRAX® without BMD to estimate fracture risk. (Although FRAX® allows input of T-score, we do not recommend this since the reference database for T-score calculation with clinical DXA systems may not be the same as that used in the FRAX® algorithm.)

Therapeutic intervention recommendations in FRAX® incorporate data on risk-benefit analyses, cost-effectiveness of treatments, and competition for resources in the USA [75, 76].These recommendations exist for guidance purposes only and are not absolute rules. Developers of FRAX® determined that for many secondary causes of osteoporosis, fracture risk is mediated primarily through impact on BMD [77]. For this reason, when low femoral neck BMD is entered into FRAX®, the secondary causes of osteoporosis button is automatically inactivated.

FRAX® scores should not deter clinicians or patients from considering intervention strategies when clinically assessed risk indicates utility. Conversely, these recommendations do not mandate treatment, particularly in patients with bone mass that is low but above the osteoporosis range. For patients with scores above FRAX® treatment thresholds, who do not have prevalent fracture of the hip or spine or secondary risk factors for accelerated bone loss, it is currently unclear if pharmacologic treatment significantly improves fracture risk with a reasonable number needed to treat. Management decisions must be made on a case-by-case basis [78, 79].

FRAX and US ethnicity data

The US adaptation of FRAX requires selecting 1 of 4 ethnicities for each patient (Caucasian, Black, Hispanic, Asian). Among these populations, data indicates differences in fracture risk even at the same BMD. Although many limitations to this methodology have been described, it provides fracture risk stratification that can direct treatment to high-risk individuals most likely to benefit and avoid treatment of those at low risk [80]. Other countries, including some with considerable ethnic diversity, have used an alternative approach, with a single version of FRAX regardless of ethnicity.

Table 8 Risk factors included in the Fracture Risk Assessment Model (FRAX®)

Clinical risk factors included in FRAX® Tool	
Age	Alcohol intake (3 or more drinks/day)
BMD at femoral neck (g/cm^2)	BMI (low body mass index, kg/m^2)
Female sex	Oral glucocorticoid intake ≥ 5 mg/day of prednisone for > 3 months (ever)
Parental history of hip fracture	Prior osteoporotic fracture (including clinical and subclinical vertebral fractures)
Rheumatoid arthritis	Smoking (current)
Secondary causes of osteoporosis: type 1 diabetes, osteogenesis imperfecta in adults, untreated long-standing hyperthyroidism, hypogonadism or premature menopause (< 40 years), chronic malnutrition or malabsorption, and chronic liver disease	

FRAX® with trabecular bone score

Trabecular bone score (TBS) is an assessment of how evenly or unevenly mineral is structurally distributed in trabecular bone. A TBS is generated from lumbar spine BMD images using software installed on a DXA machine. No additional scan time or radiation exposure is required. The TBS gray-scale texture model captures local differences in mineral concentrations, providing an index of bone microarchitecture that predicts fracture risk independent of BMD and FRAX® scores. TBS is correlated with BMD at spine and hip as well as with FRAX® risk projections for hip and major osteoporotic fracture [81, 82]. Adding TBS to FRAX®, which is possible on late-model densitometry devices, increases the ability of FRAX® to predict fractures (TBS-adjusted FRAX®) [83].

TBS is most applicable to patients who have low bone mass, rather than those with osteoporosis according to BMD criteria, for whom treatment is already indicated [84, 85]. TBS is FDA approved and provides additional utility in fracture risk assessment among people with secondary causes of bone loss and fractures, such as type 2 diabetes [83, 86, 87].

Potential limitations of FRAX®

The FRAX® tool is not a perfect predictor of fracture and its use requires clinical judgment. Because data validating the relative weight of all known risk factors are not yet available, they are not included in the FRAX® algorithm. These variables include risks associated with falls, non-DXA bone density measurements, rapidity of bone loss, specific secondary causes of osteoporosis (e.g., type 2 diabetes), and multiple fractures experienced in a short period of time. Other risks that are important in older adults not included in FRAX include frailty, multiple comorbid conditions, multiple medications associated with falls/fractures, and life expectancy.

The FRAX® tool is most useful in patients with low femoral neck BMD. The FRAX® algorithm has not been validated for use with lumbar spine BMD. Utilizing FRAX® in patients with low BMD at the lumbar spine, but relatively normal BMD at the femoral neck, underestimates fracture risk (Fig. 4).

The yes/no scoring employed by FRAX® computes average risk associated with individual clinical variables. As a result, dose–response effects of risk factors included in FRAX® are lost. For such variables, presumably higher doses increase risk more than lower doses. (Adjustments to FRAX to better account for dose effect of glucocorticoid dose have been proposed [88].)

The FRAX® algorithm is available at http://www.bonehealthandosteoporosis.org as well as at http://www.sheffield.ac.uk/FRAX. It is available on newer DXA systems or with software upgrades that provide the FRAX® scores as well as the TBS-adjusted FRAX® on the bone density report.

Alternative bone densitometry technologies

Technologies other than DXA can be used to assess BMD, bone structure, bone strength, and fracture risk.These include quantitative computed tomography (QCT) to measure volumetric (v) BMD of the spine and proximal femur and derive areal BMD values that can be used for diagnostic classification with the WHO criteria and for input for FRAX. Opportunistic QCT uses QCT images performed for non-skeletal indications to detect fractures and measure BMD with synchronous or asynchronous calibration [89]. Quantitative ultrasound (QUS) measures non-BMD parameters of bone strength that are correlated with fracture risk. Imaging technologies used in research settings and sometimes in clinical practice include: pulse echo ultrasound (PEUS), and finite element analysis (FEA) with biomechanical computed tomography (BCT) [90, 91]. Other bone imaging tools largely used in research include peripheral QCT (pQCT), high-resolution pQCT (HR-pQCT), and magnetic resonance imaging (MRI).

Biochemical markers of bone turnover

While not currently FDA approved for diagnosis of osteoporosis, measurements of biochemical bone turnover markers (BTMs) can play a role in assessing fracture risk in appropriate individuals: for example, to gauge rate of bone loss in women following treatment for breast cancer.

Products of the remodeling process can be measured as indicators of turnover activity. Biochemical markers of bone remodeling include resorption markers serum C-telopeptide (CTX) and urinary N-telopeptide (NTX) and formation markers serum amino-terminal propeptide of type 1 procollagen (P1NP), bone-specific alkaline phosphatase (BALP), and osteocalcin (OC).

BTMs may [92]:

- Predict rapidity of bone loss in untreated postmenopausal women.
- Predict extent of fracture risk reduction when repeated after 3–6 months of treatment with FDA-approved therapies.
- Predict magnitude of BMD increases with FDA-approved therapies.
- Characterize patient compliance and persistence with osteoporosis therapy using a serum CTX for an antiresorptive medication and P1NP for an anabolic therapy (least significant change [LSC] is approximately a 40% reduction in CTX).
- Potentially be used during a bisphosphonate holiday to suggest when medication should be restarted, although more data are needed to support this recommendation.

The FNIH Bone Quality Project conducted a large analysis of antiresorptive therapies to evaluate the utility of BTM

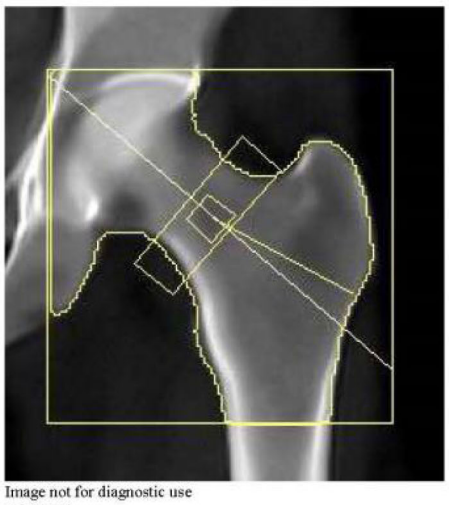


Image not for diagnostic use
100 x 104
NECK: 49 x 15

Sex: Female
Ethnicity: White

Height: 64.5 in
Weight: 115.0 lb
Age: 61

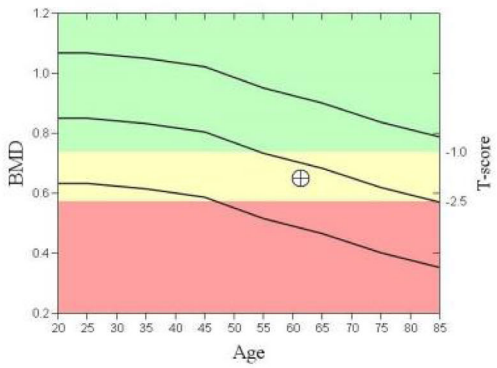
DXA Results Summary:

Region	Area (cm²)	BMC (g)	BMD (g/cm²)	T - score	PR (%)	Z - score	AM (%)
Neck	**5.14**	**3.34**	**0.649**	**-1.8**	**76**	**-0.5**	**93**
Troch	11.79	6.68	0.567	-1.4	81	-0.4	93
Inter	17.92	15.03	0.839	-1.7	76	-0.9	85
Total	34.85	25.04	0.719	-1.8	76	-0.8	88
Ward's	1.14	0.56	0.493	-2.1	67	0.0	100

Total BMD CV 1.0%
WHO Classification: Osteopenia

FRAX® WHO Fracture Risk Assessment Tool

Neck



10-year Fracture Risk[1]	Without Prior Fracture	With Prior Fracture
Major Osteoporotic Fracture	**19%**	**30%**
Hip Fracture	**2.3%**	**4.0%**

Reported Risk Factors:
US (Caucasian), Neck BMD=0.649, BMI=19.4, parental fracture, smoking, rheumatoid arthritis

[1] FRAX® Version 3.08. Fracture probability calculated for an untreated patient. Fracture probability may be lower if the patient has received treatment.

Comment:
All treatment decisions require clinical judgment and consideration of individual patient factors, including patient preferences, comorbidities, previous drug use and risk factors not captured in the FRAX model (e.g. frailty, falls, vitamin D deficiency, increased bone turnover, interval significant decline in BMD).

T-score vs. White Female. Source:BMDCS/NHANES White Female. Z-score vs. White Female. Source:BMDCS/NHANES White Female.

Fig. 4 Hip BMD showing low bone mass and a history of a fracture. The FRAX® score indicates an elevated absolute risk of major osteoporotic and hip fracture

changes as a surrogate for fracture risk reduction in drug development. In a recent pooled meta-regression analysis of antiresorptive therapies, changes in CTX or NTX did not predict antifracture efficacy. Changes in the bone formation markers BALP and P1NP, however, were strongly predictive of risk reduction for vertebral fractures, but these changes did not reach significance for non-vertebral or hip fractures [93].

Universal bone health recommendations

Several interventions to preserve bone strength can be recommended to the general population. These include adequate intake of calcium and vitamin D, cessation of tobacco use, identification and treatment of excessive alcohol intake, regular weight-bearing and muscle-strengthening exercise, and

remediation of conditions associated with falls, such as visual impairment and use of sedating medications.

Adequate intake of calcium

Sufficient calcium intakes are necessary for acquisition of peak bone mass and maintenance of bone health across the lifespan. The skeleton contains 99% of the body's calcium stores; when the exogenous supply is inadequate, bone tissue is resorbed from the skeleton to maintain constant serum calcium levels.

BHOF supports the Institute of Medicine's (IOM) calcium intake recommendations: 1000 mg/day for men aged 19–70 years and women aged 19–50 years; 1200 mg/day for women 51 years and older and men 71 years and older (Tables 9 and 10) [95]. There is no evidence that calcium intakes in excess of recommended amounts confer additional bone benefit. However, there is evidence that intake of *supplemental* calcium above 1200 to 1500 mg/day can increase risk for developing kidney stones in at-risk individuals [96].

A balanced diet rich in low-fat dairy products, select dark greens, fish with bone, fruits, vegetables, and fortified foods (like the nondairy supplemented beverages including orange juice, or soy and almond milk) provides calcium as well as numerous nutrients needed for good health. Table 9 illustrates a simple method for estimating the calcium in a patient's diet. Most people do not get enough. Average daily dietary calcium intake for adults age ≥ 50 years is 600 to 700 mg/day. Increasing dietary calcium is the first-line approach, but calcium supplements should be used when an adequate dietary intake *cannot* be achieved [97, 98].

Calcium intake recommendations refer to milligrams of *elemental* calcium in the supplement. Content varies: calcium carbonate contains 40% elemental calcium by weight, whereas calcium citrate contains 21%. Patients should be advised to read the Supplement Facts panel for elemental calcium content when choosing a supplement.

Supplemental calcium is most widely available as calcium carbonate and calcium citrate. Calcium carbonate requires stomach acid for absorption and so is best taken with food, while calcium citrate is absorbed equally well on an empty stomach. Calcium of all types is best absorbed in doses of ~ 500 mg or less. Splitting doses may be needed to ensure optimal absorption [99].

Calcium citrate is useful for people with achlorhydria, inflammatory bowel disease, absorption disorders, and those on proton pump inhibitors that reduce gastric acid. Individuals who experience gastrointestinal side effects taking calcium carbonate may benefit from taking multiple small doses, taking calcium carbonate with meals and/or switching to calcium citrate. Other varieties of calcium commonly in supplements or fortified foods include gluconate, lactate, and phosphate. Calcium citrate malate is a well-absorbed form of calcium found in some fortified juices. Elemental calcium in fortified foods varies.

Some studies have reported increased risk of cardiovascular disease linked to calcium supplements with or without vitamin D, but conflicting data are reported [100–103]. A large systematic review and meta-analysis including RCTs and cohort studies found no evidence that calcium with or without vitamin D increased cardiovascular disease [104]. The large VITamin D and OmegA-3 Trial (VITAL), sponsored by the NIH, tested supplemental vitamin D (2000 units/day) on cardiovascular outcomes and found no adverse effects [105].

Adequate intake of vitamin D

Vitamin D facilitates calcium absorption that is necessary for mineralization of bone. The BHOF recommends a daily intake of 800 to 1000 units of vitamin D for adults aged 50

Table 9 Estimating daily dietary calcium intake

Step 1: Estimate calcium intake from calcium-rich foods*

Product	# of servings/day	Estimated calcium/serving, in mg	Calcium in mg
Milk (8 oz)	_____	× 300	= _____
Almond/soy milk (8 oz)	_____	× 450	= _____
Yogurt (6 oz)	_____	× 300	= _____
Cheese (1 oz or 1 cubic in.)	_____	× 200	= _____
Fortified foods or juices	_____	× 80 to 1000**	= _____
Tofu, firm (8 oz)	_____	× 250	= _____
		Subtotal	= _____
Step 2: Add 250 mg for non-dairy sources to subtotal			+ 250
		Total calcium, in mg	= _____

*About 75 to 80% of the calcium consumed in American diets is from dairy products

**Calcium content of fortified foods varies, and it is important to review individual labels

Table 10 Recommended calcium and vitamin D intakes for women and men [2, 94].

Life stage group	Calcium IOM/BHOF (mg/day)	Calcium Safe upper limit (mg/day)	Vitamin D IOM/BHOF (units/day)	Vitamin D Safe upper limit (units/day)
51–70-year-old women	1200	2500	600/800–1000	4000
51–70-year-old men	1000	2000	600/800–1000	4000
71+-year-old men and women	1200	2000	800/800–1000	4000

years and older. The Institute of Medicine Dietary Reference Intakes for vitamin D are 600 units daily until age 70 years and 800 units/day for adults age 71 years and older. The IOM recommendations for vitamin D are based on intakes sufficient to maintain a serum 25(OH)D of 20 ng/mL in ≥ 97.5% of population [94]. A slightly higher serum 25(OH)D level (approximately 30 ng/mL) is associated with optimal calcium absorption and so is preferred by the BHOF [106–110]. The upper limits for vitamin D intake according to the IOM is 4000 units/day for adults, above which there is a potential for adverse effects. The current normal range for 25(OH)D levels is 20 to 50 ng/mL. Some studies suggest that excessive intake of vitamin D may have adverse impacts on bone through increased risk for falls and fractures [110, 111].

Chief dietary sources of vitamin D include fortified milk (400 units per quart) and breakfast cereals (generally 40–300 units per serving), saltwater fish (e.g., salmon, mackerel, tuna), and cod liver oil. Some, but not all non-dairy milk substitutes, such as rice or soy milk, are supplemented with vitamin D and calcium and so it is important to read the labels. Some calcium supplements and most multivitamin tablets contain vitamin D. Supplementation with either vitamin D_2 (ergocalciferol) or vitamin D_3 (cholecalciferol) is effective, but cholecalciferol, which is the form produced in humans, is preferable. Vitamin D_2 is derived from plant sources and may be preferred by individuals on a strict vegan/vegetarian diet.

Many conditions prevalent in older patients contribute to vitamin D deficiency, such as chronic renal insufficiency and limited sun exposure due to disability. Of note, a high prevalence of vitamin D deficiency is seen in patients with advanced osteoarthritis presenting for total hip replacement as well as in hip fracture patients with osteoporosis (including those on antifracture medications) [9, 112]. Vitamin D deficiency should be corrected to optimize surgical and/or pharmacologic outcomes.

Supplemental vitamin D should be administered in amounts capable of raising serum 25(OH)D levels to approximately 30 ng/mL (75 nmol/L) and maintaining it at this level. Adults who are vitamin D deficient are typically treated with 50,000 units of vitamin D_2 or vitamin D_3 once a week (or the equivalent daily dose of 7000 units vitamin D_2 or vitamin D_3) for 5–8 weeks to achieve a 25(OH)D blood level of approximately 30 ng/mL. This regimen should be followed by maintenance therapy of 1000 to 2000 units/day or whatever dose is needed to maintain the target serum level [113, 114]. Adults with ongoing malabsorption may require higher replacement doses of vitamin D to reach and sustain sufficiency.

Supplemental vitamin D and BMD

Systematic reviews and meta-analyses have found insufficient or conflicting evidence to support the use of supplemental vitamin D alone (without calcium) to promote musculoskeletal health in adults living in the community [115–119]. The large VITAL study in generally healthy women and men (≥ 55/≥ 50 years respectively) not selected for low bone mass or vitamin D insufficiency, reported no effect of high-dose, supplemental vitamin D (cholecalciferol 2000 units/day) versus placebo on BMD or bone structural measures over 2 years [120, 121]. Effects did not vary by sex, race/ethnicity, body mass index, or baseline 25(OH)D levels. The baseline 25(OH)D level (mean) was 27 ng/mL, suggesting that VITAL participants may already be at serum vitamin D levels sufficient to support normal bone health. These findings do not apply to persons with extremely low vitamin D levels or osteoporosis or younger adults. Ongoing studies in VITAL are examining effects of supplemental vitamin D on incident fractures among 25,871 women and men nationwide [121, 122].

Supplemental vitamin D and fall risk

A possible role for supplemental vitamin D in fall prevention has been a subject of study and inconclusive data. Results from the VITAL study, the largest placebo-controlled RCT of supplemental vitamin D on health outcomes, did not support the use of supplemental vitamin D (2000 units/day vs placebo groups) to prevent falls in generally healthy population not selected for high falls risk or vitamin D insufficiency [123]. These findings are consistent with recent meta-analyses and other randomized controlled studies in populations around the world that have *not* found supplemental vitamin D to be effective in reducing fall risk [118, 124–126].

Vitamin D absorption and synthesis

Gastrointestinal absorption of vitamin D differs between individuals and can be significantly decreased in patients with celiac disease, inflammatory bowel disease, bariatric surgery, and other disorders. Variability in skin activation and synthesis of vitamin D results from differences in pigmentation, season (weak UV light in the winter and fall), time spent outdoors, and use of sunscreens. For example, African Americans have lower 25(OH)D levels than non-Hispanic white Americans due to decreased skin activation (and possibly differences in vitamin D binding proteins). People who live in northern latitudes typically experience a decrease in serum vitamin D in winter that rebounds in spring and summer.

Cessation of tobacco use and avoidance of excessive alcohol intake

The use of tobacco products is detrimental to the skeleton as well as to overall health [127–130]. BHOF strongly recommends smoking cessation to support primary and secondary prevention of osteoporosis.

Moderate alcohol intake has no known negative effect on bone and may even be associated with slightly higher bone density and lower risk of fracture in postmenopausal women. However, alcohol intake of more than two drinks a day for women or three drinks a day for men may be detrimental to bone health. It has been associated with reduced calcium absorption and increased risk for falls. Clinicians should identify patients at risk for chronic heavy drinking and/or binge drinking who require further evaluation and treatment [131].

Regular weight-bearing and muscle-strengthening physical activity

The BHOF strongly endorses physical activity at all ages, both for fracture prevention and overall fitness. In childhood and adolescence, consistent weight-bearing and high-impact activities contribute to acquisition of optimal peak bone mass [132]. Weight-bearing exercises (in which bones and muscles work against gravity with feet and legs bearing body weight) include walking, jogging, tai chi, stair climbing, dancing, and tennis. Muscle-strengthening exercises include weight training and resistive exercises, such as yoga, Pilates, and boot camp calisthenics. To avoid injury, patients should be evaluated before initiating a new exercise program, particularly one involving compressive or contractile stressors (such as running or weightlifting).

A multicomponent program is recommended for people with osteoporosis: one that includes progressive resistance training, balance training, back extensor strengthening, core stabilizers, cardiovascular conditioning, and impact or ground-reaction forces to stimulate bone. In people with osteoporosis, improved fall outcomes have been documented following high-intensity exercise programs that combine resistance, balance, and weight-bearing activities [133–136]. In research settings, structured exercise programs have resulted in modest increases in bone density [137–139]. Muscle growth has been reported even in frail elderly individuals with established sarcopenia (age-related muscle loss) who participate in short-burst high-intensity exercise. For safety, any such program of physical activity must be developed and supervised by certified fitness personnel experienced with skeletal fragility in geriatric patients. (See "Protecting fragile bones in daily life and recreation" section.)

Motivating patients to stick with a program of physical activity

Sticking with any lifestyle change can be difficult. However, persistence is easier when that change is linked to something of value to an individual. In this case, what probably matters most is preserving independence by avoiding an injury that results in nursing home admission. Visual aids that show graphical comparisons of risk, can help patients see the connection between bone health recommendations and quality of life.

Consultation with a trained physical therapist and/or participation in group exercise led by certified fitness personnel help ensure patient safety, motivate daily participation, and promote social engagement. As long as principles of safe movement are followed, walking and daily activities such as housework and gardening are practical ways to contribute to maintenance of fitness and bone mass.

Fall prevention strategies

Among adults aged 65 or older, falls are the leading cause of both fatal and nonfatal injuries including the majority of all fractures and over 90% of hip fractures [142–144]. According to CDC statistics, in 2018, more than 32,000 adults aged ≥ 65 years were killed by unintentional fall injuries [145].

Major risk factors for falls are shown above in Table 2. Many of these are modifiable: muscle strength and balance can be improved through targeted exercise; visual impairment can be addressed; severe vitamin D deficiency can be corrected; fall hazards in the home and work environment can be remediated; and medications that induce dizziness and disorientation can be replaced or reduced.

Multiple studies have demonstrated the efficacy of therapeutic physical activity in reducing falls. A recent meta-analysis of RCTs investigating moderate-intensity multicomponent physical activity (aerobic, balance, and strength training) 3 times a week for 1 year or more reported significant fall reductions: 22% lower risk for falls and 26% lower risk for injurious falls.

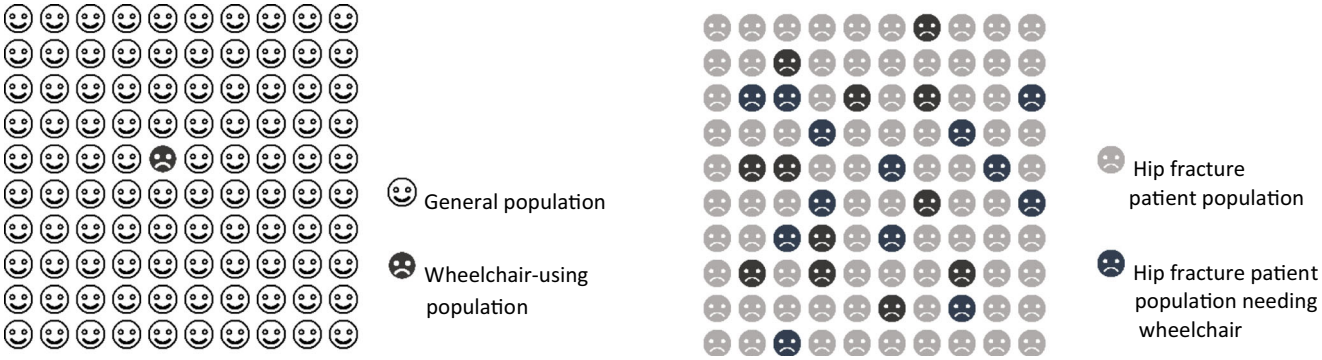


Fig. 5 This contrast between percentage of people in general population who use wheelchairs (1 in 100) and the percentage who use wheelchairs following hip fracture (25 in 100). Sources: 2010 US Census Data [140, 141]

Risk of fractures was reduced by 16%, although the significance of this finding is weakened by the small number of fractures in the study (p = .05) [146]. For individuals who have already experienced a fall, regular weight-bearing and muscle-strengthening physical activity may reduce the risk of future falls and fractures [124, 147–149].

A 12-month, single-blinded RCT among 345 high-risk older adults aged ≥ 70 years who had fallen in the year prior compared usual care (geriatrician provided fall prevention instruction) or a home-based exercise program focused on strength and balance training. At 1 year, fall incidence was 74% *lower* in the home-based exercise group than in the group that received usual care. No adverse events related to the intervention were reported [150].

Regarding fracture outcomes among persons with osteoporosis, there are few exercise/physical activity studies with fractures as a primary endpoint. However, a recent meta-analysis examining physical activity and fall outcomes in older adults in the general population provides evidence that physical activity may prevent fractures in older adults [135]. Another meta-analysis of 10 studies (n = 4047) reported that physical activity may reduce the number of older community-dwelling adults experiencing ≥ 1 fall-related fracture (RR 0.73, 95% CI 0.56 to 0.95), but the evidence is judged to be of low certainty [151].

In the WHI, among 77,206 postmenopausal women across the USA followed for a mean of 14 years, there was an association between higher levels of physical activity and lower total fracture risk and lower risk for hip fracture. It is important to note that even low-intensity activities such as walking or gardening reduced risk for hip fracture when compared to sedentary activities [152].

There are a limited number of studies with men and few RCT exercise studies with fracture outcomes comparing those who exercise to those who did not exercise.

US FDA-approved drugs for osteoporosis

Current FDA-approved pharmacologic therapeutics for prevention and/or treatment of postmenopausal osteoporosis include bisphosphonates (alendronate, alendronate plus D, ibandronate, risedronate, and zoledronic acid), estrogens (estrogen and/or hormone therapy), estrogen agonist/antagonist (raloxifene), tissue-selective estrogen complex (conjugated estrogens/bazedoxifene), parathyroid hormone (PTH [1–34], teriparatide), analog of parathyroid hormone-related peptide (PTHrP [1–34], abaloparatide), RANKL inhibitor (denosumab), fully human monoclonal antibody to sclerostin (romosozumab), and calcitonin. Please see product-specific prescribing information for details of their use (Table 11).

Antifracture benefits of FDA-approved drugs for osteoporosis have been studied primarily in postmenopausal women. We have more limited fracture data on efficacy in patients with secondary causes of osteoporosis (e.g., diabetes, glucocorticoids) and men diagnosed with osteoporosis by fracture or T-score.

Potential benefits and risks of therapy should be assessed in the context of a drug's fracture efficacy, onset of effect, duration parameters, magnitude of effect, and site of optimal fracture prevention (spine vs hip). In general, a therapy that *has been shown to reduce risk of both vertebral and non-vertebral fractures* (alendronate, risedronate, zoledronic acid, denosumab, teriparatide, abaloparatide, or romosozumab) should be considered over one that has not (raloxifene, calcitonin, ibandronate). In most of these pivotal studies, participants were on appropriate amounts of calcium and vitamin D.

The BHOF does not advocate the use of drugs that are not approved by the FDA for prevention and/or treatment of osteoporosis.

Bisphosphonates (alendronate, ibandronate, risedronate, zoledronic acid)

Bisphosphonates are a class of potent antiresorptive agents. Composed of two phosphate groups, bisphosphonates have also been called diphosphonates. All bisphosphonates can affect renal function and are contraindicated in patients with estimated glomerular filtration rate (GFR) below 30–35 mL/min. Bisphosphonates may cause or exacerbate hypocalcemia, and therefore, hypocalcemia must be corrected before treatment.

Table 11 FDA-approved drugs for osteoporosis [153]

Drug name	Brand name	Form/dosing	Approval for
Bisphosphonates			
Alendronate	Generic alendronate and Fosamax®, Fosamax Plus D™	Oral (tablet) Daily/weekly	Women and men
Alendronate	Binosto®	Effervescent tablet Weekly	Women and Men
Ibandronate	Boniva®	Oral (tablet) Monthly	Women
Ibandronate	Boniva®	Injection Quarterly	Women
Risedronate	Actonel®/Actonel® w/ calcium	Oral (tablet) Daily/weekly/twice monthly/monthly; monthly with calcium	Women and men
Risedronate	Atelvia™	Oral delayed-release (tablet) Weekly	Women
Zoledronic acid	Reclast®	IV infusion Once a year/once every 2 years	Women and men
Estrogen-related therapies			
Estrogen	Multiple brands	Oral (tablet) Daily	Women
Estrogen	Multiple brands	Transdermal (skin patch) Twice weekly/weekly	Women
Raloxifene	Evista®	Oral (tablet) Daily	Women
Conjugated estrogens/bazedoxifene	Duavee®	Oral (tablet) Daily	Women
Parathyroid hormone analogs			
Abaloparatide	Tymlos®	Injection Daily (for 2 years)	Women
Teriparatide	Forteo®	Injection Daily (for ≥ 2 years)*	Women and men
RANKL inhibitor			
Denosumab	Prolia™	Injection Every 6 months	Women and men
Sclerostin inhibitor			
Romosozumab	Evenity™	Injection (2) Monthly for 12 months	Women
Calcitonin Salmon			
Calcitonin	Fortical®/Miacalcin®	Nasal spray Daily	Women
Calcitonin	Miacalcin®	Injection Schedule varies	Women

* Use of teriparatide for more than 2 years during a patient's lifetime should only be considered if a patient remains at or has returned to having a high risk for fracture.

Alendronate, brand name: Fosamax®, Fosamax Plus D, Binosto™ (liquid preparation) and generic alendronate

Alendronate sodium is approved by the FDA for prevention (5 mg daily and 35 mg weekly tablets) and treatment of post-menopausal osteoporosis (10 mg daily tablet, 70 mg weekly tablet [most commonly used dose], 70 mg weekly tablet with 2800 units or 5600 units of vitamin D3, and 70 mg effervescent tablet). Alendronate is approved as treatment to increase bone mass in men with osteoporosis and for treatment of osteoporosis in men and women taking glucocorticoids [154].

Drug efficacy Alendronate reduces incidence of spine and hip fractures by about 50% over 3 years in patients with prior vertebral fracture and in patients who have hip T-

scores diagnostic of osteoporosis (≤ − 2.5) [155, 156]. It reduces incidence of vertebral fractures by 48% over 3 years in patients without prior vertebral fracture.

Administration Oral alendronate (generic and Fosamax®) tablets must be taken at least 30 min before the first food, beverage, or medication of the day with plain water only. Tablets must be swallowed whole with a full glass of plain water (6 to 8 oz). Effervescent alendronate (Binosto) must be dissolved in 4 oz of room temperature water and taken on an empty stomach first thing in the morning. Patients should remain upright and eat/drink nothing for 30 min following ingestion.

Side effects and drug safety Side effects are similar for all oral bisphosphonate medications and include gastrointestinal problems such as difficulty swallowing, esophageal inflammation, stomach pain, and rare cases of atypical femur fractures (AFF) and osteonecrosis of the jaw (ONJ). (See boxed discussion below.) Ocular inflammation (anterior uveitis and episcleritis) has been documented. All bisphosphonates can affect renal function and are contraindicated in patients with estimated GFR below 30–35 mL/min.

Ibandronate, brand name: Boniva® and generic ibandronate

Oral and intravenous ibandronate sodium are approved by the FDA for treatment of postmenopausal osteoporosis (150 mg monthly tablet and 3 mg every 3 months by intravenous injection). Oral ibandronate is also approved for prevention of postmenopausal osteoporosis and is available as a generic in the USA.

Drug efficacy Ibandronate reduces incidence of vertebral fractures by about 33–50% over 3 years but *does not reduce risk of non-vertebral fracture (hip/nonhip)* [157].

Administration Oral ibandronate must be taken on an empty stomach, first thing in the morning, with 8 oz of plain water (no other liquid). Tablets must be swallowed whole with a full glass of plain water (6 to 8 oz). After taking ibandronate, patients must remain upright and wait at least 60 min before eating, drinking, or taking any other medication. Intravenous ibandronate, 3 mg/3 mL prefilled syringe, is administered over 15 to 30 s once every 3 months. Serum creatinine should be checked before each injection.

Side effects and drug safety Side effects are similar for all oral bisphosphonate medications and include gastrointestinal problems such as difficulty swallowing, esophageal inflammation, and stomach pain and rare cases of AFF and ONJ. (See boxed discussion below.) Ocular inflammation has been documented. Like other bisphosphonates, ibandronate may cause or exacerbate hypocalcemia, and therefore, hypocalcemia must be corrected before treatment. All bisphosphonates can affect renal function and are contraindicated in patients with estimated glomerular filtration rate (GFR) below 30–35 mL/min.

Risedronate, brand name: Actonel®, Atelvia™, and generic risedronate

Risedronate sodium is approved by the FDA for prevention and treatment of postmenopausal osteoporosis (5 mg daily tablet; 35 mg weekly tablet; 35 mg weekly delayed-release tablet; 75 mg tablets taken on two consecutive days every month; and 150 mg tablet taken monthly). Actonel® is approved to increase bone mass in men with osteoporosis and to prevent and treat osteoporosis in men and women who are either initiating or taking glucocorticoids [158, 159].

Drug efficacy Compared with placebo, risedronate reduced incidence of vertebral fractures by 39%, hip fractures by 27%, and non-vertebral fractures by 22% in a meta-analysis conducted by Barrionuevo et al. in 2019 [160]. Significant risk reduction occurred within 1 year of treatment in patients with a prior vertebral fracture.

Administration Oral risedronate (generic and Actonel®) must be taken on an empty stomach, first thing in the morning, with 8 oz of plain water (no other liquid). Tablets must be swallowed whole with a full glass of plain water (6 to 8 oz). After taking risedronate, patients must remain upright and wait at least 30 min before eating, drinking, or taking any other medication.

Oral delayed-release risedronate (Atelvia®) is taken not on an empty stomach, but directly after breakfast with ≥ 4 oz of plain water (no other liquid). Patients should remain upright (sitting or standing) for at least 30 min.

Side effects and drug safety Side effects are similar for all oral bisphosphonate medications and include gastrointestinal problems such as difficulty swallowing, esophageal inflammation, and stomach pain and rare cases of AFF and ONJ. (See boxed discussion below.) Ocular inflammation (anterior uveitis and episcleritis) has been documented. All bisphosphonates can affect renal function and are contraindicated in patients with estimated GFR below 30–35 mL/min. Because risedronate can cause or exacerbate hypocalcemia, hypocalcemia must be corrected before treatment. All bisphosphonates can affect renal function and are contraindicated in patients with estimated glomerular filtration rate (GFR) below 30–35 mL/min.

Zoledronic acid, brand name: Reclast®

Zoledronic acid is approved by the FDA for prevention and treatment of osteoporosis in postmenopausal women (5 mg once yearly for treatment and once every 2 years for prevention). It is approved to improve bone mass in men with osteoporosis and for prevention and treatment of osteoporosis in men and women expected to be on glucocorticoid therapy for at least 12 months. (Efficacy of less-frequent dosing is currently being investigated.) Zoledronic acid is indicated for prevention of new clinical fractures in patients (both women and men) who have recently had a low-trauma hip fracture. A recent placebo-controlled study in women aged ≥ 65 years with low hip BMD found that zoledronic acid administered every 18 months for 6 years reduced vertebral and non-vertebral fractures. In this study, the number needed to treat to prevent 1 incident fracture was 15 [161].

Drug efficacy Zoledronic acid reduces incidence of vertebral fractures by 62–70% (with significant reduction at 1 year), hip fractures by 41%, and non-vertebral fractures by 21–25% over 3 years in patients with osteoporosis defined by prevalent vertebral fractures and/or osteoporosis by BMD of the hip [160].

Administration of zoledronic acid compared with placebo in postmenopausal women with low bone mass every 18 months reduces vertebral fractures by 55%, non-vertebral fractures by 34% and forearm and wrist fractures by 44% at 6 years [161].

Administration Zoledronic acid (generic and Reclast®), 5 mg in 100 mL, is given once yearly by intravenous infusion administered over at least 15 min. Some physicians infuse this over 30 min. Flu-like symptoms (arthralgia, headache, myalgia, fever) have occurred in 32% of patients after the first dose, 7% after the second dose, and 3% after the third dose. To reduce likelihood of acute-phase reactions, patients should be well hydrated, drink 2 glasses of water before the infusion and pre-treat with acetaminophen (unless contraindicated).

Side effects and drug safety We recommend a 25(OH) vitamin D level should be obtained and any vitamin D deficiency or insufficiency corrected before treatment. Zoledronic acid may cause or exacerbate hypocalcemia, and therefore, hypocalcemia must be corrected before treatment. Zoledronic acid is contraindicated in patients with creatinine clearance less than 35 mL/min or in patients with evidence of acute renal impairment. Creatinine clearance should be measured prior to each dose [162]. Ocular inflammation (anterior uveitis and episcleritis) has been documented [163]. (See boxed discussion below.)

Estrogen-related therapies (ET/HT, raloxifene, conjugated estrogens/bazedoxifene)

A variety of medications that act on estrogen receptors in bone are prescribed to prevent the bone loss associated with postmenopausal osteoporosis.

ET/HT

ET brand names: e.g., Climara®, Estrace®, Estraderm®, Estratab®, Ogen®, Premarin®, Vivelle®; HT brand names: e.g., Activella®, Femhrt®, Premphase®, Prempro®. Estrogen/hormone therapy is approved by the FDA for prevention of osteoporosis and relief of vasomotor symptoms and vulvovaginal atrophy associated with menopause. Women with an intact uterus require HT (combined estrogen and progestin) to protect uterine lining. Women who have had a hysterectomy are treated with ET (estrogen alone).

Drug efficacy The Women's Health Initiative (WHI) found that 5 years of oral HT (Prempro®) reduced incidence of clinical vertebral fractures and hip fractures by 34% and other osteoporotic fractures by 23% [164]. Meta-analysis sponsored by the Endocrine Society found that HT reduced fractures of the spine by 35%, hip by 28%, and non-vertebral skeleton by 22% [160].

Drug administration ET/HT is available in a wide variety of oral and transdermal preparations that contain estrogen only, progestin only, and combination estrogen-progestin. ET/HT dosages include cyclic, sequential, and continuous regimens. When treatment is discontinued, bone loss can be rapid. Follow-on antifracture agents should be considered to maintain BMD.

Side effects and drug safety Potential risks for women include biliary issues, breast cancer (with combined estrogen–progestin), endometrial hyperplasia/cancer (with inadequately opposed estrogen). Initial WHI data found elevated risk of myocardial infarction, stroke, pulmonary emboli, and deep vein thrombosis during 5 years of treatment with conjugated equine estrogen and medroxyprogesterone acetate (Prempro®) [165, 166]. *Subsequent analyses of WHI substudy data showed no increase in cardiovascular disease in women starting treatment within 10 years of menopause* [167].

The North American Menopause Society (NAMS) and American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) recommend tailoring ET/HT formulation, dose, and route of administration to individual postmenopausal women. Risk-benefit profiles differ by patient age, time since menopause, and other factors [168, 169].

The Endocrine Society guidelines recommend ET/HT to prevent fractures in some high-fracture-risk postmenopausal women < 60 years of age or < 10 years past menopause who

are experiencing vasomotor and/or climacteric symptoms and cannot take bisphosphonates or denosumab [170].

When ET/HT use is considered solely for fracture prevention, the FDA recommends that approved non-estrogen treatments first be carefully considered.

Raloxifene, brand name: Evista® and generic raloxifene

Raloxifene is an estrogen agonist/antagonist (selective estrogen receptor modulator/SERM) approved by the FDA for both prevention and treatment of osteoporosis in postmenopausal women. Raloxifene is indicated for the reduction in risk of invasive breast cancer in postmenopausal women with osteoporosis [171–174]. Raloxifene does not reduce the risk of coronary heart disease.

The Endocrine Society guidelines recommend raloxifene or combination conjugated equine estrogen/bazedoxifene to prevent vertebral fractures in postmenopausal women who have low risk of deep vein thrombosis for whom bisphosphonates or denosumab are not appropriate or for women with a history of or high risk for breast cancer [166].

Drug efficacy Raloxifene reduces incidence of vertebral fractures by about 30–40% in patients with a prior vertebral fracture and by about 55% in patients without a prior vertebral fracture. *Raloxifene does not reduce risk of non-vertebral fractures.*

Drug administration Raloxifene is available as a 60-mg tablet, which may be taken with or without food (60 mg).

Side effects and drug safety Raloxifene increases risk for deep vein thrombosis to a degree similar to that observed with estrogen. It can increase hot flashes and cause leg cramps.

Conjugated estrogens/bazedoxifene, brand name: Duavee®

Conjugated estrogens/bazedoxifene is FDA approved as an oral tablet for women who suffer from moderate-to-severe hot flashes associated with menopause and to prevent osteoporosis after menopause.

Conjugated estrogens/bazedoxifene combines conjugated estrogen with bazedoxifene, an estrogen agonist/antagonist. Bazedoxifene reduces risk for endometrial hyperplasia eliminating need for progestins in women who have not undergone hysterectomy.

Drug efficacy In pivotal trials, this combination drug significantly increased mean lumbar spine BMD (treatment difference 1.51%) at 12 months compared to placebo in women who had been postmenopausal between 1 and 5 years. Treatment with conjugated estrogens/bazedoxifene also increased total hip BMD. The treatment difference in total hip BMD at 12 months was 1.21% [175–178].

Drug administration Available as a tablet containing conjugated estrogens and bazedoxifene 0.45 mg/20 mg, to be taken once daily without regard to meals.

Conjugated estrogens/bazedoxifene is intended only for postmenopausal women who have not had hysterectomy. Like other products containing estrogen, its use should be consistent with treatment goals and risks for the individual woman. When being considered solely for the prevention of osteoporosis, such use should be limited to women who are at significant risk of fracture and only after carefully considering alternatives that do not contain estrogen. When treatment is discontinued, bone loss can be rapid. An antifracture agent should be considered to maintain BMD.

Side effects and drug safety Side effects of conjugated estrogens/bazedoxifene include muscle spasms, nausea, diarrhea, dyspepsia, upper abdominal pain, oropharyngeal pain, dizziness, and neck pain. Because this product contains estrogen, it is approved with the same Boxed Warning and other Warnings and Precautions that have been approved with estrogen products.

Parathyroid hormone analogs (teriparatide, abaloparatide)

Parathyroid hormone (PTH) regulates calcium homeostasis. Constant high exposure to PTH causes bone resorption, while intermittent administration of exogenous recombinant PTH stimulates bone formation. Two anabolic agents derived from synthetic analogs of PTH are currently FDA approved: teriparatide and abaloparatide.

Teriparatide, brand name: Forteo® and the bioequivalent Bonsity™

Teriparatide is a synthetic fragment of human PTH that is approved by the FDA for treatment of osteoporosis in men and women at high risk for fracture (which is defined as a history of osteoporotic fracture, multiple risk factors for fracture, or failure/intolerance to other available osteoporosis therapy). It is approved to treat glucocorticoid-induced osteoporosis in men and women at high risk for fracture [179]. The FDA has approved an expanded indication for teriparatide for treatment of osteoporosis associated with sustained systemic glucocorticoid therapy (≥ 5 mg/day of prednisone). Forteo® is currently available as 20 μg daily subcutaneous injection. Biosimilar preparations are now available as the patented expired in 2019.

Drug efficacy Teriparatide reduces risk of vertebral fractures by 65–77%, and non-vertebral fractures by 35–53% in patients with osteoporosis, after an average of 18 months of therapy [180]. The VERO trial that compared teriparatide and risedronate in postmenopausal women with severe osteoporosis reported ~ 56% fewer new vertebral fractures in the teriparatide group after 24

months [181]. It is important to follow teriparatide treatment with an antiresorptive agent, usually a bisphosphonate or denosumab, to maintain or further increase BMD.

Drug administration Teriparatide is administered by 20 μg daily subcutaneous injection. When treatment is discontinued, bone loss can be rapid and alternative agents should be considered to maintain BMD. Treatment duration was previously restricted to 24 months, but this was recently changed to open the possibility of longer treatment in high-risk patients.

Side effects and drug safety Side effects of teriparatide include transient orthostatic hypotension, leg cramps, and nausea. Teriparatide transiently increases serum calcium which may predispose patients to digitalis toxicity. It should be used with caution in patients with active or recent kidney stones, hypercalcemia and hypercalcemic disorders, and/or cutaneous calcification.

Until recently, teriparatide treatment was restricted to 2 years in response to elevated osteosarcoma seen in rodent studies. Increased osteosarcoma was not observed in humans during 15 years of post-marketing studies. As a result, the revised teriparatide label now states that use for more than 2 years during a patient's lifetime can be considered if a patient remains at or has returned to having a high risk for fracture.

Its use should be avoided in settings of increased risk for osteosarcoma: Paget's disease of the bone, prior radiation therapy involving the skeleton, open epiphyses (children and young adults), history of bone metastases or malignancies, unexplained elevated alkaline phosphatase, and hereditary disorders predisposing to osteosarcoma [182].

Abaloparatide, brand name: Tymlos®

Abaloparatide is a synthetic peptide analog of human PTH-related protein approved by the FDA for treatment of osteoporosis in postmenopausal women at high risk for fracture defined as a history of osteoporotic fracture, multiple risk factors for fracture, or failure/intolerance to other available osteoporosis therapy.

Drug efficacy Abaloparatide reduces risk of new vertebral fractures by about 86% and non-vertebral fractures by about 43% in postmenopausal women with osteoporosis, after an average of 18 months of therapy [183]. In an extension study (ACTIVE-Extend) after 18 months of abaloparatide or placebo, the addition of 6 months of oral alendronate for a total of up to 24 months of therapy resulted in a relative risk reduction of radiographic spine fractures by 87%, non-vertebral fractures by 52%, and major osteoporotic fractures by 58% [184].

Drug administration Abaloparatide is administered by 80 μg daily subcutaneous injection in the periumbilical area of the abdomen. When treatment is discontinued, bone loss can be rapid. An antiresorptive agent should be considered to maintain BMD. Abaloparatide treatment duration is recommended not to exceed 24 months.

Side effects drug safety Side effects of abaloparatide include leg cramps, nausea, and dizziness. Avoid use in patients with increased risk of osteosarcoma (e.g., Paget's disease of bone, bone metastases, prior skeletal radiation). Patients with hypercalcemia, or a history of an unexplained elevated alkaline phosphatase or skeletal malignancy should not receive abaloparatide therapy. Abaloparatide may increase urinary calcium. It should be used with caution in patients with active or recent kidney stones because of the potential to exacerbate this condition. It is common practice to follow abaloparatide treatment with an antiresorptive agent, usually a bisphosphonate or denosumab, to maintain or further increase BMD.

RANKL inhibitor (denosumab)

The cytokine RANK-ligand (RANKL) produced by osteocytes is required for osteoclast formation. Suppressing RANKL blocks osteoclast formation, leading to less bone resorption and higher bone density.

Denosumab, brand name Prolia®

Denosumab is a fully human monoclonal antibody against RANKL approved by the FDA for treatment of men and women at high risk for fracture (which is defined as a history of osteoporotic fracture and/or multiple risk factors for fracture). It is approved for treatment of patients who have failed or are intolerant to other available osteoporosis therapy, to treat postmenopausal women with osteoporosis at high risk for fracture, to increase bone mass in men with osteoporosis at high risk for fracture, to treat glucocorticoid-induced osteoporosis in men and women at high risk for fracture, to increase bone mass in men at high risk for fracture receiving androgen deprivation therapy for nonmetastatic prostate cancer, and to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer.

Drug efficacy Denosumab is one of the most potent antiresorptive drugs available to treat osteoporosis because it directly inhibits osteoclast formation and causes apoptosis of mature osteoclasts. Denosumab reduces incidence of vertebral fractures by about 68% at 1 year, hip fractures by about 40% and non-vertebral fractures by about 20% at 3 years, with continued fracture reduction in studies extended to 5 years [160, 185, 186]. Longer-term use is associated with a significant 48% reduction in the risk of all upper limb fractures and

a 43%, 43%, and 58% reduction in risk of forearm, wrist, and humerus fractures at 7 years [187, 188].

Drug administration Denosumab is administered as 60 mg subcutaneous injection by a health professional every 6 months.

Side effects and drug safety Denosumab may cause or exacerbate hypocalcemia, and therefore, hypocalcemia must be corrected before treatment. Denosumab has been associated with hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria. Studies have reported higher incidence of serious infection in women taking denosumab; however, no clear clinical pattern has emerged to suggest a relationship to duration of exposure to denosumab [189]. Safety profiles overall are similar to bisphosphonates and placebo, with no new safety concerns emerging in extension trials up to 10 years, although a theoretical infection risk exists with RANKL inhibition and prescribing information states that patients on concomitant immunosuppressant agents or with impaired immune systems may be at increased risk for serious infections [190, 191]. Denosumab has been associated with very rare cases of AFF and ONJ. (See boxed discussion below.)

Discontinuation of denosumab treatment is associated with rapid bone loss that may result in multiple vertebral fractures, especially in patients with a prior vertebral fracture [192]. For this reason, a drug holiday is not appropriate with denosumab. During periods of suspended treatment, and as recommended by the FDA, alternate antiresorptive therapy should be considered to maintain gains in bone density. Following denosumab with alendronate has been shown to preserve bone mass, while following it with teriparatide has been associated with *bone loss at some skeletal sites* [193].

Sclerostin inhibitor (romosozumab)

Romosozumab-aqqg, brand name EVENITY™

Romosozumab is a fully human monoclonal antibody to sclerostin. It is currently FDA-approved for treatment of osteoporosis in postmenopausal women at high risk for fracture—defined as a history of osteoporotic fracture, or multiple risk factors for fracture, or poor response or intolerance to other available osteoporosis therapies. (Romosozumab is approved for men with osteoporosis at high risk of fracture in some countries but not in the USA.)

Drug efficacy Romosozumab reduces fractures and increases BMD at the lumbar spine and total hip more than placebo, alendronate, and teriparatide in postmenopausal women with low bone mass [194–196]. In the pivotal FRAME trial, romosozumab compared to placebo for 12 months reduced risk of new vertebral fracture by 73% and clinical fractures by 36% [196]. In the ARCH study, high-risk postmenopausal women had significantly fewer fractures when treated with romosozumab than with alendronate (48% fewer new vertebral fractures, 19% fewer non-vertebral fractures, and 38% fewer hip fractures) for 12 months [197].

Extension studies have reported BMD trending back towards pretreatment levels after discontinuing therapy. Follow-on therapy with denosumab and, to a lesser degree, alendronate preserve or continue to accrue BMD benefits following romosozumab therapy [196, 198, 199].

Drug administration Romosozumab (210 mg) is administered in monthly doses by subcutaneous injection for 12 months. Each dose consists of two injections (105 mg each) that are given one immediately following the other by a healthcare professional. Use is limited to 1 year due to the waning of bone-forming effect after 12 months/doses.

Side effects and drug safety Romosozumab received FDA approval with a boxed warning stating that it may increase risks for myocardial infarction, stroke, and cardiovascular (CV) death. It should not be taken by women who experienced a stroke or CV event in the previous year. Romosozumab may cause hypocalcemia, and therefore, hypocalcemia must be corrected before treatment. In studies, romosozumab has been associated with hypersensitivity reactions, including angioedema, erythema multiforme, dermatitis, rash, and urticaria. Romosozumab has been associated with rare cases of AFF and ONJ (fewer cases than denosumab). (See boxed discussion below.)

Calcitonin salmon

Calcitonin is a hormone endogenous in humans that is found in salmon and other fish, reptiles, birds, and mammals. It works by preventing bone breakdown, thereby increasing bone density. Because more effective drugs are available for prevention of bone loss and reduction of fracture risk, calcitonin salmon is considered second-line therapy reserved for women in whom alternative treatments are not suitable.

Calcitonin, brand name, Miacalcin® or Fortical® and generic calcitonin

Calcitonin is FDA approved for the treatment of osteoporosis in postmenopausal women who are at least 5 years following menopause.

Drug efficacy In two RCTs, calcitonin salmon nasal spray increased lumbar vertebral BMD relative to placebo in women with low bone mass who were greater than 5 years post menopause. No increase in BMD has been demonstrated in cortical bone of the forearm or hip.

Calcitonin reduces vertebral fracture occurrence by about 30% in those with prior vertebral fractures but *does not reduce* the risk of non-vertebral fractures [200]. Calcitonin significantly reduces pain associated with vertebral, crush fractures in many patients, making early mobilization possible [201, 202].

Drug administration Calcitonin is administered in 200-unit doses delivered as a single daily intranasal spray. Subcutaneous administration by injection also is available.

Side effects and drug safety Intranasal calcitonin can cause rhinitis, epistaxis, and allergic reactions. Long-term post-marketing data meta-analysis of 21 RCTs found cancer risk was higher among calcitonin salmon-treated patients (4.1%) compared with placebo-treated patients (2.9%); therefore, the need for continued therapy should be reevaluated on a periodic basis. Because of its risk–benefit profile, calcitonin is banned in Canada and Europe; it is infrequently used in the USA [203, 204].

Possible Adverse Events Associated with Antiresorptive Therapies: ONJ and AFF

People using bisphosphonates and denosumab are at low but increased risk for ONJ, a condition in which bone is persistently exposed (usually following an extraction), and AFF, in which a femur breaks spontaneously, often with no warning. Romosozumab use has rarely been associated with ONJ and AFF according to the current studies.

Osteonecrosis of the Jaw (ONJ)
ONJ is more frequently associated with high-dose intravenous bisphosphonate treatment for cancer (96% of cases reported). For patients taking oral bisphosphonates to manage osteoporosis, the incidence of ONJ is estimated to be between 1/10,000 and 1/100,000 and is only slightly higher than the ONJ incidence in the general population [205–207]. The risk of ONJ appears to increase with bisphosphonate treatment beyond 5 years. ONJ has been reported in >2% of studied cancer patients taking high doses of denosumab (XGEVA®).[4]

The American Dental Association (ADA) reports that sound oral hygiene practices and regular dental care may be the optimal method for lowering risk of drug-related ONJ. No validated diagnostic technique is currently available to determine which patients are at increased risk. The magnitude of risk reduction associated with discontinuing antiresorptive therapy even in those with ONJ is not known but must be weighed against known negative outcomes of low bone density and fractures [207, 209, 210].

Atypical Femur Fracture (AFF)
While reports show that ONJ is more common in cancer patients treated with bisphosphonates, rates of AFF appear lower in these patients, possibly related to shorter duration of use or other mechanisms [205, 211, 212]. AFFs can occur with little or no trauma and may be bilateral. AFF incidence is very low in the general untreated population. Higher risk is associated with Asian ethnicity (North American), lateral bowing of the femur, autoimmune disease, and glucocorticoid use [213]. AFF has been reported in people taking bisphosphonates, denosumab, and romosozumab (association with duration of use is not established).

AFFs are often preceded by pain in the thigh and/or groin area. Clinicians should closely monitor symptoms related to these unusual fractures, proactively questioning patients about occurrence of any thigh and/or groin pain. Patients who present with this prodrome may have experienced stress fracture in the subtrochanteric region or femoral shaft. Bilateral femoral X-rays should be ordered, followed by an MRI or a radionuclide bone scan when clinical suspicion is high enough [214].

Another option, available on newer DXA systems, is single-energy X-ray absorptiometry, an imaging method that detects early signs of AFF [215]. The femur is imaged using a single X-ray beam to detect localized cortical abnormalities characteristic of an incomplete atypical femur fracture. The test is generally rapid (under 1 minute) and can be used to identify AFF in patients on bisphosphonates, denosumab, or romosozumab, who are experiencing groin or thigh pain suggestive of stress fracture in the subtrochanteric region or femoral shaft.

Surgical fixation of one or both femurs is required in some cases of AFF; whereas, medical conservative treatment is appropriate in other cases. If AFF is confirmed, bisphosphonates should be discontinued [14]. Although off-label treatment with an anabolic agent following AFF in association with bisphosphonate use is promising, there are limited data to support this regimen [216]

For patients taking bisphosphonates for osteoporosis, the absolute risk of AFF is low: ranging between 3.2 and 50 cases/100,000 person-years, an estimate that appears to double with prolonged duration of bisphosphonate use (> 3 years, median duration 7 years), and decline rapidly with discontinuation [206, 217].

AFF has been seen in patients taking denosumab for osteoporosis (1/2343 patients in the FREEDOM Trial extension followed for 10 years) [218, 219]. Denosumab treatment should be discontinued in the event of the rare occurrence of AFF in patients on denosumab. Another antiresorptive therapy should be started for a few years after stopping denosumab (post AFF) [220].

Romosozumab has rarely been associated with ONJ or AFF. However, because it is a weak antiresorptive, these adverse side effects are biologically plausible.

When discussing risk of ONJ and AFF with high-risk adults, it is important to make clear that the risk for fracture associated with *not treating* far exceeds the risk for these unusual adverse effects of treatment [212, 221, 222].

Treatment considerations: pharmacologic therapy

(Note: Risk reduction data for vertebral and non-vertebral fractures being discussed in this Guide come from the FDA Prescribing Information, which includes RCTs. In the absence of head-to-head trials, direct comparisons of risk reduction among drugs cannot be made.)

All patients being considered for osteoporosis treatment should be counseled on risk factor reduction, including the importance of calcium, vitamin D, elimination of tobacco use, moderation of alcohol intake, physical activity, and fall prevention (Table 12). Prior to initiating treatment, patients should be evaluated for secondary causes of bone fragility and have BMD measurements by central DXA, when available, and vertebral imaging studies when appropriate. (See vertebral imaging above.)

Postmenopausal women and men aged 50 years and older presenting with the following should be considered for treatment:

- *A hip or vertebral fracture* (clinically apparent or found on vertebral imaging) *regardless* of T-score. There are abundant data in patients with spine or hip fractures treated with approved pharmacologic agents that fracture incidence goes down. This is true for patients with previous fractures whether the T-score classification is normal, low bone mass (i.e., osteopenia), or osteoporosis [155, 157, 185, 200, 223–227]. In patients with a hip or spine fracture, T-score is not as important as fracture history in predicting future risk of fracture and antifracture efficacy from treatment.
- *A fracture of the pelvis, proximal humerus, or distal forearm in a person with low bone mass or osteopenia*, whether a postmenopausal woman or a man aged ≥ 50 years [40, 41, 228]. In persons with fractures of the pelvis, proximal humerus, or distal forearm who do not have osteopenia or low BMD, the decision to treat should be individualized [12, 13].
- *T-score ≤ − 2.5 at the femoral neck, total hip, lumbar spine, or 33% radius* (significant correlation between T-scores at the wrist, hip, and lumbar spine T-score has been reported in research). Decades of high-quality evidence demonstrate that pharmacotherapy prevents fracture in patients with osteoporosis by BMD-DXA at any clinically relevant site [65, 164, 180, 183–185, 196, 198, 224, 228–237].
- *Low bone mass and FRAX® score above recommended treatment threshold.* High fracture risk and need for pharmacologic intervention are indicated by T-score between − 1.0 and − 2.5 at the femoral neck or total hip and a 10-year probability of a hip fracture ≥ 3% or a 10-year probability of a major osteoporosis-related fracture ≥ 20% based on the US-adapted FRAX® algorithm [17, 18, 76, 238]. A major osteoporotic fracture is defined as a fracture at the hip, wrist, humerus, or spine. Although FRAX®-calculated fracture risk prediction has been confirmed in multiple studies, there are relatively few data confirming fracture risk reductions in patients selected for treatment on the basis of FRAX® score alone.

Setting and reaching goals of therapy

With the availability of measurable benchmarks such as BMD, fracture incidence, and biochemical markers of bone turnover, the "treat-to-target" strategy of outcomes-focused therapy, monitoring, and reassessment can be applied to management of osteoporosis.

For appropriate patients initiating therapy, a reasonable 3-year target outcome could be to increase T-score from − 2.8 to > − 2.5 and have no fractures. Stable BMD and a year with no new fractures could be a measurable goal for someone with low BMD and prior fragility fractures. In both cases, if the patient is not on track to reach the target or fails to reach the target, consideration should be given to clinical reassessment and possibly a change in therapy.

However, fundamental to the concept of "treat-to-target" is the principle that response to therapy is not necessarily sufficient to achieve an acceptable level of risk. A patient may reach their "target" BMD and still be at unacceptably high risk for fracture. This principle has implications for the selection of initial therapy to reduce fracture risk [239]. For example, while an oral bisphosphonate alone can reduce risk to an acceptable level in a moderate-risk patient (T-score > − 2.5, no fractures, low FRAX®), it may not be sufficient in a high-risk patient (T-score < − 2.5, multiple fractures, high FRAX® score). In the high-risk patient, an anabolic agent followed by antiresorptive therapy might have a better chance of achieving meaningful increases in bone density than antiresorptive therapy alone.

Treat-to-target management recommendations

The ideal medication for initiating therapy is one best able to sufficiently reduce risk, while accommodating a patient's needs and preferences. Consistent with the treat-to-target concept, individual patients with osteoporosis should be risk stratified before initiating treatment. Site-specific vulnerabilities can be factored in, such as recent wrist or vertebral fracture, and presented to the patient along with fracture reduction data for each of the treatments.

Speed of effect onset should be considered in relation to a patient's imminent fracture risk. In some settings, such as recent fracture or very low BMD, an agent with rapid effect onset may be preferable to one that takes longer to act. Many RCTs of osteoporosis therapies have shown benefit for fracture reduction at the spine within the first year of treatment (e.g., zoledronic acid, denosumab, and romosozumab) [33, 240]. It is important to treat

Table 12 Treatment of osteoporosis in postmenopausal women and men aged 50 years and older

General principles

- Obtain a detailed patient history pertaining to clinical risk factors for osteoporosis-related fractures and falls.
- Perform physical examination, measure height, and obtain diagnostic studies to evaluate for signs of osteoporosis and its secondary causes.
- Modify diet/supplements, lifestyle, and other modifiable clinical risk factors for fracture.
- Perform vertebral imaging when appropriate to complete risk assessment.
- Decisions on whom to treat and how to treat should be based on clinical judgment using this Guide and all available clinical information.

Consider FDA-approved medical therapies based on the following in adults ≥ 50 years

- Fracture of vertebrae (clinical or subclinical), hip, wrist, pelvis, or humerus.
- DXA T-score − 2.5 or lower in the lumbar spine, femoral neck, or total hip. Predictive value of isolated measurement of 1/3 radius is currently being investigated (use clinical judgment).
- Low bone mass (osteopenia) and a US-adapted WHO 10-year probability of a hip fracture ≥ 3% or 10-year probability of any major osteoporosis-related fracture ≥ 20%.
- Patient preferences may indicate treatment for people with 10-year fracture probabilities above or below these levels.

Consider non-medical therapeutic interventions

- Evaluate and address modifiable risk factors related to bone loss and/or falling.
- Referral for physical and/or occupational therapy evaluation (e.g., walking aids and other assistive devices).
- Encourage weight-bearing, muscle-strengthening, and balance-training activities and refer as needed.

Follow-up

- Patients not requiring medical therapies at the time of initial evaluation should be clinically reevaluated as medically appropriate.
- Patients taking FDA-approved medications should have laboratory and bone density reevaluation after 2 years or more frequently when medically appropriate.
- To identify any new vertebral fractures that have occurred in the interval, vertebral imaging should be repeated if there is documented height loss, new back pain, postural change, or suspicious finding on chest X-ray, following the last (or first) vertebral imaging test and in patients being considered for a temporary cessation of bisphosphonate therapy.
- Regularly assess compliance and persistence with the therapeutic regimen (at least annually).

patients promptly after a fracture to reduce future risk. A patient with a recent fracture and/or very low BMD (e.g., T-score < − 3.0) is at especially elevated risk and more rapid-acting aggressive antifracture therapy should be considered.

A systematic review and meta-analysis of 107 RCTs of osteoporosis interventions in postmenopausal women (mean age 66 years) with primary osteoporosis was performed and included in the 2019 Endocrine Society Clinical Practice Guideline [166]. The Endocrine Society's treatment algorithm provides guidance on the management of postmenopausal osteoporosis according to fracture risk:

Low risk: (No previous spine or hip fracture; a T-score at hip and spine above − 1.0 and a FRAX® score below treatment thresholds.) Reassess fracture risk in 2 to 4 years.

Moderate risk: (No previous spine or hip fracture; a T-score between − 1.0 and − 2.5 and a FRAX® score below treatment thresholds.) Reassess fracture risk in 2 to 4 years.

High risk: (Prior spine or hip fracture; or a lumbar spine or hip T-score of − 2.5 or below; and/or a FRAX® 10-year absolute fracture risk above treatment threshold.) Initial treatment with bisphosphonates (alendronate, risedronate, or zoledronic acid). Initial treatment with denosumab as alternative therapy to reduce fracture risk. (Ibandronate not recommended to reduce hip and non-vertebral fractures.)

Raloxifene or bazedoxifene to prevent vertebral fractures in women with a high risk of breast cancer. In postmenopausal women, estrogen treatment to reduce the risk of vertebral fractures in women with a low risk for deep vein thrombosis and for whom bisphosphonates or denosumab are not appropriate. Nasal spray calcitonin should be prescribed only in women who cannot tolerate raloxifene, bisphosphonates, estrogen, denosumab, abaloparatide, or teriparatide or for whom these therapies are not considered appropriate.

Very high risk: (Multiple spine fractures/hip fracture and T-score of − 2.5 or lower at lumbar spine or hip.) Teriparatide or abaloparatide treatment for up to 2 years or romosozumab for 1 year. Following a course of anabolic, treatment with antiresorptive osteoporosis therapies should be used to maintain bone density gains.

More information on the Endocrine Society treatment algorithm is presented in the Endocrine Society published Clinical Practice Guideline [166].

Sequential and combination therapy

Patients with recent fractures and/or very low BMD (e.g., T-score < − 3.0) are at especially high risk for future fracture(s). Monotherapy with antiresorptives may not be sufficient to lower risk to acceptable levels in such patients. Consideration of more aggressive therapy with combination or sequential use of antifracture medications may be warranted [197, 241–245].

Combination and/or sequential use of anabolic (e.g., teriparatide) and potent antiresorptive (e.g., denosumab) have been shown to increase BMD and improve bone microarchitecture and strength more effectively than monotherapy with any one agent [239, 241, 242, 246]. Combination therapy in which an anabolic agent and antiresorptive therapy are co-administered may be appropriate in a setting of very high risk, such as multiple vertebral fractures. Further studies are needed to test effects of combination therapy on incident fractures. There are no indications for combining two antiresorptive treatments.

There is accumulating evidence that BMD and fracture outcomes are significantly influenced by the order in which antifracture agents are administered. An anabolic agent administered following antiresorptive therapy has demonstrably less impact on BMD than if the anabolic is administered first [247–249]. Anabolic therapy after a potent antiresorptive agent may be followed by an attenuation of effect or even bone loss [193, 250]. When sequential treatment is considered, starting with anabolic therapy and following with an antiresorptive agent is preferred.

Multiple variables affect outcomes: agent prescribed, patient characteristics, and duration of treatment, for example. More research is needed to determine the best order and most appropriate drugs for combination and sequential therapy in individual patients.

Improving patient adherence with prescribed treatment

An estimated 25–30% of osteoporosis patients do not start taking their prescribed medication and 50% or more do not continue treatment after 1 year [251, 252]. The consequences are significant: 30% higher incidence of fracture in non-adherent patients compared to adherent patients with attendant higher morbidity, mortality, and healthcare costs [253, 254].

Patients may unintentionally fail to initiate treatment due to forgetfulness, complexity of treatment regimen, and/or drug affordability [255]. In patients who intentionally do not adhere to recommended treatment, the main reasons cited in studies include limited knowledge of osteoporosis, fear of side effects, distrust of physicians or medication in general, and a lack of belief in the need for medication and/or its effectiveness [256–259].

Acceptance of risk is sometimes influenced by competing priorities. This is reflected in findings from a systematic review of research on women's preferences and values in relation to osteoporosis management published by Barrionuevo et al. in 2019 [260]. The top-ranked consideration was a tie between drug effectiveness and side effects. Not as important were convenience and frequency of doses. (Oral doses were preferred except in the case of biannual or annual dosing, in which case, injection ranked higher.) Even less important were cost and duration of treatment.

Patients often do not understand their personal risk for fractures and the profoundly negative impact that fractures could have on their quality of life, particularly their ability to live independently [261]. This is a challenge inherent to treating "silent diseases" like osteoporosis in which symptoms do not get observably better or worse in response to therapy.

Patient awareness of risk for fractures and their devastating consequences does not guarantee acceptance of antifracture treatment. The 2019 Patient Oriented Value Report commissioned by BHOF appears to indicate that even when awareness of risks and available treatments were high, most individuals at risk for a fragility fracture choose not to take medications needed to reduce their risk. Various factors were associated with willingness to start or continue treatment: dual anabolic–antiresorptive action increased acceptance of a novel treatment agent; history of fragility fracture increased willingness to continue treatment. In a subset of patients, side effects and/or cost burden severely limited willingness to start and stay on treatment [262].

Getting off to a good start matters. Population studies of patients taking oral bisphosphonates demonstrate a strong association between optimal adherence the first year of treatment and higher rates of adherence in subsequent years. This suggests that focused support and monitoring early in treatment may help improve a patient's long-term adherence and fracture outcomes.

When discussing medication options with patients, solicit their questions and concerns regarding the drug, dosing regimen (daily, weekly, monthly, every 6 months, or yearly), its benefits, and side effects. Asking questions about patient preferences and addressing fears and misconceptions as part of the medication selection process can promote better adherence to prescribed treatment and better outcomes in the form of fractures and disability prevented.

Duration of treatment

Like any lifelong chronic disease, osteoporosis is most successfully managed with continued therapy and monitoring. Therapeutic benefits can be maintained only with treatment. Once pharmacologic therapy is stopped, BMD and fracture risk can be expected to return to baseline or worse—slowly, in the case of bisphosphonates, or quickly, in the case of non-bisphosphonates, when discontinuation is associated with accelerated bone turnover, rapid bone loss, and increased risk for spontaneous fractures.

Successful treatment can increase BMD, reduce fracture risk, and improve T-score to the low bone mass or even the normal range. However, in a person with a history of osteoporosis, a T-score in the osteopenic or normal range does not change their diagnosis. *The patient still has osteoporosis.* BMD may be improved, and fracture risk reduced; however, microarchitectural deterioration remains, as do disease processes responsible for that deterioration.

With this in mind, serial DXA scans must be interpreted in the context of past DXA T-scores, fracture history, and the

other factors that established the original osteoporosis diagnosis [263]. Changing a patient's diagnosis to osteopenia from osteoporosis could limit that patient's treatment options and may be detrimental to their bone health.

Available evidence indicates the incidence of rare adverse events such as AFF increases with longer-term antiresorptive therapy (over 3 or 5 years depending on agent) [217, 264]. Consideration of potential risks associated with continued therapy must be weighed against potential risks of discontinuing therapy.

Bisphosphonate holiday

For patients on bisphosphonates who appear to be at modest risk of fracture (e.g., T-score > − 2.5 and no recent fracture) temporary discontinuation ("holiday") can be considered after 3 years on an intravenous therapy or 5 years on an oral therapy. A bisphosphonate holiday is defined as a temporary suspension of bisphosphonate therapy (up to 5 years) [166, 265]. For patients who continue to demonstrate high fracture risk (e.g., T-score ≤ − 2.5 and/or recent fracture), continued treatment with a bisphosphonate or alternate therapy should be considered up to 10 years with an oral bisphosphonate and up to 6 years with annual IV zoledronic acid. This suggestion is consistent with ASBMR task force recommendations on managing patients on long-term bisphosphonate therapy [14].

The rationale for a bisphosphonate holiday is the expectation that prolonged skeletal retention will confer antifracture benefits for some period of time, perhaps several years, in appropriately selected patients. A period off the drug may reduce risk for ONJ and AFF [221, 229]. Decisions about how long to treat with a particular drug must be tailored to individual patients, applying the best available clinical guidelines and expert recommendations [266].

For patients treated with a non-bisphosphonate, therapeutic effect rapidly dissipates with discontinuation. Studies indicate that discontinuing denosumab results in increased bone turnover markers, reduced BMD, and increased risk of multiple vertebral fractures, especially in patients with a prior vertebral fracture [192, 267]. The Endocrine Society guideline for treatment of postmenopausal osteoporosis recommends that denosumab be continued for 5 to 10 years depending on fracture risk [166]. After discontinuing treatment with denosumab, it is recommended by the FDA that patients be switched to another antiresorptive agent, such as a bisphosphonate, to preserve bone density gains [268]. Studies are ongoing to assess the time course for starting antiresorptive therapies after stopping denosumab.

The management algorithm for bisphosphonate treatment in postmenopausal osteoporosis shown in Fig. 6 is based on ASBMR task force evaluation of data from the Fracture Intervention Trial Long-term Extension (FLEX) and the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) extension studies [14]. It suggests that women who experience a fracture before or after being treated with bisphosphonates (oral 5 years, IV 3 years) should continue bisphosphonate therapy (oral up to 10 years, IV up to 6 years). Patients who fracture on therapy should be assessed for adherence and secondary causes of osteoporosis. (Note: We lack sufficient data to make specific recommendations regarding alternative antifracture therapy after prolonged bisphosphonate treatment.)

High fracture risk in this algorithm is defined by older age (70–75 years), 1 or more clinical risk factors for fracture, and/or FRAX score above country-specific intervention thresholds. Recommended reassessment includes clinical evaluation, risk assessment, and bone density measurement by DXA. The interval between DXA scans should be based upon changes that are detectable and clinically significant. Reassessment may be necessary at less than 2 years in patients with a new fracture or in patients who can be expected to experience rapid bone loss due to new clinical risk factors (such as initiation of aromatase inhibitor or androgen deprivation therapy) (See Fig. 6).

Pharmacotherapy should be periodically reviewed to determine whether treatment should be continued, changed, stopped, or resumed. It is reasonable to evaluate patients every 1 to 2 years during any hiatus from active bisphosphonate treatment.

Further research is needed to clarify best practices in this area, although, as noted by the ASBMR in their report, due to advanced age, life expectancy, and comorbidities, it is unlikely that future RCTs will provide data for formulating definitive recommendations in this patient population.

Antifracture treatment in men with osteoporosis

Medications currently FDA approved for osteoporosis treatment in men include: bisphosphonates alendronate, risedronate, and zoledronic acid; bone anabolic teriparatide; and the RANKL inhibitor denosumab. Unless contraindicated, osteoporosis treatment in hypogonadal men with testosterone levels < 200 mg/dL and symptoms of androgen deficiency should include consideration of testosterone therapy. In hypogonadal men at high risk for fracture who are receiving testosterone, addition of a proven antifracture therapy is indicated [58].

All FDA-approved medications to treat osteoporosis in men have been demonstrated in RCTs to increase BMD. Comparable RCT data for fracture risk reduction exist but are more limited. Fixed-effects meta-analyses of 22 studies demonstrated significantly fewer vertebral fractures in men taking alendronate (67% reduction) and risedronate (57% reduction), but not in men taking calcitonin or denosumab [269]. Another meta-analysis, conducted for the USPSTF found that available

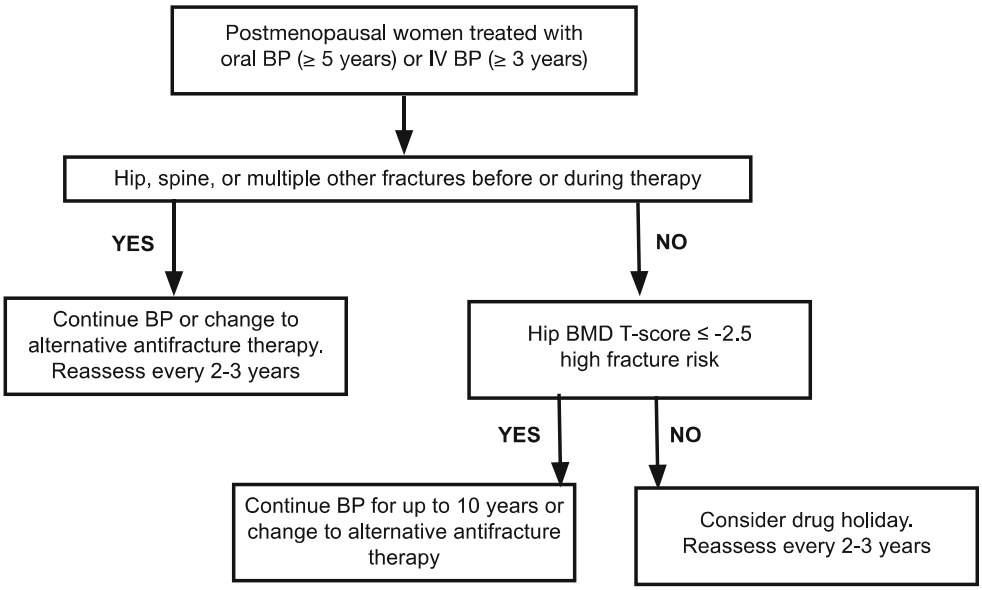


Fig. 6 Management of long-term bisphosphonate (BP) treatment in postmenopausal women. Note: This flowchart illustrates ASBMR task force recommendations for management of patients taking bisphosphonates. All other osteoporosis drugs lose effect rapidly when discontinued and must be promptly followed by alternative antifracture therapies. Adler RA, et al. (2016), *J Bone Miner Res* [14]

data suggest zoledronic acid reduces risk of morphometric vertebral fractures in men by 67%, with no comparable reduction in risk of clinical vertebral fractures or hip fractures [22].

None of the RCTs evaluating efficacy of bisphosphonates in treating men with cancer treatment-induced bone loss (CTIBL) have been powered to evaluate fracture rates as a primary outcome. However, the denosumab Hormone Ablation Bone Loss Trial (HALT) was adequately powered to demonstrate a statistically significant decrease in new vertebral fractures in men treated for 3 years with denosumab (1.5% versus 3.9% with placebo, relative risk = 0.38; 95% CI = 0.19–0.78; $P = 0.006$) [270, 271].

Antifracture treatment in patients treated with glucocorticoids

An estimated 3% of adults aged 50 years and older are treated with glucocorticoids [272]. Glucocorticoid therapy is associated with an early increased risk of fractures through multiple mechanisms, including accelerated bone resorption; alterations in PTH pulsatility; and reduction in bone formation, sex steroids, and renal calcium reabsorption [273]. Glucocorticoids cause a dose-dependent loss of BMD in the spine and hip, with the greatest loss in vertebral trabecular bone [274]. Among glucocorticoid users, fracture incidence rises with longer-term use of prednisone (over 5 years), higher doses (> 7.5 mg/day), older age (> 55 years), female sex, and Caucasian ethnicity [275].

The American College of Rheumatology (ACR) 2017 guidelines recommend risk stratifying patients when making decisions about antifracture treatment. Adults ≥ 40 years of age receiving long-term glucocorticoids should be designated as either moderate-to-high risk or low risk of fracture based on BMD, fracture history, and 10-year FRAX® fracture score (with glucocorticoid use selected on FRAX calculator). FRAX® calculations assume a prednisolone dose of 2.5–7.5 mg/day (prednisolone and prednisone doses are nearly equivalent). For people taking higher doses (> 7.5 mg/day), proportional increases in fracture risk can be approximated by *raising* the FRAX® score: a relative 15% for major osteoporotic fracture and 20% for hip fracture risk [88]. For example, a hip fracture risk estimated at 2.0% with glucocorticoid use checked in FRAX® should be increased to 2.4% if the patient's prednisone dose is higher than 7.5 mg/day.

Regardless of glucocorticoid dose, patients who exceed the adjusted FRAX® intervention threshold should receive antifracture pharmacotherapy. Likewise, treatment should be initiated in postmenopausal women and men ≥ 50 years of age on glucocorticoid therapy who experience a fragility fracture and/or have a T-score of − 2.5 or lower.

Antifracture treatment in glucocorticoid users has been shown in a Cochrane analysis of RCTs to reduce new vertebral fractures by 43%, similar to effects seen in postmenopausal osteoporosis [276]. In a 3-year study reported by Saag et al., teriparatide produced greater increases in BMD and fewer new vertebral fractures than alendronate in comparable glucocorticoid-treated patients [277]. No significant difference was observed in hip or non-spine fracture outcomes.

Meta-analysis of 3 large RCTs suggests that denosumab is effective in treating patients on glucocorticoids, outperforming bisphosphonates in its effects on lumbar spine and total hip BMD in patients with GIOP. The studies were not sufficiently powered for fracture outcomes [278].

There has been concern that, theoretically, denosumab could increase infection risk in patients on glucocorticoids or concomitant biologic therapies. Data currently available suggest any such increased risk is low and/or

comparable to that seen with risedronate and zoledronic acid [279–282].

Antifracture treatment for older-old adults

Current data show that antifracture treatment confers benefits throughout old age. In healthy community-dwelling adults over age 75 years, reported fracture reduction with zoledronic acid, denosumab, teriparatide, and abaloparatide is similar to that seen in younger community-dwelling adults [237, 283–285]. In frail elderly long-term care patients, safety and BMD improvement have been demonstrated in RCTs of alendronate and zoledronic acid treatment [286, 287].

Monitoring treatment response

Appropriate response to treatment and the need for continued medication to treat osteoporosis should be reviewed annually. Clinical assessment should be performed to identify new fractures, falls, and/or new or worsening comorbidities. Repeat bone densitometry and vertebral imaging should be done in patients exhibiting signs of vertebral fracture, such as height loss or back pain. It may be appropriate to measure biochemical markers of bone turnover in specific patients.

Ongoing clinical assessment

It is important to have accurate baseline values against which to compare serial test results. For example, significant height loss detected through yearly measurement may be an indicator of disease progression. Wall-mounted stadiometers are more reliable than freestanding devices. Patients who lose 0.8 in. or more in height either acutely or 1.5 in. cumulatively should have repeat vertebral imaging to determine if fractures have occurred since prior tests. Vertebral fracture while on treatment is associated with very high fracture risk. Consideration of untreated secondary causes of bone loss and/or changes to therapy are appropriate in such patients.

Typically, subclinical morphometric vertebral fractures are diagnostic of osteoporosis. In a patient with significant height loss, diagnosis can be confirmed with VFA performed at the same time as BMD on most modern DXA systems or with conventional lateral thoracic and lumbar spine X-ray.

Serial BMD measurement

Central DXA assessment of the total hip, femoral neck, or lumbar spine is the "gold standard" for serial assessment of BMD. Biological changes in BMD are small compared to inherent error in the test itself, and accurate interpretation of serial BMD studies requires knowing the smallest change in BMD that exceeds testing error. This least significant change (LSC) differs with the densitometry device used, patient assessed, measurement site, and technologist's skill with patient positioning and test analysis [288]. BMD changes of less than 3–6% at the hip and 2–4% at the spine may be due to precision error of the testing itself. The BHOF recommends considering monitoring BMD at the 33% radius in patients for whom BMD cannot be measured at the spine or hip and in those with hyperparathyroidism or hyperthyroidism or on androgen deprivation therapy for prostate cancer, in those undergoing orthopedic surgery of an upper extremity, or according to clinical judgment [8, 11]. Information on how to assess precision and calculate the LSC for a particular device and/or facility is available at http://www.ISCD.org.

Serial central DXA testing is an important component of osteoporosis management. Measurements for monitoring patients should be performed in accordance with medical necessity, expected response, and in consideration of local regulatory requirements. According to the ISCD, intervals between testing should be guided by the clinical status of each patient. A follow-up BMD should be done after 1 year of initial therapy or a change in therapy, with longer intervals once an effective treatment is established. The American College of Physicians recommends against monitoring BMD in postmenopausal women within a 5-year treatment interval. However, this recommendation was based on low-quality evidence and was rated *as a weak recommendation* [289]. The BHOF recommends repeating BMD assessments every 2 years in adults ages 65 and older, with the understanding that testing less or more frequently may be warranted in individual patients.

DXA is currently the preferred approach for monitoring treatment response. According the ISCD, if DXA is not available, QCT of the spine or hip or pQCT of the radius can be used in high-risk individuals for decisions regarding treatment. Information about the use of these measures and QCT-based finite element analysis for clinical decisions regarding monitoring and treatment can be found on the ISCD website at https://iscd.org/learn/official-positions/adult-positions/ [59, 290, 291]. Of note: central QCT requires high exposure to ionizing radiation [292].

Biochemical markers of bone turnover

Monitoring bone turnover markers is an alternative way of identifying poor response or nonadherence to therapy. In large RCTs, decreased biochemical markers of bone resorption after 3–6 months of treatment with specific antiresorptive therapies and increased biochemical markers of formation after 1–3 months of specific anabolic therapies have been predictive of greater BMD responses and (in some cases) fracture risk reduction [93, 293]. In order to be meaningful, changes in biochemical markers must exceed the LSC for the specific

biomarker being measured. The LSC is calculated by multiplying the "precision error" of a biochemical formation marker (laboratory provided) by 2.77 (95% confidence level). Tests should be obtained early morning after overnight fast to offset effects of diurnal variation and diet. Serial measurements should be made at the same time of day at the same laboratory. (See "Biochemical markers of bone turnover" section.)

Vertebral imaging/vertebral fracture assessment (VFA)

When current imaging by MRI and/or CT performed for other purposes is available, it should be evaluated for identification of vertebral fractures. Vertebral fractures can be directly imaged using standard lateral spine X-ray or DXA-based VFA. Once the first vertebral imaging test has been performed to determine prevalent vertebral fractures (indications above), repeat testing should be performed to identify incident vertebral fractures if there is a change in the patient's status suggestive of new fracture, including documented height loss, undiagnosed back pain, postural change, or a finding of new vertebral deformity on chest X-ray [67]. If patients are being considered for a bisphosphonate holiday, vertebral imaging can be done to identify any fractures that have occurred during treatment, which would indicate the need for continued treatment with bisphosphonates or another antifracture agent. (See "Vertebral fracture assessment" section.)

Rehabilitation following fragility fracture

Patient care following fragility fracture is a complex process involving three components: minimizing pain, reducing fracture risk, and improving function. Such multifaceted care is most effectively accomplished by a coordinated team of health professionals, often overseen by a primary care provider or, in ideal circumstances, by dedicated fracture liaison (FLS) personnel.

Ongoing physical activity that supports healing and maintenance of bone mass is a key part of rehabilitation following fracture. For patients with fractures or at high risk for fractures instruction in safe body mechanics can reduce disability, improve physical function and quality of life, and lower risk for injurious falls.

The most common fragility fractures are those of the proximal femur (hip), vertebrae (spine), and distal forearm (wrist) [294]. All contribute to disability, pain, and reduced quality of life. An estimated 21% of hip fracture patients 60 years and older die in the year following fracture [295, 296]. Vertebral fractures, which can cause pain and disability, confer smaller but significant increases in hospitalization and mortality risk [297, 298].

Hip fracture rehabilitation

Hip fracture typically requires surgical repair or replacement (proximal femur and/or acetabulum). While RCT data are sparse on the impact of specific rehabilitation protocols, settings, and durations, large observational studies conducted in Italy and Taiwan suggest a mortality benefit for patients who receive intensive, inpatient rehabilitation following hip fracture [299, 300]. Patients who received continuous inpatient rehabilitation had lower death rates at 6 and 12 months than those receiving no therapy or, in the case of the Italian study, those receiving outpatient physical therapy. Furthermore, in a small, randomized trial of functionally limited older adults who had received standard rehabilitation after hip fracture, an additional program of home-based function-oriented activities resulted in modest improvement at 6 and 9 months after randomization. Additional RCTs are needed to assess the clinical relevence of these findings [301].

Fewer than half of hospitalized hip fracture patients recover their pre-fracture competence in activities of daily living [302]. Only one fourth regains previous levels of social functioning [303]. Six months after a fracture, just 15% of hip fracture patients can walk across a room unaided [304]. Consequently, 10–20% of those living independently before a hip fracture require institutional long-term care afterwards [305].

Vertebral fracture rehabilitation

Two thirds of vertebral fractures are subclinical "silent" fractures. The typical symptomatic vertebral compression fracture is characterized by intense back pain lasting more than a couple of days that gets better when the patient lies down. If a spine fracture is suspected, further evaluation by X-ray, MRI, CT, or VFA can confirm the diagnosis.

Vertebral fractures do not usually require hospitalization [306]. However, multiple thoracic and lumbar fractures can cause spinal deformity, leading to restrictive lung disease, constipation, pain, distention, and reduced appetite [307, 308]. Chronic pain, postural weakness, and altered gait can result in impairment equal to that following a hip fracture.

Treatment for acute vertebral fracture includes use of analgesics, bracing (for 2 to 6 weeks), and partial bed rest (4 days or less). If bed rest is recommended, a few 30- to 60-min periods each day of sitting upright and walking around are valuable to avoid stiffness and prevent loss of bone and muscle tissue. Prolonged inactivity should be avoided. Removal of mechanical loads and/or resistive stresses stimulates bone resorption, further weakening bone and muscle [309, 310].

A variety of light-weight back braces and postural supports are available that restrict spinal motion near a fracture site to ease pain and promote healing. Bracing may facilitate stimulation of proprioception to improve spinal extensor muscle control. These orthoses are custom molded and can be fitted

by a physiatrist, physical therapist, or other trained clinician. A systematic review, including 4 RCTs (n = 281), investigated effects of spinal orthoses after a vertebral fracture during the acute and chronic phases post-fracture. Evidence for the benefit of bracing on pain in the acute phase (3–12 weeks after fracture) is lacking. However, there is low-quality evidence (high risk of bias due to no blinding) that bracing may have beneficial effects on pain, spinal strength, kyphosis, pulmonary volume, and quality of life at 6 months following fracture. Bracing worn 2 hours a day over 6 months appears beneficial. Type of brace does not appear to make a difference. There is no evidence that bracing improves physical function or disability [311].

Wrist fracture rehabilitation

Osteoporosis-related forearm or wrist fractures (fractures of the 1/3 radius, ulna, or both) are the most common fractures of the upper extremities. Depending on the type of fracture, treatment may consist of splint, cast, or brace immobilization. If a radius fracture is not displaced, a cast or functional brace is used until there is radiographic evidence of union. Surgical treatment has been used more recently because of faster functional recovery. Open reduction with internal fixation (ORIF) and closed reduction with percutaneous pinning (CRPP) are procedures often used for unstable distal radius fractures [39, 312, 313]. During the cast or bracing stage, arm elevation, early mobilization, and edema-control measures are implemented.

There is literature to suggest that early rehabilitation focused on digital mobility yields superior functional outcomes and patient satisfaction [314]. Targeted therapy can improve finger dexterity, even while the hand is immobilized in a cast. Unfortunately, 90% of wrist fracture patients are not referred to physical/occupational therapy during this critical period.

Management of acute fracture pain

Because pain is a barrier to movement and activity, effective pain management is a cornerstone of fracture rehabilitation, preservation of bone tissue, and ongoing fracture prevention. Conservative therapeutic options for acute pain from recent vertebral fractures include analgesics such as acetaminophen, nonsteroidal anti-inflammatory drugs, narcotics, and calcitonin, as well as limited bed rest, bracing, physical therapy, nerve root blocks, and epidural injections.

Multifactorial pain management strategies are currently underutilized. The recent US National Pain Strategy Report emphasizes the need for development and implementation of effective interdisciplinary pain treatment programs focused on patient-directed self-care that employ a range of approaches, both pharmacologic and non-pharmacologic [315]. Multimodal pain management is now a mandated performance measure for hospitals and medical facilities accredited by The Joint Commission (USA). These modalities include acupuncture therapy, chiropractic therapy, ice/heat, massage therapy, physical therapy (PT), electrical stimulation (E-Stim), relaxation therapy, and cognitive behavioral therapy (CBT) [316].

In the 3–5 days *immediately* following fracture, acetaminophen and/or low-dose narcotics administered around the clock (rather than as needed for pain) can work very well in appropriate patients [317]. When given on a regular schedule over several weeks, this regimen allows patients to remain active and avoid disuse-related muscle and bone loss. Specialist referral is advisable if neurologic involvement is suspected.

Calcitonin salmon has been shown to dramatically reduce acute pain due to recent, nontraumatic osteoporotic vertebral crush fractures. One small RCT that randomized patients to calcitonin nasal spray or placebo spray plus high-dose acetaminophen reported that calcitonin-treated patients had significantly better pain control. This was associated with weeks-earlier mobilization and functional improvement (sitting, standing, walking).

To prevent falls, it is essential to consider disorientation, sedation, and other potential side effects of pain medications, either alone or in combination with other drugs. Because many fracture patients are medicated simultaneously for multiple comorbid conditions, a medical history should include careful attention to potential polypharmacy and drug interactions that could contribute to fall-inducing side effects.

Surgical procedures for acute painful vertebral fracture

A primary source of the intense pain caused by vertebral fracture is movement of fracture margins and/or bone fragments against one another. This is a particular problem in the lumbar spine, which is highly articulated to allow free flexion and rotation. Immobilizing fractured vertebral bone dramatically reduces pain. Prolonged bed rest is not an ideal remedy given resultant deconditioning and bone loss. Extended bracing and physical therapy have been used for this purpose.

Patients with severe acute fracture pain may benefit from referral to a pain specialist and/or interventional radiologist. Unremitting pain that persists despite conservative therapy may respond to short-term specialist treatment and/or minimally invasive vertebral augmentation surgery [318, 319].

Although RCTs comparing vetebroplasty/kyphoplasty to medical management (but not to placebo) have reported conflicting results, some studies found short-term pain control with vertebral augmentation [320–323]. However, when in 2019, the second ASBMR task force compared vertebral augmentation procedures to *sham procedures (with/without*

injected analgesia), it reported little benefit of vertebroplasty for pain control in either acute or sub-acute fracture and insufficient evidence to recommend kyphoplasty over nonsurgical management [324].

Serious complications reported with these procedures include cement pulmonary embolism, osteomyelitis, and epidural cement leak. While fractures of adjacent vertebrae have been reported, analyses of study data are inconclusive [325–328]. Additional long-term data from large well-designed, placebo or sham-operated controlled RCTs are needed to clarify issues related to safety and efficacy of these procedures. Treatment for severe pain should be individualized. Whether recommending specialist surgical or nonsurgical management for pain associated with spine fractures, *clinicians should prescribe antifracture pharmacotherapy for the underlying osteoporosis*.

Managing chronic post-fracture pain

Acute pain *typically* resolves 6–8 weeks following vertebral fracture. However, some people have pain for months or years after a fracture heals. Persistent pain like this can make it difficult to sleep, walk, and eat; it can make a person irritable or depressed by depriving him or her of independence and meaningful participation in self-care and community life.

The need for continued activity to prevent loss of bone and muscle mass underlines the importance of pain control. Untreated pain is a strong incentive to avoid potentially painful activities and develop sedentary behavior. This can quickly lead to musculoskeletal deterioration and frailty. Early and sustained physical engagement is essential to restoration of function and quality of life.

Complications of analgesic drugs, such as addiction, kidney failure, and gastrointestinal bleeding, limit their long-term use for many patients. Increasingly, clinicians are employing a variety of non-pharmacologic approaches to managing persistent pain, including cognitive behavioral therapy, hypnosis, mindfulness training, biofeedback, and stress management. As there are few studies of psychological therapies for chronic pain, available evidence is of low-to-moderate quality, and data in support of one modality over another are not currently available [329–331]. Additional research is needed that focuses on risks and benefits for people with osteoporosis and related fractures [332] (Table 13).

Patients with pain following fragility fractures may benefit from one or more of the therapeutic interventions described in Table 13. Recommendations are based on available evidence with limited RCT data to support the clinical effectiveness of many of these practices. It is highly recommended that patients work alongside trained professionals and/or an interprofessional team for a given modality.

Protecting fragile bones in daily life and recreation

Following a fragility fracture, modifications to standard activities of daily life and recreation should be considered to prevent subsequent injury. A trained physical therapist and/or occupational therapist can be instrumental in educating patients about safe body dynamics (Fig. 7).

Avoidance of prolonged or excessive loading of individual skeletal sites is a fundamental principle of safety for people with osteoporosis. Distribution of skeletal load is achieved by alignment of the head, shoulders, spine, hips, knees, and ankles, which centers the body's mass over the lower extremities. The following should be avoided in patients with bone fragility. (Spine-sparing modifications provided.)

- Slouching, with head forward, trunk collapsed, and hips positioned forward of center of gravity.
  - Modification: Support back while seated to maintain aligned posture with head in neutral alignment.
  - Modification: Alternate periods of prolonged standing or sitting with 5–10 min of walking or lying supine.
- Lifting an object by bending forward from the waist with legs straight.
  - Modification: Bend with knee and hips not spine, stand close to load when bending, hold load close to body.
  - Modification: Use grabber to lift lightweight objects, step forward with back straight and knee bent to lower body.
- Vacuuming with rotated trunk and feet planted, pushing and pulling with arm fully extended, bending and twisting at waist.
  - Modification: Step to turn so that leading foot, torso, and extended arm face the same direction.
  - Modification: Shift weight from front to back foot with a straight spine to move the vacuum back and forth.

Recreational pursuits and athletic activities that exert intense forces on weakened bone and/or involve abrupt or high-impact loading can break bones in people with osteoporosis http://www.bonehealthandosteoporosis.org/wp-content/uploads/BoningUpBrochure_8.5x11.pdf [355–357]. Fortunately, many can be modified for safety with input from a trained physical therapist. Ensuring that patients understand potential risks, while focusing on safe approaches to preferred pastimes and sports enables patients to stay active. Potentially injurious activities for individuals with osteoporosis include the following:

- Jumping rope or jumping on a trampoline
- Horseback riding, downhill skiing, parasailing, sky diving

Table 13 Pain management strategies and interventions for osteoporotic fractures [333–336]

Pain management measure	Applications and considerations for osteoporosis patient care
Acetaminophen	650 mg orally every 4–6 h; maximum dose 4000 mg/day for treatment of mild to moderate pain. No evidence of benefit for neuropathic pain. Liver damage risk (overdose) [336].
Acupuncture	Acupuncture has been demonstrated to control pain in patients with chronic low back pain. Many health insurance providers now offer coverage for these therapies; however, the quality of evidence for their efficacy is low (issues of study design, placebo effect, etc.) [337].
Antidepressants Amitriptyline Duloxetine	First-line therapies for neuropathic pain. Amitriptyline (tricyclic antidepressant) 25–100 mg orally once daily or in 2 divided doses. Max single dose 75 mg, doses > 75/day should be used with caution in adults > 65 years [336]. Duloxetine serotonin–norepinephrine reuptake inhibitor (SNRI) 60–120 mg orally once daily or in 2 divided doses. Side effects common to both: somnolence, increased suicidal thoughts, headache, dizziness, dry mouth. Additional side effects amitriptyline: tremor, tachycardia, orthostatic hypotension, constipation, weight gain, urinary incontinence (multiple contraindications). Additional side effects duloxetine: increased blood pressure [338].
Anti-inflammatories (NSAIDs)	Dose depends on drug. Beneficial for suppressing mild-to-moderate inflammation-related pain. May delay bone healing following fracture, except anti-COX-2 NSAIDs. Over-the-counter NSAIDS taken every 6 h following fracture or alternating with acetaminophen can help with pain relief. Adverse reactions of concern include gastrointestinal bleeding, renal insufficiency, myocardial infarction, stroke, and dizziness. No evidence of benefit for neuropathic pain.
Antiepileptics Gabapentin Pregabalin	First-line therapies for neuropathic pain. Gabapentin 900–3600 mg orally in 3 divided doses. Pregabalin 300–600 mg/day orally in 2 divided doses [336]. Side effects in common: dizziness, somnolence, headache, peripheral edema, nausea, blurred vision, and increased suicidal thoughts. Use with caution in patients with impaired renal function. Abuse and dependence have been reported. Additional side effects/risks of gabapentin: fever, infection, lack of coordination. Additional side effects of pregabalin: weight gain and disorientation.
Antispasmodics	Efficacy in relieving pain is not well established and risk for adverse (anticholinergic) effects is high [339]. May increase risk for falls, constipation, and indigestion.
Aspirin	350–650 mg orally every 4 h; maximum dose 3600 mg/day [336]. Beneficial for mild pain (temporary uses). Adverse reactions of concern include gastrointestinal bleeding, tinnitus, insomnia, and dizziness. No evidence of benefit for neuropathic pain.
Bed rest (limited/intermittent)	While prolonged bed rest causes bone and muscle loss, immediately following vertebral compression fracture, patients are generally prescribed an initial period of strict bed rest (no sitting or standing) [340]. Even when a patient is back on his/her feet, lying flat for 10 min every couple of hours, for example, is recommended to support activity by keeping pain under control. Further RCT evidence is needed to support specific protocols for rest during recuperation from vertebral fracture [341].
Bracing and spinal orthoses	A variety of soft, semirigid, rigid, and dynamic braces are available for use following vertebral fracture to control pain, promote fracture consolidation, support posture, and improve balance, physical function, and quality of life [342]. Patients typically are instructed to wear orthoses for 12 to 24 weeks until resolution of pain and vertebral instability. RCT data are currently lacking to make evidence-based recommendations [311].
Calcitonin salmon	Calcitonin salmon has been found to mitigate acute pain from recent vertebral fractures. Limiting use duration is recommended due to potential increased risk for cancer. Not shown to be effective at ameliorating chronic pain from vertebral fractures [343].
Cognitive behavioral therapy (CBT)	Although RCT data are not available, studies have demonstrated CBT and other psychosocial complementary therapies can improve function and quality of life in patients suffering from chronic pain [344, 345].
Complementary therapies	Deep breathing, progressive muscle relaxation, guided imagery, and other relaxation techniques can help release muscle tension and direct a patient's attention away from pain and related anxiety. Biofeedback therapy can be helpful for managing acute and/or chronic pain due to fractures. Referral should be made to biofeedback specialist [336].
Electric stimulation (E-Stim)	E-Stim, also called transdermal electrical nerve stimulation (TENS), considered an effective non-pharmacologic therapy for chronic pain, uses transmission of a mild electrical current applied to a patient's skin at the site of injury or pain [346]. Referral to physiatry or physical therapy is required.
Ice and heat	Application of ice and/or heat, alternating or individually, can promote healing and be effective in reducing swelling, improving blood flow, and relieving pain of muscle spasms. Specific injury dictates appropriate method, purpose, and application (e.g., heat may not be appropriate for acute fracture with inflammation).

Table 13 (continued)

Massage	Although no large-scale RCT data exist, evidence from small studies suggest that massage may improve post-fracture pain and disability compared to sham therapies and other non-manipulative interventions (such as relaxation techniques). The ACP guideline on management of chronic low back pain includes a strong recommendation for massage therapy, chiropractic therapy, or spinal manipulation (acknowledged low-quality evidence) [347]. Intense or deep-tissue massage therapy should be avoided in people who have experienced fragility fractures. Cases of massage-induced fractures have been reported [348].
Nerve root block injection	Percutaneous dorsal root ganglion block (nerve block) has been demonstrated to provide immediate and prolonged improvement of chronic pain from vertebral osteoporotic compression fracture in patients who failed conservative treatment or had residual pain after vertebroplasty [349, 350]. Lidocaine injection provides significant short-term (up to 2 weeks) pain relief in new fractures [351] and may promote early mobilization. The AAOS includes nerve root block in its recommended treatments of acute pain following vertebral fracture [352].
Opioids	Opioids are very effective analgesia for acute pain. However, if used chronically, they lose potency, induce dependence, raise risk for addiction, and lead to constipation, falls, and central sensitization. Recommended only for very short-term use with acute fractures. Hence, non-narcotic treatments are preferred.
Topical pain relievers Capsaicin Lidocaine	Lidocaine 1.8% or 5% patch applied to intact skin at site of pain for up 12 h daily is recommended for chronic peripheral neuropathic pain. Capsaicin 8% patch is a second-line therapy that can be applied in a clinical setting every 3 months [336]. Side effects common to both: application site pain/skin irritation, pruritus, and erythema. Capsaicin can increase blood pressure transiently and can lead to desensitization. Over-the-counter preparations of menthol, methyl salicylate, or OTC capsaicin have shown little to no effect on chronic pain.
Vertebroplasty/kyphoplasty	(Not generally recommended) Little benefit of vertebroplasty for pain control and there is insufficient evidence to recommend kyphoplasty over nonsurgical management [324].

- Running/jogging (beneficial for hip BMD, can be dangerous for low spinal BMD)
- Golf, tennis/racquet ball, and bowling (done conventionally with twisting at waist)

The fear of fracture can be a powerful incentive to avoid physical activity, causing predictable harm to bone, muscle, and general health. Spine-sparing strategies for approaching tasks and pastimes help prevent injury while promoting continued mobility and self-confidence. Rather than blanket restrictions (e.g., no bending, no lifting > 10 lb). BHOF recommends guidance on spine-sparing techniques (e.g., hip hinge) by trained occupational and/or physical therapy professionals who have experience working with older individuals.

Fig. 7 Daily activities and household chores can be modified to minimize risk for vertebral fractures. (NOF [2019] Boning Up on Osteoporosis) [357]

Safety considerations for physical activity

Older adults with low bone density, osteoporosis, and fractures can safely benefit from activities that promote muscle strength and balance. In the LIFTMOR study, supervised high-intensity physical activity increased bone density, improved function, and reduced kyphosis in postmenopausal women aged 65 ± 5 years with osteoporosis and osteopenia—*without elevating risk for vertebral fractures* [358, 354].

On the other hand, when done incorrectly, high-intensity and/or impact activities can cause musculoskeletal injuries, especially in people with vertebral fractures, sarcopenia, or cognitive impairment. However, with appropriate technique, intensity, and therapeutic progression, even these vulnerable populations can realize improvements in physical performance [359, 360].

Supervision is recommended to ensure physical activities are safe and sustainable given an individual's health status, bone fragility, and overall fitness. Individuals with low bone density, osteoporosis, or spinal kyphosis should engage in physical activities with a straight or supported back. Activities that are typically performed with flexion (forward bending under stress) should be avoided unless they are modified to protect the spine. Extreme, end-of-range flexion or rotation should be avoided, especially when loaded (as in lifting objects from the floor). Slow, controlled twisting with the spine supported is acceptable as is midrange (but not end-range) spine flexion/extension

in which some of the body's weight is supported by extremities (bent knee, arm behind back, etc.) (Fig. 8).

Recommended progressive resistance training, balance training, and increased loading exercises include the following (Table 14):

- Lifting weights using back-safe position and technique
- Pulling elastic exercise bands
- Correct use of weight machines (back lying, side lying, etc.)
- Lifting one's own body weight, such as one-foot stands, and toe rises
- Balance exercises that strengthen legs and challenge balance, such as tai chi or slow/controlled dancing
- Balance exercises with cognitive element progressing in complexity, e.g., walking a pattern, walking a pattern while holding a cup (mimics real life high-fall-risk situations)
- Posture exercises that strengthen back extensor muscles and improve core stability
- Functional exercises (simulating common movements/ADLs)

The American Board of Physical Therapy Specialties offers certification to qualified physical therapists who specialize in geriatrics. Patients can find a board-certified geriatric physical therapist in their area through the public portal on the American Physical Therapy Association's website (http://apta.org).

Secondary fracture prevention

Ideally, all at-risk individuals could be identified and managed to prevent their first fracture (primary prevention). Improvements have been made in detection and management of osteoporosis in women aged 65 years and older. Medicare utilization data show many women in this age group are currently screened by DXA in compliance with HEDIS measures, an increase from 64.4% in 2006 to 72.5% in 2017. Improvements have been seen in treatment following fracture (secondary prevention). Medicare utilization data show testing and treatment rates following *any* fracture increased from 20.4% in 2007 to 41.1% in 2020 [361]. However, analysis

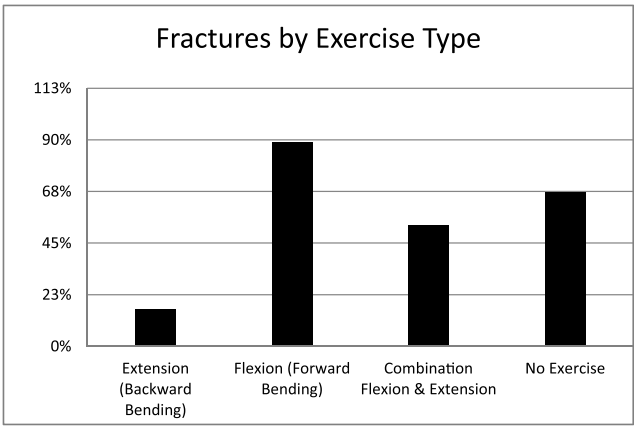


Fig. 8 For people with osteoporosis, the harm or benefit conferred by exercise depends on the specific movement involved. Activities that require spinal flexion (forward bending) increase risk of vertebral fracture, while activities that involve spinal extension decrease risk [355]. (Source: Sinaki M, Mikkelsen BA [1984] *Arch Phys Med Rehabi*)

of Medicare data from 2008 to 2014 found that following hip fracture repair, *fewer than 1 in 5 women* received recommended interventions, despite being at *very high risk for future fractures* [362].

Other studies have shown even worse rates, with up to 95% of patients discharged following hip fracture repair with no antifracture treatment and a 2.5-fold increased risk of future fracture [29, 30, 363]. Failure to treat high-risk patients can lead to disability and premature death that might have been avoided with appropriate care.

Patient perceptions and beliefs contribute to underutilization of effective osteoporosis therapies. As detailed in the ASBMR report on secondary fracture prevention, most patients do not recognize fracture as a symptom of disease [363, 364]. Clinicians may find it challenging to convince a patient that tripping and breaking a bone is not bad luck, or a particularly hard fall, it is osteoporosis and it will lead to additional fractures if untreated, particularly in the short term.

Understanding the link between treatment and fracture is critical to motivating patients to undertake the many individual steps required to reduce their risk. Simple interventions to preserve bone strength can be recommended at each office visit. In addition to antifracture medication, these

Table 14 How much physical activity? BHOF recommendations for people with osteopenia and osteoporosis [54, 357].

Weight-bearing activities	30 min on most days of the week in a single 30-min session or in multiple sessions spread throughout the day. (The stimulus has to be greater than what body is used to.)
Muscle-strengthening activities	Two to three days per week. Can be done all at once or in multiple short sessions, full body or one body part per day. (For example, arms one day, legs the next and trunk the next.)
Balance, posture, and functional activities	Every day or as often as needed. Focus on area of most need: If patient has fallen, balance activities should be emphasized. If patient is hyperkyphotic, focus should be on posture activities. If patient has trouble climbing stairs or getting up from the couch, he/she should do more functional exercises. These activities can be performed at one time or spread throughout the day.

interventions include adequate intake of calcium, vitamin D, and protein; regular participation in weight-bearing and muscle-strengthening physical activity; cessation of tobacco use; and recognition and treatment of alcohol abuse.

There are structural factors that contribute to the problem of osteoporosis underdiagnosis and undertreatment as well. Skeletal health overlaps multiple specialties of practice, in both inpatient and outpatient settings. In today's fragmented healthcare environment, it can be unclear who is responsible for bone health. The orthopedic surgeon who repairs a hip fracture may assume the primary care doctor has it covered, while the primary care doctor assumes the orthopedist took care of any needed bone-related diagnosis and/or treatment when the patient was hospitalized. Continuity of care is complicated by multiple handoffs, particularly after hospitalization: skilled nursing stay, home health, etc. Not only that, there is the challenge of identifying patients at highest risk due to the fact that most fractures occur in people with bone density above the threshold diagnostic of osteoporosis. They have low bone density, but not low enough to meet bone density criteria for intervention [365].

Institutional approaches to secondary fracture prevention have been initiated in the USA and abroad to ensure that patients who fracture are evaluated, treated, and followed so that the potential cascade of fractures is stopped after the first. Evidence-based practice models have emerged that can be adapted for various clinical practice settings. One such model gaining acceptance is the fracture liaison service (FLS).

The fracture liaison service model of care

The FLS system of care in the USA was developed through the National Bone Health Alliance (NBHA), a public–private partnership of 50-plus member organizations along with representatives from the Centers for Disease Control and Prevention, Centers for Medicare & Medicaid Services, National Institutes of Health, and the US Food and Drug Administration [13].

In an FLS system, a multidisciplinary team of healthcare providers works in coordination to implement evidence-based diagnostic and treatment protocols to follow for post-fracture care. The process is overseen by an FLS coordinator (a nurse or other allied health professional) who is charged with overall organization, tracking, and documentation of post-fracture patient care. It is a simple concept, yet its implementation is complicated, requiring planning, division of responsibilities, coordination of staff, systematic and consistent patient monitoring, and knowledge of billing and coding technicalities. Because management of osteoporosis is a multidimensional and long-term undertaking, treatment plan coordination is critical to its effectiveness. Equally critical is patient collaboration. Every aspect of the plan must accommodate patient needs, goals, values, habits, abilities, and living conditions [366, 367].

Since early pilot programs began a decade ago, FLS programs have been successful in the USA and abroad. They have markedly reduced recurrent fractures, particularly in closed medical systems, by targeting interventions at post-fracture patients, recognizing that this group is at highest risk of future fractures.

FLS pilot programs outcomes to date include the following:

- Kaiser Permanente's *Healthy Bones* program, which has led to an overall 38% reduction in their program's expected hip fracture rate since 1998.
- Geisinger Health System osteoporosis disease management program, which achieved $7.8 million in cost savings over 5 years through reduction of secondary fractures.
- American Orthopaedic Association's *Own the Bone* program has significantly improved rates of treatment and counseling, BMD testing, initiation of pharmacotherapy, and coordination of care for patients following fragility fracture [368].
- NBHA FLS Demonstration Project, a turnkey FLS solution created for sites to automate, benchmark, and improve performance related to selected osteoporosis/post-fracture quality measures demonstrated an increase in DXA and vitamin D level testing and treatment following implementation of the FLS program in three academic hospital settings [45].

The goal of the FLS model, like any practice management program is to ensure patients with a fracture are evaluated and treated for their underlying osteoporosis, while making the best use of clinician time and expertise. Creative approaches optimize use of electronic medical records and practice management software, delegate tasks, automate as much as possible, take advantage of the patient's waiting room time, and team up colleagues, specialists, allied health professionals, and support staff. There are many tools available for every type of practice, from sole practitioner to hospital-based multispecialty clinic.

Recommendations for secondary fracture prevention

In 2019, a coalition convened by the ASBMR published Clinical Recommendations for Secondary Fracture Prevention to treat the osteoporosis in women and men aged 65 years or older who suffer a spine or hip fracture. Here is a concise summary of the coalition's recommendations [363].

1. Women and men aged 65 years and older who sustain a spine or hip fracture should be managed by an FLS or a multidisciplinary team to evaluate and treat their underlying osteoporosis and reduce risk of another bone fracture in the next 1–2 years.
2. Primary care and other healthcare providers should be informed about their patient's fracture, diagnosis of osteoporosis, and future fracture risk, as well as the availability of effective treatment to reduce fracture risk.
3. These women and men should be evaluated for fall risk and provided with referrals as needed (PT, OT, ophthalmology, etc.) to initiate fall prevention measures.
4. Women and men who sustain a spine or hip fracture should be offered effective therapy to reduce their risk for future fractures. Intravenous or oral pharmacological treatments can be started in the hospital or at discharge, although some clinicians prefer to wait to start intravenous zoledronic acid for few weeks (note zoledronic acid is FDA-approved in patients with hip fractures to be prescribed with vitamin D). Treatment should not be delayed.
5. Because osteoporosis is a lifelong condition, long-term follow-up and care should be provided for all affected patients [369].

Free or low-cost fracture prevention resources

- Fall prevention: Centers for Disease Control and Prevention: STEADI (Stopping Elderly Accidents, Deaths & Injuries) tool kit for health care providers. https://www.cdc.gov/steadi/index.html
- General guidance for living with osteoporosis: *Boning Up on Osteoporosis*. Available at BHOF website: www.bonehealthandosteoporosis.org.
- Patient education videos on exercise for people with osteoporosis: https://www.nof.org/patients/fracturesfall-prevention/safe-movement-exercise-videos/
- *BoneFIT*™ an exercise training workshop developed by Osteoporosis Canada to train physical therapists and fitness instructors working with people who have osteoporosis (and are fragile). To learn about the program, including online and in-person training opportunities, please visit: https://osteoporosis.ca/health-care-professionals/bonefit.
- American Dental Association (ADA): NOF-ADA joint letter on what is known regarding risk for ONJ and risk for fracture in patients with osteoporosis. Available at http://www.bonehealthandosteoporosis.org/wp-content/uploads/ONJ-letter-FINAL-BHOF.pdf.
- ASBMR's Secondary Fracture Prevention Initiative Coalition comprised of organizations and government agencies is directed at engaging healthcare professionals across multiple disciplines to evaluate and treat women and men age 65 years and older with a hip or vertebral fracture to reduce future risk. https://www.secondaryfractures.org/about-coalition.
- American Orthopedic Association Own the Bone® Post-Fragility Fracture Quality Improvement Program. http://www.aoassn.org. (847) 318-7336.
- American Orthopedic Association Own the Bone® *Orthopaedic Bone Health ECHO*®. Each month, a panel of experts will host participants on a videoconferencing platform (Zoom) to discuss current topics related to bone health and to initiate a dialogue around patient cases presented by participants. https://www.ownthebone.org/OTB/Education/
- Bone Health & Osteoporosis Foundation (BHOF) Fracture Prevention Resources. https://www.bonehealthandosteoporosis.org/preventing-fractures/.
- FLS Bone Health ECHO (Extension for Community Healthcare Outcomes) program offers case-based clinical discussions on a wide range of topics of interest. By participating, attendees will be able to receive free CME, connect with experts in the field, share case studies, and so much more. http://www.nbha.org/projects/echo.
- Bone Source®. Through the BoneSource® website, BHOF offers a variety of programs, tools, and resources to meet the unique needs of healthcare professionals who provide bone health care. https://www.bonehealthandosteoporosis.org/?s=bone+source. (800) 231-4222.

Remaining questions

This guide has focused on prevention, diagnosis, and treatment of osteoporosis in postmenopausal women and men aged 50 years and older. Much is known about osteoporosis in this population. However, many additional issues urgently need epidemiologic, clinical, and economic research. For example:

- What can be done to improve patient adherence and persistence with prescribed antifracture medications.
- What is optimal timing and duration of bisphosphonate drug holiday?
- What can be done to determine effectiveness of FLS in different care models and to promote the FLS model to improve identification, diagnosis, and treatment following an acute fracture?
- How can FLS programs be implemented and funded nationwide to ensure treatment of patients with fragility fractures and reduce the imminent risk of fractures and other complications?
- How can the FRAX® algorithm be expanded to incorporate information on lumbar spine BMD and on multiple fractures into its quantitative risk assessment?
- Can a fracture risk calculator be developed for patients who have already initiated pharmacologic therapy? Would a calculator be helpful in determining when to initiate a bisphosphonate holiday and/or reinstitute therapy in high-risk patients?
- What is the optimal type, intensity, duration, and frequency of exercise programs for osteoporosis prevention and treatment?
- For individuals with vertebral fractures, what exercise is safe and effective in lowering incidence of fractures and falls and improving patient-centered outcomes (pain, function).

- How effective and safe are different FDA-approved treatments in preventing fractures in patients with low bone mass (osteopenia)? Do benefits exceed risks?
- What approaches are most effective in treating osteoporosis in patients with spinal cord injuries and other disabilities?
- How can we standardize radiological technologies for diagnosis of vertebral fractures (e.g., X-rays, CT, and MRI) to make them more quantitative, accurate, and consistent, particularly in the case of mild fractures?
- What is the role of DXA forearm bone density measurement in predicting wrist and other fragility fractures? Is an isolated forearm BMD diagnostically sufficient to support treatment?
- Will use of DXA to assess atypical femur fractures improve early diagnosis or will false positives result in unneeded imaging and heightened costs and/or concerns?
- How can we better assess bone strength using non-invasive technologies and thus better identify patients at high-risk for fracture?
- What is the optimal approach to treating atypical femur fracture?
- How should bone turnover biomarkers and/or BMD be used to monitor the duration of bisphosphonate holidays?
- What are the effects of combined anabolic and antiresorptive therapies on fracture outcomes?
- Can we identify agents that will significantly increase bone mass and restore normal bone structure?
- Can future osteoporosis therapies cure this prevalent disease?

The Bone Health and Osteoporosis Foundation (BHOF) is committed to continuing the effort to answer these and other questions related to this debilitating disease with the goal of eliminating osteoporosis as a threat to the health of present and future generations. For additional resources on osteoporosis and bone health, visit http://www.bonehealthandosteoporosis.org.

Summary

The osteoporosis treatment gap is truly a public health crisis, putting patients at risk for fragility fractures that cause *avoidable* suffering, disability, dependence, and premature death and cost millions in healthcare expenditures. To close this gap in care, we need to engage physicians, governmental entities, and public health organizations in efforts to improve access and insurance coverage for key fracture prevention services. Osteoporosis detection, diagnosis, and treatment must become routine components of clinical practice. Healthcare providers of all types can lend their support by raising awareness of fracture prevention and bone preservation interventions and lifestyle modifications among patients, caregivers, and fellow health professionals.

We have the tools at our disposal. Proven diagnostic technologies and bone-sparing therapies are widely available at low cost. Pharmacologic agents that build bone and/or decrease bone breakdown dramatically reduce fracture incidence. Non-pharmacologic interventions preserve bone tissue, build muscle, and help prevent falls and fall-related fractures. However, these and other effective strategies are underutilized at every stage of healthcare delivery from inpatient to at-home and continuing care.

However effective, no single intervention or modality is adequate to preserve bone and prevent fractures in vulnerable patients. Collaborative approaches piloted in FLS programs are multifactorial and wholistic. They start with the recognition that a fracture in an adult is a clinical sign of osteoporosis that warrants further investigation to identify and mitigate underlying conditions that contribute to bone loss and fractures. Multifaceted patient care must be coordinated to ensure implementation of the full range of pharmacologic, dietary, fall prevention, physical therapy, and exercise recommendations.

As our population ages, preservation of skeletal health becomes more important every year. By applying recommended fracture risk assessment, pharmacologic treatment, risk reduction counseling, and long-term monitoring, clinicians across the healthcare spectrum who care for adults can contribute to extending the healthy independent lives of their patients.

Glossary

Abaloparatide (Tymlos®): An anabolic therapy approved for the treatment of osteoporosis. The pivotal study indicates that abaloparatide, compared with placebo, reduced the risk of new vertebral fractures by 86% and non-vertebral fractures by 43% after 18 months of therapy in patients with osteoporosis.

Alendronate (Fosamax®, Binosto™): A bisphosphonate approved by the US Food and Drug Administration for prevention and treatment of osteoporosis; accumulates and persists in the bone. Studies indicate about a 50% reduction in vertebral and hip fractures in patients with osteoporosis.

Atypical femur fractures (AFF): These are atraumatic or spontaneous fractures characterized by distinct radiographic and clinical features that resemble stress fractures (transverse fracture line, periosteal callus formation at the fracture site, little or no comminution, prodromal pain, and bilaterally, in some instances). These fractures are thought to be associated with long-term use of potent antiresorptive medications and are distinguished from ordinary osteoporotic femoral diaphyseal fractures.

Biochemical markers of bone turnover: Biochemical markers of bone remodeling can be measured in serum and

urine. These include the resorption markers serum C-telopeptide (CTX) and urinary N-telopeptide (NTX) and the formation markers serum bone specific alkaline phosphatase (BALP), osteocalcin (OC), and amino-terminal propeptide of type 1 procollagen (P1NP). Elevated markers of bone turnover may predict bone loss, while declines in these markers after 3–6 months of treatment may suggest fracture risk reduction.

Bone Health and Osteoporosis Foundation (BHOF): In October 2021, the National Osteoporosis Foundation (NOF) changed its name to the Bone Health and Osteoporosis Foundation (BHOF) to reflect the Foundation's dual focus on preventing osteoporosis and fracture in addition to osteoporosis diagnosis and treatment across the lifespan.

Bone mineral density (BMD): A risk factor for fractures. By DXA, BMD is expressed as the amount of mineralized tissue in the area scanned (g/cm^2); with QCT, BMD is expressed as the amount per volume of bone (mg/cm^3). Hip BMD by DXA is considered the best predictor of hip fracture; it appears to predict other types of fractures as well as measurements made at other skeletal sites. Lumbar spine BMD may be preferable to assess changes early in menopause and after bilateral ovariectomy and may be better than hip BMD in predicting risk of spine fractures especially in women in their 50s and 60s.

Calcitonin (Miacalcin® or Fortical®): A polypeptide hormone that inhibits the resorptive activity of osteoclasts. Second-line antifracture treatment (less effective than alternatives). Nasal spray and injection available. Documented to significantly reduce acute pain of recent vertebral crush fractures. Short-term use advised due to cancer risk.

Calcium: A mineral that plays an essential role in development and maintenance of a healthy skeleton. The vast majority of the body's calcium is stored in bone. If intake is inadequate, calcium is mobilized from the skeleton to maintain a normal blood calcium level. In addition to being a substrate for bone mineralization, calcium is an inhibitor of bone remodeling through suppression of circulating parathyroid hormone.

Cancellous bone: The spongy, or trabecular, tissue in the middle of bone (e.g., vertebrae) and at the end of the long bones. Also called trabecular bone.

Cortical bone: The dense outer layer of bone.

Denosumab: A fully human monoclonal antibody to RANK-ligand (RANKL) approved by the FDA for the treatment of osteoporosis in postmenopausal women at high-risk of fracture and other indications. In the pivotal study, denosumab reduces the incidence of vertebral fractures by about 68%, hip fractures by about 40%, and non-vertebral fractures by about 20% over 3 years.

Dual-energy X-ray absorptiometry (DXA): A diagnostic test used to assess bone density at various skeletal sites using radiation exposure about one-tenth that of a standard chest X-ray. Central DXA (lumbar spine, hip) is the preferred measurement for definitive diagnosis of osteoporosis and for monitoring the effects of therapy.

Estrogen: One of a group of steroid hormones that control female sexual development; directly affects bone mass through estrogen receptors in bone, reducing bone turnover and bone loss. Indirectly increases intestinal calcium absorption and renal calcium conservation and, therefore, improves calcium balance. See hormone therapy.

Estrogen agonists/antagonists: A group of compounds that act on a subset of estrogen receptors in the body, also known as selective estrogen receptor modulators (SERMs). Examples are the pharmaceutical agents raloxifene and bazedoxifene.

Exercise: An intervention long associated with healthy bones, despite limited evidence for significant beneficial effect on BMD or fracture risk reductions. Studies evaluating exercise are ongoing; however, enough is known about the positive effect of exercise on fall prevention to support its inclusion in a comprehensive fracture prevention program.

Food and Drug Administration (FDA): The US FDA is responsible for protecting the public health by assuring the safety, effectiveness, quality, and security of human and veterinary drugs, vaccines and other biological products, and medical devices. The FDA is responsible for the safety and security of most of our nation's food supply, all cosmetics, dietary supplements, and products that give off radiation.

Fracture: Breakage of a bone, either complete or incomplete whether from trauma, repetitive stress, or bone insufficiency. Osteoporosis can contribute to any fracture at any skeletal site, but overwhelmingly affects sites that predominate in trabecular bone: femoral neck, total hip, spine, and forearm. Fractures in cortical bone dense sites are less likely to be attributed to osteoporosis, such as fingers, toes, skull, and face. Vertebral compression fractures are the most common type of osteoporotic fracture.

Fracture liaison service (FLS): A coordinated care system headed by an FLS coordinator (a nurse practitioner, physician's assistant, nurse or other health professional) who ensures that individuals who suffer a fracture receive appropriate diagnosis, treatment and support.

FRAX®: The World Health Organization Fracture Risk Assessment Tool. https://www.bonehealthandosteoporosis.org and https://www.sheffield.ac.uk/FRAX.

Hormone/estrogen therapy (HT/ET) (HT—Activella®, Femhrt®, Premphase®, Prempro®; ET—Climara®, Estrace®, Estraderm®, Estratab®, Ogen®, Ortho-Est®, Premarin®, Vivelle®): HT is a general term for all types of estrogen replacement therapy when given along with progestin, cyclically or continuously. HT is generally prescribed for women after natural menopause or bilateral ovariectomy with progestin required to protect the uterus from unopposed estrogen. ET is prescribed for postmenopausal women who have had a hysterectomy. Studies

indicate that 5 years of HT may decrease vertebral fractures by 35 to 50% and non-vertebral fractures by about 25%. Ten or more years of use might be expected to decrease the rate of all fractures by about 50%.

Ibandronate (Boniva®): A bisphosphonate approved by the FDA for the prevention and treatment of postmenopausal osteoporosis. Ibandronate reduces incidence of vertebral fractures by about 50% over 3 years. Ibandronate in the large RCTs did not reduce hip or non-spine fractures.

Least significant change (LSC): A measure utilized as part of DXA precision assessment that helps to determine if a BMD change can be ascribed to treatment effects or is due to measurement error.

Low bone mass (osteopenia): The designation for bone density between 1.0 and 2.5 standard deviations below the mean BMD of a young adult reference population (T-score between − 1.0 and − 2.5).

Modeling: The term for skeletal processes that involves shaping the bone during growth and replace damaged bone with new bone throughout the lifecycle. Modeling occurs on bone surfaces without prior bone resorption.

Non-vertebral fractures: Fractures of the hip, wrist, forearm, leg, ankle, foot, and other sites.

Normal bone mass: The designation for bone density within 1 standard deviation of the mean BMD of a young adult reference population (T-score at − 1.0 and above).

Osteopenia: See low bone mass.

Osteoporosis: A chronic, progressive disease characterized by low bone mass, microarchitectural deterioration of bone tissue, decreased bone strength, bone fragility, and a consequent increase in fracture risk; BMD 2.5 or more standard deviations below the mean BMD of a young adult reference population (T-score at or below − 2.5).

Peak bone mass: The maximum bone mass accumulated during young adult life (late teens to early 20s).

Peripheral DXA: A DXA test used to assess bone density in the forearm, finger, and heel.

Physiatrist: A physician who specializes in medicine and rehabilitation, or physiatry.

Previous fracture: A risk factor for future fractures, defined here as a history of a previous fracture after age 40 years.

PTH (1-34), teriparatide, (Forteo®): An anabolic therapy approved for the treatment of osteoporosis. The pivotal study indicates a 65% reduction in vertebral fractures and a 40 to 50% reduction in non-vertebral fractures after 18 months of therapy in patients with osteoporosis.

Quantitative computed tomography (QCT): A diagnostic test used to assess volumetric bone density; reflects three-dimensional BMD. Usually used to assess the lumbar spine but has been adapted for other skeletal sites (e.g., hip). It is also possible to measure trabecular and cortical bone density in the periphery by peripheral QCT (pQCT) or high-resolution pQCT (HRpQCT).

Quantitative ultrasound densitometry (QUS): A diagnostic test used to assess bone density at the calcaneus or tibia. Ultrasound measurements correlate only modestly with other assessments of bone density in the same patient, yet some prospective studies indicate that ultrasound may predict fractures as effectively as other measures of bone density.

Raloxifene (Evista®): An estrogen agonist/antagonist (or selective estrogen receptor modulator) approved by the FDA for prevention and treatment of osteoporosis. It lowers the risk of vertebral fracture by about 30% in patients with and about 55% in patients without prior vertebral fracture. Raloxifene is approved for the prevention of breast cancer.

RANKL: Receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL)

Remodeling: Also called bone turnover, remodeling is the process by which the skeleton repairs damage and maintains serum calcium levels through the ongoing lifelong dual processes of bone resorption (breakdown) and formation.

Resorption: The breakdown and removal of bone tissue during bone remodeling.

Risedronate (Actonel®, Atelvia®): A bisphosphonate approved by the FDA for prevention and treatment of osteoporosis. It lowers the risk of vertebral fracture by about 41–49% and non-vertebral fractures by about 36%.

Risk factors: For osteoporotic fractures, risk factors include low BMD, parental history of hip fracture, low body weight, previous fracture, smoking, excess alcohol intake, glucocorticoid use, secondary causes of osteoporosis (e.g., rheumatoid arthritis), and history of falls. These readily accessible and commonplace factors are associated with the risk of hip fracture and, in most cases, with that of vertebral and other types of fracture as well.

Romosozumab (Evenity™): The FDA-approved bone anabolic agent, romosozumab is a fully human monoclonal antibody to sclerostin that both increases BMD and decreases fracture incidence in women with postmenopausal osteoporosis. Reported 73% (95% CI 53–84%) relative risk reduction in morphometric vertebral fracture after 12 months.

Secondary causes of osteoporosis: Osteoporosis that is drug-induced or caused by many disorders such as malabsorption, hyperthyroidism, renal disease, and chronic obstructive pulmonary disease.

Secondary fracture prevention: While primary fracture prevention comprises measures to promote and maintain BMD above − 2.50 so as to prevent an initial osteoporosis-related fracture, secondary fracture prevention is antifracture treatment after a patient has had an osteoporosis-related fracture, to prevent second and subsequent fractures.

Standard deviation (SD): A statistical measure of variance in a population.

T-score: In describing BMD, the number of standard deviations above or below the mean BMD of a young adult reference population.

Teriparatide: See PTH (1-34), teriparatide, (Forteo®).

Vitamin D: A group of fat-soluble sterol compounds that includes ergocalciferol (vitamin D_2) and cholecalciferol (vitamin D_3). These compounds are ingested from plant and animal sources; cholecalciferol is also formed in skin on exposure to ultraviolet light. When activated in the liver and then the kidney, vitamin D promotes calcium absorption. Vitamin D replacement increases muscle strength in patients with severe vitamin D deficiency. A 25(OH) D level of approximately 30 ng/mL (75 nmol/L) is considered by many bone health experts to be optimal.

Zoledronic acid (Reclast®): A bisphosphonate approved by the FDA for treatment of postmenopausal osteoporosis and to reduce risk of subsequent fracture in those with prior hip fracture. It lowers risk of vertebral fractures by about 70%, hip fractures by about 41% and non-vertebral fractures by about 25%.

Z-score: In describing BMD, the number of standard deviations above or below the mean BMD for persons of the same age, sex, and ethnicity.

Abbreviations AACE, American Association of Clinical Endocrinologists; AFF, Atypical femur fractures; ASBMR, American Society for Bone and Mineral Research; BASP, Bone-specific alkaline phosphatase; BCT, Biomechanical computed tomography analysis; BHOF, Bone Health and Osteoporosis Foundation; BMD, Bone mineral density; BTMs, Bone turnover markers; CTX, Carboxy-terminal cross-linked telopeptides of type 1 collagen; CV, Cardiovascular; DXA, Dual X-ray absorptiometry; ET/HT, Estrogen/hormone therapy; FDA, US Food and Drug Administration; FLS, Fracture liaison service; FNIH, Foundation for the National Institutes of Health; FRAX®, Fracture Risk Assessment Tool; HR-pQCT, High-resolution peripheral quantitative computed tomography; IOM, Institute of Medicine; ISCD, International Society for Clinical Densitometry; LSC, Least significant change; MRI, Magnetic resonance imaging; NBHA, National Bone Health Alliance; NOF, National Osteoporosis Foundation; NTX, Amino-terminal cross-linked telopeptides of type 1 collagen; OC, Osteocalcin; ONJ, Osteonecrosis of the jaw; P1NP, Amino-terminal propeptide of type 1 procollagen; pQCT, Peripheral quantitative computed tomography; PTH, Parathyroid hormone; PTHrP, Analog of parathyroid hormone-related peptide; QCT, Quantitative computed tomography; QUS, Quantitative ultrasound; RANKL, Receptor activator of nuclear factor κB ligand; RCT, Randomized controlled trials; TBS, Trabecular bone score; USPSTF, US Preventive Services Task Force; VFA, Vertebral fracture assessment; WHI, Women's Health Initiative

Subject Specialist Contributors Kathryn E. Ackerman, MD, MPH, FACSM; Douglas Bauer, MD; Theresa Chiaia, PT, DPT; Polly deMille, RN, MA, RCEP, CSCS, USAT; Thomas F. Koinis, MD; Wendy Katzman, PT, DPTSc (Dsc), OCS; Rick Pope, MPAS, PA-C, DFAAPA, CPAAPA; Heidi Skolnik, MS, CDN, FACSM

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Declarations

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