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REVIEW ARTICLE

Osteoporosis: a clinical and pharmacological update

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Abstract
Osteoporosis is characterized by the loss of bone mass, deterioration of the bone microarchitecture, and an increased risk of fractures; these later complications are associated with significant morbidity and mortality. The asymptomatic and progressive nature of osteoporosis underscores the importance of identifying this entity in early stages. Despite the various treatments available, the prevention of the disease represents the most important aspect of management. An adequate intake of calcium and vitamin D as well as a healthy lifestyle is the basis for maintaining bone health. When osteoporosis is diagnosed, the choice of medications must be individualized considering characteristics of the patient and the risk of fractures. In this article, we review the main causes of osteoporosis, when and how to start treatment, and appropriate therapy and monitoring.

Keywords Bone mineral density · Fractures · Osteoporosis · Osteoporosis treatment

Introduction

Osteoporosis affects 200 million people worldwide. Approximately 30% of postmenopausal women in the USA have osteoporosis, and 40% of them develop fragility fractures [1].

Three elements define osteoporosis: loss of bone mass (bone quantity), deterioration of bone microarchitecture (bone quality), and increasing fracture risk [2–4]. Fractures are morbid complications causing loss of independence, chronic pain, and need for rehabilitation. Hip fracture is the most devastating subtype, and 20–40% of individuals suffering hip fractures die within a year, and 10% of survivors fracture the contralateral hip [5].

The assessment of bone mass aids in diagnosis, risk prediction, and selection and monitoring of treatment. According to the International Society for Clinical Densitometry (ISCD), bone mineral density (BMD) measurement should be performed in women ≥ 65 and men ≥ 70 years old [6]. If several risk factors exist, BMD should be assessed in postmenopausal women younger than 65 and men younger than 70. The Fracture Risk Assessment Tool (FRAX ®) is an algorithm that predicts the 10-year incidence of hip and major osteoporotic fractures (clinical spine, forearm, hip, or shoulder fracture). FRAX is valuable in both assessing fracture risk and treatment. It combines individualized models integrated with clinical risk factors and BMD at the femoral neck [7]. The National Bone Health Alliance (NBHA) and the Clinical Diagnosis of Osteoporosis Working Group [8] recommend that postmenopausal women and men aged 50 years or older are diagnosed with osteoporosis if they have: *T*-score ≤ − 2.5 at the spine or hip; low-trauma hip fracture with or without BMD assessment, osteopenia by BMD with a low-trauma vertebral, proximal humerus, pelvis, or in some cases distal forearm fracture, and FRAX risk estimates above the country-specific threshold (US threshold: 10-year probability of major osteoporotic fracture ≥ 20% or 10-year probability of hip fracture ≥ 3%) [9].

When to initiate therapy

An antecedent fragility fracture is an indication for treatment regardless of *T*-score. Guidelines recommend a fracture risk based on BMD to define populations needing treatment,

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generally using a *T*-score ≤ − 2.5 alone or in combination with clinical risk calculations (i.e., FRAX®) [10–12] (see Table 1).

New diagnoses should prompt an evaluation of secondary causes of osteoporosis. A blood count, chemistry panel, intact parathyroid hormone, and a 24-h urine calcium should be assessed, and other testing should be considered according to clinical suspicion (see Table 2). Clinicians can stress modifying clinical risk factors and adjusting or suspending medications associated with loss of BMD or increased fall risk [4, 13, 14].

Choosing therapy depends on several factors: efficacy, tolerability, safety, adverse event profile, route of administration, frequency, non-skeletal benefits, and cost. Treatments should be approved by the Food and Drug Administration (FDA), the European Medicines Agency (EMA) and local regulatory authorities [13] (see Table 3).

Correcting vitamin D deficiency

Vitamin D deficiency is associated with secondary hyperparathyroidism, osteomalacia, altered bone turnover, osteoporosis, and increased risk of falls and fractures. Etiologies of vitamin D deficiency include inadequate sunlight exposure, altered absorption of vitamin D and medications [16, 17]. Vitamin D deficiency may result in poor responses to osteoporosis treatment [4, 16].

An average calcidiol [25(OH)D] level of 26.4 ng/ml (66 nmol/L) may reduce non-vertebral fracture risk in men and women over 65 years old, while an average level of 29.6 ng/ml (74 nmol/L) may reduce hip fracture risk [18]. Some experts suggest that calcidiol levels lower than 30–32 ng/ml (74.8–80 nmol/L) are suboptimal and the physiologic range begins above this value. The level estimated to suppress PTH is between 12.8–20 ng/ml (32–50 nmol/L) and 27.2–30 ng/ml (68–75 nmol/L) depending on the analytical approach [6, 18].

800–1000 IU/day of vitamin D is sufficient to achieve a calcidiol value of 30 ng/ml (75 nmol/L), and vitamin D_2 (ergocalciferol) and D_3 (cholecalciferol) are both viable supplements [13, 18]. However, when initial values are deficient, 800–1000 IU/day may not attain desired levels, so the practical alternative is administering high doses (50,000 IU/week) for 8 weeks, followed by the routine daily dose. Another option is administering daily doses of 6000 IU/day to reach levels above 30 ng/ml, followed by 1000–2000 IU/day to maintain that level [4, 16, 19].

Table 1 Recommendations to initiate pharmacologic treatment

1. Osteopenia or low bone mass and personal history of fragility fracture (hip or spine)
2. *T*-score ≤ − 2.5 in the femoral neck, total hip, or vertebral spine
3. Osteopenia (*T*-score from − 1.0 to − 2.4 at the femoral neck, total hip, or vertebral spine); and an elevated 10-year risk of fracture using FRAX, defined as:
   - A 10-year hip fracture risk > 3%
   - A 10-year major osteoporotic fracture risk (humerus, forearm, hip, or clinical vertebral fractures) > 20%

[4, 7, 13–15]

Choosing an agent

Risks and benefits of each drug should be considered prior to prescription, and common pitfalls should be known. Parenteral drug adherence is optimal, which is useful when oral medication is contraindicated or poorly tolerated [20]. Zoledronic acid requires a single annual infusion; however, like all intravenous bisphosphonates, it may cause post-infusion arthralgias and flu-like symptoms. These symptoms are generally transient and only occur after the first infusion. Denosumab is administered subcutaneously every 6 months [21].

Alendronate and risedronate should be taken 30 min, and ibandronate 60 min, before any other medication or food or lying down [13]. Comorbidities inhibiting prolonged standing may relatively contraindicate oral bisphosphonates. Bedridden patients should avoid hormonal therapy due to risks of thromboembolism [13, 21]. Oral bisphosphonates are contraindicated when esophageal abnormalities exist, and renal insufficiency limits using any bisphosphonate. Hypocalcemia restricts bisphosphonates and denosumab and should be corrected prior to therapy. A history of bone neoplasms, metastases, or increased risk of osteosarcoma contraindicates PTH-analog therapy [21].

Alendronate, risedronate, and zoledronic acid are currently considered first-line agents due to their body of evidence showing fracture incidence reduction. In older individuals, when efficacy at multiple sites (spine, hip, and non-vertebral) is desired, alendronate, risedronate, and zoledronic acid all are good options [14, 21–23] (see Table 4). Some guidelines consider denosumab a first-line agent [4, 15, 23], but others prefer its use for high-risk individuals and therapeutic failures. Denosumab is favored in the setting of advanced renal insufficiency [24]. The UK clinical guideline for osteoporosis prevention and treatment considers alendronate and risedronate first-line and intravenous bisphosphonates or denosumab the most appropriate alternatives [12].

Teriparatide is a PTH-analog, an anabolic agent approved by FDA for patients with high fracture risk, specifically a very low *T*-score and/or failure or intolerance to previous treatments [4, 15, 22]. Teriparatide protects against vertebral and non-vertebral (non-hip) fractures but has not shown efficacy in reducing hip fracture risk [4, 12, 25]. Abaloparatide is a

Table 2 Secondary evaluation for osteoporosis

Routine panel and biochemistry	Complete blood cell count, calcium, phosphorus, total proteins, liver enzymes, alkaline phosphatase, creatinine, electrolytes, 25(OH) D, 24-h collection for calcium, sodium, and creatinine excretion, C-reactive protein, or erythrocyte sedimentation rate
Hormones	Thyroid function tests, cortisol, intact parathyroid hormone, prolactin Men: serum testosterone, sex hormone binding globulin, follicle stimulating hormone, luteinizing hormone
Markers of bone turnover	Beta C-terminal telopeptide of type I collagen (βCTX), N-terminal propeptide of type I procollagen (PINP)
Urinary tests	24-h collection for calcium, urinary free cortisol, sodium, creatinine, and electrolyte excretion, Bence Jones protein
Malignancy tests	Serum protein electrophoresis, free kappa, and lambda light chains, lactate dehydrogenase (LDH), β2 microglobulin
Malabsorption tests	Endomysial and/or anti-tissue transglutaminase antibodies
Imaging	Lateral spine X-ray (dorsal spine with focus on T7 and lumbar spine with focus on L2-L3), bone mineral densitometry

[4, 13, 14]

synthetic analog of PTH-related peptide (PTHrP) that retains anabolic activity with less bone resorption compared with PTHrP. In the ACTIVE trial, abaloparatide was more effective preventing vertebral fractures compared to placebo at 18 months, and in a secondary endpoint, significantly reduced the non-vertebral fracture risk over placebo [26]. Duration of PTH-analog therapy should be less than 24 months and followed by antiresorptive therapy to preserve gains in BMD [4, 25].

Estrogens and selective estrogen receptor modulators (SERMs) are no longer considered first-line therapy but may be a preventative option for women with significant risk who cannot receive non-estrogenic treatment, have climacteric symptoms, or have menopause-associated vaginal atrophy [13, 17, 21, 22, 28]. Raloxifene reduces the risk of vertebral fractures in women with osteopenia and osteoporosis but failed to consistently reduce non-vertebral fracture risk [21].

Novel therapies include romosozumab, a monoclonal antibody-producing anabolic effect by inhibiting sclerostin, an inhibitor of Wnt pathways that suppresses the proliferation of osteoblasts [29]. Romosozumab was more effective than alendronate at preventing vertebral fractures in postmenopausal women, but safety signals revealed increased risks of serious cardiovascular events, thus delaying approval pending further review [30]. Next, odanacatib selectively inhibits cathepsin K, an extracellular protease produced by osteoclasts to degrade bony matrix. This mechanism hypothetically spares anabolic effects of osteoblasts by preserving cell-to-cell signals from osteoclasts [31, 32]. The study evaluating odanacatib also had to be discontinued because of major adverse cardiovascular events [33].

Table 3 Classification of therapy

Antiresorptive agents
- Bisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid)
- Raloxifene
- Denosumab

Anabolic agents
- Teriparatide
- Abaloparatide
- Romosozumab[a]

[a] Pending approval by the FDA for the treatment of osteoporosis

Combination treatment

Osteoporosis therapies have been combined to attain greater yields in increasing bone density. In severe, advanced, or refractory disease, combining therapies may be considered, especially administering anabolic therapy (i.e., abaloparatide or teriparatide) followed by antiresorptive drug (i.e., bisphosphonates or denosumab). This combination strategy has shown superiority over monotherapy in increasing BMD [25, 34–36].

The DATA (Denosumab and Teriparatide Administration) study examined denosumab and teriparatide over 12 months and compared BMD in individuals receiving each alone or a combination of the two. The combination group had the greatest increases in BMD in the spine, femoral neck and total hip, as measured by dual-energy X-ray absorptiometry (DXA) [35]. In the DATA-HRpQTC study, the combination of denosumab and teriparatide after 12 months demonstrated improvement in bone quality compared with either alone via high-resolution quantitative tomography. At 24 months, this combination continued to demonstrate improvements in bone microarchitecture suggesting that efficacy may improve during the second year [37–39].

Special populations

Osteoporosis in men

Osteoporosis in men is a growing problem due to an aging population. An estimated 1–8% of men suffer from osteoporosis in industrialized countries [40] and about 1 in 8 men over

Table 4 Recommendations for antiresorptive drugs

Drug	Zoledronic acid	Risedronate	Alendronate	Ibandronate	Raloxifene	Denosumab
Dose	5 mg/year (EV)	5 mg/day 35 mg/week	10 mg/day 70 mg/week	2.5 mg/day 150 mg/month 3 mg every 3 months (EV)	60 mg/day	60 mg every 6 months (SQ)
Vertebral Fx	A	A	A	A	A	A
Hip Fx	A	A	A	NAE	NAE	A
Non-vertebral Fx	A	A	A	A+	NAE	A
Indication	Postmenopausal OP Male OP with a high risk of fracture GIO	Postmenopausal OP Male OP with a high risk of fracture GIO prevention	Postmenopausal OP Male OP GIO prevention	Postmenopausal OP	Postmenopausal OP	Postmenopausal OP Male OP GIO Bone loss secondary to the use of aromatase inhibitors or androgen deprivation

EV, intravenous; *Fx*, anti-fracture efficacy; *A*, grade A recommendation; *NAE*, not adequately evaluated; *OP*, osteoporosis; *GIO*, glucocorticoid-induced osteoporosis; *SQ*, subcutaneous [4, 13, 14, 27]
+: in subsets of patients only (post-hoc analysis)

50 years of age will suffer an osteoporotic fracture [41]. Mortality after fracture was higher for men than women, and some authors report that men have twofold mortality rates after hip fractures [42, 43]. Male-specific determinants of bone mass like the peak bone mass occur later in life because of later onset of puberty. Males also have larger periosteal deposition of bone conferring a better resistance to mechanical forces [44].

Trabecular bone mass decreases with age in both sexes, but this loss is accelerated by menopause. Cortical bone mass remains stable until menopause for women and even later ages for men. Women mainly experience trabecular bone perforation and loss of connectivity, while men predominantly experience trabecular thinning. Perforation is structurally more detrimental and could partially explain the higher fracture risks of women [41].

Two hundred thirty-two patients were studied to describe the etiology and characteristics of osteoporosis in men, and results revealed 57% had idiopathic osteoporosis, which was more common under the age of 60. Forty-three percent of men developed secondary osteoporosis, which was more frequent in individuals older than 60 years. The risk factors of osteoporosis are similar despite sex; however, men with idiopathic osteoporosis have higher frequencies of hypercalciuria and family history [45].

Common secondary causes of osteoporosis in men are excessive consumption of alcohol, hypogonadism, tobacco use, and prolonged treatment with corticosteroids [45–49]. Kanis et al. found up to 68% of both sexes suffering a hip fracture and 38% suffering any fragility fracture excessively consumed alcohol (≥ 3 units/day) [45, 46]. A meta-analysis including 3,730,424 participants revealed that heavy alcohol consumption was associated with a trend toward increased hip fracture risk, but there was significant heterogeneity between studies ($P < 0.001$, $I^2 = 72.6\%$). Analyses based on amount of alcohol consumption revealed the RR of hip fractures was 0.88 (95% CI 0.83–0.89) with light alcohol consumption (0.01–12.5 g/day), 1.00 (95% CI 0.85–1.14) with moderate consumption (12.6–49.9 g/day), and 1.71 (95% CI: 1.41–2.01) with heavy consumption (≥ 50 g/day) [47].

A meta-analysis of 59,232 participants found an association between smoking and the risk of any fracture (RR = 1.25, 95% CI 1.15–1.36). The relative risk (RR) of suffering a hip fracture was 1.84 (95% CI 1.52–2.22). The male subgroup (26% of the study population) had elevated risks of osteoporotic fractures at any site [48].

Another risk common in older men is androgenic hormone suppression in individuals with prostate cancer. Hormonal therapy is associated with a fracture risk of 20% in the first 5 years [49] and a rapid loss of bone mass after the first year of treatment (approximately 2–4% in the lumbar spine and hip) [50]. Clinically, we assume that BMD scores (*T*-scores ≤ − 2.5) can be used similarly in both men age 50 and older and postmenopausal women; however, fractures in men have been

associated with higher absolute BMD values in comparison to women [43, 49, 50].

Therapeutic studies in men are scarce but bisphosphonates, denosumab, and teriparatide are FDA-approved options. Bisphosphonates, including alendronate, increase BMD and decrease bone turnover markers (BTMs) [12, 13, 51], and in a study of men with hypogonadism, alendronate reduced the incidence of vertebral fractures to 0.8% versus 7.1% of controls ($P = 0.02$) [52]. For men at high risk of vertebral fracture, especially with glucocorticoid-induced osteoporosis, bisphosphonates, denosumab, or teriparatide all seem reasonable [12].

Denosumab is efficacious in increasing BMD at the lumbar spine, total hip, femoral neck, trochanter, and radius. Denosumab was associated with a lower incidence of new vertebral fractures in men with prostate cancer receiving androgen deprivation therapy [53].

Glucocorticoid-induced osteoporosis

Glucocorticoid-induced osteoporosis (GIO) is a very common cause of secondary osteoporosis. Around 1–3% of the world population and 1% of the US adult population receives prolonged GC therapy [54, 55]. Fracture risk increases during the first 3–6 months of treatment, even with doses of 5 mg/day of prednisone, or its equivalent, due to high rates of trabecular bone loss [56].

GCs decrease function and promote apoptosis of osteoblasts via suppressing IGF-1 and TGF-β, both factors that promote bone formation. GCs also upregulate Wnt inhibitors, such as sclerostin and Dickkopf-1 (Dkk-1). Additionally, GCs prolong the lifespan of osteoclasts, increasing bone resorption [57, 58].

Doses of ≥ 7.5 mg/day of prednisolone (or equivalent) have an RR of 5.18 (95% CI 4.25–6.31) for vertebral fractures and 2.27 (2.16–3.10) for non-vertebral fractures [58]. An English cohort evaluated the RR of fracture of 244,235 patients on treatment with oral corticosteroids compared with 244,235 controls. Prednisolone ≥ 7.5 mg/day, or equivalent, produced a RR of 1.44 (95% CI 1.34–1.54) for non-vertebral fracture, 2.21 (95% CI 1.85–2.64) for hip fractures, and 2.83 (95% CI 2.35–2.40) for vertebral fractures, when compared to lower doses (< 2.5 mg/day) [59].

According to ACR guideline-based therapy, fracture risk should be stratified in each patient. For patients under 40 years of age, high-risk individuals are those with previous osteoporotic fractures, and moderate risk are those expected to continue GCs at > 7.5 mg/day for 6 months with either a hip or spine Z-score < −3 or a rapid decline in hip or spine BMD (≥ 10% loss in 1 year) during GC treatment. Low risk is assigned when no risk factor other than GC treatment is present [55]. In patients over 40 years of age, the risk outline is seen in Table 5.

Table 5 ACR stratification of the risk of fracture in patients over 40 years

	High	Moderate	Low
FRAX®* (major osteoporotic fracture)	≥ 20%	10–19%	< 10%
FRAX®* (hip fracture)	≥ 3%	> 1 and < 3%	≤ 1
BMD (hip or spine) T score	≤ −2.5[+]	–	–
Prior fracture	+	–	–

*FRAX-10-year risk of fracture (GC-adjusted): increase the risk generated with FRAX by 1.15 for major osteoporotic fracture and 1.2 for hip fracture if GC treatment is > 7.5 mg/day

[+] For men ≥ 50 years and postmenopausal women [55]

All individuals receiving doses ≥ 2.5 mg/day of prednisone, or equivalent, for 3 months or more should optimize the intake of calcium (1000–1200 mg/day) and vitamin D (600–800 IU) along with enacting lifestyle modifications (maintain appropriate weight, smoking cessation, etc.). Those ≥ 40 years of age with a moderate risk of fracture may be treated with oral bisphosphonates (this recommendation is stronger in the high-risk population), but if oral therapy is contraindicated or poorly tolerated, intravenous bisphosphonates may be used. If bisphosphonates are contraindicated, teriparatide or denosumab are recommended, preferably in that order. If none of the above can be used, raloxifene may be considered in postmenopausal women [55].

Individuals < 40 years of age at moderate or high risk of fracture should be treated with oral bisphosphonates. If contraindications exist, the same alternative medications listed for adults ≥ 40 years of age are recommended; however, raloxifene should not be used in men or premenopausal women. The guidelines also include recommendations for special populations (women of childbearing potential, adults with organ transplantation, etc.) [55].

For individuals receiving ≥ 7.5 mg/day of prednisone (or equivalent), denosumab is superior to risedronate in increasing bone mineral density at the lumbar spine for patients on chronic GCs (4.4% [95% CI 3.8–5.0] vs. 2.3% [1.7–2.9], $p < 0.0001$) as well as those who had recently started GC therapy (3.8% [3.1–4.5] vs. 0.8% [0.2–1.5], $p < 0.0001$). Denosumab is also associated with improvements in cortical bone structure assessed by high resolution peripheral quantitative computed tomography (HR-pQCT) of the radius and tibia when compared to risedronate after 12 and 24 months of treatment [60].

Monitoring treatment

The National Osteoporosis Foundation (NOF) recommends monitoring with DXA every 2 years or less in certain clinical circumstances [13]. The ISCD recommends repeating a DXA in the following circumstances: once the expected change in

BMD equals or exceeds the least significant change (LSC) of DXA measurement, 1 year after starting treatment, and/or when changing therapy. Subsequent intervals may be lengthened after therapeutic effect is established [6, 11]. AACE (American Association of Clinical Endocrinologists) recommends repeating bone densitometry 1 to 2 years after initiating treatment until BMD has stabilized [4].

Osteoporosis therapy induces rapid and large changes in BTMs; thus, they have the potential to predict treatment responses in individual cases, which could assist in treatment decisions. BTM assessment is recommended between 3 and 6 months after treatment initiation. Antiresorptive treatment significantly decreases markers of bone resorption within days or weeks followed by a decline in bone formation markers [62, 63]. Anabolic agents elevate markers of bone formation 1–3 months after treatment initiation [13]. βCTX is a preferred marker of bone resorption, and the PINP is a marker of bone formation. Changes in BTMs during treatment indicate adequate therapy and can be re-assessed earlier during treatment compared to BMD [61].

Defining therapeutic success and failure

Therapeutic success of treatment is poorly defined. Carey defines therapeutic success for bisphosphonates based on clinical, densitometric, and laboratory parameters (see Table 6) but notes that bisphosphonates reduce the risk of fracture even without elevation of BMD or significant changes in BTMs [64]. The Committee of Scientific Advisors of the International Osteoporosis Foundation (IOF) examined three parameters that may help define treatment failure: incident fractures, bone mineral density, and BTMs [65]. Previous fragility fractures confer high risk for incident fractures.

Gehlbach found that women with 1, 2, or ≥ 3 previous fractures had 1.8-, 3.0-, and 4.8-times greater risk of incident fracture, respectively, and women with ≥ 3 previous vertebral fractures have a 9.1-times greater risk of a new vertebral fracture [66]. Importantly, within the first 6 months of treatment, fractures may occur without implying a therapeutic failure [65, 67]. After an early fracture while on therapy, the incidence of second and third fractures is markedly reduced by 80–90%; therefore, the IOF considers a second fragility fracture, not the first, a marker of therapeutic failure [65].

Logically, increases of BMD during treatment should represent a good therapeutic response, but changes in BMD do not always correlate with changes in fracture risk [65, 68, 69]. Biological changes (gain or loss) in BMD are usually small, while the precision error of the measurement of BMD is much larger. But, BMD changes can be reliably detected when considering the least significant change (smallest change in BMD that is beyond the range of error of the machine). The IOF proposes that a decrease in BMD greater than the LSC is an indicator of treatment failure [65].

BTMs may predict fracture risk reduction over time. In a meta-analysis involving 18 clinical trials, antiresorptive therapy associated with a 70% decrease in BTMs conferred a 40% reduction in non-vertebral fracture risk [70].

The inter-laboratory variability and the precision error of BTMs may be significant, even when using the same method [71]. Taking into account variability of BTM measurement, the IOF proposes that a decrease in βCTX less than the least significant change (LSC) at 95% confidence is an indicator of antiresorptive treatment failure. Conversely, the increase in PINP less than the LSC at 95% confidence is an indicator of failure to respond to teriparatide [65].

Non-compliance can lead to treatment failure, and it is likely responsible for a significant number of "non-responders," especially to oral bisphosphonates [64, 69]. Compliance should be addressed after therapy initiation and regularly at follow-up to detect poor tolerability [72–74, 76]. Despite the importance of adherence, only 25% or less of patients are adherent 1 year after initiating therapy [75]. Bisphosphonates are associated with an early decrease in the levels of PINP and CTX beyond the least significant change (LSC), so BTM assessment may predict adherence problems. The LSC is estimated as a decrease of more than 38% for PINP and 56% for CTX. If decreases do not exceed the LSC, adherence to treatment must be re-assessed and secondary causes of osteoporosis should be evaluated [63].

Table 6 Therapeutic success with bisphosphonates

•The absence of definite fractures or symptoms and signs that suggest them
•Preservation of height (< 1 cm of loss)
•No change or increment in BMD (more than least significant change) measured by central DXA
•A decrease of bone resorption markers of 30% or more, measured in blood or urine
•Compliance with therapy

[64]

When to consider a change in treatment?

Prior to changing therapy, the IOF recommends ensuring good adherence and evaluating secondary causes of osteoporosis. After 1 year of therapy, a change from antiresorptive therapy should be considered in the following circumstances:

(1) The occurrence of two or more incident fragility fractures (fractures of hand, digits, skull, feet, and ankle are not fragility fractures)
(2) The occurrence of a single incident fracture along with either:

(a) The lack of an appropriate reduction in serum βCTX or PINP
(b) A significant decrease in BMD

(3) The lack of a significant decrease in serum βCTX or PINP
(4) A significant decrease in BMD.

A significant decrease in BMD is ≥ 5% at the lumbar spine and ≥ 4% at the proximal femur as measured by two DXA scans. Regarding BTM measurements (using the same assay), a significant decline is 25% from baseline for antiresorptive treatments. A 25% increase in BTMs is considered significant for anabolic agents after 6 months [65].

Long-term security aspects

The most common adverse events observed with oral bisphosphonates occur in the gastrointestinal tract. Acute influenza-like symptoms are commonly seen with intravenous bisphosphonates. All bisphosphonates have warnings or contraindications for use in patients with renal impairment [77]. Oral bisphosphonates are poorly absorbed (< 1%), so the risk of renal injury is higher with intravenous administration, it has been reported following zoledronic acid administration, and this may be related to rapid infusion rates or high dose. The recommended infusion time is at least 15 min with adequate hydration prior to administration [77, 78].

Long-term bisphosphonate or denosumab use is associated with a potential risk of medication-related osteonecrosis of the jaw, which may be related to cumulative high doses given for treatment of malignant disease [77, 79]. The incidence ranged from 1 to 15% in oncologic cohorts but only 0.001 to 0.01% in osteoporosis cohorts [80]. Risk factors include GC use, maxillary or mandibular bone surgery, poor oral hygiene, periodontal disease, diabetes mellitus, dental implants, suppuration, and dental extraction [79, 81]. Discussing this risk with patients and completing dental treatments 2 weeks before starting antiresorptive agents is advised. Good oral hygiene, the use of antibiotics post-procedure, mouth rinsing and appropriate wound closure following tooth extraction may reduce the risk [79, 81].

Atypical fractures of the femur (subtrochanteric or femoral diaphysis) are potentially related to the cumulative dose and have been reported with long-term bisphosphonate use and denosumab [4, 82].

The age-adjusted incidence rates for atypical femoral are 1.78/100,000 per year with a 2-year exposure or less; this increases to 113/100,000 per year with exposure of 8–9.9 years [83]. Receiving antiresorptive drugs in addition to bisphosphonates, GC use, and proton-pump inhibitors use increase the risk of atypical fracture. Some genetic susceptibilities have also been reported [83–85].

When to stop treatment

Bisphosphonates accumulate in bone resulting in a "residual effect" differing for each bisphosphonate. Effects on bone remodeling are preserved for months to years without therapy [13, 86]. A temporary suspension or "holiday" is common practice assuming the benefit of discontinuing treatment exceeds the risk of new fractures.

Treatment holidays reduce the risks of atypical fractures, but fragility fracture risk increases with drug holiday duration [87–89]. Drug holiday recommendations must consider the varied residual effects of each bisphosphonate. After 3–5 years of bisphosphonate therapy (3 years of zoledronic acid and 5 years of alendronate or risedronate), drug holidays are reasonable considerations [90–92]. Evidence-based guidance on the appropriate duration of holidays is lacking, but 2 to 3 years seems reasonable [90]. When offering a risedronate holiday, a shorter duration is preferred because 1 year or greater is associated with a significant loss of protection [93]. Holiday duration must be individualized weighing each overall fracture risk, the BMD and BTMs.

A theoretical holiday period applies only to bisphosphonates and no other therapies, like teriparatide and denosumab. Both act via different mechanisms and effects are rapidly reversed after discontinuation [94, 95]. Teriparatide should always be followed by antiresorptive treatment to prevent rapid loss of bone mass [4]. Several case reports and series suggest increased bone loss and rebound vertebral fractures after denosumab discontinuation [96, 97]. Denosumab discontinuation should be carefully planned, and bisphosphonate administration following denosumab cessation may inhibit rapid BMD loss [95, 97].

A working group from the European Calcified Tissue Society (ECTS) proposes re-evaluation after 5 years of denosumab treatment. In individuals with low fracture risk and increased BMD, cessation of denosumab followed by bisphosphonate therapy may be safe. Individuals still considered high-risk may continue denosumab for up to 10 years followed by a single infusion of zoledronic acid or one or more years of oral bisphosphonates. High-risk individuals wishing to stop denosumab after 5 years may be offered an additional 5 years of oral or 3 years of intravenous bisphosphonates [95].

Conclusions

Osteoporosis is a disabling disease and a serious health problem worldwide. Diagnosis in advanced stages is common, usually after fractures have occurred often reducing the quality

of life indefinitely. Clinicians should focus on prevention and early recognition of risk factors leading to osteoporosis. A multidisciplinary approach is essential to prevent, treat, and rehabilitate fractures after occurrence [98].

The presence of a diminished bone mass measured by DXA is useful in predicting fracture risk, but adding clinical risk factors to DXA measurements, as used in the FRAX, improves overall risk predictions. Evaluation of secondary causes of osteoporosis helps ensure therapeutic responses. Vitamin D deficiency leads to poor treatment efficacy, and normal serum values are important for bone health. Values above 32 ng/ml (80 nmol/L) help reduce fracture risk in both sexes. Adequate calcium and vitamin D intake are vital in osteoporosis prevention.

Therapy should be individualized to promote adherence. Bisphosphonates are the most commonly prescribed agents, so awareness of the effectiveness and benefits of each drug is important. Choosing therapy to match patient comfort (route of administration, frequency, etc.) and associated comorbidities can mitigate risks of therapeutic failure. When confronting chronic kidney disease and/or gastrointestinal comorbidities, denosumab may offer therapeutic advantages. Combination therapy for severe and/or refractory osteoporosis consists of simultaneous or sequential administration of both anabolic and antiresorptive agents. Finally, clear guidance on stopping osteoporosis treatment is lacking, so providers must weigh the individualized risks of new fractures against treatment duration.

Compliance with ethical standards

Disclosures None.

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