

Recent advances in managing osteoporosis

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Abstract

Osteoporosis is a common disease associated with increased morbidity and mortality. However, osteoporosis continues to be under-recognized, and the majority of men and women with fractures go untreated. FRAX[®] is a tool that has been developed by the World Health Organization to better identify people at high absolute risk of fracture. Modalities to assess bone quality, an important component of bone strength, have also emerged. Combined with new therapeutic options that promise increased compliance with therapy, the burden of this ever-growing and costly disease may be reduced.

Introduction and context

Osteoporosis is an under-diagnosed and under-treated serious disease

From individual and societal perspectives, the consequences of osteoporotic fractures are devastating, being associated with tremendous costs as well as increased mortality and morbidity [1-3]. The projected rise in the prevalence of osteoporosis with the ageing of the population will likely increase the current burden. Unfortunately, less than one-third of patients who have sustained a fragility fracture are diagnosed and treated for osteoporosis [4]. Among those who have not yet sustained a fracture but who are at high risk based on clinical risk factors (CRFs) and bone mineral density (BMD) measurement, the treatment rate is also disappointingly low [5].

Limitations of dual-energy X-ray absorptiometry in identifying individuals at high risk of fracture

Identification by physicians of people at high risk of fracture is the key step in initiating appropriate treatment. Measurement of BMD at the lumbar spine and proximal femur by dual-energy X-ray absorptiometry (DXA) is the current gold standard used to diagnose osteoporosis, with at least 2.5 standard deviations below the mean BMD of healthy young adults set as the threshold (T score \leq -2.5). It is also a good predictor of

fracture risk, with each standard deviation decline in BMD approximately doubling the fracture risk [6]. However, assessment of fracture risk and the decision to start treatment should not rely solely on BMD. Approximately half of fractures occur in people with osteopenia (T scores of -1.0 to -2.5) or a normal BMD, highlighting the importance of other factors, such as age, past history of fragility fracture, bone quality, and so on, on fracture risk [7]. Failure to identify people at high risk of fracture could be explained by the low accessibility to DXA machines and the limited time to evaluate CRFs for fracture in routine practice. Efforts have thus been made to develop easy-to-use tools (such as FRAX) that do not necessitate the inclusion of BMD data to calculate the individual's absolute risk of fracture [8]. As DXA measures only one component of bone strength, imaging techniques that evaluate bone quality are also emerging.

A need for new therapeutic modalities for osteoporosis

Oral bisphosphonates are the cornerstone of osteoporosis treatment, having been on the market for more than a decade. However, low adherence is a major issue and concerns about their long-term safety have been raised [9,10]. Indeed, bisphosphonate use has been associated with an increased risk of osteonecrosis of the jaw, mainly in oncology patients receiving high-dose intravenous

bisphosphonate therapy [11]. Atypical subtrochanteric femoral fractures in patients treated with bisphosphonates have also been reported, although results from a large cohort study suggest that these fractures are more likely osteoporotic by nature than a complication of bisphosphonate therapy [12]. Strontium ranelate is another option for postmenopausal women, but data in men are lacking. Teriparatide [recombinant human parathyroid hormone (PTH) (1-34)] and PTH (1-84) are the only anabolic agents currently available. However, they are costly and require daily subcutaneous injections. New options that are likely to enhance adherence to osteoporosis treatment, namely monthly oral bisphosphonate dosing and annual zoledronic acid infusions, have been released. A novel therapy, subcutaneous injections of denosumab every 6 months, is imminent. New antiresorptive and anabolic agents are also in the early stages of development.

Recent advances

Prediction of absolute risk of fracture using FRAX

FRAX[®] is a recently released, web-accessed fracture assessment tool that has been developed by the World Health Organization using primary data from nine population-based cohorts from North America, Europe, Asia, and Australia and validated in 11 independent cohorts [8,13]. It allows quick calculation of the 10-year likelihood of hip and major osteoporotic fractures (hip, clinical spine, humerus, or wrist fracture) for men and women between 40 and 90 years of age. The algorithm uses CRFs, alone or in combination with femoral neck BMD, to estimate fracture risk. CRFs included in the model are age, sex, body mass index calculated from weight and height, history of fragility fracture (including radiographic vertebral fracture), parental history of hip fracture, current smoking habits, current or past use of oral glucocorticoids (prednisolone ≥ 5 mg daily for at least 3 months), rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol use (≥ 3 units daily). As fracture risk varies worldwide, selection of a specific country is required. (If a specific country is not available, the country for which the epidemiology of osteoporosis most closely approximates it can be used.)

FRAX is a major advance in systematizing fracture risk assessment. However, it has a number of limitations that need to be taken into account when evaluating fracture risk in an individual [14]. First, dose responses exist for many CRFs (number of previous fractures, smoking, alcohol, and glucocorticoids) and need to be weighted when calculating fracture probabilities. Moreover, important factors that modulate fracture risk, such as propensity to fall, increased bone turnover markers

(BTMs), vitamin D deficiency, medications that accelerate bone loss (such as aromatase inhibitors and androgen deprivation therapy), and use of osteoporosis therapy, are not included in the model. FRAX also does not consider low spine BMD. Finally, epidemiological data are lacking for many countries and ethnic groups outside the US, and data for men are limited.

New imaging techniques for osteoporosis

Given that the majority of vertebral fractures are asymptomatic and that X-rays are not routinely performed unless symptoms are present, an important proportion of high-risk individuals may be inadequately identified and remain untreated for osteoporosis. Vertebral fracture assessment by DXA (VFA-DXA) involves minimal radiation exposure and is a convenient low-cost screening procedure that has been shown to adequately detect moderate to severe vertebral fractures in older women as compared with conventional X-rays [15]. However, reimbursement of VFA-DXA is still not uniformly available worldwide.

BMD measurement by DXA evaluates only one determinant of bone strength. Imaging techniques such as high-resolution peripheral computed tomography, three-dimensional micro-computed tomography, and micro-magnetic resonance imaging assess other bone strength components such as trabecular and cortical bone microarchitecture and could enhance the detection of people at high risk of fracture [16]. However, at present, the lack of normative data and the high cost and low availability of these modalities preclude its use in clinical practice.

Vertebroplasty for painful vertebral fractures

Findings from two recent methodologically rigorous Australian and international randomized placebo-controlled trials of vertebroplasty for painful acute vertebral fractures show, for the first time, that vertebroplasty is no better than a sham procedure in reducing pain for up to 6 months after an acute vertebral fracture [17,18]. The safety of vertebroplasty will also be assessed in longer-term follow-up of patients enrolled in the current studies.

Novel therapies for osteoporosis

Risedronate 150 mg once a month was approved by the US Food and Drug Administration (FDA) in 2008 for the treatment of postmenopausal osteoporosis. In a non-inferiority trial comparing risedronate 150 mg monthly with risedronate 5 mg daily, similar increases in BMD at the lumbar spine and hip, decreases in BTMs, and reductions in the incidence of radiologic vertebral fractures were seen at 1 year [19].

Approval of zoledronic acid by the FDA in 2007 was a major addition to the armamentarium of osteoporosis treatment, being both effective and requiring annual intravenous infusions, thus eliminating some drawbacks of oral bisphosphonate therapy. Zoledronic acid has been shown to reduce vertebral and non-vertebral fractures by 70% and 25%, respectively, as well as hip fractures by 41%, over 3 years in postmenopausal women [20]. This is also the only medication to date to reduce all-cause mortality by 28% and all clinical fractures by 35% in older men and women who received zoledronic acid 5 mg versus placebo within 3 months of sustaining a hip fracture [21]. Recently, a single zoledronic acid infusion was reported to be non-inferior and possibly superior to daily oral risedronate in the prevention and treatment of glucocorticoid-induced bone loss [22]. Furthermore, the 36-month interim results of the Zometa-Femara Adjuvant Synergy Trial (Z-FAST) suggest that up-front zoledronic acid at a dose of 4 mg every 6 months is more effective in preventing aromatase inhibitor-associated bone loss than delaying treatment until bone loss or a fracture has occurred in women with breast cancer [23]. Of interest, the effects of a single zoledronic acid infusion on BMD and BTMs have been shown to persist for at least 2 years, suggesting that a greater interval between infusions could possibly maintain its anti-fracture efficacy in patients with osteoporosis [24].

Novel osteoporosis therapies are also going through the final steps of approval and should become available shortly. Denosumab is a human antibody to RANKL (receptor activator of nuclear factor-kappa-B ligand), an inhibitor of osteoclast differentiation, proliferation, and function. Phase II and phase III clinical trials of denosumab in the treatment and prevention of postmenopausal osteoporosis and the treatment and prevention of bone loss in patients undergoing hormone ablation for prostate or breast cancer have been performed. Denosumab is administered subcutaneously at a dose of 60 mg every 6 months in the treatment of postmenopausal osteoporosis. It reduced the 3-year incidence of new vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis by 68%, 20%, and 40%, respectively, compared with placebo [25]. Treatment with denosumab also resulted in greater increases in BMD and reductions in BTMs than alendronate [26]. In men with non-metastatic prostate cancer undergoing androgen deprivation therapy, BMD increased and the risk of new vertebral fractures was decreased by 62% after 3 years of denosumab versus placebo [27]. Novel SERMs (selective estrogen receptor modulators) (e.g., lasofoxifene) are also in development. Lasofoxifene at a dose of 0.5 mg/day has been shown to

decrease vertebral and non-vertebral fractures by 42% and 22%, respectively, as well as the risk of estrogen-positive breast cancer by 67%, in postmenopausal women [28].

Briefly, new anti-resorptive and anabolic agents are also in the early stages of clinical development. Cathepsin K is an enzyme present in osteoclasts and is necessary for bone matrix degradation during bone resorption. A 2-year course of 50 mg of oral weekly odanacatib, a selective inhibitor of cathepsin K, increased lumbar spine and total hip BMDs by 5.5% and 3.2%, respectively, while the BTMs urinary N-telopeptide and bone-specific alkaline phosphatase decreased by 52% and 13%, respectively [29]. Our improved understanding of the molecular pathways involved in bone formation has led to the identification of new anabolic therapeutic targets. For example, activation of the Wnt signaling pathway has been shown to promote bone formation. Association of Wnt proteins with the membrane receptors Frizzled and LRP5/6 (low-density-lipoprotein (LDP) receptor-related proteins 5 and 6) results in the accumulation of β -catenin, a molecule important for the transcription of genes involved in bone formation, through the disruption of a protein complex (comprising glycogen synthase kinase 3), responsible for phosphorylation and degradation of β -catenin. Blockade of natural antagonists of the Wnt pathway such as sclerostin, the *SOST* (sclerosteosis) gene product secreted by osteocytes, and Dickkopf (*Dkk*)-1 could potentially lead to new anabolic drugs. Preclinical studies of anti-sclerostin antibody treatment in a rat model of postmenopausal osteoporosis showed promise as a potential anabolic agent by increasing bone formation, bone mass, and bone strength [30]. A single subcutaneous dose of sclerostin antibody administered to healthy postmenopausal women resulted in a mean increase in the bone formation marker serum P1NP by 60-100% at 21 days and a trend of decrease in the bone resorption marker serum C-telopeptide [31]. Finally, targeting the calcium-sensing receptor in parathyroid or bone cells is also a potential way of treating osteoporosis [32].

Implications for clinical practice

FRAX is a quick accessible tool that uses readily available CRFs, without necessitating BMD data, to calculate 10-year absolute probabilities of fracture. When used properly, it provides valuable and meaningful information to both clinicians and patients. Given the limitations of FRAX, clinical judgement is required when interpreting the results. The ultimate application of FRAX is to identify high-risk individuals who would be candidates for therapy, especially those in the osteopenic range. Treatment guidelines based on expert opinions or

cost-effectiveness analyses are emerging, using thresholds of FRAX-calculated 10-year fracture probabilities of hip and major osteoporotic fractures for intervention [33-35]. It is likely that FRAX will be incorporated into the reporting software for bone densitometry.

Low adherence and persistence with daily and weekly oral bisphosphonates have a great impact on anti-fracture efficacy [36]. Whether the availability of less frequent oral and intravenous regimens will improve persistence with treatment is yet to be determined. Cost, potential side effects, and contraindications are also important factors that restrain treatment options in some patients. Novel anti-resorptive and anabolic therapies are being developed as alternatives for patients with osteoporosis.

Abbreviations

BMD, bone mineral density; BTM, bone turnover marker; CRF, clinical risk factor; DXA, dual-energy X-ray absorptiometry; FDA, US Food and Drug Administration; LRP5/6, low-density-lipoprotein (LDP) receptor-related proteins 5 and 6; PTH, parathyroid hormone; RANKL, receptor activator of nuclear factor-kappa-B ligand; SERM, selective estrogen receptor modulator; VFA-DXA, vertebral fracture assessment by dual-energy X-ray absorptiometry; Z-FAST, Zometa-Femara Adjuvant Synergy Trial.

Competing interests

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