Osteoporosis

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Fractures resulting from osteoporosis become increasingly common in women after age 55 years and men after age 65 years, resulting in substantial bone-associated morbidities, and increased mortality and health-care costs. Research advances have led to a more accurate assessment of fracture risk and have increased the range of therapeutic options available to prevent fractures. Fracture risk algorithms that combine clinical risk factors and bone mineral density are now widely used in clinical practice to target high-risk individuals for treatment. The discovery of key pathways regulating bone resorption and formation has identified new approaches to treatment with distinctive mechanisms of action. Osteoporosis is a chronic condition and long-term, sometimes lifelong, management is required. In individuals at high risk of fracture, the benefit versus risk profile is likely to be favourable for up to 10 years of treatment with bisphosphonates or denosumab. In people at a very high or imminent risk of fracture, therapy with teriparatide or abaloparatide should be considered; however, since treatment duration with these drugs is restricted to 18–24 months, treatment should be continued with an antiresorptive drug. Individuals at high risk of fractures do not receive adequate treatment and strategies to address this treatment gap—eg, widespread implementation of Fracture Liaison Services and improvement of adherence to therapy—are important challenges for the future.

Introduction

Osteoporosis is defined as a systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture.[1] This well established definition, developed by international consensus in 1993, captures two important characteristics of the disease: its adverse effects on bone mass and microstructure, and the clinical outcome of fracture. The following year, diagnostic criteria were produced by WHO using SD scores of bone mineral density (BMD) related to peak bone mass in healthy young women, with osteoporosis being defined as a BMD T score of –2·5 or less and low bone mass (osteopenia) as a BMD T-score between –1 and –2·5.[2] The diagnostic criteria recognised the importance of low BMD in the pathogenesis of fragility fractures and provided a tool that could be used in epidemiological studies to quantify the prevalence of osteoporosis. However, the utility of BMD as a clinical indicator of osteoporosis is limited, because BMD is only one of a number of important risk factors for fracture, and the majority of fragility fractures occur in individuals with BMD values above this threshold.[3,4]

Search strategy and selection criteria

We searched PubMed, Embase, and the Cochrane Library for articles and reviews in the English language published between Jan 1, 2013 and Aug 2, 2018, although older references were also used when appropriate. We used the search terms "osteoporosis" and "fracture" and limited the search to the following study designs: human, clinical studies, clinical trials (phases 2, 3, and 4), controlled clinical trials, guidelines, meta-analyses, observational studies, practice guidelines, pragmatic clinical trials, randomised controlled trials, and systematic reviews. We also searched the reference lists from articles and reviews identified by the search.

Rachner and colleagues'[5] 2011 review on osteoporosis provided a detailed report on bone biology. This Seminar covers advances that have been made in our knowledge of the epidemiology, pathogenesis, and clinical management of osteoporosis in adults, and is primarily focused on postmenopausal osteoporosis. We review emerging therapies with novel mechanisms of action, controversies in the field, and the future for new treatment paradigms and precision medicine.

Epidemiology

Because of the systemic nature of osteoporosis, the associated increase in fracture risk affects virtually all skeletal sites.[6] Hip fractures and vertebral fractures are strongly associated with reductions in hip BMD and spine BMD, respectively, and have historically been considered the prototypical osteoporotic fractures.[7] However, the incidence of all other fractures (non-hip, non-vertebral) is numerically much greater and collectively these fractures result in much larger economic costs for the population.[8,9]

Hip fractures, which present with symptoms of pain and an inability to bear weight, almost always require surgical fixation and are associated with greater reduction in functional status and quality of life than all other types of fracture, with a high risk for short-term mortality, and substantial direct medical costs. The epidemiology of hip fractures is well described, with an exponential increase as a function of age (most occurring after age 80 years), predominance among women (only about a quarter of hip fractures occur in men), and marked geographical variation (>10 fold differences in incidence). An estimated 2·7 million hip fractures occurred in 2010 worldwide, of which 1 364 717 (51%) were calculated to be potentially preventable (264 162 in men, and 1 100 555 in women), if osteoporosis (defined as a femoral neck T score of –2·5 SD or less) could be avoided.[10]

Vertebral fractures are much more variable in their presentation, ranging from those causing severe pain that requires admission to hospital, to those that produce

few symptoms and are diagnosed only on imaging.[11–13] The majority of studies show that most vertebral fractures are not clinically recognised but retain importance as markers of skeletal fragility that portend increased risk for other fractures, including those affecting the hip.[14–16] Worldwide variation in the prevalence and incidence of vertebral fractures has been observed, with the highest rates in North America and Asia.[17] Although the variable clinical presentation and differences in the criteria used for vertebral fracture diagnosis decrease the quality of the epidemiological data, research is helping to refine the understanding of osteoporotic vertebral fractures, and will hopefully lead to greater consistency in their recognition and taxonomy.[18,19] Importantly, vertebral fractures are the most common fracture associated with skeletal fragility, and are a source of substantial morbidity, mortality, and other adverse health outcomes.[13]

Historically, the greatest hip fracture incidence has been reported in people of European ancestry (particularly from northern Europe) with the lowest in eastern Asian populations.[20] The basis for these differences is not well understood and cannot be explained by differences in BMD. Hip fracture occurences have also been subject to divergent secular trends over the past few decades, such that the incidence has been decreasing in North America but is increasing in many Asian countries.[21,22] Trends for non-hip fractures have been less consistent.[22] Factors postulated to be contributing to these changes are lifestyle, urbanisation, obesity, birth period cohort effects, and consequences of screening.[23]

Mechanisms of action of drugs used to prevent fractures

Normal bone remodelling and modelling

The adult human skeleton is composed of cortical and cancellous bone, the proportions of which vary according to the skeletal site. In the vertebrae, cancellous bone predominates whereas long bones contain mostly cortical bone. Bone remodelling is a process by which old bone is replaced by new bone, resulting in renewal of the skeleton approximately every 10 years. The process occurs at discrete sites termed bone remodelling units, where recruitment of osteoclasts is followed by resorption of a quantum of mineralised bone, a reversal phase in which osteoclasts undergo apoptosis and osteoblasts are recruited to the site, and finally the formation and mineralisation of new bone within the resorption cavity. The sequence of events is always bone resorption followed by bone formation, and these two processes are coupled both spatially and temporally. In the young adult skeleton, the amount of bone resorbed and then formed is quantitatively similar (remodelling balance).[24,25]

Bone modelling sculpts the bones during skeletal development, optimising their shape and structure to respond to the prevailing mechanical stresses. In contrast to bone remodelling, resorption and formation are not coupled, either temporally or spatially. Although bone modelling is most evident during growth, it can also occur in the adult skeleton, particularly (although not exclusively), in response to mechanical loading.[26,27]

BMD is influenced by environmental and genetic factors, of which the genetic factors account for 50–85% of normal variance in bone mass. Genome-wide association studies have identified around 100 loci associated with bone density and other variables related to bone strength and fracture risk, although causal mechanisms have not been established for many of these loci.[28] Gene expression studies implicate a possible role for many other loci. Generally, the effects of genetic factors on the skeleton result from a large number of genes with small effect sizes, but rare monogenic skeletal diseases have provided valuable insights into key pathways that regulate bone remodelling and affect bone density and strength, particularly the RANK, RANKL, OPG, and Wnt signalling pathways.[5]

Pathophysiology of age-related bone loss

The process of ageing in women is associated with an increase in the rate of bone remodelling in both cancellous and cortical bone, combined with a negative remodelling balance, resulting in bone loss and disruption of bone microarchitecture. Trabecular thinning and loss of trabeculae can be observed in cancellous bone,[29,30] whereas in cortical bone, endocortical and intracortical bone loss lead to reduced cortical thickness and increased cortical porosity.[31] In men, ageing is predominantly associated with reduced bone formation, and low bone turnover. Changes in matrix and mineral composition of bone can also contribute to increased bone fragility.

Osteoporosis drugs: effects on bone remodelling and modelling

Antiresorptive drugs

The predominant effect of antiresorptive drugs (figure 1) is to inhibit the recruitment and activity of osteoclasts, thus decreasing the rate of remodelling and reversing the transient deficit created by resorption cavities in which formation has not yet occurred or been completed, allowing for a modest increase in BMD. These drugs probably do not fully correct the negative remodelling balance, but since the number of remodelling units is greatly reduced, the effect of any negative imbalance is decreased. Reduced remodelling is associated with increased secondary mineralisation of bone, which further contributes to the increase in BMD.[32]

Essentially, antiresorptive therapy preserves existing bone mass and structure and increases the degree and homogeneity of mineralisation. In cortical bone, denosumab can improve cortical bone structure at several sites, including the hip, increasing cortical thickness and decreasing porosity.[33–36] A possible explanation for this observation is that denosumab maintains physiological bone modelling.[37,38] In addition, the accessibility of

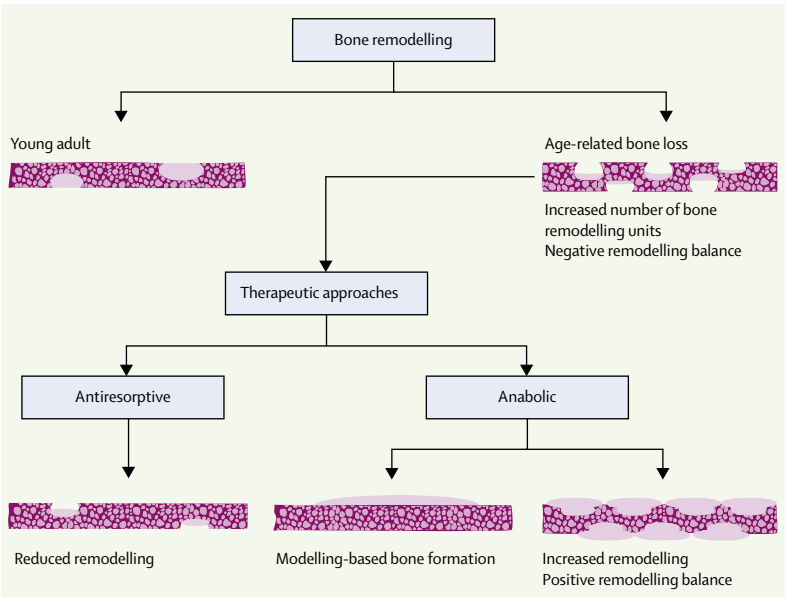

Figure 1: **Effects of antiresorptive and anabolic drugs on bone remodelling and modelling**
Age-related bone loss is associated with an increase in remodelling and a negative remodelling balance in individual bone remodelling units. Antiresorptive agents act predominantly by reducing remodelling rate. Anabolic agents produce their effects by increasing remodelling in combination with a positive remodelling balance, or stimulating bone modelling.

cortical bone to denosumab might be greater than the accessibility to bisphosphonates, because of differences in pharmacokinetic properties.[39]

Anabolic drugs

Anabolic skeletal effects can be achieved through changes in bone remodelling, bone modelling or a combination of the two (figure 1). In iliac crest bone, intermittent administration of teriparatide stimulates modelling-based bone formation on cancellous, endosteal, and periosteal surfaces, an effect that is most evident in the early stages of treatment.[40,41] However, the majority of the anabolic effect in cancellous bone is achieved through remodelling with overfilling of remodelling units. In cortical bone, the effects vary according to site; increased total bone area, increased cortical porosity, and the formation of hypomineralised new bone can occur in the early stages of treatment, which results in little change, or a decrease in BMD at sites such as the hip and radius.[42] However, increased bone strength has been reported with longer-term treatment in the hip, and cortical thickness mapping has shown localised increases at sites that are subjected to mechanical loading.[43–46] Effects of abaloparatide, an analogue of parathyroid hormone-related protein (PTHrP), on bone modelling have not been reported; however, in postmenopausal women treated for 12–18 months with abaloparatide, bone remodelling indices in cancellous iliac crest bone were generally similar to those in a placebo group, and to those treated with teriparatide.[47]

Sclerostin is an osteocyte-derived inhibitor of bone formation.[5] The anabolic effects of sclerostin inhibition are mediated through an early and transient increase in bone formation combined with a sustained decrease in bone resorption. In iliac crest biopsy samples obtained from postmenopausal women in the Fracture study in Postmenopausal Women with Osteoporosis (FRAME),[48] large increases in bone formation were seen in cancellous and endocortical bone after 2 months of treatment with romosozumab (a monoclonal antibody that binds and inhibits sclerostin), although the effect was no longer evident after 12 months of treatment. The eroded surface was significantly reduced at both timepoints, and trabecular bone volume, microarchitecture, and cortical thickness were significantly improved at 12 months.Data from animal studies have shown increased modelling bone formation in response to sclerostin inhibition, but the relative contributions of bone remodelling and modelling to bone formation in humans remain to be established.[49]

Risk assessment

BMD, which is usually measured with dual energy x-ray absorptiometry (DXA) in clinical practice, strongly correlates with fracture risk. For every reduction of 1 SD, fracture risk increases by 1·5–2 times overall, and by approximately 2·5 times when hip fractures are predicted from hip BMD.[7,50] As a result, most risk assessment paradigms incorporate BMD. The limitation of BMD is that most fractures occur in individuals with a BMD T-score that does not meet the conventional definition for osteoporosis (–2·5 or lower), and therefore has low sensitivity when used alone for osteoporosis screening.[4,6,7,51] Fortunately, many easily identified clinical risk factors (such as age, sex, previous fracture) are associated with fracture risk independently of BMD and can be used for fracture risk assessment with or without BMD. Several fracture risk assessment tools have been developed to estimate absolute fracture risk from these clinical factors. The three tools that have been independently validated are summarised in table 1.[52]

The Fracture Risk Assessment Tool (FRAX) has been the most widely studied tool and has been incorporated into clinical practice guidelines. It differs from other tools in that it can be directly calibrated to fracture incidence rates in the target population (defined by countries and ethnicity, with over 60 tools available) and considers death as a competing risk (since higher mortality reduces the chance that individuals will survive long enough to have a fracture).[56] FRAX estimates the 10 year probability of major osteoporotic fracture (a composite of hip, clinical spine, forearm, and proximal humerus fracture) or 10 year probability of hip fracture alone. Over 100 different clinical practice guidelines have incorporated FRAX, although they differ in how it is used to set the threshold for treatment.[57] Two general approaches have evolved and emphasise differences in the role of BMD testing (table 2). Under the UK National Osteoporosis Guidelines Group

	Risk factor inputs	Outputs	Unique features
Fracture risk assessment tool[53]	Age, sex, body-mass index, previous fragility fracture, glucocorticoid use ≥3 months, secondary osteoporosis, rheumatoid arthritis, parental hip fracture, current cigarette smoking, alcohol intake of ≥3 units per day, femoral neck bone mineral density or T score (optional)	10 year major osteoporotic fracture (clinical vertebrae, hip, forearm, proximal humerus); 10 year hip fracture	Nine international prospective cohorts (46 340 participants); meta-analyses for clinical risk factors; population-specific calibration; includes competing mortality
Garvan Fracture risk calculator[54]	Age, sex, fractures after age 50 years (none, 0, 1, 2, ≥3), history of falls in the previous 12 months (none, 0, 1, 2, ≥3), femoral neck bone mineral density or T score, weight	5 or 10 year osteoporotic fracture (hip, clinical vertebrae, wrist, metacarpal, humerus, scapula, clavicle, distal femur, proximal tibia, patella, pelvis, and sternum); 5 or 10 year hip fracture	Dubbo Osteoporosis Epidemiology Study (1358 Australian women and 858 men); includes dose–response for number of previous fractures and falls
QFractureScores-2016[55]	Age, sex, height, weight, smoking, alcohol, diabetes, previous fracture, parental osteoporosis or hip fracture, living in a nursing or care home, history of falls, dementia, cancer, asthma or COPD, cardiovascular disease, chronic liver disease, advanced chronic kidney disease, Parkinson's disease, rheumatoid arthritis, systemic lupus erythematosus, malabsorption, endocrine problems, epilepsy or anticonvulsant use, antidepressant use, steroid use, hormone replacement therapy	1–10 year osteoporotic fracture (clinical spine, hip, distal forearm), or humerus fracture); 1–10 year hip fracture	357 general practices in England and Wales (>1 million women and >1 million men); includes dose–response for smoking (four levels), alcohol intake (five levels), type of diabetes; bone mineral density is not an input variable

COPD=chronic obstructive pulmonary disease.

Table 1: **Fracture risk prediction tools with at least one independent validation cohort**

	UK National Osteoporosis Guidelines Group[58]	US National Osteoporosis Foundation[59]
Treatment initiation	The intervention threshold at each age is set at a risk equivalent to that associated with a previous fracture, and therefore increases with age up to 70 years	Vertebral fracture (clinical or asymptomatic), or hip fracture; hip dual energy x-ray absorptiometry (femoral neck or total hip), or lumbar spine T score ≤–2·5 SD; 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 can indicate treatment for people with 10 year fracture probabilities above or below these levels
Follow-up	Treatment should be reviewed after 5 years for alendronate, risedronate, or ibandronate, and after 3 years for zoledronic acid; continuation of an osteoporosis treatment, including assessment of renal function, can generally be recommended in the following groups: high-risk individuals (aged ≥75 years, previous hip or vertebral fracture, continuous oral glucocorticoids at a dose of ≥7·5 mg per day prednisolone or equivalent); individuals who sustain one or more low trauma fractures during treatment, after exclusion of poor adherence to treatment; individuals with total hip or femoral neck bone mineral density T score ≤–2·5 SD; if treatment is discontinued, fracture risk should be reassessed after a new fracture regardless of when this occurs, and if no new fracture occurs, after 2 years	Patients that do not require medical therapies at the time of initial evaluation should be clinically re-evaluated when medically appropriate; patients taking FDA-approved medications should have laboratory and bone density re-evaluated after 2 years or more frequently when medically appropriate; vertebral imaging should be repeated if the patient has documented height loss, new back pain, postural change, or suspicious findings on chest x-ray, following the last (or first) vertebral imaging test or in patients being considered for a temporary cessation of drug therapy to make sure no new vertebral fractures have occurred in the interval; regularly, and at least annually, assess compliance and persistence with the therapeutic regimen

FDA=US Food and Drug Administration.

Table 2: **Two clinical approaches in the management of osteoporosis in postmenopausal women and men aged 50 and older**

(NOGG), FRAX is first used without BMD to estimate fracture risk; individuals with sufficiently high fracture risk are considered for treatment, whereas those with a very low fracture risk are managed without medication, and an intermediate group undergoes BMD testing for refinement of their fracture risk.[58] The intervention threshold is set at the risk for a woman of the same age who has already had a fragility fracture, under the assumption that such individuals would already be considered for treatment (figure 2). The US National Osteoporosis Foundation (NOF) approach is dependent upon BMD testing to identify individuals for treatment (in the absence of previous spine or hip fracture). BMD screening at age 65 years in healthy women, and 70 years in healthy men, is recommended, and treatment is initiated on the basis of an osteoporotic BMD T-score or, in those with low bone mass (osteopenia), elevated fracture risk estimated from FRAX with BMD (major osteoporotic fracture 20% or greater, hip fracture 3% or greater).[59] The US Preventive Services Task Force (USPSTF) recommends BMD screening for osteoporosis in women aged 65 years or older, whereas in younger women, screening is recommended using one of several clinical risk assessment tools, followed by BMD testing in those at increased risk of fracture. The USPSTF found insufficient evidence to assess the benefits and risks of screening for osteoporosis in men.[60]

These UK NOGG and US NOF strategies have not been directly compared in terms of their ability to prevent fractures. The first randomised controlled trial (SCOOP)[61] was a pragmatic study in more than 12 000 eligible women, half of whom were assigned to screening according to the NOGG approach. Treatment was recommended in 14% of women found to meet the intervention threshold, with a high uptake (78% of women in the screening high-risk group) at 6 months. Although the primary endpoint of a reduction in all osteoporosis-related fractures was not met, the screened group had a

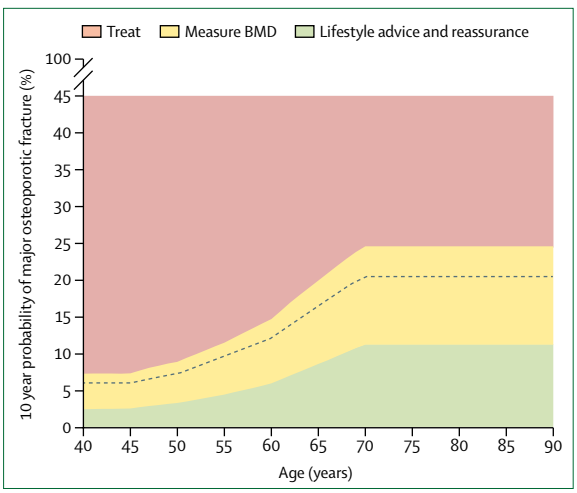

Figure 2: **UK National Osteoporosis Guidelines Group assessment and treatment thresholds**
Green denotes that an individual's risk lies below the intervention threshold—ie, pharmacological intervention is not required. Red denotes that the fracture probability is consistently above the upper assessment threshold, and pharmacological intervention is strongly recommended in most cases. Patients with fracture probabilities in the intermediate category (yellow) should be considered for BMD assessment using dual energy x-ray absorptiometry, and fracture probability should then be recomputed using the Fracture Risk Assessment Tool. Pharmacological intervention would be recommended if the recomputed fracture probability exceeds the intervention threshold (dashed line). BMD=bone mineral density.

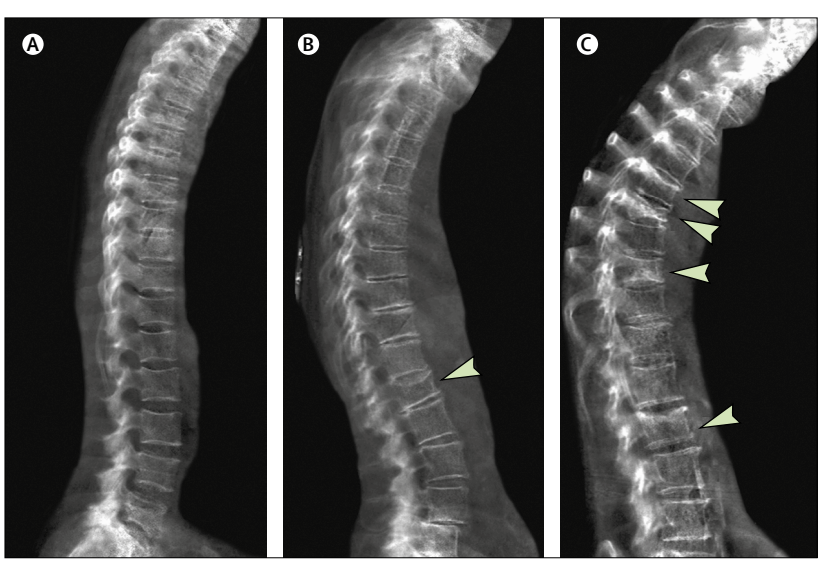

Figure 3: **Previously unrecognised vertebral fractures**
Vertebral fracture assessment can be done with the dual energy x-ray absorptiometry scanner at the time of bone mineral density assessment to identify unsuspected vertebral fractures. In the absence of an alternative cause, their presence indicates high fracture risk due to underlying osteoporosis and usually warrants treatment initiation. (A) Normal spine. (B) Single moderate fracture (L1). (C) Multiple vertebral fractures (T7 moderate, T8 severe, T10 mild, L2 mild). L=lumbar vertebra. T=thoracic vertebra. Arrows point to specific fractures.

significant 28% reduction in incident hip fractures. This study is important as it provides evidence of the ability of FRAX to identify a risk that is amenable to treatment. Moreover, this approach was shown to be highly cost-effective.[62] A subsequent randomised study was done in 34 229 postmenopausal women using a two-step screening process.[63] Although no significant differences were seen in the intention-to-treat analyses, significant reductions in hip (26%), major osteoporotic (13%), and all fractures (11%) were shown in those identified by FRAX as being at moderate or high risk of fracture (major fracture probability 15% or greater) who underwent DXA scanning.

Several new measures have been proposed to enhance fracture risk assessment in routine clinical practice. These include trabecular bone score (TBS), a texture measure derived from spine DXA that can be used to refine the output from FRAX;[64–66] vertebral fracture assessment, the use of lateral spine DXA to detect previously unrecognised vertebral fractures (figure 3) that are associated with adverse clinical outcomes including hip fractures;[16,67] hip geometry measures, particularly longer hip axis length, which increases susceptibility of the hip to fracture;[68,69] and use of previously acquired clinical CT scans to detect unrecognised vertebral fractures, or estimate BMD (so-called opportunistic screening).[70,71] Ongoing initiatives directly assess skeletal strength non-invasively from clinical CT and perhaps DXA using mechanical engineering principles based on finite element analysis.[72,73] Identification of individuals at high fracture risk in the 1–2 years following screening (imminent fracture risk) is a new concept that might be helpful in selecting individuals who would benefit from more potent, rapidly acting, but more expensive medications.[74,75] Importantly, falls are not included in FRAX but are incorporated into the other risk calculators. A meta-analysis found that past falls predicted incident fracture independently of FRAX probability.[76] Other measures of frailty such as reduced muscle mass and impaired muscle function (sarcopenia) are not directly considered by any of the tools, but contribute to fracture risk.[77–81] Future fracture prediction tools will directly incorporate a variety of measures including hip geometry, non-invasive strength assessment, and falls.

Type 2 diabetes is associated with an increase in fracture risk that is independent of FRAX probability. Adjustments that improve the predictive ability of FRAX in affected individuals include use of the rheumatoid arthritis input to FRAX, use of the TBS adjustment, reduction of the femoral neck BMD T-score input by 0·5 SD, and increasing the age input to FRAX by 10 years.[82]

Management of osteoporosis

Despite advances that have been made in fracture risk assessment, and the range of effective options available to reduce fracture, treatment rates are low among high-risk individuals.[83] Prescription of bone protective medications has decreased over the past decade with falling treatment rates even in people at very high risk. For example, in the USA it was shown that in the proportion of people admitted to hospital following hip fracture between 2001 and 2011, those who were

prescribed bone protective medication fell from 40% to 21%,[84] and low proportions have been reported from elsewhere in the world.[85–88] Probable reasons for under-treatment of osteoporosis include fear of adverse effects, scarcity of awareness of osteoporosis both among health-care professionals and affected individuals, issues related to reimbursement, and poor coordination of health-care systems involved in the care of people who have sustained a fracture. The problem is compounded by poor adherence to therapy, which has been particularly well documented for oral bisphosphonates [89,90]

Lifestyle measures

The objective of treating osteoporosis is to reduce the likelihood of fragility fractures by strengthening the skeleton or decreasing fall frequency, or both. General measures (good nutrition, regular physical activity, avoiding harmful lifestyle habits) are recommended for all patients at risk of osteoporosis.[91–93] However, results of studies evaluating effects of calcium and vitamin D on fracture risk are inconsistent, perhaps because these factors might be threshold nutrients for which the benefit of supplementation is only observed in individuals with low intakes.[94–99] Most studies that have investigated calcium and vitamin D have not evaluated outcomes specifically in patients with deficiencies in these nutrients. The correction of deficiencies, by ensuring a total daily intake of calcium of 800–1200 mg and a serum 25-hydroxyvitamin D of at least 50 nmol/L can be beneficial, but supplements in calcium-replete and vitamin D-replete individuals appear to have little or no benefit. Excessive intake of calcium (more than 1500 mg total daily) might be associated with an increased risk of renal stones and, less certainly, cardiovascular events.[94,100] Intermittent high doses of vitamin D (60 000 IU monthly or 500 000 IU annually) have been associated with increased risk of falls and fractures and the recommended daily dose should not exceed 4000 IU, unless the patient has documented malabsorption.[101–103]

Results of studies of relationships between protein intake and either BMD or fracture risk have also been inconsistent.[104] Among fall-prone older patients between 67 and 93 years who were losing weight, higher protein intake was associated with reduced fall frequency.[105] Comprehensive fall prevention programmes, including exercise programmes for muscle strengthening, balance training, and correction of visual impairment, can reduce fall frequency but have not been shown to reduce fracture risk.[106] These general measures can slow bone loss in older adults but do not restore BMD and are not sufficient therapy for patients at high risk of fracture.

Pharmacological interventions

Pharmacological therapy is appropriate for high-risk patients, in the absence of contraindications and after thorough clinical evaluation and exclusion of secondary causes (panel).[107] In placebo-controlled trials, several therapies of different classes have been shown to substantially reduce fracture risk. Vertebral fracture risk is usually reduced by 30–70%. Some agents reduce hip fracture risk by as much as 50% and non-vertebral fracture risk by 15–35%. Absolute reduction of fracture risk is determined as much by the risk of the individual being treated as by the choice of medicine.

The overall aim of osteoporosis therapy, namely reduction in fracture risk, cannot be judged in the clinical setting in an individual patient, since neither clinicians nor patients know when a fracture has been prevented by treatment. The availability of newer therapies that induce progressive increases in BMD provide the possibility that a target, such as a specific BMD value or level of fracture risk, could eventually be developed to guide osteoporosis treatment decisions, similar to the use of targets for the management of diabetes and hypertension.[108] This strategy is unlikely to be successful with bisphosphonates, which have a modest effect on BMD.[109]

Because very few studies have directly compared fracture efficacy among therapies, the choice of drug for the initial treatment of a patient with osteoporosis is based on a combination of cost and clinical judgment, including knowledge of the effectiveness and safety of specific drugs; the magnitude of fracture risk; and other considerations such as patient preference, age, and renal function. A synopsis of the efficacy and safety of each class of drug is provided in tables 3 and 4.

Bisphosphonates

Bisphosphonates, which are the most commonly used osteoporosis drugs, are potent antiresorptive agents. Alendronate, risedronate, and zoledronic acid effectively reduce the risk of vertebral, non-vertebral, and hip

Panel: **Procedures proposed in the investigation of osteoporosis**

Routine

- History and clinical examination
- Blood count, sedimentation rate, or C-reactive protein
- Serum calcium, phosphate, alkaline phosphatase, liver transaminases, creatinine
- Serum 25-hydroxyvitamin D (recommendations vary according to resources, but routine measurement in patients with osteoporosis is recommended in some guidelines)
- Thyroid function tests
- Bone densitometry (dual energy x-ray absorptiometry)

Other procedures (if indicated)

- Lateral x-rays of thoracic and lumbar spine or dual energy x-ray absorptiometry-based vertebral fracture assessment
- Serum immunoelectrophoresis and urinary Bence-Jones proteins
- Parathyroid hormone, urinary calcium
- Serum testosterone, sex hormone binding protein, follicle-stimulating hormone, luteinising hormone
- Markers of bone turnover
- 24 h urinary free cortisol, overnight dexamethasone suppression test
- Endomysial and tissue transglutaminase antibodies
- Isotope bone scan

fractures.[110,111] In a further study, Ibandronate reduced spine fracture risk, but the study was not powered to evaluate effects on non-vertebral or hip fracture.[119] The prevalence of upper gastrointestinal symptoms is increased with oral bisphosphonates, and flu-like symptoms occur in about a third of patients with their first (but not subsequent) intravenous doses of zoledronic acid. Muscle and joint pain of unknown mechanism are described with both oral and intravenous agents. Bisphosphonates must be used with caution in patients with substantially impaired renal function or hypocalcaemia. Osteonecrosis of the jaw occurs very rarely in patients receiving osteoporosis doses of bisphosphonates.[120] Invasive dental procedures and poor oral hygiene are risk factors for osteonecrosis of the jaw. Preoperative improvement of oral hygiene and topical antimicrobial therapy with dental extraction might reduce the risk of osteonecrosis of the jaw. A duration-dependent risk of subtrochanteric or femoral shaft fractures with atypical radiological features becomes evident after 2–3 years of therapy and is about 1/1000 after 8–10 years of therapy.[121]

RANK ligand inhibitor

Denosumab, a fully human monoclonal antibody, binds to and inhibits RANK ligand, resulting in marked but reversible inhibition of bone remodeling.[5] Administered by a subcutaneous injection of 60 mg every 6 months, denosumab reduces the risk of vertebral, non-vertebral,

	Route of administration	Fracture risk reduction*		
		Vertebral	Hip	Non-vertebral
Bisphosphonate[110,111]				
Alendronate	Oral once daily or weekly	Yes	Yes	Yes
Risedronate	Oral once daily, weekly, or monthly	Yes	Yes	Yes
Ibandronate	Oral once monthly or intravenous every 3 months	Yes†	ND‡	ND‡
Zoledronic acid	Intravenous once yearly	Yes	Yes	Yes
RANK ligand inhibitor				
Denosumab[112]	Subcutaneous injection every 6 months	Yes	Yes	Yes
Oestrogen§[113]				
Estradiol, estropipate, conjugated oestrogen	Oral, transdermal, implant	Yes	Yes	Yes
Selective oestrogen receptor modulators				
Raloxifene[114]	Oral once daily	Yes	ND‡	No
Bazedoxifene[115]	Oral once daily	Yes	ND‡	No
Bazedoxifene and conjugated oestrogen¶[116]	Oral once daily	No	No	No
Parathyroid hormone receptor agonist				
Teriparatide[117]	Subcutaneous injection daily	Yes	ND‡	Yes
Abaloparatide (only available in the USA)[118]	Subcutaneous injection daily	Yes	ND‡	Yes

ND=not determined. *Significant fracture risk reduction in primary analysis of a clinical trial. †Fracture risk reduction only shown with oral dosing. ‡Studies not powered to observe effect on hip or non-vertebral fracture risk. §Fracture risk reduction observed in low-risk women; approved for prevention but not treatment of osteoporosis. ¶No evidence of fracture prevention with this preparation; approved in some countries for prevention but not treatment of postmenopausal osteoporosis.

Table 3: **Approved pharmacological interventions for osteoporosis**

	Adverse events	Contraindications and important warnings
Bisphosphonate	Common: upper gastrointestinal adverse reactions with oral dosing, acute phase reaction with intravenous dosing; uncommon: bone, joint and muscle pain; rare: eye inflammation, femoral shaft or subtrochanteric fractures with atypical radiographic features, osteonecrosis of the jaw	Hypersensitivity, hypocalcaemia; oral drugs: oesophageal abnormalities that delay emptying, inability to remain upright; zoledronic acid: impaired renal function (creatinine clearance less than 35 mL/min); warning: patients with severe renal impairment should use oral drugs with caution
RANK ligand inhibitor	Uncommon: skin rash; rare: cellulitis, femoral shaft or subtrochanteric fractures with atypical radiographic features, osteonecrosis of the jaw	Hypocalcaemia, pregnancy, hypersensitivity; warning: multiple vertebral fractures have occurred when denosumab has been discontinued
Oestrogen	Breast pain, headache, oedema	Undiagnosed uterine bleeding, breast cancer, oestrogen-dependent neoplasia, venous or arterial thromboembolic disease or thrombophilic disorders, substantial liver impairment, pregnancy
Selective oestrogen receptor modulators	Common; vasomotor symptoms, muscle cramps; uncommon: venous thrombosis	Venous thromboembolism, pregnancy
Parathyroid hormone receptor agonist	Common: muscle cramps, increased serum or urine calcium or serum uric acid; uncommon: orthostatic hypotension	Hypersensitivity, nephrolithiasis; warnings: should not be used in children or adolescents with open epiphyses, or patients with Paget's disease of bone, previous external beam or implant radiation involving the skeleton, bone metastases, history of skeletal malignancies, other metabolic bone diseases, or hypercalcaemic disorders; maximum duration of therapy over patient's lifetime is 24 months

Table 4: **Adverse events and contraindications for approved pharmacological interventions for osteoporosis**

and hip fractures, and the effects are evident within the first year of therapy.[112] BMD increases progressively over 10 years of therapy and is consistent with persistence of protection from fracture for this period.[122] Skin rash and infection occur more frequently with denosumab than with placebo. The theoretical concern about possible immune dysfunction and increased risk of serious infection has not been observed in follow-up studies of up to 10 years. Very rare cases of atypical femoral fractures and osteonecrosis of the jaw have been observed with long-term therapy, but the relationship between duration of denosumab therapy and these possible side-effects is unclear.

Upon stopping treatment with denosumab, indices of bone remodelling quickly rise above baseline levels before returning to pre-treatment levels. Rapid decreases in BMD and loss of vertebral fracture protection occur, and multiple vertebral fractures have been reported to occur 3–18 months after stopping denosumab treatment.[123] Patients and their health-care providers should be counselled about the importance of adherence to a regular treatment regimen and, if treatment is stopped, maintenance of treatment benefits with another antiresorptive drug is usually indicated.

Hormone replacement therapy

Oestrogen therapy, with or without a progestin, effectively prevented bone loss in postmenopausal women and reduced the risk of vertebral and hip fractures by 34% in the low risk population of the Women's Health Initiative study.[113] Initiation of oestrogen therapy is not recommended in women more than 10 years beyond menopause because of concerns about cardiovascular safety, but starting soon after the menopause does not appear to be associated with increased cardiovascular risk.[124] Guidelines recommend the use of oestrogen for management of menopausal symptoms in early menopausal women, and as therapy to prevent bone loss and reduce fracture risk in women at high risk of fracture when alternate therapies are not appropriate.[125]

Selective oestrogen receptor modulators

Raloxifene, an oestrogen agonist and antagonist, is a weak antiresorptive agent known to reduce the risk of vertebral but not non-vertebral or hip fracture in women with postmenopausal osteoporosis.[114] Raloxifene might worsen hot flashes, carries an oestrogen-like risk of venous thrombosis, and in women with risk factors for coronary heart disease (average age 67·5 years), was associated with an increased risk of death from stroke.[126,127] However, the therapy substantially reduces the risk of invasive breast cancer. Raloxifene is an appealing treatment option for younger postmenopausal women with osteoporosis without pronounced vasomotor menopausal symptoms, who are at risk for vertebral but not hip fractures, and who have no risk factors for venous thrombosis, especially if they are concerned about breast cancer risk. As the patient ages and hip fracture becomes a greater clinical concern, switching to a drug known to reduce hip fracture risk might be appropriate.

The effects of bazedoxifene on fracture risk in women with postmenopausal osteoporosis and its safety profile are similar to that of raloxifene.[115] The combination of conjugated oestrogen and bazedoxifene is approved in the USA for prevention of postmenopausal osteoporosis.[116]

Teriparatide

Teriparatide, administered daily by subcutaneous injection for 18–24 months reduced the risk of vertebral and non-vertebral fracture.[117] In a randomised, matched comparison study, teriparatide was significantly more effective in protecting postmenopausal women with osteoporosis from fracture than was risedronate.[128] Teriparatide should not be used in patients with hypercalcaemia, previous radiation therapy to the skeleton, skeletal malignancies, or bone metastases and use is limited to 18–24 months because of theoretical concerns about increased risk of osteosarcoma. Upon discontinuing therapy, switching to a bisphosphonate or denosumab is associated with preservation of, or increase in, BMD.[129]

Abaloparatide

Abaloparatide, a synthetic analogue of PTHrP, has skeletal effects similar to teriparatide. In a study of postmenopausal women with osteoporosis, administration of 80 µg abaloparatide daily by subcutaneous injection was compared with teriparatide 20 µg daily, and placebo. After 18 months treatment with abaloparatide, the risk of vertebral and non-vertebral fractures was significantly reduced, by 86% and 43%, respectively, when compared with placebo.[118] Hypercalcaemia was significantly less common in abaloparatide-treated than teriparatide-treated women (3·4% *vs* 6·4%). This drug has been approved in the USA, but registration was denied in Europe on the grounds of concerns about its effectiveness in reducing non-vertebral fractures, and increases in heart rate and palpitations.

Combining osteoporosis therapies

Studies have not yet justified the use of two antiresorptive agents simultaneously.[129] The combination of bisphosphonates and teriparatide does not produce any meaningful benefit over monotherapy. Beginning treatment with both teriparatide and denosumab results in faster and greater gains in BMD than with either therapy alone, but whether this combination results in greater protection from fracture is not known. Conversely, using drugs in sequence to accomplish long-term management is encouraged. Oestrogen and raloxifene are appropriate in younger postmenopausal women, and teriparatide and abaloparatide are appropriate for patients at imminent risk of vertebral fracture. Following each of these therapies, continuation of treatment with a bisphosphonate or

denosumab should be considered in patients with a high risk of fracture.

Osteoporosis in men

The safety and effects of therapies on BMD and bone turnover appear to be similar in men and postmenopausal women with osteoporosis.[130] Although few studies have evaluated fracture risk in response to treatment in men, recommendations for use of bisphosphonates, denosumab, and teriparatide are similar in men and women.

Glucocorticoid-induced osteoporosis

Because fracture risk increases rapidly after initiation of glucocorticoid therapy, bone protective treatment should be started as early as possible in high-risk individuals. Alendronate, risedronate, zoledronic acid, denosumab, and teriparatide are all approved for use in glucocorticoid-treated patients at increased risk of fracture, because of their effects on BMD.[131–135] Post-hoc or safety analyses from clinical trials also indicate that alendronate, risedronate, and teriparatide reduce vertebral fracture risk, and large cohort studies provide evidence that bisphosphonates can also reduce non-vertebral fractures, including hip fractures.[136,137] In a BMD comparator study of teriparatide and alendronate, significantly fewer new vertebral fractures were seen at 18 and 36 months in teriparatide-treated individuals.[135] Denosumab has been shown to be more effective than risedronate in increasing BMD in glucocorticoid-treated individuals.[138]

Potential new treatments

Romosozumab, which is a humanised antibody that binds sclerostin, markedly but transiently activates bone formation and inhibits bone resorption, which results in large increases in BMD.[139] Results of two fracture endpoint studies showed that beginning treatment with romosozumab therapy for 12 months, followed by either denosumab or alendronate, is more effective than treatment with either denosumab alone (initiated after 12 months of placebo) or alendronate alone (initiated at baseline).[140,141] An increased risk of cardiovascular adverse events with romosozumab was observed compared with alendronate, but not compared with placebo. Results of these studies have been submitted for regulatory review.

Fracture liaison services

Fracture liaison services (FLS) provide a model that delivers comprehensive assessment and management for people who have sustained a fragility fracture.[142] When operating to best practice standards, FLS are cost-effective, improve treatment rates and adherence, and lower re-fracture rates and mortality.[143] Although FLS have been set up in many parts of the world, they serve only a small minority of individuals with fragility fracture, and wider coverage is an important priority for the future.

Duration and monitoring of therapy

In most people at high risk of fracture with irreversible risk factors, life-long management is usually required. Pivotal clinical trials of bisphosphonates have mostly been limited to 3 years, and evidence for their efficacy with longer treatment duration is based on the results of extension studies. Evidence has shown that fracture reduction is maintained for up to 5 years of treatment, but few data are available for effects beyond this period.

Bisphosphonates are retained in bone for some time after therapy is withdrawn and continue to have beneficial effects for varying periods of time, depending on the bisphosphonate. Decreases in BMD are seen within 2–3 years after cessation of alendronate or zoledronic acid therapy and after 1–2 years for risedronate or ibandronate.[144] Post-hoc analyses of extension studies of alendronate and zoledronic acid suggest that continuation of treatment for 5 years for alendronate and 3 years for zoledronic acid is associated with a decrease in vertebral fractures when compared with placebo; no reduction in non-vertebral fractures was shown, although the power to analyse a reduction was limited.[145,146] Women most likely to benefit from continued therapy were those with a low hip BMD (T score –2·0 or less; or less than or equal to –2·5), a prevalent vertebral fracture, or incident fracture during the initial treatment period.

Recommendations for clinicians are to advise an initial treatment period of 5 years for oral bisphosphonates and 3 years for intravenous zoledronic acid (figure 4).[58,144,147] The evidence base for longer durations of treatment is weaker, but continuation of treatment for a further 5 years or 3 years should be considered in individuals with persistently low hip BMD, prevalent vertebral fracture, history of hip fracture, incident fracture during

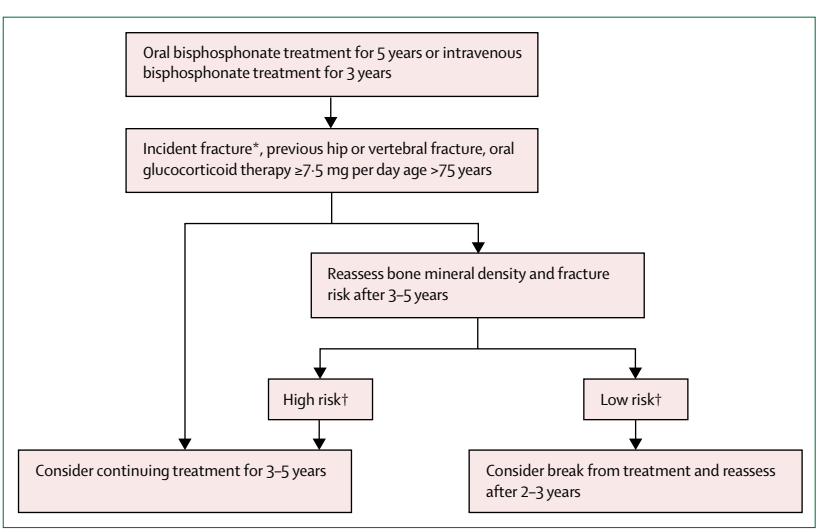

Figure 4: **Suggested approach for management of individuals on long-term bisphosphonate therapy**
*In patients who have a fragility fracture during therapy, check adherence, exclude secondary causes of osteoporosis, and re-evaluate treatment choice. †Use country-specific intervention thresholds for treatment decision, based on bone mineral density or fracture probability or both.

treatment, oral glucocorticoid therapy, age older than 75 years, or high fracture probability as estimated by FRAX. In patients who do not fall within these categories, fracture risk should be reassessed after the initial treatment period, and a period of 2–3 years with no treatment should be considered, with subsequent fracture risk assessment at the end of this period. These recommendations are based solely on evidence from studies of postmenopausal women, and there is not yet evidence to guide treatment durations of over 10 years.

For non-bisphosphonate therapies, reversal of the beneficial effects of treatment on BMD is seen within the first year after cessation of therapy, and maintenance of treatment benefits with other drugs is therefore often required.

Routine monitoring using BMD or bone turnover marker measurements during the initial 3–5 year period of treatment is controversial. Although treatment-related increases in hip BMD are associated with reduced fracture risk compared with stable BMD, and decreases in BMD are associated with greater risk for fractures, whether such information usefully informs treatment decisions and leads to improved fracture outcomes is uncertain.[148] However, in people who sustain a fracture while receiving treatment, adherence to therapy should be checked, BMD measured, secondary causes of osteoporosis excluded, and a switch to an alternative therapy considered. Evidence suggests that review of therapy 3 months after starting treatment by a health-care professional could be helpful to improve adherence to therapy.[149] The role of biochemical turnover markers in monitoring therapy requires further investigation. However, a reduction in these markers following initiation of antiresorptive therapy might be useful to establish treatment adherence and response, whereas an increase in markers can aid decisions about restarting treatment after a break from drugs.

Conclusion

Fractures resulting from osteoporosis are a major cause of morbidity and mortality in older people. Despite substantial advances in fracture risk assessment and the availability of a range of pharmacological options to reduce fracture risk, many high-risk individuals do not receive adequate investigation and treatment. Challenges for the future include wider implementation of integrated systems of care such as Fracture Liaison Services, improving treatment adherence, and establishing effective and safe long-term treatment regimens to provide sustained reductions in fracture risk.

Contributors

All authors contributed equally to the first and subsequent drafts of the manuscript. WDL did the literature search.

Declaration of interests

JEC has received consulting fees and honoraria from Gilead and Amgen and is Chair of the National Osteoporosis Guideline Group. MRM has received consulting fees and honoraria from Amgen and Radius Health. WDL declares no competing interests.

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