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Postmenopausal osteoporosis: Assessment and management

René Rizzoli, Emeritus professor of medicine

Service of Bone Diseases, Geneva University Hospitals and Faculty of Medicine, 1211 Geneva 14, Switzerland

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Osteoporosis increases the risk of fractures, which are associated with increased mortality and lower quality of life. Patients with prevalent fracture are at high risk to of sustaining another one. Optimal protein and calcium intakes, and vitamin D supplies, together with regular weight bearing physical exercise are the corner stones of fracture prevention. Evidence for anti-fracture efficacy of pharmacological interventions relies on results from randomised controlled trials in postmenopausal women with fractures as the primary outcome. Treatments with bone resorption inhibitors, like bisphosphonates or denosumab, and bone formation stimulator like teriparatide, reduce vertebral and non-vertebral fracture risk. A reduction in vertebral fracture risk can already be detected within a year after starting therapy.

Introduction

Osteoporosis is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and in susceptibility to fracture risk [1]. The diagnosis of the disease relies on the quantitative assessment, using dual energy x-ray absorptiometry (DXA), of areal bone mineral density (aBMD) at hip or spine, which represents an important determinant of bone strength and thereby of fracture risk. The operational definition of osteoporosis is based on aBMD lower than the lower limit of normal range of young healthy women, as defined in a WHO document [2]. An osteodensitometry-based diagnosis of osteoporosis together with a prevalent fragility fracture defines severe osteoporosis. Indications to

E-mail address: rene.rizzoli@unige.ch.

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treatment depend on the evaluation of fracture risk, which also integrates other clinical risk factors than osteoporosis densitometric diagnosis [1].

Epidemiology

Bone mass decreases and the risk of osteoporotic fracture increases with ageing, with an accelerated bone loss after menopause. As the populations become older, the numbers of individuals who face the problem of bone fragility and increased fracture risk increases inexorably. In 2010, it was estimated that 22 million women in the EU had osteoporosis using the diagnostic criterion of the WHO [3]. At the age of 50, the lifetime risk of sustaining an osteoporotic fracture is close to 50% for women and more than 20% for men [1,4]. Major osteoporotic fractures comprise spine, hip, distal forearm and proximal humerus fractures.

The number of new fractures in 2010 in the EU was estimated at 3.5 million, comprising approximately 610,000 hip fractures, 520,000 vertebral fractures, 560,000 forearm fractures and 1,800,000 other fractures such as pelvis, rib, humerus, tibia, fibula, clavicle, scapula, sternum, and other femoral fractures [3]. Hip fracture event cannot remain unrecognized, being nearly always surgically treated in hospitals. Most, if not all, hip fractures associated with osteoporosis result from a fall from standing height, which defines fragility fractures. More than 50% of patients admitted to hospital with hip fracture are over 80 years old [5]. Around 2% of falls in the elderly lead to fractures.

Only a fraction of all x-ray determined vertebral fractures comes to clinical attention and is diagnosed. Furthermore, even if the criteria used to define vertebral fracture may vary, deformities of vertebral body on conventional x-ray examination remain largely under-recognized, or not mentioned in the radiologist report [6].

The incidence of osteoporotic fractures varies from region to region (Fig. 1). This may be related to population age distribution, genetic background, or life-style conditions, but are unlikely to be explained by regional variations in BMD levels. Up to 40% of hip fractures occur in patients living in nursing homes [7]. This is probably related to advanced age, to a high prevalence of comorbidities requiring long-term care and high risk of recurrent falls in this population.

Despite a rising number of old subjects and a forecasted increase of absolute number and incidence of hip fractures, a decrease in age-adjusted incidence has been observed in several regions, thus a reversal of a secular trend [5]. However, the incidence of other osteoporotic fractures is continuing to increase, as is the total number of days in orthopedic and rehabilitation wards, because of more frequent multiple fractures and higher number co-morbidities [8].

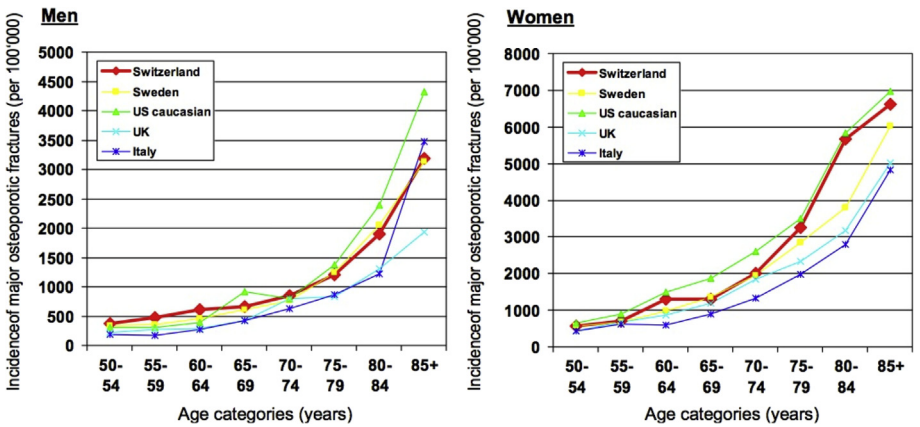

Fig. 1. Comparative incidence of major osteoporotic (hip, spine, distal radius and proximal humerus) (number of fractures per 100'000 inhabitants). There is an exponential increase in fracture incidence particularly in the oldest old. From Lippuner et al. Ref. [4].

Burden of the disease

Among the complications of osteoporosis, hip fracture represents the most dramatic expression of the disease, in terms of morbidity, mortality and medical costs. Increased mortality has been consistently demonstrated after hip or vertebral fracture. Hip fracture is associated with a 20% excess mortality within the first year after surgery [7,9]. Reduced survival cannot be attributed directly to the fracture, but to underlying cardiovascular or pulmonary diseases, which might become decompensated because of the fracture event. By the prolonged handicaps they cause, fractures are a major threat for the quality of life of the elderly and represent a significant cause of health expenses. By one year after hip fracture, close to 20% of the patients still require rehabilitation in hospital [7]. This burden is a major consumer of health care. Consequences of osteoporotic fractures are going to compromise the economy and social equilibrium in many countries in which the proportion of elderly is exploding.

Pathophysiology of bone loss

From the age of 50 in women, bone loss accelerates through bone cortex thinning, increased cortical porosity and trabeculae destruction by thinning and perforation [10]. Bone loss does not attenuate with age, but continues throughout the whole life, at least in peripheral skeletal sites. Various factors contribute to age-related bone mass decrease and microstructural alterations.

Hormones

Estrogen deficiency increases bone turnover with an imbalance between bone formation and resorption, and appears to be a main cause of osteoporosis observed in women after the fifth decade. It is associated with an increased production of a variety of cytokines released in the bone marrow environment, which stimulates bone resorption by raising the number and/or the activity of the bone resorbing cells osteoclasts. Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF), Tumor Necrosis Factor-alpha (TNF-alpha), Interleukin-1, Interleukin-6, and Receptor Activator Nuclear Kappa-b Ligand (RANKL) are cytokines implicated in sex hormones deficiency induced bone loss. GM-CSF and RANKL are necessary for osteoclast generation [11].

Primary hyperparathyroidism increases bone turnover and is associated with some bone loss. An excess of thyroid hormones also increases the rate of bone remodelling. Thus, bone loss can occur in hyperthyroidism and in patients under long-term thyroid hormone therapy at doses suppressing TSH. The main net effect of glucocorticoid excess is the reduction of bone formation, early bone loss and increased fracture risk [12]. In addition, glucocorticoids excess causes muscle wasting.

Nutrition

Nutritional deficiencies play a significant role in osteoporosis in elderly [13]. Nutritional insufficiency and malnutrition are frequent in older people, and particularly prevalent in patients with hip fracture. With ageing there is a decrease in calcium intake, in the intestinal absorption of calcium, in the absorptive capacity of the intestinal epithelium to adapt to a low calcium intake, in the exposure to sunlight and the capacity of the skin to produce vitamin D. A state of chronic secondary hyperparathyroidism resulting from calcium and vitamin D deficiencies increases bone turnover and favours a negative bone balance, hence osteoporosis.

The prevalence of protein-energy malnutrition is as high as 4–10% in elderly persons living at home, 15–38% in those in institutional care, and 30–70% in hospitalized elderly patients [14]. Malnutrition and particularly protein-energy malnutrition is a risk factor for osteoporosis, sarcopenia and frailty [13,15]. Various studies have found a relationship between protein intakes and calcium-phosphate or bone metabolism and have come to the conclusion that either a deficient or an excessive protein supply could negatively affect the balance of calcium. Questionnaires such as the Mini Nutritional Assessment (MNA) or the SNAQ65+, which have been validated in older persons are useful in this respect to assess nutritional status [14].

Protein intakes influence the production of Insulin-like growth factor-I (IGF-I), which is an important trophic hormone, mediating the effects of growth hormone (GH), having growth-promoting effects on almost every cell in the body, especially skeletal muscle, cartilage and bone. It regulates phosphate reabsorption in the kidney and has a stimulatory effect on the active uptake of calcium and phosphate from the intestine via the renal synthesis of calcitriol [16]. The plasma IGF-I concentration has utility as a nutritional biomarker. A sufficient protein intake is mandatory for bone health, particularly in elderly [13,17,18].

A state of undernutrition on admission can adversely influence their clinical outcome. Intervention studies using supplements, or even an oral dietary preparation that normalize protein intake, can improve the clinical outcome after hip fracture, by lowering the rate of complications, such as bedsore, severe anemia, intercurrent lung or renal infections [13] and shorten the length of stay in rehabilitation wards.

Mechanical causes

Immobilisation is an important cause of bone loss. Enforced immobilisation in healthy volunteers or motor deficits due to neurological disorders such as hemiplegia or paraplegia result into a decrease in bone mineral mass. This underlines the importance of weight bearing in the maintenance of bone mass [19,20]. Immobilisation results in a negative uncoupling, the amount of resorbed bone being greater than formed at the tissue level, is associated with increased osteoclastic resorption and decreased osteoblastic formation at the cellular level, and there is an increase in the bone formation inhibitor sclerostin produced by the osteocytes at the molecular level [21].

Toxic causes

Excessive alcohol consumption is a risk factor for osteoporosis [22]. Reduced rate of bone formation has been associated with alcohol abuse. High intake of alcohol is often associated with marked dietary disturbance such as low protein intake, other changes in lifestyle, liver disease, and decreased testosterone production. An increased risk of both axial and appendicular osteoporotic fractures is found in smokers [23].

Diagnosis of osteoporosis

The objectives of bone mineral density measurements are to provide diagnostic criteria, information on the probability of fractures, and a baseline value on which to monitor treated or untreated patient. Bone mineral density (BMD) is the amount of bone mass per unit volume (volumetric density), or per unit area (areal density). Areal BMD accounts for about two thirds of the variance of bone strength as determined *in vitro* on isolated bones [24]. The most widely used are based on X-ray absorptiometry in bone, particularly dual energy X-ray absorptiometry (DXA) [1]. Other techniques include quantitative ultrasound (QUS), quantitative computed tomography (QCT) applied both to the appendicular skeleton and to the spine, peripheral DXA, digital X-ray radiogrammetry, radiographic absorptiometry, and other radiographic techniques. Other important determinants of bone strength for both cortical and trabecular bone include macro- and microarchitecture [1].

Moderate or severe vertebral fractures, even when asymptomatic, are strong risk factors for subsequent fracture. Vertebral fracture assessment should therefore be considered in high-risk individuals, using either lateral lumbar and thoracic spine radiographs or lateral spine DXA imaging. Vertebral fracture assessment should be considered in postmenopausal women if there is a history of $\geq$4 cm height loss, hyperkyphosis, recent or current long-term oral glucocorticoid therapy, or a BMD T-score ≤ -2.5, as in individuals with a history of non-vertebral fracture [1].

The operational definition of osteoporosis (endorsed by the World Health Organization [WHO]) is an areal bone mineral density (aBMD) T-score (T-Score = [measured BMD − Young Adult BMD]/Young Adult SD) of −2.5 or lower (i.e. at least 2.5 standard deviations below average bone mineral density of healthy young individuals), where aBMD is assessed by dual X-ray absorptiometry (DXA) at spine or hip [1]. Between −1.0 and −2.5 standard deviations corresponds to low bone mineral mass or osteopenia.

Areal BMD integrates the size of the bone and its thickness, as well as the true volumetric density. Above the age of 65, osteoarthritis makes the measurement of lumbar spine BMD less reliable for diagnosis purpose. Femoral neck aBMD appears to be a good predictor of fracture of the proximal femur [25]. Proximal femur measurements are influenced by a variety of factors likely to impair accuracy and decrease precision of the measurement. The size of the region of interest as well as its location along the hip axis, the degree of leg rotation or abduction can affect proximal femur aBMD measurement. The potential for error in terms of both accuracy and precision emphasizes the need for strictly controlled conditions of measurements.

The resistance to loading or bending of bones is influenced not only by the amount of bone mass, but also by its geometrical distribution and its microstructure, included cortical porosity [10,24] as well as cortical and trabecular bone material level properties. Microstructure variables can be evaluated using high-resolution peripheral quantitative computerized tomography. Bone strength can be estimated from quantitative computerized tomography data using finite element analysis [26].

The prediction of low-trauma fractures in postmenopausal women can be improved beyond DXA and FRAX with the assessment of peripheral cortical and trabecular volumetric BMD and microstructure. Cortical area and trabecular BMD predict low-trauma fractures independently of each other [27]. The best prediction is obtained with the combination of trabecular and cortical variables at the radius. The associations are higher for the risk of multiple and imminent low-trauma fractures. Estimated bone strength has similar performance than the combination of cortical area and trabecular BMD, but aBMD measured by DXA at the same bone site (ultra-distal radius) captures a substantial proportion of the information provided by this combination or failure load [27].

The degree of bone remodelling can be assessed by the measurement of biochemical markers of bone turnover under specified pre-analytical conditions [28]. The potential use of biochemical markers of bone turnover includes the prediction of bone loss (the higher the bone turnover, the greater the postmenopausal bone loss), the prediction of fracture risk and the monitoring of therapy with anti-catabolic agents (prediction of response and verification of the compliance) [28]. The International Osteoporosis Foundation and the International Federation of clinical Chemistry and Laboratory Medicine (IFCC) have proposed two of several markers as reference analytes in the prediction of fracture risk; serum procollagen type I N propeptide (s-PINP) and serum C-terminal cross-linking telopeptide of type I collagen (s-CTX) as markers of bone formation and bone resorption, respectively [29]. Pre-analytical conditions are of major importance, with blood samples drawn on fast and in the early morning.

After the diagnosis of osteoporosis it is important to determine if the patient has primary osteoporosis (age-related bone loss) or secondary osteoporosis, caused by underlying diseases, amenable to interventions, such as metabolic diseases, nutritional deficiencies, or medication (particularly glucocorticoids).

Risk assessment and intervention thresholds

A diagnosis threshold as determined by aBMD, should not be automatically translated into a therapeutic threshold. Other factors such as age, clinical risk factors (prevalent fracture, parental hip fracture history, current smoker, $\geq$ 3 alcoholic drinks/day, rheumatoid arthritis, current corticosteroid use, body mass index (BMI) < 20 kg/m^2, or secondary osteoporosis), bone turnover or treatment cost/benefits, should be included into the treatment decision [1]. Thus, the risk of fracture for an individual is related to aBMD and to a series a number of factors independent from aBMD. For instance, the same T-score with the same technique at any one site has a different significance at different ages. For any aBMD value, fracture risk is much higher in the elderly than in the young [1]. The objective of the risk estimation is to identify the individuals at higher fracture risk, and to provide treatment accordingly [1].

Of the various risk assessment tools developed in osteoporosis, the FRAX® model is the most widely used. FRAX® is a computer based algorithm (http://www.shef.ac.uk/FRAX) that calculates the 10-year probability of a major osteoporotic fracture (hip, clinical spine, humerus or wrist fracture) and the 10-year probability of hip fracture, but is also capable of predicting asymptomatic vertebral fractures. Since its first release, it has been updated to take into account glucocorticoid dose [30], large differences in femoral neck and lumbar spine aBMD [31]. It adjusts also the result in very old patients for the

competing hazard of death, and for country specific fracture epidemiology. The intervention thresholds for osteoporosis depend on regional guidances and country specific reimbursement policies, and these are increasingly guided by economic evaluations to determine cost-effective intervention thresholds.

There are 2 main approaches for determining an intervention threshold Fig. 2. One approach recommends a fixed threshold, irrespective of age. A treatment is recommended for T-score of ≤ -2.5 at femoral neck; or, if the T-score is between -1.0 and -2.5, for a 10-year probability of fracture (based on FRAX) of $\geq$3% for hip or $\geq$ 20% for a major fragility fracture. Another approach is to treat when the age-related fracture probability exceeds a threshold given by FRAX, equivalent to the fracture risk of a woman with a prior fragility fracture [1]. The argument for an age-dependent intervention threshold is to avoid under-prescription of treatment in eligible younger patients as well as the over-prescription in older age groups that could arise from a fixed threshold [32]. For instance, using an anti-osteoporosis treatment intervention threshold of 20% for major fractures 10-year probability would concern 70% of a population older than 75 years [33]. Most guidelines recommend that women with a prior fragility fracture should be considered for intervention without the necessity for a BMD test (other than to monitor treatment). Therefore, a prior fragility fracture can be considered to carry a sufficient risk that treatment can be recommended. FRAX tool can be applied as an osteoporosis screening approach, as shown in the SCOOP trial (SCreening of Older wOmen for the Prevention of fractures). In this study, women aged 70–85 years were randomised to receive a care algorithm including FRAX and drug targeting, or usual primary care for osteoporosis [34]. Over the five-year period of follow-up, there was a reduction in the risk of hip fracture (HR 0.72; 95% CI 0.59–0.89; $p = 0.002$), in the group with screening. The screening algorithm resulted in an increase in the use of anti-osteoporosis medication, and greater compliance with therapy.

Strategies to prevent falls and to prevent bone loss in older individuals

Patients who have recovered from a major fracture are significantly more likely to fall. Intrinsic risk factors include gait deficits, dizziness and orthostasis, visual impairment, depression, functional and cognitive impairment, low body mass index, urinary incontinence, chronic musculoskeletal pain, and aged 80 years and older.

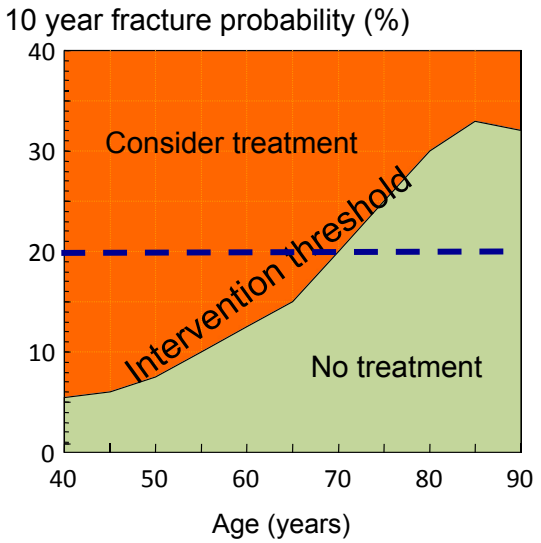

Fig. 2. Intervention threshold according to FRAX-determined 10-year fracture probability. The age-dependent threshold corresponds to the risk equivalent to that associated with a prevalent fragility fracture.

Although a number of risk factors for falling are not modifiable, such as age, others are amenable to changes, like decreased visual acuity, medications that can diminish awareness and/or balance, and home environment (slippery floors and mats, poor lighting) [35]. Exercise programs focussing on gait, co-ordination and functional tasks, as well as muscle strengthening exercises other than just walking seem to improve clinical balance outcomes in older people [36,37]. Concomitant medication to be avoided in older adults has been addressed in the updated Beers criteria from the American Geriatrics Society [38]. A multi-task music-based training like Jaques-Dalcroze eurhythmic exercise, has been shown to reduce gait and balance variability, and lower fall risk [39,40]. Some studies, some not, have reported fall risk reduction in the elderly with Tai Chi [41]. Reducing falls can be associated with a lower fracture risk [42].

Weight bearing exercise forms an integral component of osteoporosis management [43]. At all times, increased muscle strength through resistance training contributes to reduce fracture risk by maintaining bone mass, by stimulating bone formation and decreasing bone resorption [44]. Mixed loading exercise appears to be effective to reduce bone loss in postmenopausal women [19,20]. Some prevention of hip fracture by physical activity has been consistently reported [45].

The American Heart Association and the American College of Sports Medicine encourage older adults to accumulate 30–60 min of moderate intensity aerobic exercise per day (150–300 min/week) or 20–30 min of vigorous intensity exercise per day (75–150 min/week) [46]. For healthy older adults, exercise of 10–15 min per session with 8 repetitions for each muscle group is a reasonable goal. Dietary proteins following physical exercises magnify de novo muscle protein synthesis and improves muscle strength [47].

Nutritional supplementation and vitamin D

Vitamin D supplementation

Vitamin D plays an essential role in the maintenance of bone strength and muscle function [48]. This nutrient/cofactor is involved in the absorption of calcium and phosphorus from the intestine, for the mineralization of bone and maintenance of muscle quality as well as potentially a variety of beneficial effects on other organ systems. Vitamin D is synthesised in skin during sun exposure or ingested as part of a balanced diet. Older individuals synthesise lower amounts of vitamin D in skin (they also tend to expose their skin less than younger adults) and they frequently have nutritionally impoverished diets. Thus, many older people suffer from hypovitaminosis D. This is particularly true in patients with hip fracture [49].

A large number of clinical studies have tested the effects of vitamin D supplementation (often in combination with calcium) on fracture risk in older and/or osteoporotic population samples. Meta-analyses of these trials have returned equivocal results. However, it is generally recognized that a positive relationship exists between vitamin D intake and the reduction in risk of non-vertebral and hip fracture [32,48]. For example, in a pooled analysis of 11 trials ($N = 31{,}000$) a lower fracture risk was associated with patients having a plasma concentration of 25-hydroxy vitamin D (25-(OH)D) of at least 60 nmol/L at baseline as compared with those having levels below 30 nmol/L [50]. Vitamin D supplementation has beneficial effects beyond a direct effect on bone health. Raising the levels of 25-(OH)D decreased the incidence of falls in older persons by 19%. Other studies and meta-analyses on vitamin D supplementation have concluded that it is associated with a reduction in all-cause mortality [51].

Sufficient levels of vitamin D are a prerequisite for the efficacy of anti-osteoporosis medication, as all studies on these agents have been conducted in calcium and vitamin D-supplemented patients. The recommendation of a dose of 800 IU/day (20 μg/day) in older adults (>70 years) has been adopted by most European guidelines, as well as the International Osteoporosis Foundation (IOF) and the Institute of Medicine (IOM) and was also advised in a ESCEO consensus paper [48,52,53]. There is no strong necessity to systematically measure circulating levels of 25-(OH)D in older patients with suspected high fracture risk since the cost of testing far exceeds that of supplementation. Vitamin D supplementation should precede any anti-osteoporosis therapy. The adverse effects of hypercalcemia/hypercalciuria and nephrolithiasis are more frequently associated with high serum 25-(OH)D levels

(>125 nmol/L), which has been set as the potential upper limit of adequacy. Studies with large annual doses of vitamin D have reported an increased risk of falls and hip fracture [54]. Thus, a yearly regimen of vitamin D high dose supplementation should be avoided.

Calcium supplementation

It is important to ensure a sufficient calcium intake through a balanced diet. Calcium and vitamin D supplements decrease secondary hyperparathyroidism and reduce the risk of proximal femur fracture, particularly in the elderly living in nursing homes [55]. Intakes of at least 1000 mg/day of calcium in addition to 800 IU of vitamin D can be recommended in the general management of patients with osteoporosis [53].

A meta-analysis has concluded that calcium supplements without co-administered vitamin D were associated with an increased risk of myocardial infarction [56]. There was no increased risk when calcium was of dietary origin. Large long-term observational studies have not confirmed this hypothesis [57,58]. Overall, it can be concluded that 1) calcium and vitamin D supplementation may lead to a modest reduction in fracture risk, although population-level intervention has not been shown to be an effective public health strategy; 2) supplementation with calcium alone does not reduce fracture risk; 3) side effects of calcium supplementation include renal stones and gastrointestinal symptoms; 4) vitamin D supplementation, rather than calcium, may reduce falls risk; and 5) increased cardiovascular risk consequent to calcium supplementation is not convincingly supported by current evidence; 6) calcium and vitamin D supplementation is recommended for patients at high risk of calcium and vitamin D insufficiency, and in those who are receiving treatment for osteoporosis [59].

Dietary protein intakes

Correction of protein insufficiency can lead to a rapid normalisation of IGF-I levels in frail older adults and in patients with a recent hip fracture [13]. In view of the impaired protein assimilation of older individuals, the RDA (0.8 g/kg body weight) should be increased to 1.0 or 1.2 g/kg per day in the older age group without adverse event [17,18].

Dairy products are a source of both protein and calcium, since one litre of milk provides 32 g of protein and 1200 mg of calcium. Dairy products, some being fortified with calcium or vitamin D, decrease circulating PTH, increase IGF-I, and decrease bone resorption markers [60]. Dairy products are associated with higher bone strength [61]. In older US men and women, higher milk consumption is associated with a lower hip fracture risk [62].

Pharmacological strategies

Efficacy of anti-osteoporotic drugs

Anti-osteoporosis drugs are either anti-resorbers or stimulators of bone formation. The efficacy of the available anti-osteoporotic agents in increasing bone strength and reducing osteoporotic fracture risk is well established [1,32]. For some of the anti-osteoporosis agents, the beneficial effect of treatment has also been demonstrated on hip fractures (Table 1). Agents that have been approved for the treatment of osteoporosis in postmenopausal women include selective estrogen receptor modulators (SERMs), bisphosphonates (alendronate, risedronate, zoledronic acid and ibandronate), denosumab and teriparatide [1].

Selective estrogen-receptor modulators

Selective estrogen-receptor modulators (SERMs) are nonsteroidal agents that bind to the oestrogen receptor and act as estrogen agonists or antagonists, depending on the target tissue. Raloxifene is available for the prevention and treatment of postmenopausal osteoporosis. Raloxifene prevents bone loss and reduces the risk of vertebral fractures by 30–50% in postmenopausal women with low bone mass, with osteoporosis, with or without prior vertebral fractures as shown in the MORE trial [63].

Table 1
Antifracture efficacy of the most frequently used treatments for postmenopausal osteoporosis when given with calcium and vitamin D, as derived from randomized controlled trials [updated from Ref. [1]].

	Effect on vertebral fracture risk		Effect on non-vertebral fracture risk	
	Osteoporosis	Established osteoporosis[a]	Osteoporosis	Established osteoporosis[a]
Alendronate	+	+	NA	+ (including hip)
Risedronate	+	+	NA	+ (including hip)
Ibandronate	NA	+	NA	+ [b]
Zoledronic acid	+	+	NA	+ [c]
HRT	+	+	+	+ (including hip)
Raloxifene	+	+	NA	NA
Teriparatide	NA	+	NA	+
Denosumab	+	+ [c]	+ (including hip)	+ [c]

NA, no evidence available.
+, Effective drug.
[a] Women with a prior vertebral fracture.
[b] In subsets of patients only (post-hoc analysis).
[c] Mixed group of patients with or without prevalent vertebral fractures.

There is no significant reduction of non-vertebral fractures, except in women with severe vertebral fractures at baseline [64].

As adverse events, there is an increase of deep venous thrombo-embolism, of hot flushes and of lower limb cramps. The risk of invasive breast cancer is reduced by about 60% [65]. In the RUTH study, raloxifene had no effect on cardiovascular death and on the incidence of coronary heart disease and stroke [66]. Raloxifene is approved for the prevention and treatment of postmenopausal osteoporosis.

Though approved in Europe, bazedoxifene is only available in Spain and Germany. It reduces the risk of new vertebral fracture, with favourable effects on bone mineral density, bone turnover markers and lipid profile [67,68]. In a subgroup of women at increased risk of fracture, bazedoxifene decreases non-vertebral fracture risk. Like with raloxifene, venous thromboembolic events, deep vein thromboses, leg cramps and hot flushes are reported adverse events [69]. Bazedoxifene is also combined with conjugated equine estrogen to create a tissue selective estrogen complex for the management of vasomotor symptoms and the prevention of osteoporosis associated with menopause (bazedoxifene 20 mg/conjugated equine estrogen 0.45 mg) [70]. This association improves vasomotor symptoms while opposing breast and endometrial proliferation, preventing bone resorption, increasing BMD and improving lipid profile [70].

Bisphosphonates

Bisphosphonates are stable analogues of pyrophosphate characterized by a P-C-P bond. Their potency depends on the length and structure of the side chains [71]. Bisphosphonates have a strong affinity for bone hydroxyapatite and are potent inhibitors of bone resorption. They reduce the recruitment and activity of osteoclasts and increase their apoptosis. Aminobisphosphonates (alendronate, risedronate, ibandronate, zoledronic acid) inhibit the farnesyl pyrophosphate synthase step in the mevalonate pathway, thereby modifying the isoprenylation of guanosine triphosphate binding proteins. Non-nitrogen containing bisphosphonates (clodronate, etidronate, tiludronate) act as ATP competitors. The potency and chemical affinity to bone of bisphosphonates determines their effect to inhibit bone resorption and varies greatly from compound to compound [71]. Potency differences can range 10,000-fold *in vitro*, so that the doses used clinically also vary.

Oral bioavailability of bisphosphonates is around 1% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea, and orange juice. The oral formulation needs a 30- to 60-minute fast after ingestion and before any meal, without stretching out, to ensure optimal intestinal absorption and prevent oesophageal damages. Bisphosphonates are quickly cleared from plasma, about 50% being deposited in bone and the remainder excreted in urine. Their half-life in bone is very prolonged.

Alendronate

Oral alendronate lowers the incidence of vertebral, wrist, and hip fractures by approximately 50% in women with prevalent vertebral fractures [72,73]. In women without prevalent vertebral fractures,

there is no significant decrease in clinical fractures in the overall population, but a reduction in those patients with baseline hip BMD T-score lower than −2.5 SD [74]. In a case–control study performed in more than 90'000 men and women aged 80 years and older and with a prevalent fracture, alendronate use is associated with a 34% decrease in hip fracture risk, and a 12% lower mortality risk, but with a 58% increase in the risk of mild upper gastro-intestinal symptoms [75]. Pivotal trials have been conducted with a daily dose. The efficacy of the weekly 70 mg regimen has been shown in bridging studies with aBMD and bone turnover markers as outcome [76].

Risedronate

Oral risedronate reduces the risk of vertebral and non-vertebral fractures by 40–50% and 30–36%, respectively, in women with prevalent vertebral fractures [77,78]. In a large population of elderly women, risedronate decreases the risk of hip fractures by 30%. This effect is greater in osteoporotic women age 70–79 years (−40%), but not significant in women over the age of 80 years without evidence of osteoporosis [79]. A delayed-release formulation of 35 mg risedronate weekly allows osteoporotic patients to take their risedronate dose immediately after breakfast, offering thereby a potentially improved adherence to treatment [80].

Ibandronate

Daily oral ibandronate (2.5 mg) reduces the risk of vertebral fractures by 50–60%, whereas a lower non-vertebral fracture risk was only demonstrated in a post hoc analysis of women with a baseline aBMD T-score below −3 SD [81–83]. In bridging studies, oral ibandronate 150 mg once monthly or intravenous ibandronate 3 mg every 3 months are equivalent or superior to daily regimen in increasing aBMD and decreasing biochemical markers of bone turnover [84,85]. In post-hoc analyses, ibandronate regimens with annual cumulative exposure $\geq$10.8 g increase time-to-fracture for all clinical fractures versus placebo [86].

Zoledronic acid

In a large phase III trial comprising 7,700 postmenopausal osteoporotic patients, the yearly infusion of zoledronic acid 5 mg over three years, reduces the incidence of vertebral and hip fractures by 70% and 40%, respectively [87]. Intravenous zoledronic acid decreases fracture risk and mortality when given shortly after a first hip fracture [88]. From an extension study to 6 [89] and 9 [90] years, it appears that prolonging treatment beyond 6 years does not provide additional benefits.

Denosumab

Receptor activator of nuclear factor NFkB (RANK), its ligand RANKL, a member of the tumour necrosis factor (TNF) superfamily, and osteoprotegerin (OPG), which acts as a decoy receptor for RANKL, are critical molecules for differentiation and action of osteoclast and hence for bone resorption. The fully human antibody against RANKL denosumab prevents the interaction of RANKL with the receptor RANK.

Over a 3-year placebo-controlled pivotal trial, there is a 68% reduction in the incidence of new vertebral fractures with denosumab given subcutaneously every 6 months at a dose of 60 mg. Non-vertebral fracture risk is reduced by 20% and hip fractures by 40% [91]. In an extension study, women from the denosumab group had 7 more years of treatment (long-term group) and those in the placebo group received 7 years of denosumab (cross-over group) [92]. The yearly incidence of new vertebral fractures remained low during the extension, whereas non-vertebral fractures further decreased to reach a stable level [92].

Discontinuation of denosumab is associated with a rapid increase in bone turnover, even above pretreatment levels, an aBMD decrease, and a marked increase in vertebral fracture rate [93]. Multiple vertebral fracture risk was even higher than in the placebo group. A short duration of bisphosphonate could be considered when discontinuing denosumab to prevent the rebound in turnover [94,95].

Regarding adverse events, 7 cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the cross-over group [92]. In a meta-analysis of four trials, a non-statistically significant relative risk of serious adverse events for the denosumab group compared with the placebo group was 1.33, of serious adverse events related to infection 2.10, of neoplasm 1.11, of study discontinuation due to adverse events 1.10, and of death 0.78 [96].

Menopausal hormone therapy (MHT)

Estrogens prevent the accelerated bone turnover and bone loss following menopause at all skeletal sites. They decrease the risk of vertebral and non-vertebral fractures (including hip fracture) by about 30%, regardless of baseline BMD [97,98]. In a recent re-assessment of the long-term outcomes of WHI trials, MHT with conjugated oestrogen and medroxyprogesterone acetate for a median of 5.6 years or with conjugated estrogen alone for a median of 7.2 years was not associated with an increased risk of all-cause, cardiovascular, or cancer mortality during a cumulative follow-up of 18 years [99].

Teriparatide

Whilst a continuous increase of endogenous production of parathyroid hormone (PTH) is deleterious for the skeleton, intermittent administration of PTH (e.g. with daily subcutaneous injections) leads to an increase in bone mass and an improvement in skeletal microstructure at both cancellous and cortical skeletal sites [100].

At a daily subcutaneous dose of 20 μg, the 1-34 N-terminal fragment (teriparatide) reduces the risk of vertebral fractures (−65%) and non-vertebral fractures (−53%) [101]. Treatment with PTH is registered for 18–24 months, and beneficial effects on non-vertebral fracture with teriparatide persist for up to 30 months after stopping teriparatide [102].

Adverse events with teriparatide are nausea, pain in the limbs, headache and dizziness. Slight and transient elevations of serum calcium concentrations have been observed following the injection of teriparatide. The use of peptides of the PTH family is contra-indicated in conditions such as hypercalcemia, metabolic bone diseases other than osteoporosis, Paget's disease, prior radiation therapy to the skeleton, in malignancies or bone metastasis or severe renal impairment. In rats, very high doses of teriparatide since weaning increase the risk of osteosarcoma [103]. There is no confirmation of these findings in human.

Perspectives

Abaloparatide is a 34-amino-acid peptide with 76% homology to parathyroid-related protein (PTHrP) (1–34) and 41% homology to PTH (1–34) [104]. Abaloparatide is a potent and selective activator of the PTH receptor type 1 (PTHR1) signaling pathway.

At a daily dose of 80 μg subcutaneously, abaloparatide, increased aBMD more than teriparatide and reduces major osteoporotic fractures to a greater extent than teriparatide, with a possible more rapid onset of action [105]. Use of abaloparatide for 18 months followed by alendronate for 24 months improved spine, total hip and femoral neck aBMD and reduced vertebral, non-vertebral, major and clinical fractures compared to that observed after 18 months of placebo followed by 24 months of alendronate [106]. Adverse events were nausea, dizziness, headaches and palpitations, which are generally mild to moderate in severity [107].

Romozumab is an anti-sclerostin monoclonal antibody, which transiently stimulates bone formation and more persistently inhibits bone resorption [108]. In a one-year placebo controlled study, followed by one year of denosumab in both groups, romosozumab given subcutaneously monthly reduceda vertebral fracture risk by 73%, whilst the −25% observed for non-vertebral fracture was not statistically significant [109]. In another trial, romozosumab was compared to weekly alendronate during the first year and then both groups received the bisphosphonate for one year. By 2 years, vertebral, non-vertebral and hip fracture risk was decreased by 48, 19 and 38%, respectively [110]. In the latter trial, a higher number of adjudicated severe cardiovasccular events were recorded in the romozosumab treated patients. These results open the way to sequential regimens for the treatment of osteoporotic patients.

Early onset of anti-fracture efficacy

Anti-osteoporosis treatments are frequently under-prescribed, even in women who have sustained an osteoporotic fracture and are at increased risk of a subsequent fracture [111]. Clinicians may be reluctant to prescribe treatment because of doubts they might have over the effectiveness of treatment in a short period of time in patients with a limited life expectancy. Clinically significant benefits in terms of fracture reduction have been demonstrated within the first year of treatment (Table 2) [32]. Thus, even in an oldest old patient population, treatment with an anti-osteoporosis agent is worth to be

Table 2
First year treatment vertebral fracture risk reduction.

Anti-osteoporosis agent	Type of fracture	Percent risk reduction
Alendronate	Clinical	59
Clodronate	Morphometric	46
Risedronate	Clinical	69
	Morphometric	81
Zoledronic acid	Morphometric	60
	Morphometric (Men)	68
Denosumab	Morphometric	61
Raloxifene	Clinical	68
Teriparatide [a]	Morphometric	65

Clinical refers to symptomatic fracture.
[a] 18 months data.
Adapted from Ref. [32] where the references of the various trials can be found.

introduced, because of an early onset of fracture risk reduction. Over the long-term, anti-osteoporosis treatments seem to maintain effectiveness and remain safe [112]. Various guidelines recommend treatment re-evaluation every 3 for parenteral administration and 5 years for oral formulations [113].

Cost-effectiveness

Pharmaceutical anti-osteoporosis treatments are generally cost-effective, and even cost-saving in the oldest old [33]. When the costs threshold for one Quality-adjusted Life-Year (QALY) was set at twice the gross domestic product per capita and a first-line treatment with alendronate (original molecule) was evaluated, treatment was cost effective in women having a 10-year risk for a major osteoporotic fracture as low as 13.8% or more, whereas for men the risk estimate should exceed 15% [33].

Safety of anti-osteoporotic drugs

Gastrointestinal effects

Upper GI events with oral bisphosphonates include irritation of the oesophagus, dysphagia and heartburn. The risk of upper GI events is lower when the drug intake instructions are properly followed (including an appropriate quantity of water and post-dosing postural positioning). In placebo-controlled trials, the reported rates of upper GI events in the active and placebo arms are often very similar. Patients with upper GI disorders, such as oesophageal stricture, achalasia, or poorly controlled gastro-oesophageal reflux disease, should not be treated with oral bisphosphonates.

Generic versions of bisphosphonates are associated with higher rates of GI events and greater risk of treatment discontinuation [114]. This might be due to their faster disintegration times. Weekly or monthly dosing formulations are associated with lower rates of upper GI effects than daily dosing. Intravenous bisphosphonates are also generally associated with fewer GI side effects, although nausea, vomiting and diarrhoea are still listed as common in the Summary of Product Characteristics (SmPC) of zoledronic acid. Of potential interest for the oldest old, is the development of an alendronate formulation in effervescent forms that are easier to swallow.

Vascular effects

Selective estrogen receptor modulators (SERMs), such as raloxifene or bazedoxifene, are associated with cutaneous flushing ('hot flushes'), sweating and leg cramps. Venous thromboembolism (VTE) is a known adverse drug reaction with SERMs. In the pivotal regulatory study of raloxifene (MORE), the incidence rates of VTE were about 8–12/1000 in the treated arms (RR vs placebo: 3.1).

Musculoskeletal pain

Bone pain, as well as joint and muscle pain, have been frequently associated with bisphosphonates use, both oral and IV (about 5–10% of patients) and also to some extent with raloxifene and teriparatide

[115]. Intravenous bisphosphonates are associated with the highest rates. Headache and limb pain are commonly reported adverse reactions with teriparatide.

Immune reactions

Intravenous bisphosphonates are associated with transient flu-like symptoms (myalgia, arthralgia, headache and fever), collectively called an acute phase reaction (APR) [115]. Rates of fever of about 30% have been reported post-dosing with zoledronic acid. The symptoms of APR seem be evoked by the release of pro-inflammatory cytokines from circulating T cells, generally appear 24–48 h after administration and resolve within 48 h. The likelihood of having an APR after an IV bisphosphonate may be reduced by administration of acetaminophen (paracetamol) prior to dosing.

Denosumab has been associated with higher rates of skin infections and eczema. Meta-analysis indicates that the increased risk is very limited. In the FREEDOM trial, the incidence of (serious) cellulitis (including erysipelas) was significantly higher in the active arm (0.3% versus <0.1%).

Cancer

Rare cases of oesophageal cancer have been reported in patients exposed to oral bisphosphonates. But the results from epidemiological studies on prescription databases have been conflicting. In the most recent analysis performed on the UK GPRD, 95 out of the 4442 annually reported cases of upper gastro-intestinal cancer could be linked to bisphosphonate use (Odds Ratio of 1.34 for bisphosphonates) [116].

Cardiac effects

An increased risk of atrial fibrillation (AF) reported as a severe adverse event was observed in the pivotal HORIZON study with zoledronic acid. The incidence of AF was 1.3% in the active arm of zoledronic acid trial in postmenopausal osteoporosis versus 0.5% on placebo ($p < 0.001$). Post-hoc analyses of other bisphosphonate trials and several large population-based studies have not confirmed this suspicion. No increase in risk of cardiovascular mortality with use of bisphosphonates is reported and indeed a decrease in myocardial infarction has been associated with bisphosphonate use in patients with rheumatoid arthritis [117].

Fracture healing

There is no evidence for impaired fracture healing. Cases of osteonecrosis of the jaw (ONJ) have been reported [118]. They are defined as exposed bone in the maxillofacial region that shows negligible healing over a period of 8 weeks. They are mostly reported in cancer patients receiving high-dose IV bisphosphonates for the prevention or treatment of cancer-related bone disease. There are a few reports of denosumab-related ONJ, but the incidence rates seem be similar to those of zoledronic acid [119].

Atypical subtrochanteric, low-trauma, femur fractures in bisphosphonate-treated patients have been reported, some with prodromal thigh pain in the preceding period. Although there is an association with duration of bisphosphonate use, atypical fractures can also be observed in untreated patients [120,121]. While it is possible that the duration of bisphosphonate exposure beyond 5 years may be a risk factor, it is generally not recommended that patients with the highest risk of osteoporotic fractures should stop all treatments.

Renal safety

Impaired renal function is common in older patients causing concern for various drug treatments, including bisphosphonates, since these are excreted via the kidney [71]. Therefore, these products (both oral and IV forms) are not recommended in patients with creatinine clearance < 30–35 ml/min. Post hoc analyses of clinical trial data indicate however preserved anti-fracture efficacy and stable serum creatinine levels, suggesting that there is no evidence to suggest that the oral forms confer any increased risk in patients with chronic kidney disease (stage 1, 2 or 3). Denosumab is not excreted by the kidney and could therefore be used in patients with impaired renal function. However, the administration of such a potent bone resorption inhibitor in patients with terminal renal failure and possibly adynamic bone disease may further inhibit bone turnover.

Pain management

The management of chronic pain can be a challenge in older patients in view of likely polymedication and age-related metabolic changes [122]. Opioids can be of help, but a careful selection should be made to minimize CNS and gastrointestinal effects. Slow dose titration and regular creatinine clearance monitoring are advised. Buprenorphine shows a distinct benefit as its half-life of drug activity is not increased in older patients or in those with renal dysfunction.

Surgical techniques such as vertebroplasty (an injection of a cement into the vertebral body) or kyphoplasty (a similar procedure but with the inflation a small balloon in the bone cavity in an attempt to restore the original height and form of the compressed vertebra) in case of painful vertebral fracture are still debated in the oldest old.

Treatment adherence in osteoporosis

Yearly persistence rates in osteoporosis are from 26% to 56% for daily anti-osteoporosis regimens and from 36% to 70% for weekly regimens. Estimates of compliance (medication possession ratio) range from 46% to 64% and 58% to 76%, for daily and weekly regimens, respectively. Compliance tends to diminish with increasing follow-up duration and the drop is particularly rapid over the first 2 years of treatment. In a meta-analysis of 6 studies (171,063 patients), the increase in fracture risk for non-compliant patients was 28% for hip fractures and 43% for clinical vertebral fractures [123].

The main reason underlying non-adherence are the financial limitation of paying for the treatment, the fear or experience of side-effects, concerns about pharmacological treatments in general and lack of perceived need for a anti-osteoporosis treatment. Given the rather wide range of side effects outlined earlier, many patients are likely to believe that the negative effects of anti-osteoporosis medication outweigh any possible benefits. Patients with fragility fractures may deny that their facture is related to bone health, attributing all causality to the fall [124].

Conclusions on osteoporosis treatment

The risk of osteoporotic fractures is a major healthcare concern. The impact of a major fracture on patients' lives is immense, often heralding the transition to frailty and dependence. The costs borne by society are also significant, both in terms of immediate care and rehabilitation and over the longer term if dependence begins to take hold.

Many people at high risk of fracture receive no treatment or highly inadequate treatment [1]. There is now sufficient evidence of the short-term benefits of treatment and of the long-term safety profile of anti-osteoporosis treatments. Many older people are under nourished and vitamin D deficient. These are situations that should be easily improved.

In order to promote awareness and encourage proactive treatment in high-risk patients, the *Capture the Fracture Campaign* of the International Osteoporosis Foundation and a wide implementation of fracture liaison services [124] to strengthen secondary fracture prevention should be strongly advocated.

Summary

- Osteoporotic fractures are associated with increased mortality and lower quality of life.
- Patients with prevalent fracture are at high risk to of sustaining another one.
- Optimal protein and calcium intakes, and vitamin D supplies, together with regular weight bearing physical exercise are the corner stones of fracture prevention.
- Treatments with bone resorption inhibitors, like bisphosphonates or denosumab, and bone formation stimulator like teriparatide, reduce vertebral and non-vertebral fracture risk.
- A reduction in vertebral fracture risk can already be detected within a year after starting therapy.

Practice points

- Correct or prevent vitamin D insufficiency (≥800 IU/d)
- Ensure dietary calcium intake ≥ 1000 mg/d
- Ensure adequate dietary protein intake ≥ 1 g/kg body weight x d
- Promote weight-bearing physical exercise
- Treat any disease that might be causing bone loss
- Reduce the risk of falls
- Prescribe pharmaceutical treatment when indicated by risk assessment
- Follow-up patients with enquiries of compliance and persistence
- Re-evaluate therapeutic options after 3 or 5 years

Research agenda

1. To validate management models aimed at improving identification of patients at increased risk of fracture and implementation of available therapies
2. To validate sequential or combined therapies regimens to make them more convenient, safer and thereby with better adherence, and with limited treatment offset
3. To investigate and implement non-pharmacological approaches as preventive strategies
4. To show antifracture efficacy of nutritional intervention
5. To explore new pathways to increase bone strength, with limited reversibility

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