

Age- and gender-related macro- and micro-architecture changes in bone structure and implications for treatment

Bone is a dynamic tissue, which has the ability to adapt its shape and size in response to mechanical loads through the modeling process, and to be constantly renewed by remodeling. These processes are influenced by genetic, hormonal and lifestyle factors. Age-related variation in bone strength, which depends both on bone density and bone structure, are gender-specific, and this explains the difference in the incidence of osteoporotic fractures at specific sites between men and women. Even though estrogen deficiency is more pronounced in women, it appears to be one of the major causes of osteoporosis in both genders. Most of the drugs used to treat osteoporosis have been tested on postmenopausal women; nevertheless, some drugs have been shown to be effective also in men. An accurate examination of the medical history of the patient, possibly with the aid of radiological and advanced techniques to image bone quality should direct the physician in selecting the most appropriate therapy.

KEYWORDS: aging ■ biphosphonates ■ bone macro- and micro-architecture ■ bone strength ■ osteoporosis ■ parathyroid hormone ■ strontium ranelate

**Loredana Cavalli¹
& Maria Luisa Brandi^{1*}**

¹Mineral & Bone Metabolism Disease Unit, Department of Internal Medicine, University of Florence, Italy
*Author for correspondence:
Tel.: +39 055 794 6303
m.brandi@dmf.unifi.it

Bone strength, which is resistance to fracture, depends not only on the bone mass, but also on its spatial distribution (micro- and macroarchitecture) and the intrinsic properties of the materials that constitute the bone [1]. A particular feature of the bone is the ability to adapt its size and shape in response to mechanical loads, through the process of modeling achieved by the independent action of osteoblasts and osteoclasts. Modeling occurs principally during growth, but also in the adult, according to Wolff's law, in response to a mechanical load, as the use of a certain limb in a sport player, resulting in a thickening of bone cortex and an enlargement of external bone diameter, or conversely to the unloading of the skeleton, as during bed rest or space flight [2,3].

Another process, known as remodeling, allows the skeleton to maintain mechanical integrity through the constant osteoclastic resorption of damaged bone followed by osteoblast-mediated deposition and mineralization of new matrix. Overall remodeling rates average 8–10% per year in the adult [3], but individual bone sites can vary widely depending on the level of accumulated microdamage.

At a macroscopic level, two types of bone can be distinguished: the cortical bone, located in the shaft of long bones and on outer surfaces of the flat bones, and the trabecular bone, found at the extremity of long bones and at the inner parts of flat bones. The two compartments differ for micro- and macro-architecture and speed of

turnover. Bone loss starts at the bone surfaces; therefore, changes in bone mass occur earlier and more intensively in trabecular bone than in cortical [3].

When bone remodeling is unbalanced

Sex hormones influence bone remodeling: in the elderly, with decreasing of estrogen and testosterone, bone resorption exceeds bone formation, resulting in a loss of bone mass.

Osteoporosis, the most common metabolic bone disease, characterized by low BMD and microarchitectural deterioration of bone tissue, with a consequent increase in the susceptibility to fragility fractures, has become an increasingly important public health problem due to the rapidly aging population. Currently every third postmenopausal woman and every fifth man older than 50 years suffer from osteoporosis [4].

It is important to identify the possible pathological mechanisms underlying bone fragility in old age; in particular, it is of interest to consider sexual dimorphism in age-related skeletal changes, which is reflected in the gender differences in bone fracture rates [5].

■ Age-related bone structure changes in men & women

The age-related changes underlying the increase in skeletal fragility include bone mineral loss by trabecular resorption, endocortical

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thinning and increasing cortical porosity, while a smaller amount of bone is gained by apposition on the exterior cortex [6]. Spine fractures usually occur less commonly in men than in women. Contrary to the prevailing view, close examination of the literature suggests that the amount of bone lost on the inner (endocortical and trabecular) surfaces of the vertebra during aging, measured using quantitative computed tomography (QCT), is similar in men and women. Likewise, trabecular bone loss at the iliac crest, measured using quantitative histomorphometry, is similar in men and women. By contrast, studies in long bones confirm that cortical bone loss is less in males than in females. However, this lesser fall in cortical bone mass across age in men, at least in the appendicular skeleton, is due to greater periosteal bone formation in men, not due to less resorptive removal of bone on the inner (endocortical) surface of the cortical shell in men than women [6].

Age-related changes in the density and cross-sectional area of the femoral neck are closely related. A loss of trabecular bone with age causes femoral neck stiffness to decrease, leading to elevated strains at the periosteal surface during habitual activities such as walking. Bone cells respond to these increased strains by adding new bone tissue at the periosteal surface, maintaining homeostasis of femoral neck stiffness. The result is an ongoing increase in femoral neck size with declining trabecular volumetric BMD. Elderly male femoral necks have a larger cross-sectional area than those in elderly women, and these disparities increase with age [7].

Measures of net cortical and trabecular BMD obtained by QCT performed at lumbar spine, hip and mid-femoral shaft, show a higher age-related decline in elderly women than in men, with comparable increments of periosteal apposition across genders. Based on indices of bone strength that integrate the volumetric bone density and geometry measures, parameters of bone fragility such as compressive strength, bending/torsional strength and buckling ratio also show greater decrement with age in women than in men, a difference which far exceeds that of bone density evaluated by dual-emission x-ray absorptiometry (DXA). These data suggest that the sex difference in bone strength continues to increase into old age, due to greater bone loss in women than men rather than due to greater bone gain in men than women [5].

■ Sexual dimorphism in macro- & micro-structure of the skeleton as the result of gender-specific genetic & environmental factors

Differences between the genders in both skeletal development and aging are not limited to BMD, affecting also the structural components of bone strength (e.g., skeletal dimensions, cortical thickness), biomechanical responses, mineral mass and turnover, and even trabecular microstructure [8].

Sexual dimorphism in the skeletal dimensions and shape constitutes the basis of sex evaluation for archeological and forensic applications [9].

For example, in the Framingham cohorts, adult men have longer femora, with more obtuse neck-shaft angles, as well as longer and wider femoral necks, in addition to higher BMD. Thus, the greater prevalence of fragility fractures with advancing age in women compared with men may largely be explained by the smaller skeletal size and bone mass of women [10], after adjustment for body size [11,12]. It should be noted, however, that peak volumetric BMD is no different by sex [8,13]. Bone structure changes in men and women are summarized in TABLE 1.

■ Role of hormones

Although women and men both lose BMD and bone microstructure with aging because of endocrine, paracrine and cellular factors, these effects are more pronounced in women, particularly a decrease in cortical thickness, a decrease in number of trabeculae, and an increase in spacing between trabeculae compared with men [14], notably accelerating after menopause with the rapid decline in estrogen levels [15–17].

Estrogen may influence peak bone mass in males as in females, as demonstrated by the lower BMD in young females with late menarche [18] as well as in men with loss-of-function mutations in the estrogen receptor α (ER α) gene [19] and aromatase gene [20]. Age-related declines in BMD in men are also directly related to declining levels of estradiol, probably more important than the BMD relationship to testosterone in aging men [21–23].

Conversely, the androgen receptor (AR) also plays a role in modulating bone mass and structure in females [24], and periosteal expansion in women may also be enhanced by androgens, as seen in polycystic ovary syndrome (PCOS).

Further knowledge on the mechanism by which these hormones modulate bone metabolism could justify, in the future, the analysis of genes in both the androgen and estrogen

pathways, including androgen receptor, ER α (*ESR1*) and ER β (*ESR2*), and aromatase (*CYP19*), in association with osteoporosis in men as well as women [8].

Recent findings have redefined the traditional concept of sex hormones as the main regulators of skeletal sexual dimorphism. GH-IGF1 action is likely to be the most important determinant of sex differences in bone mass [25]. Estrogens limit periosteal bone expansion but stimulate endosteal bone apposition in females, whereas androgens stimulate radial bone expansion in males. Androgens not only act directly on bone through the AR but also activate ER α or ER β following aromatization into estrogens. Both the AR and ER α pathways are needed to optimize radial cortical bone expansion, whereas AR signaling alone is the dominant pathway for normal male trabecular bone development. Estrogen/ER α mediated effects in males may partly depend on interaction with IGF1. AR and ER β signaling may limit the osteogenic response to loading in males and females respectively, while ER α may stimulate it in the female skeleton [25].

Deficiency or resistance to either GH or androgens impairs bone modeling and decreases muscle mass [26].

Environmental factors

Environmental covariates might explain some of the apparent differences in the heritability of bone mass between genders, particularly in men. Therefore, in quantitative genetic studies of bone mass, BMD should be adjusted not only for age, BMI, height, and estrogen use in females, but also for alcohol, caffeine, calcium and vitamin D consumption, smoking, and physical activity [8].

Peripheral QCT (pQCT) measurements performed at the proximal nondominant forearm in a group of healthy subjects from 6 to 19 years of age showed that during puberty, the bone mineral content/muscle cross-sectional area ratio increases in girls but not in boys. Girls and boys have a similar muscle–bone relationship regarding external bone size, but girls have a relatively smaller marrow cavity. These observations are in accordance with the hypothesis that estrogen lowers a mechanostat set point on endosteal bone surfaces [27].

Not enough to say “osteoporosis”

Two principal types of involutional osteoporosis can be distinguished: postmenopausal (type 1) and senile (type 2) osteoporosis.

Table 1. Bone structure in men and women.

	Male	Female
Bone features		
Skeletal size and bone mass	++	+
Peak volumetric BMD	+	+
Bone structural changes with aging		
Bone loss in trabecular and endocortical surfaces of vertebra	++	++
Trabecular bone loss at the iliac crest	++	++
Cortical bone loss in long bones due to:	+	+++
– Endocortical bone resorption	+	+
– Periosteal bone formation	-	---
Cross-sectional area increase in femoral neck	++	+
<i>The plus and the minus signs indicate the dimension of a bone characteristic in a gender compared with the opposite gender.</i>		

Type 1 osteoporosis refers to the rapid phase of bone loss starting approximately 2 years prior to last menses, and continuing for 2 years after, at which point the rapid bone loss reduces to a constant, slower decline phase; caused by estrogen deficiency, it involves mainly trabecular bone, and is manifested clinically by low-impact fractures of the distal radius and vertebrae. Biochemical markers of bone turnover reflect a high remodeling rate in this phase, with excessive bone resorption and rapid bone loss, as shown also on bone histomorphometry.

Type 2 osteoporosis, attributed to aging processes such as osteoblast dysfunction, involves both trabecular and cortical bone. In addition to vertebral fractures, low-trauma hip fractures are also characteristic for this type of osteoporosis.

However, more recently, estrogen deficiency seems to be the main cause of bone loss in early and also late postmenopausal women and elderly men. The type 1/type 2 model was reformulated as a “unitary model of osteoporosis in postmenopausal women and aging men” (TABLE 2) [28].

Estradiol inhibits the generation and activity of osteoclasts by upregulating osteoprotegerin. In addition to its effect on the RANKL/osteoprotegerin system, estrogen deficiency leads to activation of T cell and antigen presentation, as well as an enhanced production of RANKL and TNF- β , which results in increased osteoclastogenesis. A progressive proinflammatory status has not only been associated with the postmenopausal phase but also with aging in general; this phenomenon, referred to as ‘inflamm-aging’, appears to be gender specific: IFN- γ production by T cells increased with age in women, but not in men [28].

Estrogen levels correlate better than testosterone levels with BMD and intervention studies in elderly men show a greater suppressive effect of estradiol on bone resorption than

Table 2. Classic types of primary osteoporosis.

Osteoporosis	Type 1: postmenopausal	Type 2: senile
Who is affected	Women	Men and women
When	From 2 years prior to last menses to 2 years after, then it slows	After 65–70 years of age
Due to	Estrogen deficiency	Osteoblast dysfunction for aging, often associated with vitamin D deficiency
Bone affected	Trabecular	Trabecular and cortical
Sites of related low-trauma fractures	Vertebrae and distal radius	Vertebrae, distal radius and hip
Bone turnover (biochemical markers)	↑↑ Bone resorption	↓ Bone formation
↑: Increase; ↓: Decrease.		

testosterone [29]. In men with idiopathic osteoporosis, estradiol levels are decreased, whereas sex-hormone-binding globulin (SHBG) levels and bone resorption markers are elevated [28]. SHBG levels in men increase with aging. High SHBG levels could significantly contribute to the development of osteoporosis by decreasing the bioavailability of estradiol.

Apart from sex hormones, vitamin D levels decrease with aging, as a result of a lack of sunlight exposure, in particular in residents of nursing homes, inadequate dietary intake or medical conditions such as renal insufficiency. In vitamin D deficiency intestinal calcium absorption is decreased, leading to hypocalcemia; as a consequence, parathyroid hormone (PTH) levels increase, thus enhancing bone degradation, which counteracts hypocalcemia, but in the long run leads to bone loss.

As vitamin D receptors are expressed in many tissues other than bone, including skeletal muscle, vitamin D deficiency has been associated with muscle weakness and an increased frequency of falls and fracture; accordingly, vitamin D supplementation is necessary in order to reduce the risk of falling [28,30].

Osteoporosis-specific treatments

Calcium and vitamin D supplementation is widely accepted as a fundamental basic measure for the prevention and treatment of osteoporosis. However, large clinical trials conducted over the past 20 years clearly established that osteoporotic patients should receive specific pharmacologic treatment.

Antiestrogen drugs can be classified on the basis of their action on bone remodeling [31].

Antiresorptive drugs (such as bisphosphonates or raloxifene – a selective estrogen receptor modulator) decrease bone remodeling and reduce fractures by preserving skeletal microarchitecture and moderately increasing bone mass.

Anabolic drugs such as teriparatide or PTH(1–84), on the other hand, reduce fractures by enhancing remodeling: in addition to increasing BMD, they appear to repair bone microarchitecture and improve bone geometry.

Strontium ranelate, available for osteoporosis in Europe, falls outside the aforementioned classification because it decouples the two processes, inhibiting bone resorption and stimulating bone formation. However, bone anabolic effect has not been demonstrated in paired bone biopsies.

There is a large body of scientific evidence derived from randomized controlled trials (RCTs) concerning the treatment of postmenopausal osteoporosis. Three different aminobisphosphonates (alendronate, risedronate and zoledronic acid), teriparatide, strontium ranelate and hormone replacement therapy (the lattermost is no longer recommended for the prevention or treatment of osteoporosis) were shown to be effective against both vertebral and non-vertebral fractures. Evidence of efficacy against vertebral fractures is available for ibandronate (an aminobisphosphonate), raloxifene and PTH(1–84) (TABLE 3) [28].

■ Antifracture efficacy of drugs goes beyond the increase in BMD

In women with osteoporosis, each 1% improvement in spine BMD (by DXA) is expected to reduce vertebral fracture risk by approximately 4%. However, randomized trials of antiresorptive agents show that a 1–6% improvement in spine BMD can reduce vertebral fracture risk by 35–50%. Less than 20% of the decreased spine fracture risk produced by alendronate or raloxifene could be explained by improvement in spine BMD. The discrepancy is even greater during the first year or two of treatment when 1–4% improvements in BMD are associated with 65–68% decreases in spine fracture risk.

Bisphosphonates continue to increase BMD but the reduction in fracture risk wanes to 20–45%. DXA underestimates the change in bone density of spinal trabecular bone and this might explain part of the discrepancy between expected and observed reductions in spine fracture risk. Even more accurate measurement of BMD would not explain the rapid onset and later waning of effect despite gradually increasing BMD [32].

The effect of drugs on nonspine fracture risk is more complex and cannot be predicted from changes in DXA BMD. Long-term (>10 years) use of estrogen, for example, has been associated with >50% reduction in risk of hip and wrist fracture, which could not be explained by improvements in BMD, and increased section modulus versus nonusers with a net increase in predicted femoral neck strength despite losing approximately 0.4% per year in femoral neck BMD [33].

Parathyroid hormone reduces spine fracture risk and this effect is more completely explained by improvement in spine BMD. This suggests that sustaining the increased BMD produced by PTH may maintain long-term reductions in fracture risk.

The choice of the most appropriate therapy for individual patients should be based on the level of turnover rate indicated by biochemical markers, therefore preferring an anticatabolic drug in case of high bone turnover in a postmenopausal woman and an anabolic or decoupling drug in an old patient with low turnover indices or a very low spinal and/or hip BMD. Importantly, patient compliance with medical therapy should be considered when choosing drugs with a certain frequency of administration.

Alendronate, risedronate and ibandronate were marketed with administration schedules that increasingly simplified oral therapy from once daily, to weekly, to monthly. A third generation bisphosphonate, zoledronic acid, is provided in the form of a brief intravenous infusion administered yearly.

Moreover, osteoporosis type – postmenopausal, senile, secondary to pathologies or the use of drugs – potential side effect, allergies, drug-specific contraindications, and last but not least the cost of a treatment should be considered (TABLE 4).

Antiresorptive drugs: applications

■ Bisphosphonates

Direct inhibitory effect of glucocorticoid on bone formation and promotion of apoptosis of bone cells are thought to be the major mechanism of glucocorticoid-induced osteoporosis (GIO), the most common form of secondary osteoporosis. Glucocorticoid reduces not only BMD but also bone quality; therefore, patients with GIO have a higher risk of fracture than those with postmenopausal osteoporosis with the same level of BMD.

Intravenous ibandronate is a potent nitrogen-containing bisphosphonate with established therapeutic efficacy and tolerability for patients with established GIO [34].

Other bisphosphonates with similar effects are risedronate, alendronate and zoledronic acid. The oral preparation of ibandronate, however, has not been shown to be effective in GIO osteoporosis, although it is efficacious in preventing bone loss in postmenopausal women, with a significant reduction in vertebral fracture risks. Ibandronate shares a similar molecular mechanism with alendronate and risedronate; thus it should also be useful in the prevention and treatment of GIO [34,35].

Zoledronic acid is a third-generation amino-bisphosphonate displaying the highest inhibition of farnesyl diphosphate (FFP) synthase and greatest affinity for bone mineral to date. In ovariectomized rats, zoledronic acid prevented estrogen-deficient bone loss in vertebrae and showed a prominent protective effect on trabecular thinning [36]. In a substudy of the HORIZON pivotal fracture trial, in which yearly intravenous zoledronic acid 5 mg was

Table 3. Osteoporosis therapies in use.

Drug class	Drugs	Action on bone remodeling	Action on BMD	Action on V and NV fracture risk
Antiresorptive agents	Aminobisphosphonates	↓↓	↑	V ↓; NV ↓
	Raloxifene	↓	↑	V ↓
	Denosumab	↓↓↓	↑	V ↓; NV ↓
Uncoupling agent	Strontium ranelate	↓ OC; ↑ OB	↑	V ↓; NV ↓
Anabolic agents	PTH(1–84)	↑	↑↑	V ↓; NV ↓
	Teriparatide	↑	↑↑	V ↓; NV ↓

↑: Increase; ↓: Decrease; NV: Nonvertebral; OB: Osteoblast; OC: Osteoclast; PTH: Parathyroid hormone; V: Vertebral.

Table 4. The various formulations and dosages of drugs available and their clinical indications.

Drug	Dosage and formulation	Indication
Alendronate	70 mg, one tablet per week	Postmenopausal osteoporosis
Alendronate	10 mg, one tablet per day	Male osteoporosis
Risedronate	5 mg, one tablet per day 35 mg, one tablet per week 75 mg, two tablets on 2 consecutive days per month	Postmenopausal osteoporosis; glucocorticoid-induced osteoporosis
Risedronate	30 mg, one tablet per day	Paget's disease
Ibandronate	150 mg, one tablet per month 3 mg, one intravenous infusion every 3 months	Postmenopausal osteoporosis at high risk of fracture; glucocorticoid-induced osteoporosis
Zoledronate	5 mg, one intravenous infusion per year	Osteoporosis in postmenopausal women and in men at increased risk of fracture including those with a recent low-trauma hip fracture; Paget's disease
Zoledronate	4 mg, intravenous infusion every 3–4 weeks	Multiple myeloma; bone metastases from solid tumors
Strontium ranelate	2 g, oral suspension, one sachet per day	Postmenopausal osteoporosis
Denosumab	60 mg/ml, one subcutaneous administration every 6 months	Prevention and treatment of postmenopausal osteoporosis, or bone loss in hormone ablation-treated prostate and breast cancer
Teriparatide	20 µg, one daily subcutaneous administration, for 18 months	Severe osteoporosis
PTH(1–84)	100 µg, one daily subcutaneous administration, for 18 months	Severe osteoporosis

found to significantly reduce risk of various fracture types in patients with postmenopausal osteoporosis, 152 patients underwent bone biopsy. Zoledronic acid reduced bone turnover by 63% and preserved bone structure and volume, with evidence of ongoing bone remodeling in 99% of biopsies obtained [37].

■ Strontium ranelate

Strontium ranelate has been shown to increase bone formation *in vitro*, enhancing preosteoblastic cell replication and osteoblastic differentiation and decreasing abilities of osteoblasts to induce osteoclastogenesis via the calcium sensing receptor and an increase in the OPG/RANKL ratio [38].

Oral administration of strontium ranelate 2 g/day to postmenopausal osteoporotic women, leading to continued increases in BMD at all sites, has proven efficacy against vertebral and nonvertebral fracture over 5 years, as demonstrated in the Spinal Osteoporosis Therapeutic Intervention (SOTI) trial and in the Treatment Of Peripheral Osteoporosis Study (TROPOS) [39–41], although many women require longer-term treatment [42]. No studies have been performed on strontium ranelate efficacy in men.

■ Denosumab

RANKL, a member of the TNF superfamily expressed on the surface of precursors of osteoblasts, is essential for the differentiation,

activation and survival of osteoclasts. RANKL accelerates osteoclastogenesis when it binds to its receptor, RANK, on osteoclast precursor cells. Osteoprotegerin, produced by osteoblasts, acts as a soluble decoy receptor for RANKL and blocks its effects. McClung *et al.* report that denosumab, a breakthrough fully human monoclonal antibody against RANKL, mimicking the function of osteoprotegerin, caused especially rapid, potent, dose-dependent decreases in biochemical markers of bone resorption, as determined by levels of serum and urine telopeptide products of bone-collagen degradation. Subsequent decrements in serum bone-specific alkaline phosphatase, a marker of osseous tissue formation, indicated an overall reduction in skeletal remodeling [43].

Recently, some bisphosphonates, especially pamidronate and zoledronic acid, have been associated with osteonecrosis of the maxilla and mandible, particularly after tooth extraction and in persons previously treated with corticosteroids or chemotherapy. A dynamic bone disease could result from excessive suppression of bone remodeling, which allows microdamage to accumulate and leads to fracture, known as subtrochanteric atypical fractures. McClung *et al.* demonstrate that denosumab can cause rapid and potent suppression of bone resorption but also that this suppression seems to be reversible [43]. Perhaps short-acting bone antiresorptive agents (e.g., lower doses of denosumab), coordinated with anabolic agents for bone,

might best augment skeletal mass and improve bone quality while preventing depressed skeletal turnover [44].

Denosumab was approved by both the US FDA and EMA in 2010. It had been fast tracked by FDA for treatment and prevention of postmenopausal osteoporosis, and treatment and prevention of bone loss in hormone ablation-treated prostate and breast cancer patients.

Anabolic therapy

■ Parathyroid hormone

Parathyroid hormone, the major hormonal regulator of calcium homeostasis, is a potent stimulator of bone formation and can restore bone to an osteopenic skeleton, when administered intermittently. Osteoblasts are the primary target cells for the anabolic effects of PTH in bone tissue. Anabolic effects of PTH on bone have been demonstrated in animals and humans, by numerous measurement techniques including BMD and bone histomorphometry. Recent 2D and 3D assessments of cancellous bone structure have shown that PTH can re-establish lost trabecular connectivity in animals and humans by a novel mechanism in which trabeculae are first thickened and then split by longitudinal tunneling [45].

These results provide new insight into the positive clinical effects of PTH in osteoporosis. In recent randomized controlled clinical trials of intermittent PTH treatment, PTH decreased incidence of vertebral and nonvertebral fractures in postmenopausal women [46]. Thus, PTH shows strong potential as therapy for osteoporosis. However, 2D and 3D structural analysis of advanced osteopenia in animals has shown that there is a critical limit of trabecular connectivity and bone strength below which PTH cannot completely reverse the condition. Given that PTH treatment fails to completely restore trabecular connectivity and bone strength in animals with advanced osteopenia, early treatment of osteoporosis appears important and efficacious for preventing fractures caused by decreased trabecular connectivity [46].

There is evidence from RCTs regarding the efficacy of antiresorptives in reducing the risk of fracture, but none of these agents completely abolish the fracture risk. The reduction of relative risk ratio by different therapies in RCTs is relatively constant but it is important to note that the proportion of inadequate-responders (i.e., patients fracturing despite adequate pharmacological treatment) increases with the severity of the disease. The beneficial effect of introducing

a treatment with antiresorptives after the treatment course with teriparatide (TPTD) or PTH has been demonstrated and is supported by a good rationale. TPTD increases bone mass but, at the same time, the new bone is less mineralized. Treatment with antiresorptives after TPTD prevents the accelerated osteoclastic resorption of the new bone tissue built during TPTD therapy, increases mineralization and rapidly lowers cortical porosity; this leads to further increases in BMD. For these reasons the introduction of an antiresorptive after the treatment course with TPTD is recommended and in the long term estimation of efficacy the complete scheme (e.g., TPTD followed by a bisphosphonate) should be always taken into account. The cost of TPTD treatment is considerably higher than that of antiresorptives. For this reason its use is indicated for patients with severe osteoporosis; in Italy, for example, TPTD is fully reimbursed in patients incurring a new vertebral or hip fracture while on chronic treatment with antiresorptives or in patients never treated with AR, with three or more vertebral or hip fractures [47].

Compared with bisphosphonates, the effect of which persists for many months after drug withdrawal [48], the protective action of TPTD on BMD vanishes with time in both genders but not up to the baseline values [49–53].

After weaning from the drug, in 1 year, a decrease of lumbar spine BMD of 7.1% (SD: 3.8) in postmenopausal women and of 4.1% (3.5) in eugonadal men was measured by DXA in one study, whereas measured by QCT, trabecular BMD at the lumbar spine decreased by 17.0% (8.9) in women versus 11.1% (12.2) in eugonadal men [50–53]. In women, total hip and femoral neck BMD decreased in 1 year by 3.8% (3.9) and 3.1% (4.3), respectively, whereas in eugonadal men, no loss was observed in both sites. Such a bone loss does not seem to endanger the bone mechanical resistance [54]. However, this should justify thinking about starting antiresorptive therapy (bisphosphonates or raloxifene) when stopping TPTD in postmenopausal women, but not in eugonadal males [55].

■ Antisclerostin antibodies

Sclerostin is a secreted protein from osteocytes that inhibits Wnt signaling. Wnt signaling plays important roles in osteoblastic differentiation, and hence bone formation. Therefore, inhibition of sclerostin promotes bone formation. A monoclonal antibody has been generated against sclerostin, which has been shown to stimulate bone formation and increase bone

volume in rodents and primates. Preliminary data in humans showed that this antibody increases markers for bone formation [56]. Two clinical Phase II studies using this antibody in postmenopausal osteoporosis, fragility tibia and femoral fracture was initiated in 2009 and are ongoing.

What about men?

With aging of the population in recent years, the number of male osteoporosis patients is increasing. As osteoporosis can progress without symptoms until a fracture, diagnosis and treatment of osteoporosis are often delayed, especially in men, because the concept of male osteoporosis has not been fully penetrated. Even after fragile fracture caused by osteoporosis, it is frequent that an appropriate treatment for osteoporosis has not been provided in men [57]. Indeed, in contrast to osteoporosis in postmenopausal women, the treatment of osteoporosis in men has been scarcely reported. Nevertheless, some drugs commonly used for the treatment of osteoporosis in women also appear to be effective in men [28].

Overall, the data from the two alendronate studies clearly document the efficacy and safety of alendronate in osteoporotic men [58,59].

The positive effects of alendronate on BMD, markers and fractures are very consistent between studies and also with the results of multiple clinical studies conducted in postmenopausal osteoporotic women. Treatment with 10 mg alendronate for 2 years produced significant and clinically meaningful increases in BMD, similar to those previously observed in postmenopausal women. Data from studies including men and women confirm the similarity of response suggested by single-gender studies. As in much larger studies in postmenopausal women, alendronate 10 mg/day also reduced the incidence of new vertebral fracture and, correspondingly, reduced height loss. The safety and tolerability of alendronate in men was favorable and consistent with the safety profile previously observed in postmenopausal women.

Alendronate 10 mg/day, risedronate 35 mg/week and denosumab 120 mg subcutaneous injection every 4 weeks represents an important and needed therapeutic advancement in the management of osteoporosis in men [60].

Furthermore, it has been reported that approximately half of male osteoporosis patients have secondary causes. In management of osteoporosis patients, particular attention should be paid to background diseases and lifestyle of the patients (Table 5).

Conclusion & future perspective

The choice of the appropriate treatment for osteoporosis should first take into account any underlying conditions at the base of osteoporosis and possibly correct them. Second, bone turnover rate and bone quality should be evaluated through biochemical analysis and imaging techniques, respectively, thus stopping bone resorption in case of high turnover rate, or stimulating bone formation in case of low turnover. Sex hormonal deficiency in both genders might need a correction, as well as calcium and vitamin D, particularly with aging. Lifestyle factors such as exercise, sun exposure, balanced diet, abstention from smoking and the use of alcohol are also essential for the maintenance of a healthy and strong bones.

Each class of drugs for osteoporosis is distinguished by side effects, contraindications, costs, efficacy in terms of BMD increase at different sites and in terms of antifracture efficacy. Alendronate 10 mg/day, risedronate 35 mg/week and denosumab 120 mg subcutaneous injection every 4 weeks are the only drugs approved for male osteoporosis treatment. Strontium ranelate is the drug that has been tested in the oldest group of patients.

Further research is required for improving knowledge on molecular basis of the different types of osteoporosis, and for testing antifracture drugs not only on postmenopausal women but also men and the elderly.

Table 5. Elements on which to base the choice of therapy.

To consider	Example
Type of osteoporosis → turnover markers	Postmenopausal osteoporosis usually first requires an antiresorptive drug
Severity of BMD reduction	In cases of very severe osteoporosis → anabolic agent
Contraindications to specific drugs	Oral bisphosphonates are not indicated in cases of esophagitis; parenteral intake of vitamin D is indicated in cases of malabsorption
Patient's compliance	If patient is not available or reliable in taking drugs, a parenteral long-lasting formulation should be preferred
History of previous long-term therapy with the same drug	Bisphosphonates should not be taken for more than 5 years, in order to avoid adynamic bone disease

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Executive summary

- Bone strength depends not only on the bone mass but also on micro- and macro-structure of the tissue.
- Bone tissue adapts its size and shape in response to mechanical loads through the modeling process.
- The constant remodeling process, bone resorption followed by bone formation, which maintains mechanical integrity throughout life, is influenced by sex hormones.
- In the elderly, with decreasing sex hormones, bone resorption exceeds bone formation.
- The elderly often have a deficiency of vitamin D, which contributes to bone fragility.
- Even if peak BMD is similar between genders, adjusted for body size, women have smaller skeletal size, bone mass and cortical thickness than men, and this partly explains the greater risk of osteoporosis fracture in women than in men.
- Age-related trabecular bone loss measured by quantitative computed tomography on vertebra or by quantitative histomorphometry on iliac crest are similar between genders, while in the appendicular skeleton men have a smaller cortical bone loss, due to greater periosteal formation than women.
- Estrogen influences peak bone mass in both genders.
- Androgens seem to play a role in periosteal expansion in men and women.
- GH-IGF1 action is also important in determining bone mass.
- Environmental factors can significantly influence bone strength.
- During puberty, girls show a major increase of bone mineral content/muscle cross-sectional area ratio.

Bibliography

Papers of special note have been highlighted as:

▪ of interest

▪▪ of considerable interest

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