Osteoporosis: An Age-Related and Gender-Specific Disease – A Mini-Review

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Abstract
Osteoporosis, a classical age-related disease and known to be more common in women than in men, has been reported increasingly often in men during the past few years. Although men at all ages after puberty have larger bones than women, resulting in greater bending strength, mortality after a hip fracture, one of the major complications of osteoporosis, is more common in men than in women. Sex hormone deficiency is associated with unrestrained osteoclast activity and bone loss. Even though estrogen deficiency is more pronounced in women, it appears to be a major factor in the pathogenesis of osteoporosis in both genders. 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. The aim of this study is to review primary osteoporosis in the elderly with particular emphasis on gender-related aspects.

Introduction

Osteoporosis is one of the most common conditions associated with aging. It is defined as a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture. Bone strength primarily reflects the integration of bone density and bone quality [1]. The risk of fracture increases 1.5- to 3-fold or more for each standard deviation (SD) decrease in bone mineral density (BMD). A BMD value between 1 and 2.5 SD below the mean value for young adults is defined as low bone mass or osteopenia. A person with a BMD more than 2.5 SD below the adult mean value is considered to suffer from osteoporosis. This classification has been established for lumbar spine bone mineral densities of postmenopausal women only. Nevertheless, the above-mentioned diagnostic categories are used for men as well as women.

Many risk factors contribute to the pathogenesis of osteoporosis. Age-specific variations in bone density are mainly determined by genetic factors. Nevertheless, lifestyle factors such as bone-loading physical activities, nutrition (calcium and vitamin D intake, alcohol consumption), nicotine abuse, illnesses or the intake of medica-
tracellular bone matrix (osteoid) and orchestrate its mineralization. Bone-forming processes take about 4–6 months. After the formation and mineralization of new bone, the bone remodeling unit enters a resting phase.

Osteoblasts, as adipocytes, fibroblasts, chondroblasts and myoblasts, differentiate from mesenchymal stem cells. After bone formation osteoblasts convert into inactive lining cells, terminally differentiate into osteocytes, or undergo apoptosis. In contrast to osteoblasts, osteoclasts are derived from the hematopoietic lineage and can be generated from mononuclear precursors. A highly coordinated communication between bone forming and bone-degrading cells is needed to maintain bone homeostasis. Two cytokines – mainly produced by bone marrow stromal cells and osteoblasts – are essential and adequate for osteoclast generation: macrophage colony-stimulating factor (M-CSF), and receptor activator of nuclear factor-kappa B ligand (RANKL). RANK, a receptor for RANKL, is expressed on osteoclast precursors. RANKL-RANK interactions stimulate the differentiation and activation of osteoclasts and inhibit osteoclast apoptosis. These processes are antagonized by osteoprotegerin, a natural decoy receptor of RANKL also mainly produced by stromal cells and osteoblasts [for review, see 7]. These interactions are already under clinical investigation with regard to their potential therapeutic application [reviewed in 8]. Whereas the RANKL/RANK/osteoprotegerin system mediating osteoblast-osteoclast coupling was identified as early as 10 years ago, signaling molecules for osteoclast-osteoblast communication were only recently discovered. Osteoclasts express ephrinB2, whose receptor ephB4 is expressed by osteoblasts [9]. The interaction between ephrinB2 and ephB4 appears to limit osteoclast activity and promote osteoblast differentiation.

Generally speaking, osteoporosis results from any imbalance between the activity of osteoblasts and that of osteoclasts, which leads to bone degradation. With regard to aspects of bone formation, a number of experimental and clinical studies have been published on the effect of age on the generation, differentiation and function of osteoblasts. Most – but not all – investigators registered a decrease in the osteoprogenitor pool of bone marrow with advancing age [10]. Decreased osteoblastogenesis is also seen in the senescence-accelerated mouse P6 (SAMP6), a model of involutional osteoporosis associated with spontaneous fractures in old age [11].

An important and characteristic feature of the aging bone marrow is a shift from osteoblastogenesis to adipogenesis, leading to the accumulation of bone marrow fat. Runx2 is the first osteoblast-specific transcription factor.
that was described. Runx2-deficient mice completely lack ossification because of the absence of osteoblast differentiation [12]. In contrast, peroxisome-proliferator-activated receptor γ2 (PPARγ2) inhibits osteoblast but promotes adipocyte proliferation. Several studies indicate that the expression of runx2 in osteoblasts decreases with age (fig. 1), while that of PPARγ2 increases [13]. Thus, alterations in these transcription factors appear to explain – at least in part – the age-related shift from osteoblastogenesis to adipogenesis, and thus the transition from red to yellow bone marrow.

More insights into age-related process especially in bone can be appreciated from the pathogenesis of the Hutchinson-Gildford progeria syndrome. This is a disease caused by a mutation in the lamin A/C gene and is characterized by premature aging, including atherosclerosis, alopecia and osteoporosis with spontaneous fractures [14].

Lamins are intermediate filaments that are important constituents of the inner nuclear membrane, and its expression has been found to decrease in osteoblasts of aged mice. Very recent data from our group indicate that knock-down of lamin A/C in human mesenchymal stem cells leads to a decrease of osteoblast proliferation, a reduction of runx2 mRNA expression and an increase in the RANKL/OPG ratio [15]. Thus, these findings indicate a novel link between lamin A/C deficiency and age-related osteoblast insufficiency, a feature that is also seen in klotho-deficient mice (which exhibit many pathologies resembling human aging).

With regard to the effects of aging on osteoclast generation, contradictory data have been reported in the published literature. Perkins et al. [16] suggested that age-related bone loss in mice is associated with an increase in the osteoclast progenitor pool, and that bone marrow cells from aged mice exhibit a greater ability to form osteoclasts. A greater capacity for osteoclast generation in mice was also registered by Cao et al. [17], as well as our group (fig. 2), and was found to be related to increased mRNA expression of RANKL. In contrast, osteoclastogenesis is impaired in senescence-accelerated mice, possibly due to osteoblast insufficiency [11]. Data from our laboratory [18] show that, in aged male rats, serum

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**Fig. 1.** Gene expression of runx2 and alkaline phosphatase (ALP) decrease in bone tissue and in osteoblasts with age. **a** Bone marrow was flushed out of the femora of young (6-weeks) and old (18-months) BALBc mice. The bone tissue was crushed in liquid nitrogen. RNA was isolated and subjected to real-time PCR analysis for runx2 and ALP. Gene expression was normalized to GAPDH. **b** Bone marrow stromal cells were isolated from the bone marrow of young (6 weeks) and old (18 months) mice and cultured for 21 days under osteoinductive conditions. RNA was isolated and subjected to real-time PCR analysis for runx2 and ALP. Gene expression was normalized to GAPDH. *p < 0.01.

**Fig. 2.** Number of osteoclasts increases in old mice. Osteoclasts were derived from murine (C57BL/6J) bone marrow stromal cells and were cultured for 7 days in the presence of 10 nM 1,25-dihydroxyvitamin D3. Cells were stained for tartrate-resistant acid phosphatase (TRAP). Multinucleated, TRAP-positive cells were counted as osteoclasts. **p < 0.01.
RANKL levels and ex vivo osteoclast generation are diminished despite demonstrable evidence of increased bone resorption. A decline in serum RANKL levels with age has also been registered in human studies [19] and is in line with the age-related decline of RANKL expression in T cells (fig. 3). Thus, data on effects of aging on RANKL expression, and osteoclast generation as well, are contradictory.

Alternative approaches to investigate changes in the number and/or activity of cells involved in bone remodeling are bone histomorphometry and the determination of biochemical markers of bone turnover. Most, but not all authors who used bone histomorphometry registered a decline in bone formation with age [11, 20]. In men, serum levels of markers of bone formation (such as osteocalcin or bone-specific alkaline phosphatase) decline until the 6th decade. Older men, on the other hand, were shown to demonstrate stable or increased as well as decreased bone formation markers [21, 22]. A considerable number of studies have reported an increase in markers of bone formation and bone resorption in postmenopausal women compared to premenopausal women [21], reflecting a high remodeling rate on histomorphometry. In older men, bone degradation as determined by biochemical markers appears to increase [21, 22]. Thus, particularly with regard to bone formation, age-related changes in bone remodeling appear to be gender specific.

A Model of Involutional Osteoporosis

In 1983, Riggs and Melton [23] proposed the existence of two distinct types of involutional osteoporosis: postmenopausal (type 1) and senile (type 2) osteoporosis. Type 1 osteoporosis refers to the rapid phase of bone loss observed approximately 5–10 years after menopause, involves mainly trabecular bone, and is manifested clinically by fractures of the distal radius and vertebrae. While postmenopausal osteoporosis was recognized to be caused by estrogen deficiency, senile osteoporosis was attributed to aging processes such as osteoblast dysfunction. Type 2 osteoporosis involves both trabecular and cortical bone. In addition to vertebral fractures, hip fractures are also characteristic for this type of osteoporosis.

In 1998 the type1/type 2 model was reformulated as a 'unitary model of osteoporosis in postmenopausal women and aging men' [23]. In the unitary model, estrogen deficiency was deemed to be the main cause of bone loss in early and also late postmenopausal women and elderly men. Estrogens have multiple effects on bone cells and mineral homeostasis. Estradiol inhibits the generation and activity of osteoclasts [24], effects mediated by an upregulation of osteoprotegerin. As mentioned above, estrogen withdrawal results in a high remodeling rate with excessive bone resorption and rapid bone loss. Eghbali-Fatourechi et al. [25] showed that upregulation of RANKL
in the bone marrow is an important mediator of high bone degradation in early postmenopausal women.

In addition to its effect on the RANKL/osteoprotegerin system, estrogen deficiency leads to dysregulation of T cell function and antigen presentation. Pacifici et al. [26] demonstrated that estrogen withdrawal results in increased production of interleukin-7 (in part due to a decrease in transforming growth factor-β), leading to T cell activation and greater release of interferon-γ by T cells. Interferon-γ upregulates the expression of major histocompatibility complex II molecules, which results in augmented antigen presentation by bone marrow macrophages and dendritic cells. Consequently, T cells are further activated and enhance the production of RANKL and tumor necrosis factor-α, which results in increased osteoclastogenesis [26]. Notably, a progressive proinflammatory status has not only been associated with the postmenopausal phase but also with aging in general; this phenomenon has been referred to as ‘inflamm-aging’ [27]. Data from our laboratory suggest that some phenomena of ‘inflamm-aging’ are gender specific: interferon-γ production by T cells increases with age in women, but not in men [22].

The rapid phase of postmenopausal bone loss approximately 5–10 years after menopause is followed by a slower phase of continuous bone loss (‘senile bone loss’). Notably, extraskeletal consequences of estrogen deficiency (such as reduced intestinal calcium absorption) lead to a progressive elevation of PTH and further stimulate bone degradation [23].

Although testosterone deficiency in men is clearly associated with bone loss, estrogens appear to be even more important than androgens for male bones. This notion derives from several lines of evidence: the description of a mutated estrogen receptor gene in a young man with osteoporosis, observational studies demonstrating that estrogen levels correlate better than testosterone levels with bone mineral density [28], and intervention studies in elderly men showing a greater suppressive effect of estradiol on bone resorption than testosterone [28]. In men with idiopathic osteoporosis, estradiol levels are decreased, whereas sex-hormone-binding globulin (SHBG) levels and bone resorption markers are elevated [29]. SHBG levels in men increase with aging. High SHBG levels could significantly contribute to the development of osteoporosis by decreasing the bioavailability of estradiol (and testosterone), thus facilitating unrestrained osteoclast activity that exceeds bone formation. Recently, it has been suggested that the increase of serum SHBG is due to complex interactions between the reduction of pituitary growth hormone secretory capacity and decreased testosterone production by the testes [28]. Despite the fact that estrogens are crucially important for bone health in women and men, it should be borne in mind that – in contrast to the abrupt cessation of ovarian function during menopausal transition – there is a slight but steady decrease in estradiol and testosterone levels with aging in men.

Apart from estrogen deficiency, vitamin D deficiency is a major factor accounting for bone fragility in the elderly. It is well established that vitamin D levels decrease with aging [22]; in particular in residents of nursing homes, extremely low concentrations of vitamin D have been reported. If vitamin D levels are very low, the clinical picture of osteomalacia may develop; the concomitant existence of osteoporosis and osteomalacia has been referred to as ‘osteoporomalacia’. Low levels of vitamin D in elderly subjects may result from a lack of sunlight exposure, inadequate dietary intake, or medical conditions such as renal insufficiency. One of the major effects of the active metabolite of vitamin D, i.e. 1,25(OH)2vitamin D, is to increase the intestinal absorption of calcium and phosphate. Thus, in vitamin D deficiency intestinal calcium absorption is decreased and may lead to hypocalcemia; as a consequence PTH levels increase. High PTH levels result in enhanced bone degradation which on the one hand counteracts hypocalcemia, but on the other hand in the long run leads to bone loss.

As will be discussed in more detail later, frequent falls in elderly subjects clearly increase the risk of fractures. Vitamin D receptors are not only expressed in bone but also in other tissues, including skeletal muscle. Vitamin D deficiency has been associated with muscle weakness and an increased frequency of falls; accordingly, vitamin D supplementation may reduce the risk of falling [1].

### Biomechanics

Low bone mass is not the only factor contributing to the frequency of fractures in the aging population. As early as 20 years ago it was shown that, for a given bone mass, the risk of fractures increases with age, indicating the existence of other factors besides bone mass that predispose an individual to sustain a nontraumatic fracture.

Factors most likely to influence the resistance to fracture include the overall composition (i.e. proportion of mineral, collagen, water and matrix proteins), the physical and biochemical characteristics of these components.
(i.e., nature of collagen, degree of mineralization), the morphology and architecture (i.e., bone size, geometry, trabecular microarchitecture), and the severity and nature of pre-existing microdamage (i.e., crack length and location) [30]. One example of trabecular bone loss and trabecular architectural disruption with aging is shown in figure 4. A balance between the mineral stiffness of bone and its flexibility is achieved by varying its mineral content [31]. The greater the mineral content, the greater the material stiffness and the lesser its flexibility. The association between areal BMD and vertebral fracture risk is explained by its correlation with more specific parameters of bone density, structure, and strength. Besides, bone structure, strength, and load-strength ratios contribute to forearm fracture risk independently of areal BMD [32].

As long as bone grows in length, periosteal apposition increases in diameter while concurrent endocortical resorption excavates the marrow cavity. There is little difference between the genders with regard to the extent of periosteal apposition and net endocortical remodeling until puberty [33]. Estrogen in girls inhibits periosteal bone formation, limiting the diameter of bone and simultaneously promoting net bone formation on the endocortical surface. In boys, pubertal androgen production increases periosteal apposition, bone diameter, and cortical thickness. Continued widening of the inner diameter shifts the cortex even farther from the neutral axis than the displacement that occurs in girls [31]. Thus, young men have greater bending strength than do young women because bending strength increases with the distance from the neutral axis. However, cortical thickness is similar in both sexes [31]. The fact that men have larger bones at all ages compared to women [31] may explain why stresses are higher in women compared to men when simulating a fall on the greater trochanter [34]. A simulated investigation of forearm behavior when falling showed that women had significantly less failure strength, bone mineral content, trabecular density and cortical area than did men [35]. In premenopausal women, periosteal apposition increases the width of the radius, partly offsetting endocortical resorption [36]. During menopause, increased periosteal apposition partially preserves bone strength [36]. The postmenopausal period is characterized by a further acceleration of endocortical resorption, whereas periosteal apposition increasingly declines [36]. Thus, the estimated cortical area and bending strength decrease in the postmenopausal period.

Gender-related differences are found not only in peripheral bones. Men have greater vertebral strength at all ages, largely because of the greater cross-sectional area of vertebrae. The latter is estimated to be 25% less in women than in men [37]. According to another study, periosteal bone formation increases vertebral body cross-sectional area to a 3-fold greater extent in men than in women, distributing loads over a larger cross-sectional area (CSA) so that the load imposed per unit CSA decreased twice as much in men than in women [37]. The fact that women generally experience greater relative loads is in accordance with other studies [38]. The age-associated decline in vertebral strength is greater in women than men. In women, the ultimate load of the spine and the fracture risk score (i.e., quotient of estimated spinal load and estimated ultimate strength) begin to decrease significantly after the fifth decade, whereas this occurs in men after the sixth decade [39]. For bending and lifting, the risk of vertebral fractures, defined as the ratio of spinal load to vertebral strength, exceeded 1.0 in 30% of women and 12% of men aged at least 50 years [40].

Loading factors include the incidence and mechanics of falls, which occur more frequently in the elderly. One third of community-dwelling individuals older than 65
years of age experience falls every year. Obviously, the more times an individual falls, the greater is the risk of fracture. Hip fractures are almost always due to a fall, but only 5% of falls result in fractures [41]. The risk of hip fractures is greatest for a sideways fall that impacts on the greater trochanter. In such a case, the risk of hip fracture has been shown to rise up to 6-fold [42]. Disturbance type and gait speed significantly affect the direction of a fall and location of the impact. Slipping or fainting while walking slowly is more likely to result in an impact on the hip, suggesting a greater risk of hip fracture [43]. In the latter study, four types of disorders (faint, slip, step down and trip) were investigated at fast, normal and slow speed. A meta-analysis showed that a low body mass index is a risk factor for hip fracture even after adjustment for femoral areal BMD [44]. In women, a threefold increase in soft tissue thickness has been shown to reduce predicted peak force by 35% [45]. In a recent investigation of human cadaveric specimens, it was found that each SD decrease in trochanteric soft tissue thickness was associated with a 1.8-fold increase in the risk of hip fracture [46].

**Treatment**

**Osteoporosis-Specific Medication**

Although there is still some discussion on the optimal dose, 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 15 to 20 years clearly established that – in addition to calcium and vitamin D – patients with osteoporosis should receive specific pharmacologic treatment. In 2005, Riggs and Parfitt [47] proposed a classification of drugs used to treat osteoporosis, based on their action on bone remodeling. Anticatabolic 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 substantially increasing bone mass, anabolic drugs appear to repair bone microarchitecture and improve bone geometry. Strontium ranelate, which is available for the treatment of osteoporosis in Europe, does not fit into the aforementioned classification because it inhibits bone resorption and stimulates bone formation.

There is a large body of scientific evidence derived from randomized controlled trials concerning the treatment of osteoporosis in postmenopausal women; for a detailed discussion the reader is referred elsewhere [1, 48]. To summarize, a number of substances were shown to be effective against both vertebral and nonvertebral fractures: three different aminobisphosphonates (alendronate, risedronate, zoledronic acid), teriparatide, strontium ranelate and hormone replacement therapy (the lattermost is no longer recommended for the prevention or treatment of osteoporosis). Evidence of efficacy against vertebral fractures is available for ibandronate (an aminobisphosphonate), raloxifene and PTH(1–84).

In contrast to postmenopausal women, osteoporosis in men is scarcely investigated. In 2000, the first large controlled trial on osteoporosis treatment in men showed that alendronate increased bone mineral density and prevented vertebral fractures [49]. In men receiving glucocorticoids, risedronate reduced the risk of vertebral fractures [50]. In a randomized open label study performed in men with primary or secondary osteoporosis, Ringe et al. [51] found a significantly lower incidence of new vertebral fractures in men treated with risedronate when compared to alphacalcidol. Although the above mentioned studies constitute a rationale for the treatment of osteoporosis in men, undertreatment of elderly men with osteoporosis is very common in clinical practice. Thus, further research needs to be conducted on gender-related aspects of the treatment of osteoporosis.

**Training**

The public health burden of fractures cannot be resolved by drugs alone because drug trials have been largely focused on women at the highest risk of fractures due to osteoporosis. However, a large number of individuals who suffer fractures have a bone mineral density even less than –2.5 SD below the normal value in young adults. Therefore, one goal is to achieve an acceptable bone mineral density in the general population. Prophylaxis should be started in childhood, with the aim of increasing peak bone mass. A 7-month exercise program of gradually increasing intensity in pre- and early-pubertal girls showed greater changes in the cross-sectional area of femoral neck bone, cortical thickness, and section modulus in the intervention group than in controls [52]. According to experimental studies, the response to exercise is gender specific; the greatest effects are seen in male animals [53].

**Vertebroplasty/Kyphoplasty**

These methods of percutaneous cement injection provide minimally invasive options for the management of osteoporotic vertebral compression fractures. According
to a recent review, a mean restoration of 6.6° in the kyphotic angle is achieved by both procedures [54]. A large number of subjects experience some pain relief: 87% with vertebroplasty and 92% with kyphoplasty. With regard to complication rates, cement leaks occur in 41% and 9% of vertebrae treated by vertebroplasty and kyphoplasty, respectively. Following either procedure, new fractures of adjacent vertebrae occur at rates higher than those registered in the general osteoporotic population, but approximately equivalent to the general osteoporotic population that had experienced a previous vertebral fracture.

Hip Protectors
As mentioned above, the risk of hip fracture is greatest for a sideways fall that impacts on the greater trochanter [42]. An increase in the thickness of soft tissue has been shown to reduce the predicted peak force on the trochanter [45]. Thus, trochanteric padding systems designed to absorb part of the impact on the hip when falling may reduce the risk of hip fractures. However, the results of studies investigating hip protectors for prevention of hip fractures in the elderly are contradictory. Pooling data from eleven trials conducted in nursing or residential care settings, including cluster-randomized studies, demonstrated a significant reduction in the frequency of hip fractures [55]. However, pooling data from three individually randomized trials involving more than 5,000 community-dwelling persons showed no reduction in the frequency of hip fractures [55]. In line with the doubts expressed in this review concerning the effectiveness of hip protectors in the elderly, a more recent meta-analysis [56] reported limited evidence of hip protectors preventing hip fractures in care homes. Many hip fractures occur in persons with a low risk for hip fractures or under circumstances that preclude the use of hip protectors. This may be the reason why the actual preventive effect of hip protectors is lower than its maximum potential preventive effect [57]. Cost-effectiveness analyses are inconsistent in that they report positive as well as negative results. The primary acceptance of hip protectors as well as compliance rates are low.

Compliance can be raised by providing information on the dangers of hip fractures as well as improving the design and mechanical properties of hip protectors [58]. Soft-shell protectors are possibly more acceptable to users than the traditional hard-shell designs. However, in simulated sideways falls, soft-shell protectors were shown to achieve no more than a marginal reduction of the total impact force [59]. Further clinical trials are needed to clarify this issue.

Conclusion
Osteoporosis is an age-related disease with several gender-specific differences. Its prevalence is higher in women than in men. Due to their larger bones, men have greater bending strength than do women. However, once a hip fracture has occurred, mortality is higher in men. Differences in sex hormone production – especially the abrupt decline of estrogen in women – are responsible for inter-gender differences in the pathophysiology of osteoporosis. Finally, the treatment of osteoporosis also differs between genders; some therapy options can only be used in women.

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Conflict of Interest Statement
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References
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