Of mice and men: pathophysiology of male osteoporosis

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Abstract

In both old and young men osteoporosis is a severe but frequently neglected condition. This review deals with the multifactorial pathogenesis of impaired bone strength in men. Male bones are not only influenced by androgens, but, somewhat surprisingly – according to the current state of knowledge – female sex hormones may be the major players in calcified tissue remodelling. As a matter of principle, gender shapes bone geometry on a life-long basis. In men, age-dependant bone loss is outweighed by increased periosteal apposition. Contrary to women, the male gender-specific resorption pattern is mainly based on trabecular thinning. Therefore the connectivity remains rather intact, which again positively influences the biomechanical tissue properties and the resistance to fractures. Since affected patients often present with a family history of fractures or low bone density, the genetics of male osteoporosis is one of the main fields of interest in current bone research. Several gene polymorphisms involving the α1 chain of type 1 collagen (COL1A1), aromatase, vitamin D receptor (VDR), low-density lipoprotein receptor-related protein 5 (LPR5) and the lactase phlorizin hydrolase (LCT) have recently been described. But apart from such exciting research novelties, the classical every-day violaters of both male and female bone health (vitamin D deficiency, low calcium intake and inadequate life-style) must still be taken into account.

Introduction

Osteoporosis 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. Bone density is expressed as grams of mineral per area or volume, and in any given individual is determined by peak bone mass and the amount of bone loss. Bone quality refers to architecture, turnover, damage accumulation (e.g. microfractures) and mineralization [1]. Histomorphometric findings in osteoporotic bone typically include reduced trabecular bone volume (BV/TV), low trabecular number (Tb.N), impaired trabecular thickness (Tb.Th) and poor connectivity. Although osteoporosis more frequently occurs in postmenopausal women, male individuals are not resistant to the disease; indeed about 15% of all patients affected are men. In contrast to women they more often suffer from secondary bone loss. Idiopathic osteoporosis (including the senile type) accounts for only less than half of the cases. Development of impaired bone strength in men must be considered as a multifactorial process involving changes in hormones, growth factors and cytokines. Vitamin D deficiency, gene polymorphisms, renal calcium loss and lifestyle factors moreover contribute to the disease.

Sex hormones

Estrogen deficiency is traditionally associated with postmenopausal osteoporosis, but also plays a prominent role in the pathogenesis of male osteoporosis. Estrogens are C18 steroids
formed by aromatization of androgens. The aromatase enzyme catalyses the conversion of androstenedione to estrone and the conversion of testosterone to estradiol. The vast majority of circulating estrogens are protein-bound; about two-thirds are transported via albumin, one-third is sex hormone binding globulin (SHBG)-bound and the remainder is free. Several studies have suggested that in male idiopathic osteoporosis increased serum levels of SHBG lead to a decrease in free androgens and estrogens [2,3]. Since estrogens normally suppress the generation and activation of osteoclasts [4], bone remodelling is consecutively shifted towards resorption as seen in postmenopausal hormone deficiency. Further menopause-triggered effects are overexpression of pro-inflammatory cytokines (IL-6, IL-11, TNFα), reduced expression of the osteoclast suppressor TGF-β and the enlargement of the bone marrow pool of resorptive progenitor cells [5,6]. Despite the fact that these results add up to a conceivably pathogenetic concept in women that could be partially suitable for men, concise results from corresponding studies in males are still pending. Like other steroids, estrogens bind to intracellular receptors (estrogen receptor α (ERα) and estrogen receptor β (ERβ)) to regulate gene transcription. Their distribution differs between target tissues. Although bone expresses both receptor types, broad consent on the cellular location and mechanisms of action has not yet been reached. Impaired ERα expression in osteoblasts and osteocytes was found in bone biopsies of younger men with idiopathic osteoporosis [7]. Moreover, lack of estrogen in aromatase deficiency results in decreased mineral density, delayed epiphyseal closure and tall stature in affected humans [8]. Similar findings were reported in a man with a disruptive mutation of the estrogen receptor (α) [9]. Although estrogen effects seem to predominate in mature male bone, androgens must not be forgotten. The presence of corresponding receptors (androgen receptor (AR)) and essential enzymes for the generation of male steroid hormones indicate a certain role for androgens within local bone metabolism [10,11]. Moreover, men and male rats that are by birth insensitive to androgens (testicular feminization) not only develop a pseudo-female phenotype but also exhibit impaired bone density. Astonishingly their bone mass is lower than that in healthy females, which again emphasizes the distinct role of both female and male sex hormones within bone biology [12,13]. Furthermore, dihydrotestosterone (DHT) or other non-aromatizable androgens can prevent trabecular and cortical bone loss in both orchidectomized or ovariectomized rats [14,15].

**Bone geometry**

Gender implicates significant differences in bone geometry; during growth and puberty the presence of androgens leads to the development of the male phenotype. Female bones are smaller in size and total diameter since estrogens significantly suppress the amount of periosteal apposition but stimulate the narrowing of the medullary cavity by increased endosteal bone formation. Astonishingly cortical thickness neither varies in race nor in gender. This can be simply explained by cortical inward-growth in females and expansive size growth in males [16]. Androgens mainly act on growing bone while estrogen rather preserves the postpubertal state [17]. Therefore it is easy to understand how postmenopausal estrogen deficiency gives rise to the development of osteoporosis. Since men do not encounter an equivalent midlife hormonal change, their pattern of bone loss is slower. In terms of precise pathogenetic mechanisms no difference can be made between idiopathic and senile osteoporosis. Compared to women, bone loss in older men is limited by increased periosteal bone apposition [18]. Furthermore, the pattern of trabecular bone loss varies between the genders. Women mainly lose connectivity while in men thinning predominates [19]. Hypothetically male body composition could also play a relevant role in bone formation activity. Since a greater amount of muscle transfers more mechanical load, an additional increase of bone remodelling seems obvious [20].

**Vitamin D**

Although often seen in postmenopausal women, osteoporosis is not always the consequence of bone loss; it can originate from impaired bone growth in childhood or adolescence. Even if malnutritional diseases such as
rickets have become rare, vitamin D deficiency still poses a major problem to bone health. Vitamin D and its hydroxylated derivatives are secosteroids that can be produced either endogenously after exposure to sunlight or gained from dietary intake. After binding to the corresponding steroid receptor the complex itself acts as a transcription factor. Vitamin D deficiency is a widespread condition predisposing whole populations to secondary hyperparathyroidism. Elevated parathyroid hormone (PTH) serum levels, as seen in primary, secondary and tertiary hyperparathyroidism, lead to demineralization of bone. While primary disease is usually caused by a benign parathyroid tumor, secondary hyperparathyroidism frequently arises from hypocalcemia, as seen in chronic renal failure or vitamin D deficiency. Even in healthy males significant correlations between low spinal bone mineral density (BMD) and corresponding D hypovitaminosis can be detected [21]. Since vitamin D represents a key regulator of intestinal calcium absorption, its association with osteoporosis (“osteoporomalacia”) does not come as a surprise. Apart from the generally high prevalence of vitamin D deficiency certain risk groups have been identified (e.g. long-term residents of nursing-homes, immigrants to higher latitudes with darker skin and therefore reduced penetration of sunlight). Although in osteomalacia broad osteoid layers are produced, the material properties of properly mineralized bone are not reached: as a consequence these patients are also predisposed to fractures. Simple exposure of the hands and face for several minutes a day could lead to a sufficient vitamin D supply, but promotion of that easy method remains strongly controversial. Since dermatologic anti-skin-cancer incentives have cost much effort to be widely accepted among the population, the recommendation of supplements, vitamin D-rich or enriched nutrition should be preferred instead.

**Molecular signalling – the RANK/RANKL/OPG system**

Receptor activator of nuclear factor κ-b ligand (RANKL), a member of the tumor necrosis family (TNF) superfamily, is secreted by osteoblasts and regulates, via the receptor activator of nuclear factor κ-b (RANK), the differentiation, activation, and survival of osteoclasts. RANKL-expression on marrow stromal cells (MSCs) is upregulated two- to threefold by estrogen deficiency and directly correlates with increases in bone resorption markers [22]. Osteoprotegerin (OPG), which is produced by preosteoblastic MSCs and osteoblasts, acts as a decoy receptor that competitively inhibits RANK signalling. Mice overexpressing OPG develop an osteopetrotic phenotype [23]. In several clinical studies OPG levels in humans have been shown to rise with age. Men exhibit a steep increase in OPG levels from about 70 years onwards, which is later than in women, where it occurs in their sixties [24]. Somewhat surprisingly increased OPG serum concentrations could be demonstrated in osteoporotic patients [25]. Since, as mentioned above, studies on serum OPG levels yielded rather unexpected results, the legitimate question has been raised whether circulating OPG levels indeed depict the microenvironment of its action. A similar paradox involves low serum RANKL levels, which could be identified as an independent risk factor for non-traumatic fractures [26]. When OPG knockout mice were shown to exhibit severe arterial calcification, the already suspected linkage between atherosclerosis and osteoporosis began to seriously awake international scientific interest [27]. Apart from the fact that these diseases share several risk factors (e.g. ageing, inflammation, glucocorticoid use, estrogen deficiency), aortic calcification can frequently be found in lateral spine radiographs from osteoporotic patients [28]. As in bone, OPG might act as a “vasculo-protegerin” in the blood vessels. In spite of this suggested function, blood tests have again shown the opposite result; for instance, OPG plasma levels were positively correlated with clinical stage in patients with peripheral artery disease [29].

**GH/IGF-1 axis**

The growth hormone (GH)/insulin-like growth factor-1 (IGF-1)-axis plays an essential role in the development, growth and maintenance of the skeleton. The peripheral effects of pituitary GH secretion are mostly mediated via hepatic or locally produced IGF-1. Androgens, for example, stimulate osteoblastic IGF-1 production and thereby their proliferation [30].
Another pathogenetic approach to male osteoporosis has suggested the etiologic involvement of low IGF-1 plasma levels [31]. Although adults with GH-deficiency also develop secondary bone loss, idiopathic osteoporosis is, rather, associated with hepatic GH-insensitivity than with pituitary hyposecretion [32]. Thus GH replacement therapy is unlikely to be offered to the average male suffering from idiopathic osteoporosis.

**Secondary osteoporosis and renal calcium loss**

As already mentioned, when compared to women, men more often suffer from secondary bone loss. The spectrum of such underlying diseases ranges from endocrine (e.g. both endogenous and exogenous glucocorticoid excess, hyperthyrosis, hypogonadism) to gastrointestinal (e.g. malnutrition, malabsorption) and malignant diseases. Cancer-related bone loss can be directly tumor-mediated (e.g. RANKL secretion in multiple myeloma) [33] or treatment-dependent (e.g. antiandrogen therapy in prostate cancer). Furthermore, impaired bone strength can occur along with chronic inflammation (e.g. rheumatoid arthritis, chronic inflammatory bowel disease, ankylosing spondylitis) or after organ transplantations [34–36]. The absence of mechanical stress (e.g. immobilisation) also deprives bone of its remodelling capacity. Renal calcium loss may be another pathogenetic co-aspect of male osteoporosis, since hypercalciuric patients often present with reduced spinal bone density [37], but vice versa, in osteoporotic men significantly increased urinary calcium excretion has been found [38].

**Genetics**

Osteoporosis should be considered mainly as a multifactorial, polygenic disease; several specific genes are considered to be major candidates for susceptibility to bone fragility. Patterns of inheritance barely follow Mendelian laws, except in mutations within the ERα and aromatase genes. In these rare familial osteoporotic syndromes, a monogenic gene defect causes reduced bone density. Recently much attention has been drawn to the gene encoding the α1 chain of type 1 collagen (COLIA 1). A single nucleotide polymorphism (SNIP) affecting an Sp1 binding site within a key regulatory region of COLIA 1 has been reported to be associated with lower BMD and increased fracture risk [39–43]. Moreover, polymorphisms within the aromatase, IGF-1 and vitamin D receptor (VDR) genes have been observed to correlate with bone mass [44–47]. Lactose malabsorption is not only widespread among the caucasian and asian populations but is also associated with reduced skeletal calcium content. At the genetic level, a corresponding polymorphism (LCT: a 13910 T/C dimorphism near the lactase phlorizin hydrolase gene) has recently been identified. Lactose-intolerant individuals differ from milk-drinkers anthropometrically as they are significantly lighter and shorter [48]. Recently another study has identified low-density lipoprotein receptor-related protein (LPR5) as a genetic susceptibility factor for idiopathic male osteoporosis [49]. But, in the end, individual BMD is neither the quantitative nor the qualitative result of a certain gene set only, rather it reflects a given potential that is modulated by various endo- and exogenous factors.

**Life-style**

Exogenous factors such as nutrition, exercise, exposure to sunlight, nicotine and alcohol abuse are thought to strongly influence the development of this disease. Since such an impact on bone health has been well established in women, an equivalent role for male lifestyle can be assumed [50,51]. Low dietary calcium intake and smoking have been associated with a reduction in both spinal and hip BMD in young otherwise definitely healthy cadets entering the US military academy of Westpoint. Moreover, prior exercise history was accompanied by an increase in calcaneal BMD [52]. In addition body weight strongly influences bone health. In particular, in osteoporotic patients, low body mass index (BMI) is significantly associated with all sorts of fractures [53]. As an extreme example, male adolescents with anorexia nervosa often show osteopenic or even osteoporotic bone density [54]. Alcohol abuse is considered to be an important risk factor for impaired bone strength and fractures [55]. Apart from conditions such as malnutrition, hypogonadism and cirrhotic...
liver disease, which jeopardize bone health in chronic drinkers, ethanol seems to have directly toxic effects on osteoblast function. Osteocalcin is a protein that is synthesized by osteoblasts and that can easily be measured by blood testing. Levels correlate well with bone formation. In both social drinkers and alcoholics reduced osteocalcin levels could be shown [56]. Moreover calcium excretion is elevated after ethanol intake. The long term effects of alcohol further involve significant fluctuations of serum PTH levels, with acute intoxications resulting in intermittent hypoparathyroidism with a subsequent rebound rise [57]. Although vitamin D deficiency plays a central role in cirrhotics in particular, histomorphometric findings in non-cirrhotics indicate a low turn-over osteoporosis rather than osteomalacia [58].

**Conclusion**

Although many pieces from the puzzle of male osteoporosis have been collected, no comprehensive model for the pathogenesis of this multifactorial polygenetic disease can be generated so far. In both men and women osteoporosis arises from a severe imbalance in bone remodelling, i.e. from reduced formation and/or increased resorption of bone. Even though their bone geometry basically protects men from fractures, this advantage becomes useless once resorption has been uncoupled from bone formation. It does not matter if it is vitamin D deficiency, low calcium intake, inadequate life-style, genetics or hormonal changes (Fig. 1) that are to blame, uncoupling of bone remodelling may result in a significantly increased fracture risk.

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