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Osteoporosis in Men - A Crucial Role of Sex Hormones

Michał Rabijewski and Lucyna Papierska
Department of Endocrinology,
Medical Centre for Postgraduate Education, Warsaw,
Poland

1. Introduction

Osteoporosis is a disorder characterized by reduced bone mass, impaired bone quality and a propensity to fracture. Traditionally, osteoporosis has been viewed as a syndrome characterized by back pain and vertebral fractures. Osteoporotic fractures have long been regarded as a female ailment, but with the increasing longevity of men, it appears that the incidence and prevalence of osteoporotic fractures in men is not very different from the rate in women although it occurs approximately 10 years later in the lives of men. Morbidity and mortality associated with fractures and their (surgical) treatment is considerably greater than in women. A multitude of factors determine bone strength: genetic, nutritional (calcium), vitamin D, physical activity, and hormonal factors. Hormonal factors are significant throughout life, from puberty onwards. In adolescence they are indispensable for the formation of peak bone mass. Throughout life, sex steroids maintain bone formation. Surprisingly, in men estrogens appear to be more significant for the development of peak bone mass and the maintenance of bone mineral density than androgens. In men estrogens are derived from androgens and levels of both of them are strongly interrelated (adequate androgen levels imply adequate estrogen levels).

2. Qualities of bone in men

Fracture is the result of failure of the material composition and the structural design of bone to tolerate the loads imposed upon it. These properties, or bone 'qualities', are compromised with the emergence of age-related abnormalities in bone modelling and remodelling, the cellular machinery responsible for the attainment of peak bone strength during growth and its maintenance during adulthood. The abnormalities contributing to material and structural decay are: a negative bone balance produced by each basic multicellular unit (BMU), a sustained increase in remodelling intensity in midlife in women but not in men unless frankly hypogonadal, reduced periosteal apposition after completion of longitudinal growth and secondary hyperparathyroidism (Khosla et al. 2006). However, the most important cause of bone loss is the increase in the intensity of bone remodelling on the trabecular, intracortical and endocortical bone surfaces (Amin & Felson 2001; Benito et al. 2004). The trabecular bone loss proceeds mainly by thinning in men - see Figure 1. Remodelling on intracortical surfaces results in intracortical porosity, particularly in cortex adjacent to the

marrow cavity, trabecularisation of the endosteal cortex and a decrease in cortical width. The effect is likely greater in women than in men. Periosteal apposition slows after completion of growth. Some studies suggest that men have greater periosteal apposition than women (Vanderschueren et al. 2004).

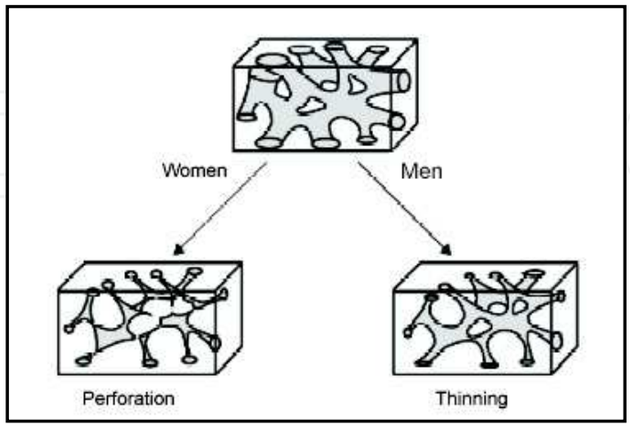

Fig. 1. Gender differences in pattern of trabecular bone loss resulting in trabecular thinning in men and increased cortical porosity and trabecular perforation in women.

Compared with women, men have greater bone strength not because of increased bone mineral density, but because of greater bone size, resulting from bone acquired at the periosteal surface. Periosteal bone formation is a result of two endocrine effects: androgen-mediated stimulatory effects on periosteal bone formation and estrogen induced inhibitory effects on periosteal expansion. So, greater periosteal bone expansion in men has been traditional assumed to result from exposure to higher levels of androgens and/or lower levels of estrogens (Vanderschueren et al. 2006).

3. Hormonal determinants of bone mass

3.1 Androgens and bone

Androgens are pivotal for the acquisition of bone mass in adolescence and the maintenance of bone mass in adulthood (Finkelstein et al. 1996). In men, chronically low androgen levels are associated with low bone mass, and testosterone replacement can enhance BMD. However, it is not yet precisely clear what role androgens play in the maintenance of bone mass in men. Peak bone mass is acquired between the ages of 12–16 years, and even beyond. It represents the sum of several processes including a marked increase in bone formation. Boys tend to reach peak 2 years later than girls and their BMD is higher than that in women at all skeletal sites. In part this relates to a greater cross-sectional bone area in males. The timing of gonadal steroid surges are critical for bone acquisition since there is a relatively short window of time in which bone formation is favored and matrix synthesis is markedly enhanced (Rochira et al. 2006). In adulthood normal testosterone levels are required for the maintenance of BMD. Hypogonadal men suffer from osteoporosis, and bone fractures in men in their forties or fifties may well be the first manifestation of undiagnosed hypogonadism (Vanderschueren et al. 2004). Variations of free testosterone within the normal range are an independent predictor of cortical bone density, and also of previous osteoporosis-related fractures. Elderly men and older men with a deficiency in

total testosterone and estradiol are more likely to be osteoporotic and at greater risk of hip fracture. Men with a deficiency of total testosterone were more likely to have rapid bone loss from the hip or to suffer from hip fractures following minimal trauma. Also men with osteoporosis were more likely to have a deficiency of testosterone and estradiol (Khosla et al. 2006).

3.2 Estrogens and bone

Estrogens play also an essential role in maintaining bone mass in men.. Men with estrogens deficiency or impaired estrogens action have delayed epiphyseal closure and osteopenia (Monshima et al. 1991). It was shown that in men with aromatase deficiency the administration of estrogen had a significant beneficial effect on skeletal growth and bone maturation (Rochira 2000). In elderly men, estrogen seems to play a more dominant role than testosterone in regulating bone resorption. In elderly men, lower than normal levels of estrogen appeared to be associated with vertebral fractures (Rochira et al. 2006). Age-related decreases of estradiol, especially levels below 40 pmol/l, may be the major cause of bone loss (Barrett-Connor et al. 2000).

Estrogens in men are predominately the product of peripheral aromatization of androgens. Androgens (androstenedione, dehydroepiandrosterone produced by the adrenal gland, and testosterone produced by the testis) serve as precursors for chemical conversion to estrone and estradiol via the enzyme aromatase. The testis itself produce approximately 20% of the total estradiol. Adipose tissue is the most important source of estrogens in men. Plasma testosterone levels show an age-related decline while plasma estrogen levels in men remain relatively constant with aging resulting in an increased estrogen/androgen ratio. Estrogen deficiency in elderly men is tightly coupled to androgen deficiency since all estrogens are derived from androgens through aromatization. Restoring plasma testosterone to normal also normalizes plasma estradiol levels.

3.3 Current model of influence of sex hormones on bone in men

Recently data have challenged the traditional concept of stimulatory *vs.* inhibitory effects of androgens and estrogens. The role of androgens as the main determinant of male bone acquisition has been challenged by observations in men with aromatase deficiency (Carani et al. 1997; Rochira et al. 2000). These men, who have normal androgen concentrations, but undetectable levels of endogenous estrogen, have surprisingly low bone mass and areal density and respond very well to estrogen therapy. Reduced bone mass in these subjects is not due to reduced volumetric bone density, but reflects a deficit in bone size and the increase in bone mass during estrogen therapy was found to be driven primarily by an increase in bone size, without treatment effect on volumetric density. The enlargement of cortical bone reflected *periosteal apposition*. As evidenced in the aromatase-deficient adolescent androgens alone may not be sufficient to drive periosteal expansion. Moreover, the periosteal expansion observed in response to estrogen therapy demonstrates that estrogens stimulate rather than inhibit periosteal apposition. While, exposure to estrogens is essential for the process of periosteal bone expansion in men.

Thus, the interaction of estrogen with the periosteum has been studied. Animal data suggest that estrogens may decrease the set point of the mechanostat and thereby increase the sensitivity of bone for mechanical stimuli (Lee 2003). This may indirectly impact on the response of the bone to androgens, because androgens increase lean body mass and the

mechanical loading of the male skeleton and this mechanical loading constitutes one of the main triggers for androgen induced periosteal apposition. Androgens indirectly induce mechanical loading through their anabolic action on muscle, and there is growing evidence that estrogens interact with this process. Exposure to estrogen may be critical to allow the increased loading to be translated into periosteal bone formation and radial expansion (Vanderschueren 2003).

Estrogen action on bone may reflect an interaction with GH and/or IGF-I, two main determinants of cortical bone growth (Bateman et al. 1998). Estrogens are known to have a biphasic effect on pubertal skeletal growth. During early puberty, low estrogen concentrations increase the secretion of GH and IGF-I synthesis. As a consequence, estrogens stimulate skeletal growth. Hence, sex steroid-related changes in GH and IGF-I secretion may impact on bone size and cross-sectional area. By the end of puberty, elevated concentrations of estrogen limit skeletal longitudinal growth through a direct effect on growth plate closure. By the end of puberty, estrogens may inhibit radial growth in men (Juul 2001). Estrogen-related changes in serum IGF-I may be more important than direct estrogen-mediated stimulation of the periosteal surfaces. Estradiol stimulates radial bone growth as a result of an up-regulation of hepatic IGF-I synthesis and secretion, but only ER activation results in changes in serum IGF-I, indicating that AR-mediated androgen action, is independent of GH and/or IGF-I.

Effects of estrogen on periosteal bone are dose dependent. Low levels of estrogen might increase the mechanical sensitivity of the periosteum and/or affect circulating IGF-I levels, while higher concentrations of estrogen might inhibit periosteal bone apposition and its interaction with mechanical loading, possibly through an ERβ effect (Moverare et al. 2003). The inhibitory effect of estrogen is not observed in men, because men are exposed to low endogenous estrogen concentrations. Also disruption of ERβ does not affect the male cortical phenotype. Men exhibit more periosteal expansion because they are more exposed to the stimulatory effects of androgens and less exposed to the inhibitory effects of estrogens. Androgens may primarily affect lean body mass and the loading of the male skeleton; exposure to low-dose estrogen may allow this loading to induce bone expansion.

In addition to the changes in trabecular and cortical morphology, abnormalities in bone remodelling produce changes in bone 'qualities' at higher levels of resolution. Advancing age is associated with a reduction in osteonal size, accompanied by an increase in haversian canal diameter due to the reduced bone formation by each BMU. Smaller osteons result in less resistance to crack propagation through interstitial bone (Khosla et al. 2006). Also, smaller osteons give rise to a greater proportion interstitial (rather than osteonal) bone which has a higher tissue mineralization density, fewer osteocytes and is liable to accumulate microdamage and offer less resistance to crack propagation. These phenomena are likely to occur in both sexes but in women, osteonal density (the number per unit volume) may increase because of the high intracortical remodelling; the osteons are smaller but there are more of them (Amin et al. 2001).

Sex differences in bone size are contributing to the lower incidence of fractures in men. Men also have larger muscle mass and higher body weight so that compressive stress (load/area) is similar in young adult men and women. Men and women have similar cortical thickness which confers a greater cortical area in men (because their bones have a larger perimeter). Peak trabecular number and thickness is similar in men and women at the iliac crest and vertebral bone. Men have thicker trabeculae at the distal radius which may be more resistant

to perforation. Reasons for sex differences in bone fragility are multifaceted: sex differences in trabecular morphology (thinning in men and perforation in women), less cortical porosity, endocortical remodelling and thinning in men, particularly and possibly greater periosteal apposition in men. Other factors that may contribute to sex differences in bone fragility include differences in osteonal morphology, tissue mineralisation and matrix composition (Amin et al. 2001; Seeman et al. 2002;Vanderschueren et al. 2004). Model of sex hormones action on bone is shown on Figure 2.

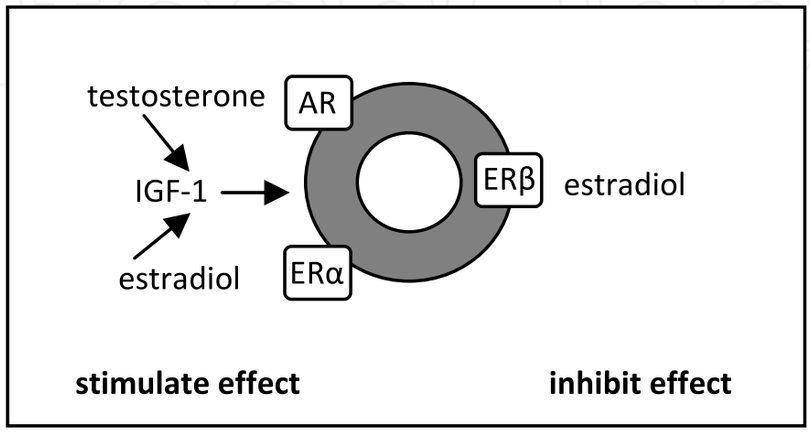

Fig. 2. Model of sex hormones action on bone: testosterone stimulates periosteal expansion, whereas estradiol has a double action on periosteal bone apposition. Estrogen action on the periosteum may be also result of indirectly changes in IGF-I.

4. Epidemiology of osteoporosis in men

It is agreed that the life-time risk of osteoporotic fracture in men is around one-third of that in women About 4 to 6 percent of men older than 50 have osteoporosis, and 33 to 47 percent have osteopenia. The prevalence of osteoporosis is 7 percent in white men, 5 percent in black men, and about 3 percent in Hispanic-American men. Because men have greater bone mass, they present with osteoporotic fracture about 10 years later than women. Thus, starting at about age 75, the incidence of hip fracture increases rapidly. The life-time risk of a hip fracture in Caucasian men is 13 to 25% (Cooper et al.1992; Johnell et al. 2005). Because of the predicted growth in the number of elderly persons, the number of men with osteoporotic fracture is expected to increase.

5. Fractures in men

Fractures represent the primary clinical consequence of osteoporosis. The difference in fracture incidence observed between men and women is due not only to a difference in their bone strength but also to the type and frequency of trauma experienced by men over life. Fractures of the hip, vertebrae and forearm are more likely to occur after minimal trauma in aging men. Of these fractures, those involving the hip and vertebrae are associated with some of the greatest morbidity and mortality for men (Anderson et al.1999). The fracture incidence in men follows a bimodal distribution tending to peak in adolescence and with advanced age. Although women have a greater incidence of fractures with aging, men are

actually more likely than women to sustain a fracture at younger ages, what is related, in part, to the greater frequency of severe trauma associated with their fractures. The incidence rate for a work-related fracture for male employees is more than twice that for female employees, These fractures appear to be related to high-energy trauma events (Anderson & Cooper 1999). After the age of 50 yr, the trend reverses, with women tending to have a higher incidence of overall fractures than men. In both men and women, there is an exponential rise in fracture incidence after age 75 yr, particularly for hip fractures; however, the absolute incidence tends to be lower in men. Osteoporotic fractures in men appear to involve fractures of the hip, vertebrae, forearm, and humerus, although fragility fractures at other sites, including the pelvis, ribs, and clavicle, also occur in aging men. Of all the hip, forearm and clinical vertebral fractures, approximately 30, 20, and 40% occur in men, respectively. The lower absolute incidence in osteoporotic fractures in older men may be due to the an increased frequency of falls in women (Bilezikian 1999; Campion & Maricic 2003).

5.1 Hip fractures

Among all osteoporotic fractures, hip fractures account for the greatest morbidity and mortality for men. Overall, the incidence of hip fractures in men is uncommon until after the age of 75 yr, when the risk increases exponentially. The age-adjusted female to male ratio for hip fractures has been observed to be highest for whites, with a ratio up to 3–4:1 (Maggi et al.1991). With the improving longevity of men and the increasing size of the population, the number of men with hip fracture worldwide is estimated to reach 1.8 million in 2050 (Khosla et al. 2006). The mortality and morbidity associated with hip fractures are greater for men than women (Forsens et al. 1999). Men are twice as likely to die in hospital after a hip fracture as women. Estimates for the 1-yr mortality rate after hip fracture ranges from 31–35% in men compared with 17–22% in women (Bass et al. 2007). Greater number of comorbid conditions at the time of fracture contribute to mortality risk and up to 50% of men may need institutionalized care after hip fracture. Men are less likely to return to autonomous living circumstances than women at 1 yr after hip fracture. In men ages 60–69 yr, the decrease in life expectancy after a hip fracture is 11.5 yr, compared with men ages 70–79 yr and age 80 yr or older, where the decrease in life expectancy is 5 and 1.5 yr, respectively (Center et al.1999). Despite these facts, men are less likely to be investigated or treated for osteoporosis after hip fracture.

5.2 Vertebral fractures

Vertebral fractures are not always associated with pain that would bring them to clinical attention. The true incidence of these fractures is often underestimated. The age-standardized prevalence of vertebral deformity in Europe is estimated to be the same for both men and women, either 12 or 20%, depending on the criteria used to define vertebral deformity (O'Neill et al.1996). Below age 65 yr, men had a higher prevalence of vertebral deformity than women, whereas after this age the trend was reversed. The prevalence of vertebral deformity increased with age. The age-adjusted incidence for radiographically defined vertebral fractures in men is half the rate of women. In a 10-yr study prevalent vertebral deformity was a predictor of mortality in men during the forthcoming decade (age-adjusted hazard ratio, 2.4) (Hasserius rt al. 2003). Severe vertebral deformity is related to functional impairment and the association between vertebral deformity and negative health outcomes appears to be even stronger in men than in women.

6. Risk factors for osteoporosis in men

Development of osteoporosis in men is primarily related to aging and genetic factors but30 to 60 percent of cases of osteoporosis are associated with one or more secondary risk factors. The three major causes of secondary osteoporosis in men are alcohol abuse, glucocorticoid glucocorticoid therapy and hypogonadism. Of these, glucocorticoid-induced osteoporosis is the most common.

6.1 Glucocorticoid therapy

Long-term oral glucocorticoid therapy accounts for nearly one in six cases of male osteoporosis. The extent of bone loss is related to the duration of therapy and the dosage of the steroid. Because of the high risk of bone loss, treatment of osteoporosis is recommended for any patient taking 5 mg or more of steroids per day for longer than six months. The recommended treatment is a bisphosphonate supplemented with calcium and vitamin D (Recommendation of American Collefe of Rheumatology 2001).

6.2 Tobacco and alcohol use

Tobacco use and excessive alcohol consumption are more prevalent in men than in women, and both are independently associated with an increased incidence of osteoporotic fractures (Anderson et al.1997). Tobacco-related bone loss is linked to smoking duration and quantity. The mechanism may be a combination of decreased body weight, decreased calcium absorption, decreased estradiol levels, and a direct toxic effect on bone metabolism. Alcohol in modest amounts may have a protective effect on bone density, but sustained high consumption causes bone loss. It is likely that alcohol has a direct toxic effect on osteoblastic function. Excessive alcohol consumption is also often associated with poor nutrition and decreased physical activity, both of which are associated with bone loss (Seeman et al. 1983). Further studies are needed to determine the quantity of alcohol above which the protective effect ceases and bone loss occurs.

6.3 Hypogonadism

Hypogonadism induces a state of high bone turnover with accelerated bone loss and increased fracture risk which results from combined deficiency of testosterone and estradiol (Goderie-Plomp et al. 2004). Symptomatic hypogonadism is an indication for testosterone substitution in all causes (primary and secondary hypogonadism). .Also in men with history of delayed poberty peak bone mass in significant lower than in healthy men, what can be the reason of greater risk of fracture and high incidence of osteoporosis in this population (Finkelstein et al. 1996).

Aging is accompanied by progressive moderate decrease in the population mean serum concentration of total testosterone. A marked age-related increase of serum sex hormone-binding globulin (SHBG) levels is also found which results in a decrease in the non-SHBG-bound fractions of testosterone available for biological action, i.e. decreased free- and bioavailable testosterone, as well as a moderate decrease of free- and bioavailable estradiol (Araujo 2004)/ . Aging in men is also accompanied by increasing prevalence of signs and symptoms, including osteoporosis, that are reminiscent of those observed in young hypogonadal men, but which in the elderly are at most only in part related to the decline of testosterone production. With age, both low serum testosterone and symptoms and signs

consistent with hypogonadism become increasingly prevalent but also less specific (Zitzmann et al. 2006). The minimal testosterone levels needs in the elderly are not clearly established and may to vary between individuals. In this elderly population, effects of testosterone treatment on BMD have been inconsistent, with the most convincing effects being observed in men with very low serum testosterone (Katznelson et al. 1996; Snyder et al. 2000; Wang et al. 2001). In elderly men, testosterone treatment may have additional beneficial effects on muscle mass and strength, which may help decrease fracture risk through a reduced propensity to fall (Snyder et al.1999).

6.4 Estradiol deficiency

Declining levels of estrogens levels with age contribute to bone loss and fracture risk in men. Estrogen plays an important role in regulating bone density, bone resorption and bone loss in elderly men as well as in the acquisition of peak bone mass. It seems, that free estradiol and SHBG, but not free testosterone, are independently associated with fracture risk, clinical vertebral fractures, non-vertebral osteoporotic fractures and hip fractures. Specifically, the yearly incidence of fractures was inversely associated with serum estradiol levels at estradiol levels less than 16 pg/ml; above this level, there was no relationship between fracture incidence and estradiol levels (Amin et al., 2000, Barrett-Connor et al. 2000)
These findings have clinical implications: measurement of serum sex steroid levels, particularly estradiol levels, in men with osteoporosis and use of selective estrogen receptor modulators (SERMs) in preventing bone loss in aging men may be usefull.

6.5 Vitamin D deficiency

Vitamin D deficiency is a widespread condition and still poses a major problem to bone health in wide population. Vitamin D and its hydroxylated derivatives can be produced either endogenously after exposure to sunlight or gained from dietary intake. Vitamin D deficiency results in secondary hyperparathyroidism (elevated parathyroid hormone serum levels) followed by demineralization of bone. Secondary hyperparathyroidism usually arises from hypocalcemia, as seen in chronic renal failure or vitamin D deficiency (Campion & Maricic 2003). Significant correlations between low spinal bone mineral density and low vitamin D levels can be observed. Vitamin D represents a key regulator of intestinal calcium absorption and its association with bone metabolism and osteoporosis - osteomalacia - is clear. Aging in males is connected with decreased renal hydroxylation of 25OH-vitamin D to calcitriol what is associated with low action of 1-alpha hydroxylase and may lead to low serum levels of active vitamin D derivatives . In patients with osteomalacia the material properties of properly mineralized bone are not reached and these patients are predisposed to fractures (Bilezikian 1999; Khosla et al. 2006).

6.6 Others risk factors and causes of secondary osteoporosis in men

Others risk factors which also could be associated with idiopathic osteoporosis in men (Harper & Weber 1998) and the more common others medical conditions which could lead to osteoporosis are listed in Table 1.
Secondary causes of osteoporosis should be excluded before the diagnosis of idiopathic osteoporosis can be made. Low bone mass and falls are both determinants of osteoporotic fracture in men. The following are a list of risk factors which could be associated with idiopathic osteoporosis in men.

High risk causes
History of nontraumatic fracture (hip, vertebrae or wrist)
Osteopenia seen on plane radiograph
Glucocorticoid use of 5mg of more for longer than six months
Hypogonadism
Hyperparathyroidism
Medium risk causes
Anticonvulsant grug use
Excess alcohol consumption and tobacco use
Rheumatoid and other inflammatory arthritis
Multiple myeloma ot lymphoma
Hyperthyroidism and hypothyroidism
Family history of osteoporosis
Prolonged immobilization, lack of physical activity
Conditions associated with increased risk of falling
Infrequent causes
Chronic renal and liver diseases
Cushing's disease
Low body mass index
Gastric or bowel resection, celiac disease

Table 1. Risk factors for osteoporosis in men.

7. Diagnosis

Osteoporosis can be defined as ''a skeletal disease'' characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk. The World Health Organization has definitions for osteopenia and osteoporosis in women, but not in men. In women, osteopenia is defined as a T score of between -1 and -2.5, and osteoporosis as a T-score of -2.5 or more. The T-score is the number of standard deviations by which the bone mineral density of an individual person differs from that of the young, normal mean of the same population. A strength of this diagnostic threshold has been the fashioning of a common approach to describe the disease. The WHO have supported the use of a single reference population (white women aged 20-29 years), a single reference site (the femoral neck) and a single technology (DXA) (Kanis et al. 2008).

Osteoporosis in men would be defined as a BMD value at the femoral neck that lay 2.5 SD or more below the average value of young healthy women The many studies that have examined fracture risk in men have come to disparate conclusions concerning the relationship between fracture risk and BMD. The relation between BMD and fracture risk changes with age, so that age-adjustment is required. The comparative studies show that the

risk of hip fracture is similar in men and women for any given absolute value for BMD measured mainly at the hip. In the meta-analysis described above the relationship between hip fracture incidence and BMD at the proximal femur was identical in men and women at any given age (Johnell 2005). These studies indicate that a similar cut-off value for femoral neck BMD that is used in women should be used in the diagnosis of osteoporosis in men. The implementation of probability based fracture risk assessment (e.g. FRAX) will decrease the clinical utility of the T-score but diagnostic criteria remain of value in diagnostic of osteoporosis in men (Orwoll 2000).

Osteoporosis in men commonly presents with vertebral body fracture or hip fracture, whereas in women it is often diagnosed by routine bone density screening, but osteoporosis can be identified in men before fractures occur. Men with history of nontraumatic fracture, particularly of the hip, vertebral body, or distal wrist; radiographic evidence of osteopenia (because 30 to 50 percent of bone mass must be lost before evidence of loss is seen on a plain radiograph); long-term glucocorticoid use; hypogonadism; hyperparathyroidism; and other risk factors for osteoporosis, including disease states, medications affecting bone metabolism, or gait disorder, should be considered for formal osteoporosis testing (Khosla et al.2006).

Physicians might consider routinely screening men aged 70 or older, because this is the age when fracture rates increase most rapidly. Men with asymptomatic vertebral body fractures, who are at substantially increased risk of future fractures, can be identified using serial measurements of height. A man with a loss of height or whose distal ribs touch the pelvic brim should be considered for thoracic and lumbar spine radiographs to look for vertebral fractures. Screening measures include diagnostic radiologic studies using dual-energy x-ray absorptiometry (DXA) of the hip and spine, heel ultrasonography, or quantitative computed tomography. In men, declining BMD and T scores (the comparison with peak BMD adjusted for sex and race) correlate with an increased risk of hip and other fractures similar to that occurring in women.

Once osteoporosis is diagnosed, the cause should be determined, if possible, to identify the various risk factors and medical conditions causing secondary osteoporosis. The search for risk factors should include review of the history and physical examination findings plus a laboratory evaluation. Routine laboratory tests include complete blood cell count, liver and kidney panels, and measurement of calcium, phosphorus, alkaline phosphatase, thyroid-stimulating hormone level, and total testosterone levels - table 2.

Initial screening	Additional tests
Complete blood cell cunt	Serum protein
Calcium	24+hour urine calciuria
Phosphorus	Estradiol level
Alkaline phosphatase	Parathyroid hormone level
Kidney and liver function tests	
25-hydroxyvitamin D	
TSH	
Total testosterone	

Table 2. Laboratory evaluation for osteoporosis in men

8. Treatment of osteoporosis in men

Few randomized controlled clinical trials on drug treatment for osteoporosis have been conducted in men. This is due to the fact that data from earlier trials on mixed female–male populations are not accepted as a source of guidelines for men and only a few of the requested randomized controlled studies on purely male cohorts have been performed. Older drugs were approved for osteoporosis in general without the need for separate trials in men (e.g. calcium, fluoride, calcitonin, alfacalcidol) and, therefore, these are still available for treating men. It was suggested that significant differences in bone biology might exist between the sexes. This is a severe therapeutic disadvantage for men with osteoporosis. Interestingly, so far, for all drugs that have also been studied in men, similar therapeutic results, in terms of BMD and fracture reducing potency, have been reported in men and women, disproving the argument of significant differences in bone biology of the female and male skeleton.

8.1 General measures for prevention of osteoporosis in men.

Calcium and vitamin D intake probably provide beneficial effects on bone mass and fractures. Reducing modifiable individual risk factors of diet and lifestyle, including alcohol and nicotine intake, remain important throughout life. For men suffering from one or more diseases or medical conditions with a high risk for the development of secondary osteoporosis (see early detectionand counteractionmeasures are important, e.g. reduction of glucocorticoid dosage if possible, androgen therapy in cases of hypogonadism, thiazides for idiopathic hypercalcuria and early surgical treatment of primary hyperparathyroidism. In the elderly who are at risk for falls (e.g. those with reduced muscle strength, poor balance, previous falls) attempts to increase strength and balance or the use of a hip protector may be beneficial. Table 3 summarises general recommendations for the prevention of osteoporotic fractures in men.

Long-term regular physical activity and exercise
Maintenance of adequate calcium and vitamin D intake (total intake 1000–1500 mg calcium and 600–800 IU vitamin D per day)
Routine calcium/vitamin D supplementation after age 70 years
Limit alcohol intake and smoking
Recognize and treat testosterone deficiency
Identify other risk factors and consider specific prophylactic measures

Table 3. General measures for the prevention of osteoporotic fractures in men

8.2 Aetiological therapy in secondary osteoporosis

Since about 50% of men are diagnosed with secondary osteoporosis, an aetiology-adapted treatment is more important in male than in female. The treatment in such cases is often complicated. eg: glucocorticoids cause bone lose in dose-dependent manner, in corticotherapy of rheumatic disease however, too great a reduction in corticoids may increase the risk of osteoporosis, since an insufficient immunosuppressive effect will allow further degradation of bone tissue by proinflammatory cytokines. Furthermore, insufficient

disease control is associated with less mobility. For a number of mono-aetiolgical, and for the majority of polyaetiological, secondary osteoporoses no aetiological therapies are available, i.e. the therapeutic strategy is no different from that used in idiopathic osteoporosis.

8.3 Treatment of idiopathic osteoporosis

In men with secondary osteoporosis, with no options for aetiology-related treatment, and in all cases of primary or idiopathic osteoporosis, an individually adapted therapeutic strategy has to be planned. Since osteoporosis is a chronic disease that has to be treated over several years, it is important to inform the patient carefully about modifiable risk factors, future fracture risk, chances of improving pain, therapeutic mechanism of the selected medications and their possible side effects. With the exception of estrogen and raloxifen, the same specific drugs as those used with women can be adopted in men. However, not all are approved for this application in men. Calcitonin, alfacalcidol and fluoride do not exclude male osteoporosis and they are listed as second-line treatments. Bisphosphonates, strontium ranelate and teriparatide are firstline treatments, but only alendronate and risedronate have been approved for men. Teriparatide is not approved for men in the European Union countries.

8.4 Calcitonin and fluoride

There are only small studies on these two treatments in men with osteoporosis. There is one double blind, placebo-controlled study with the physiological osteoclast inhibitor calcitonin. In this study 28 men with osteoporosis received either 200 IU of salmon calcitonin nasal spray plus 500 mg calcium per day or a placebo nasal spray plus calcium. Lumbar spine BMD increase of 7.1% in the calcitonin group vs. 2.4% in the controls, in parallel with a higher decrease in bone resorption markers (Trovas et al.2002). In prospective controlled, 3-year trial of 60 men with primary osteoporosis a significantly lower vertebral fracture rate with low-dose-intermittent fluoride therapy compared to controls receiving only calcium plus vitamin D was found (Ringe et al. 1998).

8.5 Bisphosphonates

Bisphosphonate therapy has been shown to be effective in increasing BMD in men with primary osteoporosis, as well as in men with secondary osteoporosis, including hypogonadism and glucocorticoid-induced osteoporosis. The results of a randomized, controlled clinical trial showed that alendronate, given with calcium and vitamin D, was effective in preventing bone loss in men. The BMD increased by 7.3% at the lumbar spine and 2.5% at the femoral neck in the treatment group. Moreover, vertebral fracture risk was significantly reduced (0.8% in the treatment group compared with 7.1% in the placebo group). The efficacy of alendronate in treating osteoporosis in men has been confirmed (Orwoll et al.2000; Miller et al. 2004; Ringe et al. 2004) .

Risedronate is a potent bisphosphonate that has been demonstrated to reduce vertebral fractures in patients with glucocorticoid-induced osteoporosis within 1 year. Risedronate 35 mg once weekly has been approved recently as a second bisphosphonate for the treatment of men with a high fracture risk (Boonen et all.2006, Harrington et al.2004; McClung et al. 2001; Ringe et al. 2006).

Zoledronic acid is a potent intravenously administered bisphosphonate whose effects on fracture risk been assessed in a recent randomized placebo-controlled trial involving elderly

men and women who had recently suffered a hip fracture. Yearly administration of 5 mg of zoledronic acid for a median of 1.9 years within 3 months of the fracture reduced the occurrence of overall new clinical fractures and mortality, but not hip fractures (Orwoll et al. 2010).

Bisphosphonates increased BMD and reduced fracture risk in men with glucocorticoid or leuprolide-induced bone loss. They are currently the treatment of choice for idiopathic osteoporosis in men.

Bisphosphonates are generally well tolerated. However, both intravenous and oral bisphosphonates have been linked in rare cases to osteonecrosis of the jaw, although current limited data suggest no clear increase in the risk of this complication in patients with osteoporosis. Rare case reports of atypical femoral diaphyseal fractures in patients on bisphosphonate therapy have also recently emerged in the literature and raise concerns about the long-term safety of this treatment in some individuals. However, more data are required on these atypical fractures

Although most trials of oral bisphosphonates in men have been either underpowered or not primarily designed to assess their effect on fracture incidence, some trials showed a significant 60%–88% reduction in the occurrence of new radiologic vertebral fractures. Although the increase in BMD with bisphosphonate therapy is similar in men and women and could therefore theoretically translate into a reduction of fracture risk similar to the one observed in women, more data are required to ascertain the benefits of oral bisphosphonates on non-vertebral and hip fractures in men (Orwoll et al. 2004).

8.6 Calcium and vitamin D

In two recent studies, injections of vitamin D2 (ergocalciferol) in men living in nursing homes resulted in reduced appendicular fractures. On the other hand, the antifracture efficacy of D3 (calciferol) 1,25 (OH)2D3 (calcitriol) in men without serious D3 deficiency remains controversial (Heikinheimo et al. 1992; Orwoll et al.1992).

Calcium intake should be 1,000 to 1,500 mg per day, and vitamin D intake should be 400 to 800 IU per day. Only 50 to 60 percent of older adults meet recommendations for calcium intake (Amin & Felson 2001). Older adults also have decreased vitamin D levels because skin synthesis, oral intake, and gastrointestinal absorption are diminished. Skin synthesis of vitamin D decreases because older patients tend to remain indoors and incur less exposure to sunlight.

8.7 Strontium ranelate

Strontium ranelate exerts dual – antiresorptive and anabolic action in bone. In recent study in men with primary osteoporosis it produced even significantly greater mean increases in BMD over 12 months compared with alendronate (Meunier et al.2004). However, the antifraxture effect of SR in men must be proved in further studies.

8.8 Androgen replacement therapy

Symptomatic hypogonadism is considered an indication for testosterone substitution at all ages (Wang 2009). In clinical trials in patients with Klinefelter syndorme and hypogonadism hypogonadotropic with low bone mineral density testosterone replacement therapy was associated with increase of BMD and decreasing of resorptions markers (Finkelstein et al. 1989). These effects may probably reduce the risk of fracture in part of patients. Also in

patiens witj primary and secondary hypogonadism due to testis diseases or hypothalamo-pituitary disriders, testosterone replacement therapy may reduce bone turnover and prevent further bone loss, and even increase BMD, at least in some patients (Behre et al.1997; Snyder et al. 2000). Effects on fracture risk have not been assessed.

In the case of low serum testosterone due to long-term treatment with systemic glucocorticoid administration, beneficial effects of testosterone treatment on BMD were observed (Crawford et al. 2003). In view of the lack of documentation of antifracture efficacy of testosterone, treatment of osteoporosis should include bisfosfonates or other antiosteoporotic agents, whether or not on testosterone substitution (Khosla et al.2006). In men with profound hypogonadism due to androgen deprivation therapy for prostate cancer, treatment with testosterone is contraindicated and the other therapeutic options should be considered such as SERMs, bisphosphonates and denosumab, can effectively reduce bone turnover, prevent bone loss and reduce fracture risk (Adlet et al. 2011; Khosla rt al. 2006).

As noted above, aging is accompanied by progressive moderate decrease in the population mean serum concentration of testosterone and increasing prevalence of men with serum (free, bioavailable) testosterone levels that lie below the range for young men (Araujo et al.2004). In this elderly population, effects of testosterone treatment on BMD have been inconsistent, with the most convincing effects being observed in men with very low serum testosterone (Katznelson et al.1996; Snyder et al. 2000; Wang et al 2001). In elderly men, testosterone treatment may have additional beneficial effects on muscle mass and strength, which may help decrease fracture risk through a reduced propensity to fall (Snyder et al. 1999). Nevertheless, the effect of testosterone treatment on fracture risk is unknown. By contrast, treatment with bisphosphonates and teriparatide has been shown to be effective in men with low baseline serum testosterone in subgroup analysis of clinical trials of treatment.

In this context, hypogonadism in older men requires a conservative approach and testosterone treatment should be considered only for men with frankly low serum testosterone, in the presence of unequivocal signs and symptoms of hypogonadism, In view of the lack of documentation of anti-fracture efficacy of testosterone, treatment of osteoporosis should include established osteoporosis treatments whether or not on testosterone substitution. Nevertheless, the effect of testosterone treatment on fracture risk is unknown and the long-term risk-benefit ratio of prolonged treatment in elderly men is not yet established. The potential adverse effects on haematocrit, prostate and cardiovascular risk requires alertness.

9. Teriparatade

A favourable effect of treatment with parathyroid hormone (PTH) on BMD in men with advanced osteoporosis has also been demonstrated in a small pilot study with daily injections of 400 IU PTH (1–34) [Teriparatide]. After 18 months, the average lumbar spine BMD had increased by 13.5% in the PTH-group and was unchanged in placebo group. In a larger trial of 437 men with osteoporosis (daily dose of 20 mg or 40 mg rhPTH or placebo, subcutaneously) over 11 months plus 18 months follow-up similar effects on BMD and a significantly lower rate of vertebral fractures for the pooled PTH groups were found. The similarity of those effects on BMD with the effects observed in clinical studies of women where the influence of the treatment on fracture incidence was assessed, clearly indicates the therapeutic usefulness of teriparatide in both sexes (Kaudman 2001; Kurland 2000)

10. Conclusion

In conclusion, osteoporosis is a prevalent health problem in men. An evidence-based approach should be adopted in the clinical investigation and drug treatment for this condition. Further research into the validity of diagnostic criteria, risk factors and emerging therapeutic agents for osteoporosis in men is however urgently required.

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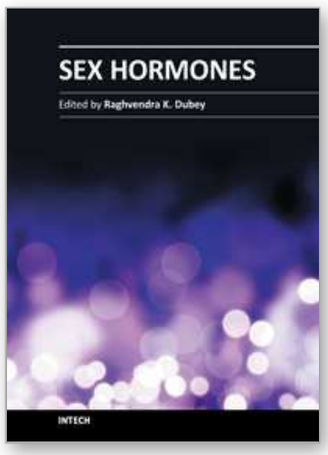

Sex Hormones

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Sex Hormones not only regulate reproductive function, but they also play a prominent role in the biology and physiology of several organs/tissues and in the pathophysiology of several diseases. During the last two decades, the information on the mechanisms of action of sex hormones, such as estrogens and androgens, has rapidly evolved from the conventional nuclear receptor dependent mechanisms to include additional non-nuclear, non-genomic and receptor-independent mechanisms. This highlights the need to update the current knowledge on sex hormones and their mode of action. Increasing evidence that exogenous/epigenetic factors can influence sex hormone production and action highlights the need to update our knowledge on the mechanisms involved. This book provides a systematic and updated overview of the male/female sex-hormones and their impact in the biology and physiology of various organs. Additionally, the book discusses their positive and negative association with the pathophysiology of various diseases (e.g. osteoporosis, cardiovascular-disease, hypogonadism, reproduction, cancer) and their therapeutic potential.

InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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