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REVIEW PAPER

Osteoporosis in men

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Abstract

Osteoporotic fractures are the leading cause of morbidity and mortality among aging men. 30% of all hip fractures occur in men, and mortality resulting from not only the hip fracture, but also the spine and other major osteoporotic fractures, is significantly higher in men than in women. As in women, hypogonadism is the best documented risk factor for developing osteoporosis in men. In older men, testosterone levels are negatively correlated with the risk of fractures, and it seems that this age-related testosterone deficiency should not be considered as one of the many causes of secondary osteoporosis, rather one of the major and most important mechanisms of senile osteoporosis. Acute hypogonadism induced by ablation treatment for prostate cancer (surgical or pharmacological castration, antiandrogen therapy) is associated with an extremely high risk of fracture. Other documented causes of bone loss in men are cigarette smoking and alcohol abuse, and a number of diseases that require corticosteroid treatment. Pharmacotherapy of osteoporosis should be recommended to all men with a diagnosed osteoporotic fracture and all men with a high 10-year absolute fracture risk (FRAX™). Not all drugs registered for the treatment of postmenopausal osteoporosis have been registered for the treatment of osteoporosis in men, and others have not been the subject of long-term and costly clinical trials required for such registration. The risk reduction of new fractures was documented only for treatment with zoledronic acid. Risedronate, strontium ranelate, teriparatide, and denosumab in men increase in bone mineral density comparable to that seen in postmenopausal women.

Key words: male osteoporosis, hypogonadism, fracture risk, treatment.

Introduction

While most studies of osteoporosis have focused on postmenopausal women, older men are also at increased risk of fragility fractures [1-4]. The incidence of osteoporotic fractures in men and in women is increasing rapidly, which is related to the fact that both women and men live longer and longer [5, 6]. Hence, the number of aging men, predisposed to such fractures, is increasing worldwide. At the same time, the lack of widespread awareness of the risk of osteoporotic fractures in men is currently comparable to that of osteoporosis in women 30 years ago. Osteoporotic fractures are the leading cause of morbidity and mortality among aging men [7, 8]. The risk of at least one typical osteoporotic fracture in a 50-year-old male is estimated to be about 13% (in women about 40%) and for an 80-year-old man this figure increases to 25% [9-11]. The risk of vertebral fragility fracture in men is only half as much as in women, and cross-sectional radiological findings suggest that up to one third of men over 65 years old have suffered a fracture [12]. The risk of fracture of the proximal femur (hip) in aging men is 5-6%, compared to 16-18% in women. This means that 30% of all hip fractures occur in men [13-15]. At the same time, from unexplained causes, mortality in the hip [16-18] as well as in the spine [19] and other major osteoporotic fractures, is significantly higher in men than in women.

The basic factors determining the current bone mass are: the peak bone mass achieved after the age of 20 years and the rate of its loss. During adolescence, bone mass increases rapidly in response to increased secretion of sex hormones. The total increase in bone mineral density (BMD) observed in men, however, only partially reflects the actual increase in the bone mass. It seems that in a greater proportion of women it depends also on the increase in bone size [20, 21]. Peak bone mass is achieved in about the twentieth (spine) to the thirtieth (peripheral bones) years of life [22-25]. Bone loss, beginning in most men after 40 years of age, is in fact comparable to the loss of bone mass in women, but in men it is better compensated for by depositing some of the newly formed bone on the outer surface of the bone (periosteal apposition). This increases bone size, and so maintains the strength of the wider bone as well as offsetting bone loss from the inside of the bone.

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Aetiology

The causes of osteoporosis in men are similar to those of women: hypogonadism, glucocorticoid therapy, gastrointestinal diseases, vitamin D deficiency, anticonvulsant therapy, and alcohol abuse are the most common aetiological factors [26-30].

As in women, hypogonadism is the best documented risk factor for developing osteoporosis in men. In boys with androgen resistance, despite high growth, peak bone mass is not achieved [31, 32]. Also, in Klinefelter syndrome, low bone mass is observed. Androgens play an extremely important role in bone tissue homeostasis. They directly stimulate the proliferation, differentiation, and function of osteoblasts, inhibit osteoclast recruitment, and influence interactions between osteoclasts and osteoblasts. They stimulate growth hormone secretion (GH), increase the sensitivity of bone cells to IGF-1, and stimulate the production of bone matrix [21]. Androgen receptors have been localised in both osteoblasts and osteoclasts [33]. However, it appears that also oestrogens play a significant role in the aetiopathogenesis of osteoporosis in men, as in women [33-35]. There is a positive correlation between serum oestradiol concentrations and bone mineral density of men [23]. Severe osteoporosis has been reported in men with deletion of oestrogen receptor gene, and aromatase-deficient males. It worth stressing, however, that a risk of fracture in men correlates with oestradiol concentration only in the range of extremely low (post-castration) values: less than 16-20 pg/ml [36]. It appears therefore, that there is a threshold value for oestradiol concentration in men, necessary for the proper functioning of bone metabolism, above which oestradiol no longer plays a key role in protecting men from osteoporosis.

In elderly men, testosterone levels are inversely correlated with fracture risk [37], which may reflect not only the direct anabolic effects of androgens on bone mass, but also the periosteal apposition and bone size increase, favouring biomechanics of fractures. Androgens also act indirectly by affecting non-skeletal factors such as muscle mass and strength, balance, and risk of falls. Taking into account that about 70% of men with osteoporosis also experience other symptoms of testosterone deficiency syndrome (TDS), it seems that age-related testosterone deficiency should not be considered as a one of the many causes of secondary osteoporosis, but rather as one of the major and most important mechanisms of involutive (senile) osteoporosis [38, 39]. It also should be stressed that, in contrast to the rapid decrease in oestrogen levels in postmenopausal women, the decrease of testosterone secretion in aging men is much more extended in time. Consequently, men do not experience rapid acceleration of bone loss. As a consequence, the exponential increase in frequency of osteoporotic fractures with age is approximately five to seven years delayed in men, compared to women [40-44].

Androgen deficiency in younger males may result mainly from castration or hyperprolactinaemia, with particular attention to the increasing group of men with acute hypogonadism induced by androgen-deprivation therapy for prostate cancer (surgical or pharmacological castration, antiandrogen therapy) and at the highest risk for fractures [45].

Documented causes of bone loss in men are cigarette smoking and alcohol abuse [26, 30]. Also, a number of diseases that require treatment with corticosteroids, such as rheumatoid arthritis or asthma, can result in secondary osteoporosis and bone fractures, as in women.

Diagnosis

Due to the painless early period of osteoporosis, there is no symptom of its development until a fracture occurs. Thus, of utmost importance in diagnosing osteoporosis is the possibility of early detection of the risk of this disease. Unfortunately, often the only time a patient realises he has a problem is when he breaks a bone – and even then, the diagnosis of osteoporosis is frequently overlooked. DXA densitometry should be recommended for all men over the age of 70 years, who have experienced clinical risk factors for fracture or a significant (2 cm or more) reduction in growth.

Comprehensive assessment of fracture risk over a ten-year period (FRAX™) integrates selected clinical risk factors (age, sex, previous fragility fracture after 45 years, corticosteroid therapy, smoking and alcohol abuse, rheumatoid arthritis, and other secondary causes of bone loss) and diagnostic findings (DXA densitometry). A fracture probability of more than 10% is indicative of pharmacotherapy [46]. In the case of a moderate fracture probability (5-10%), additional factors increasing actual fracture risk, such as corticosteroid dose and risk of falls, should be taken into account. In particular, imaging of thoracic and lumbar spine (X-ray, VFA) to exclude or to confirm the presence of "silent" vertebral fractures should always be considered. In men, up to 80% of fragility vertebral fractures are made without a clear clinical manifestation. At the same time, previous osteoporotic fracture is the most important risk factor for subsequent fractures, multiplying it by several or even several times. Therefore, according to current recommendations, an osteoporotic fracture of the spine or the hip is an absolute indication for the implementation of the treatment – both by the primary care physician and by a specialist, regardless of the stage of the disease and the occurrence of other fracture risk factors [46].

Due to the fact that osteoporosis reflects rather quantitative but not qualitative, the results of traditional biochemical research in patients with uncomplicated osteoporosis remain generally normal. They are, however,

crucial for excluding the secondary causes of bone loss or pathological fractures. Basic laboratory tests for differential diagnosis of osteoporosis include OB and blood morphology, Ca, creatinine and total protein levels, serum alkaline phosphatase, and vitamin D (serum 25OHD). At further stages of the diagnostic procedure, the daily urinary calcium excretion and serum PTH (hyperparathyroidism), TSH (hyperthyroidism), and PSA (prostate cancer) or other tumour markers and monoclonal proteins or bone marrow biopsy are used.

Treatment: Fewer medicines registered for the treatment of osteoporosis in men

The aim of the treatment in osteoporosis is to prevent all-life fractures in those who have not yet suffered, and to reduce the risk of fractures in patients with advanced osteoporosis. Comprehensive fracture prevention should address all men over the age of 65 years and should be aware of the risks, modifications of lifestyle, and nutrition, and, as far as possible, the elimination of risk factors for fracture, and prevention of falls.

Pharmacotherapy of osteoporosis should be recommended to all men diagnosed with osteoporotic fracture and to all men with a high 10-year absolute fracture risk (FRAX) [46]. However, there is much less research on the treatment of osteoporosis in men compared to women. Not all drugs registered for the treatment of postmenopausal osteoporosis have been registered for the treatment of osteoporosis in men, and others have not been the subject of long-term and costly clinical trials required for such registration.

Supplementation of calcium and vitamin D is the basis of both prophylaxis as well as the pharmacotherapy in the prevention of osteoporotic fractures. It should be emphasised that, in addition to the direct effect on bone metabolism, vitamin D has a strong, beneficial effect on muscle strength and function, and thus reduces the risk of falling [47].

There have been few trials of osteoporosis therapies performed specifically in male populations, the available trials are relatively small, and in most the endpoint has been a change in BMD, compared to the results obtained in appropriate postmenopausal osteoporosis studies. Only one (zoledronic acid) was originally designed to assess the impact on fracture risk as a primary end point. None of the studies predicted prolonged follow-up or follow-up as an open study.

Testosterone increases bone mineral density in men with low levels of this hormone. However, this effect is limited to patients with baseline serum testosterone levels below 2.0 ng/ml (7.5 nmol/l) [48]. The impact of such treatment on the risk of fractures has not been documented. In 241 men treated for two years with alendronate 10 mg/d vs. placebo, a significant increase in BMD was shown. Significant reductions in the number of morphometric vertebral fractures have also been reported in comparison with placebo (OR = 0.10; 95% CI: 0.00-0.88) [49]. Risedronate in 284 men effectively increased bone mineral density in comparison with placebo, but no significant effect on the risk of fractures was found [50]. In a randomised, placebo-controlled study of 1199 men with osteoporosis, treatment with zoledronic acid resulted in a significant reduction in the risk of new vertebral fractures, by 67% (RR: 0.33; 95% CI: 0.16-0.70) [51]. Strontium ranelate also significantly increases bone mineral density in men with osteoporosis, to a similar extent as in women, but the study did not have sufficient statistical power to demonstrate significant reductions in fracture risk [52]. Teriparatide (1-34 rhPTH) has been registered for the treatment of "severe" osteoporosis in men: after numerous fragility fractures, with multiple risk factors or ineffective prior therapy [53]. In men treated with denosumab for two years, there was a significant increase in BMD in lumbar vertebrae, total hip, femoral neck, trochanter, and 1/3 radius, respectively, by 8.0%, 3.4%, 3.4%, and 4.6% ($p < 0.01$ for all values). In men who received a placebo in the first year of the study, the change to denosumab in the second year of follow-up resulted in an increase in BMD similar to the one obtained by men from the beginning of treatment with denosumab. The amount of bone mineral density obtained is comparable to that seen in postmenopausal women and men receiving androgen-deprivation therapy for prostate cancer [54].

Disclosure

Author reports no conflict of interest.

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