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Editorial

Osteoporosis in Men

Pawel Szulc,[1] Jean Marc Kaufman,[2] and Eric S. Orwoll[3]

[1] *INSERM UMR 1033, Hôpital Edouard Herriot, University of Lyon, Pavillon F, Place d'Arsonval, 69437 Lyon, France*
[2] *Department of Endocrinology, University Hospital Ghent, B-9000 Gent, Belgium*
[3] *Department of Medicine, Endocrinology, Diabetology & Clinical Nutrition, Oregon Health & Science University, Portland, OR 97239, USA*

Correspondence should be addressed to Pawel Szulc, pawel.szulc@inserm.fr

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Osteoporotic fractures (fragility fractures) are more frequent in postmenopausal women than in older men [1]. However, osteoporosis in men is one of the major and the most neglected public health problems for several reasons.

First, morbidity, mortality, and loss of independence after major fragility fracture are greater in men than women [2, 3]. The interpretation of data concerning mortality after fragility fracture should be, however, cautious. As life expectancy is lower in men than women, it is not appropriate to compare mortality after hip fracture between men and women of the same age. Therefore, it is important that, for a given age, the additional increase in mortality after a hip fracture is greater in men than women [4]. In addition, the fraction of the potential time of life lost after a hip fracture (taking into account the sex-specific life expectancy) is greater in men than women [5]. Thus, these studies show that the mortality after a hip fracture is really higher in men than in women.

Secondly, the number of osteoporotic fractures in men increases rapidly. The overall number of fractures is on the rise because the elderly population increases due to the lengthening of the lifespan. However, several studies have shown that the age-specific incidence of major osteoporotic fractures in postmenopausal women, especially hip fracture, has been slightly, but consistently, decreasing for the last 15 years [6–8]. Such trends have been observed in North America, Australia, and several European countries. By contrast, in these countries, the age-specific incidence of hip fracture in men decreased less than in women or even remained stable [8–10]. In addition, in some European countries and in Japan, age-specific hip fracture incidence continues to increase in both sexes [11, 12]. Therefore, over the next decades, the number of osteoporotic fractures is expected to increase faster in men than in women. Consequently, fragility fractures in men will constitute higher percentage of all the osteoporotic fractures than they do now.

Thirdly, the identification of men at high risk of fracture is not satisfactory. Increasing age, history of fragility fracture, and low bone mineral density (BMD) measured by dual energy X-ray absorptiometry (DXA) are important risk factors of fracture. Nevertheless, only 20% of men who sustain a hip fracture or major osteoporotic fracture have osteoporosis diagnosed by DXA using the sex-specific T-score < -2.5, half as many compared with women from the same cohort [13–15].

The diagnostic criteria of osteoporosis in men are a matter of controversy. The International Society for Clinical Densitometry (ISCD) recommends sex-specific T-score < -2.5 [16]. By contrast, International Osteoporosis (IOF) recommends the threshold corresponding to T-score $= -2.5$ in premenopausal women [17]. It corresponds to a T-score of approximately -2.75 compared with peak BMD in young men. The justification for using a female-based threshold is that the risk of fracture is similar in both sexes for the same absolute BMD, not for the same sex-specific T-score. If we accept the threshold recommended by ISCD, men with lower risk of fracture will be treated and we will have to treat more men to avoid one fracture. If we accept the threshold recommended by IOF, fewer men will be treated and fewer fractures will be avoided. Does it mean that the threshold of ISCD should be preferred? Not necessarily. Aside from the individual fracture risk, there is also variation from country

to country in the willingness to pay for therapy and in the choice of the treatment criterion. If the sex-specific T-score = −2.5 identifies men at a lower risk of fracture than women, the health authorities may refuse the reimbursement of any antiosteoporotic treatment in men. If the IOF threshold is recommended in these countries, it will be easier to obtain the reimbursement for the osteoporosis treatment in men. Fewer men will be treated, but at least, it will be possible to reduce the risk of fracture in those who have the most severe osteoporosis and the highest risk of fracture.

An additional problem is that other bone parameters do not provide much improvement in the prediction of fracture in men. Classical biochemical bone turnover markers (BTMs) are not predictive of fracture in the multivariable models adjusted for BMD [18, 19]. Ultrasound parameters predict fractures in men similarly to BMD, but their joint use does not improve fracture prediction compared with BMD alone [20]. Quantitative computed tomography (QCT) predicts hip fracture, but not better than DXA alone [21]. Young healthy men with prevalent fractures had lower cortical bone volume assessed by peripheral QCT than men without fracture [22]. However, these analyses were not adjusted for BMD measured by DXA. High-resolution peripheral quantitative computed tomography (HR-pQCT) allows assessment of bone microarchitecture at the distal radius and tibia. Men with vertebral fractures had thinner cortex and lower cortical volumetric BMD assessed by HR-pQCT compared with men without vertebral fracture, even after adjustment for BMD measured by DXA [23]. However, these cross-sectional data have to be confirmed in the prospective studies.

Several studies have assessed other approaches that aimed to improve fracture prediction in men. The FRAX algorithm is a significant landmark in the assessment of the individual risk of fracture [24]. It takes into account several risk factors, which determine bone fragility, for example, history of fracture, parental history of hip fracture, corticotherapy, and so forth. Another algorithm is the Garvan nomogram [25]. It takes into account history of fractures and that of falls. Falls, especially multiple falls, seem to be associated with a substantial increase in the risk of peripheral fracture in the elderly men [26]. However, both FRAX and the Garvan nomogram have been introduced only recently and few studies assessed their utility in men [27, 28].

Limited data suggest an association between bone size and risk of fracture. Low bone width was associated with higher risk of fracture independently of BMD [29]. History of fracture was associated with lower cross-sectional area (CSA) measured by peripheral QCT [23]. However, no method of measurement of bone width or CSA could be recommended currently for the clinical practice. Several studies showed that longer femoral neck axis and wider neck-shaft angle were associated with higher risk of hip fracture, mainly cervical fracture [30, 31]. However, these associations were weak and not consistent between the investigated groups.

More and more studies suggest utility of the finite element analysis (FEA) for fracture prediction in men. The load-to-strength ratio remained significantly associated with the risk of hip fracture after adjustment for BMD [32]. More recently, vertebral compressive strength improved vertebral fracture risk assessment in comparison with DXA-measured BMD [33]. However, FEA is not available in the clinical practice.

Serum and urinary levels of C-terminal telopeptide of type I collagen did not predict fracture after adjustment for BMD in men. By contrast, measurement of serum levels of native, nonisomerized form of CTX-I (α-CTX-I) and of beta-isomerized form (β-CTX-I) showed that higher α-CTX-I/β-CTX-I ratio is associated with higher risk of fracture in men [34]. However, it is not clear if the increased α-CTX-I/β-CTX-I ratio reflects higher bone turnover rate or an intrinsic defect of posttranslational modifications of bone collagen. The use of these measures has not been shown to improve the prediction of fracture or the management of care in men with osteoporosis.

In most of the cohorts, decreased levels of total or bioavailable 17β-estradiol were associated with higher risk of fragility fracture in men [35–37]. However the analyses were not systematically adjusted for BMD. Decreased serum level of 25-hydroxycholecalciferol was associated with higher risk of hip fracture in American men aged >65 and with higher risk of clinical fracture in Swedish men aged >65 [38, 39]. However, this association was markedly attenuated after adjustment for hip BMD [38]. Low serum level of insulin-like growth factor I (IGF-I) was associated with a higher risk of ostoporotic fracture in men, also after adjustment for BMD [40]. The potential mechanism underlying this association is not clear. This observation is, however, interesting because serum IGF-I concentration was not correlated with BMD in older men [41, 42]. Finally, increased level of fibroblast growth factor 23 was associated with higher risk of nonspine fracture in the elderly men, even after adjustment for confounders including BMD and parathyroid hormone concentration [43]. However, the exact mechanism underlying this association has not been elucidated.

Thus, FRAX appears to improve the assessment of the fracture risk in both sexes; however, it needs to be verified in a higher number of cohorts of men. By contrast, other available studies do not provide reliable methods permitting to identify with a satisfactory probability older men at high risk of fracture.

Fourthly, fewer studies concern the antiosteoporotic treatment in older men compared with the studies carried out in postmenopausal women. Most studies assessed only changes in BMD measured by DXA and in the BTM levels induced by antiosteoporotic treatment [44–48]. Then, the antifracture efficacy of the investigated medications in men is inferred indirectly from these bridging studies by comparing their results with the data obtained previously in postmenopausal women. By contrast, few studies assessed the antifracture efficacy of the antiosteoporotic therapies in men [48–52]. Moreover, some of these studies were not powered to this type of analysis. Some of these studies were observational surveys, not randomized pharmaceutical trials. The effect of the antiosteoporotic medications on the risk of fracture in men was assessed specifically only in few studies.

The antifracture efficacy of denosumab and toremifene has been investigated in men receiving androgen-deprivation therapy for prostate cancer [53–55]. In older osteoporotic men, zoledronic acid decreased significantly the incidence of vertebral fractures [56].

Fifthly, even men with an increase in fracture risk are rarely treated. In men, the parameter that indicates higher risk of fracture most consistently in epidemiological studies is prevalent fragility fracture [26, 57]. A history of osteoporotic fracture is associated with a two- to fourfold higher risk of another osteoporotic fracture. This is a very similar situation to that found in postmenopausal women. However, about 50 percent of women who sustained fragility fracture benefit from bone densitometry and/or antiosteoporotic treatment [58–60]. By contrast, less than 10 percent of men who sustained an osteoporotic fracture will have bone densitometry and/or osteoporotic treatment [58–60]. In some studies, only 1 out of 20 men having sustained a hip fracture (and were hospitalized for this fracture) benefited from bone densitometry and/or antiosteoporotic treatment [60]. Even men receiving chronic glucocorticoid therapy or androgen deprivation therapy are not systematically screened and, whenever appropriate, treated for osteoporosis [61, 62].

In conclusion, on one hand, osteoporosis in older men is a major public health problem. The number of fragility fractures in men is rapidly increasing, the consequences of these fractures are more severe in men than in women, and the identification of men at high risk of fracture is suboptimal. On the other hand, osteoporosis in older men should be considered a neglected public health problem. There are fewer data on the appropriate measures to assess fracture risk, less information on the antifracture efficacy of the available medications in men than in women, and only few men with the evidently increased risk of fracture obtain adequate treatment.

Pawel Szulc
Jean Marc Kaufman
Eric S. Orwoll

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