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PERSPECTIVES

Pathophysiology and Diagnosis of Osteoporosis in Aging Men

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Abstract

Osteoporotic fractures in older men are a major public health problem due to their morbidity, mortality and costs. Older men have a lower fracture risk than age-matched women for several reasons. Young men have larger bones than women even after adjustment for differences in body size. Age-related cortical thinning is lower in magnitude in men than in women because in men, endocortical expansion is more efficiently offset by periosteal apposition. The principal mechanism of trabecular bone loss in men is trabecular thinning in contrast to trabecular perforation and loss in women.

The definition and the diagnostic criteria of osteoporosis in men are still subject to debate and controversy. In men aged 50 and older, osteoporosis may be diagnosed if the sex-specific T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less. In certain circumstances, the one-third distal radius may also be utilized. Assessment of clinical risk factors can help clinicians identify asymptomatic men at risk for low bone mineral density (BMD). For instance, in men with prostate cancer, both surgical bilateral orchidectomy and androgen-deprivation therapy result in rapid bone loss and high risk of fracture. The fracture risk assessment tool (FRAX®) helps identify individuals at high risk of fracture on the basis of several clinical criteria associated with an increased fracture risk regardless of BMD. Especially in the elderly, the assessment of the risk of fracture must include assessment of the risk of falls. *IBMS BoneKEy*. 2008 October;5(10):370-380.

Osteoporosis in Aging Men – Burden of the Disease

Osteoporosis-related fractures (fragility fractures) in older men are a major public health problem. There are fewer fragility fractures in men than women because men have stronger bones and shorter life expectancy (1-2). The risk of fragility fracture in a man is equal to a risk of fracture in a woman who is five to ten years younger, except for old men who have a higher risk of death than that of fracture (3-5). Currently, an increase in life expectancy results in a higher number of men at high risk of fracture and a higher number of fractures in this population (1-2). Conversely, the age-specific incidence of fractures does not increase in more recent generations (3;5-7).

Fragility fractures in older men are responsible for 20 to 30% of the overall costs of fractures in the elderly (8). The proportion of years of life lost after a fragility fracture is significantly higher in men than in women (9). By contrast, data on the significantly higher mortality after fracture in men in comparison with women should be interpreted more cautiously because of the difference in life expectancy.

Pathophysiology of Bone Fragility in Men

Bone size and strength in young adults

Older men have a lower risk of fracture than age-matched women because: 1) young men have stronger bone than women and 2) age-related loss of bone strength is lower in magnitude in men than women.

In comparison with young women, young men have larger bones (higher external diameter, higher cross-sectional area [CSA]) due to higher cortical area and higher medullary area (11-12). These differences persist after adjustment for body size. Consequently, men have higher peak areal bone mineral density (aBMD). However, the proportion of total bone area occupied by

cortical bone is similar in both sexes. Cortical bone mass is higher in young men than women because a ring of similar thickness is distributed around a larger perimeter, whereas volumetric BMD (vBMD) of cortical bone is similar. As a large part of load applied to bone is carried by the cortical bone, a larger cortical mass contributes to greater bone strength in men. Trabecular vBMD is not higher in young men than women; it is equal in both sexes or even slightly lower in men (13). Microarchitecture of trabecular bone (trabecular number and connectivity) is similar in young men and women (14-16). Other parameters (bone turnover rate, bone mineralization, etc.) have not been studied enough in young adults to determine their role in the difference in bone strength between young men and women.

Age-related decrease in bone mass and strength in men

The age-related decrease in bone mass and strength is lower in magnitude in men than women. Bone resorption measured by urinary excretion of total deoxypyridinoline (DPD) increases slightly and progressively with age in men (17-19). Bone formation remains stable or slightly increases in very old men. This imbalance between increased bone resorption and relatively stable bone formation may underlie bone loss in elderly men. However, the high scatter of individual values of biochemical bone turnover markers (BTM) renders the assessment of age-related changes in bone turnover in men difficult (18). Moreover, these changes are slow, progressive and concomitant with other age-related changes such as a decrease in glomerular filtration, a decrease in muscle mass and creatinine excretion used to calculate creatinine-adjusted urinary levels of bone resorption markers, possible impairment of catabolism of peptides, and a decrease in the content of cross-links in bone (17).

The structural basis of bone loss in men is poorly understood. Cortical thickness decreases with age in both sexes but less so in men (11;20). Age-related endocortical expansion (an increase in medullary area) is significant and similar in both sexes but more efficiently offset by periosteal apposition in men than women (11;21). Therefore, the age-related decrease in cortical area in men is weak or non-significant and lower in magnitude than in women (11). Cortical porosity increases with age more in women than men, which is consistent with a greater decrease in cortical vBMD in women (22). The stability of cortical mass in men preserves resistance to compression, whereas distribution of the same amount of cortical bone around a larger perimeter can even improve resistance to bending.

The decrease in trabecular vBMD is greater in women or similar in both sexes according to the age range and skeletal site (11;20) (Fig. 1). As men have bigger bones, the decrease in trabecular bone mineral content (BMC) may be similar in both sexes or higher in men. Age-related trabecular bone loss proceeds in men mainly by trabecular thinning whereas the principal mechanism in women is trabecular perforation and loss. This is consistent with age-related deterioration of trabecular connectivity and a decrease in trabecular surface in women but not in men (14-16). However, it appears that, also in men, it is the loss of trabecular connectivity that determines the decrease in bone strength (23). Histomorphometric studies show a decrease in bone formation in older men (14-15;24), which is consistent with a decrease in mean wall thickness (25). Some, but not all, studies also suggest a decrease in depth of resorption cavities leading to an increase in the thickness of interstitial bone (26-30).

Periosteal apposition continues during adult life at various skeletal sites, regardless of the age range, ethnic group, design of the study and method of measurement (31-32) (Fig. 2). Periosteal expansion is observed in both sexes; however, various studies provide seemingly discordant data concerning the difference in age-related periosteal expansion in men and women (11;21;32-34). Men have larger bones, thus, an increase in the external diameter by the same absolute value in both sexes may correspond to a higher increase in total CSA in men (because the deposited bone is distributed around a larger perimeter) but to

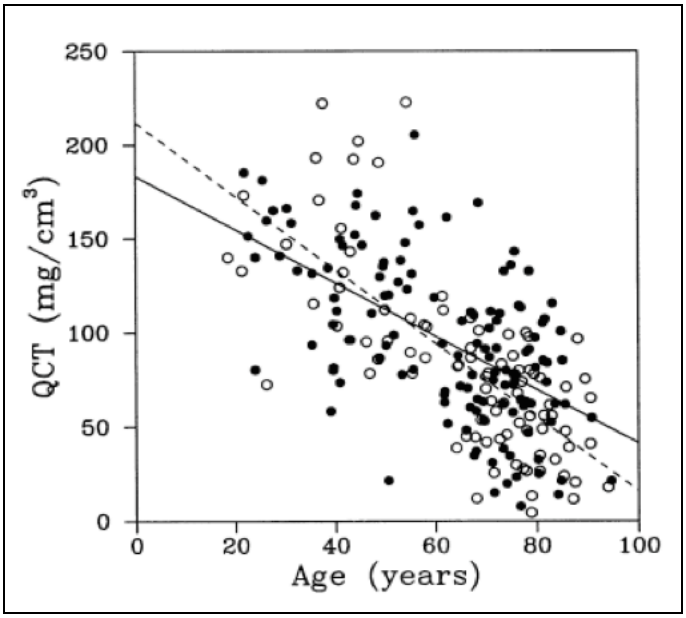

Fig. 1. Age-related changes in volumetric bone mineral density of the trabecular bone of the third lumbar vertebra, measured by quantitative computed tomography in vertebral blocks obtained at autopsy from 90 women aged 18 to 94 years and 131 men aged 21 to 94 years (13). Reproduced from Ebbesen *et al*. Vertebral bone density evaluated by dual-energy X-ray absorptiometry and quantitative coputed tomography in vitro. *Bone*. 1998 Sep;23(3):283-90, with permission from Elsevier.

a higher relative increase in total CSA in women (because initial values used for calculation of the percentage are lower in women).

Periosteal expansion in young adults probably reflects an intrinsic mechanism (residual radial bone growth after adolescence) or adaptation to applied loads (body mass, the playing arm in tennis players) (35). In older men, the prospectively assessed rate of periosteal apposition remains relatively constant (36-37). In contrast, in women, data are discordant and should be interpreted cautiously. In the OFELY cohort, periosteal expansion at the distal radius slowed after the menopause (38). By contrast, in women from the InCHIANTI cohort, periosteal expansion at the distal tibia accelerated with age and was even faster in older women than in age-matched men (36). One possible explanation is that periosteal apposition is an attempt by the bone weakened by endosteal bone loss to adapt to the prevailing load. At the non-weight-bearing distal radius, where applied loads are very low, the low rate of periosteal apposition might reflect the intrinsic age-related decrease in periosteal apposition occuring in women but not men. In contrast, at the weight-bearing distal tibia, an increasing rate of periosteal apposition in women (which becomes even greater than in men) might reflect an attempt of the periosteum to adapt to greater endosteal bone loss. Although these data may shed new light on the regulation of periosteal expansion in older individuals, this interpretation is only a speculation. We lack experimental evidence that periosteal apposition is a reaction and an adaptation to endosteal bone loss.

Overall, age-related changes in bone size should be interpreted cautiously. Age-related changes in bone geometry vary according to the skeletal site and even for different parts of the same bone. The disparate trends may reflect different mechanical loads and show that results from one skeletal site cannot be extrapolated onto other sites. Cross-sectional studies can be influenced by the secular trend – more recent generations are taller. Prospective data are scanty and can be influenced by methodological limitations of techniques used for the evaluation of bone size.

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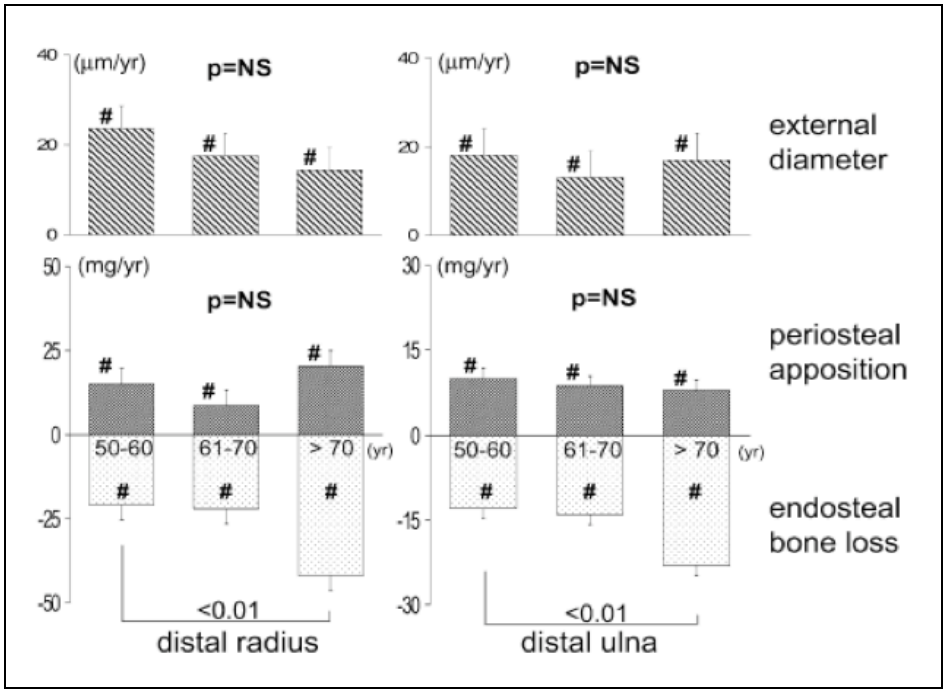

Fig. 2. *Upper panel:* Comparison of absolute values of annual rates of increase in external diameter at the distal radius and ulna according to age group (37). *Lower panel:* Comparison of absolute values of rates of deposition of bone mass by periosteal apposition *(positive hatched bars)* and rate of endosteal bone loss *(negative pointed bars)* at the distal radius and ulna according to age group. The slopes are significantly different from 0 (<0.005–0.0001) for periosteal apposition and for endosteal bone loss for both bones and for all age groups. (*Please note, in the lower panel, the scales are different for the radius and ulna).* Reproduced from Szulc P, Delmas PD. Bone loss in elderly men: increased endosteal bone loss and stable periosteal apposition. The prospective MINOS study. *Osteoporos Int*. 2007 Apr;18(4):495-503, with permission from Springer.

Diagnostic Approach in Clinical Practice – Osteoporosis or Fracture Risk

The definition and, consequently, the diagnostic criteria of osteoporosis in men are still subject to debate and controversy (39). The principal question is as follows: what does the diagnosis of the same severity of osteoporosis in both sexes mean in clinical reality? Would it mean a similar decrease in BMD, or a similar percentage of fractures identified by a given cut-off, or similar absolute fracture risk, or similar cost-effectiveness of treatment in both sexes? As mentioned above, young men have larger, and consequently stronger, bones than young women. Then, age-related endosteal bone loss in men proceeds mainly by trabecular thinning, which is less detrimental to bone strength than when the loss of trabecular connectivity is the principal mechanism of postmenopausal osteoporosis. In men, endosteal bone loss is better offset by periosteal apposition that improves the resistance to bending and torsion, but is only partly captured by aBMD, because it increases both BMC and projected area. Thus, similar bone loss in both sexes (expressed as a percentage of peak aBMD, as the number of standard deviations, etc.) will leave higher residual bone strength in men than in women.

The decrease in BMD measured by DXA is associated with an exponential increase in the risk of fracture that is similar in both sexes (40). Also, variation in the gradients of risk of fracture (relative risk per standard deviation) according to age, type of fracture and time since assessment are similar in both sexes. However, the percentage of incident fractures identified by a given cut-off of sex-specific T-score is lower in men than women (41-43). According to current guidelines from the International Society for Clinical Desitometry, osteoporosis may be

diagnosed in men aged 50 and older of all ethnic groups, if the sex-specific T-score of the lumbar spine, total hip, or femoral neck is -2.5 or less (44). The T-score should be calculated by using a normative reference database of Caucasian men. The 33% distal radius (also called the one-third distal radius) may be utilized if the hip and/or spine cannot be measured or interpreted, in case of hyperparathyroidism and in very obese patients (over the weight limit for the DXA table). Caution in interpreting spine DXA is warranted because of artifact from lumbar arthritis.

Use of the female specific T-score in men identifies severely osteoporotic men with the highest risk of fracture (45). Although this cut-off identifies fewer fractures, these men will benefit the most from anti-osteoporotic treatment, which may improve the cost-effectiveness of this treatment.

DXA is the primary method to identify asymptomatic men who might benefit from osteoporosis treatment. Analysis of clinical risk factors can help clinicians identify men at risk for low BMD and determine which men should be tested (46). Critical assessment of clinical risk factors in older men shows that some factors have been thoroughly studied, and their negative role as risk factors for low BMD was convincingly demonstrated, *e.g.*, age of 70 years and above, low body mass index (BMI < 25 kg/m^2), weight loss of more than 10%, smoking, physical inactivity, a family history of fracture, a previous osteoporotic fracture, prolonged systemic corticosteroid therapy, androgen deprivation therapy, and spinal cord injury (few studies). Other factors were assessed in studies whose design was suboptimal (small groups of men, vague definition of the risk factor, a biased cohort, no prospective data, and few cases in an investigated cohort). These factors include thyroid disease or replacement therapy, gastrointestinal and metabolic malabsorption disorders, respiratory disease, hyperparathyoidism and rheumatoid arthritis (see below). Other factors were not associated with low BMD, but they may be associated with a higher risk of fracture due to a higher risk of falling. These factors include dietary intake of calcium and vitamin D, alcohol use, and type 2 diabetes.

It is recommended that clinicians periodically perform individualized assessment of risk factors for osteoporosis in older men (47). In men aged 65 years and older, this assessment should be performed systematically. In men aged 50 to 65 years, this assessment may be beneficial, especially in those who have evident risk factors. For instance, a slender 55-year-old smoker should be interrogated about other risk factors for low BMD. In men who have risk factors for low BMD or falling, DXA measurement of BMD should be obtained. In men who choose not to be screened, risk assessment should be updated periodically.

An important aid improving identification of men (and women) at high risk of fracture is the recently published fracture risk assessment tool (FRAX®) (48). FRAX® calculates the risk of fracture on the basis of several criteria such as sex, age, BMI, a personal history of fragility fracture, a parental history of hip fracture, current smoking, long-term use of oral glucocorticoids, daily alcohol intake, the presence of other causes of secondary osteoporosis and femoral neck BMD transformed into a T-score or Z-score by using the reference value for Caucasian women from the NHANES III cohort. Calculation of ten-year probability of fracture takes into account life expectancy according to sex, age and femoral neck BMD, as low BMD is associated with higher mortality independently of other confounders (49-50). Analysis of these clinical factors shows that the additional increase in the probability of fracture varies according to the risk factor, *e.g.*, a prior fragility fracture has a higher impact than smoking. The effect of different factors is similar in men and women, but varies according to age and the type of fracture. For instance, the impact of a prior fragility fracture is stronger at the age of 50 than at the age of 80. A parental history of hip fracture increases the risk of hip fracture more than that of other osteoporotic fractures (clinical spine, humerus, and distal radius).

Limitations of FRAX® have been described in detail in the reference paper. However, some caveats specific for the use of FRAX® in men should be mentioned. Men have more high-trauma fractures. Thus, the physician will have to be careful to establish circumstances of prior fracture in order to avoid overestimation of individual risk. Men are generally not good at giving the history of their families and may provide erroneous information concerning a parental history of hip fracture (forgetting an actual fracture or confusing hip fracture with a hip prosthesis worn because of arthritis). Surgical bilateral orchidectomy and androgen-deprivation therapy in men with prostate cancer are important and not fully recognized risk factors of osteoporosis. In these men, rapidly developing severe hypogonadism results in a prompt acceleration of bone resorption, bone loss and an increase in the risk of fracture (51-53). The advantage is that these men can be easily identified.

The situation is more difficult with late onset hypogonadism (LOH), also called androgen deficiency in the aging male (54). In older men, an androgen deficit is partial, develops gradually over decades and occurs in 20 to 35% of men. The symptoms of LOH can be evaluated using standardized scales. However, both subjective symptoms and clinical signs are not specific. Laboratory investigations permitting a confirmation of a diagnosis of LOH are low total testosterone concentration (specific but not sensitive) and concentrations of free testosterone (measured by the dialysis method) or bioavailable testosterone (measured by ammonium sulphate precipitation) (55). These two methods provide meaningful and clinically useful results; however, their technical difficulties should be acknowledged. Severe LOH can be associated with low BMD and higher bone turnover (56). Although it is possible that LOH carries a fracture risk over and above that provided by low BMD itself by increasing the risk of falling, data are limited (57-58). Thus, for now, it is not possible to provide practical guidelines on how LOH can be included in the calculation of individual probability of fracture.

An important message of FRAX® is that the clinical assessment of a patient should be focused on the risk of fracture and not only on low BMD or on osteoporosis defined by some other criteria. This assessment should concern not only bone fragility but also the risk of falling. Low-energy trauma is responsible for the majority of fragility fractures and its contribution to the occurrence of fracture increases with age (59). Especially in the elderly, a decrease in the risk of fracture may be achieved by a reduction in the risk of falling, which may occur through better pharmacological control of diseases such as arterial hypertension, diabetes, arrhythmias, Parkinsonism, etc. It may necessitate modification of medications, *e.g.*, neuroleptics, antidepressants or benzodiazepines. Other aspects may also be important at the individual level, *e.g.*, using appropriate glasses (to avoid diplopia and one-eye non-stereoscopic vision), wearing comfortable shoes, removing loose rugs in the home or fixing handrails in staircases.

Conclusions, and Tasks for the Future

Osteoporosis in older men is recognized as a major public health problem and a clinical problem that should be dealt with in clinical practice. It is recognized that an increase in the number of fragility fractures in older men is expected over the next decades due to increasing life expectancy in men. Recent studies provide new data on the pathophysiology of bone fragility in men and on the structural basis underlying differences in bone fragility between men and women. Several of these factors have been described above (bone size in young adults, periosteal expansion during aging, trabecular thinning or loss, etc.). Although the importance of bone size seems evident, it is necessary to remember that periosteal expansion depends largely on local factors and results from one skeletal site cannot be extrapolated onto other sites.

However, practical management of osteoporosis in older men remains subject to debate and controversy. BMD measured by DXA is not sufficient to identify men at high risk of fracture regardless of the selected threshold. It is not established

which BMD value is the optimal trade-off between a threshold that improves cost-effectiveness of anti-osteoporotic treatment but identifies few fractures (*e.g.*, female-specific T-score = -2.5) and a threshold that identifies more fractures but lowers the cost-effectiveness of the treatment (*e.g.*, male-specific T-score = -2.5).

Some clinical factors for fracture risk have been established. They improve the identification of men at high risk of fracture but are not always modifiable. We need more studies on the modifiable determinants of bone fragility in men that can be a potential target for treatment.

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