Hot topics from the 4th International Conference on Osteoporosis in Men

With the aging of the population worldwide, osteoporotic fractures are becoming a serious problem in the Western world. Male osteoporosis is associated with a significant burden in terms of morbidity, mortality and economic cost. Although less frequent in men than women, osteoporosis is a relatively common problem. The increasing prevalence and awareness of osteoporosis and fractures in men, together with the development of easy-to-measure tools and risk indicators to optimize case-finding strategies, has increased the demand for a better understanding of the pathogenesis of this condition and, in turn, for appropriate and effective treatments. This article reports recent findings regarding the pathophysiology and treatment of male osteoporosis that have been discussed by some of the most outstanding scientists in this field at a meeting held in Santa Margherita, Italy, on 6–8 November 2008.

KEYWORDS: fractures, male, osteoporosis, pathogenesis, treatment

Gerolamo Bianchi[1], Andrea Giusti[2†], Ernesto Palummeri[2] & Giuseppe Girasole[1]

[†]Author for correspondence:
[1]Rheumatology, La Colletta Hospital, Arenzano, Italy
[2]EO Galliera Hospital, Department of Gerontology and Musculoskeletal Sciences, Corso Mentana 10, Genova 16128, Italy
Tel.: +39 105 634 395
Fax: +39 105 634 402
andrea.giusti@galliera.it

Osteoporosis in men is far from a rare problem, and seems to be an important issue for males as well as for females. In the last few years, several investigators have better defined this heterogeneous condition by improving the understanding of the pathophysiology and defining the epidemiology of male osteoporosis [1]. In this context, the identification of evidence-based case-finding strategies and treatments for the management of men at risk of fracture will be of crucial importance for the future.

In a recent meeting held in Santa Margherita, Italy, the pathophysiology, diagnosis and treatment of male osteoporosis were discussed by some of the most outstanding scientists in this field from around the world.

Structural basis of bone fragility in men & women

The ability of the bone to resist fracture for any given load is related to the amount of bone tissue, the intrinsic properties of that tissue, and the structural and spatial design of bone (at the macro- and micro-structural level), for both men and women. The aging process is accompanied by deterioration of these properties, which are responsible for resistance to structural failure [2,3].

Several changes occur in bone tissue during aging:

- A decline in periostal bone formation (more in women than men);
- A decrease of bone formation and bone resorption in basic multicellular units (BMUs), with a lesser decrease of resorption, resulting in a negative BMU balance (probably in both sexes);
- An increase in the remodeling rate, which worsens the negative BMU balance in postmenopausal women and perhaps in men with estrogen deficiency [2].

Overall, these age-related changes produce bone loss in the endocortical, intracortical and trabecular components. In addition, secondary hyperparathyroidism due to hypovitaminosis D increases the remodeling rate, producing a trabecularization of cortical bone, which is characterized by an increase in porosity, a higher surface sustaining remodeling activity and cortical thinning [4].

Histomorphometric studies have clearly defined the changes in bone remodeling responsible for bone loss in women, but this has been less well defined in men [5]. Bone biopsies from the iliac crest have shown a reduction in cancellous bone volume with age in both sexes, although this was greater in women in some studies. In addition, histomorphometry has demonstrated an age-related decrease of the amount of bone formed within the BMUs, indicating a reduction of osteoblast activity. This decrease was shown to be comparable between men and women, and to start early in life after the peak bone mass is achieved. Finally, published data suggests that in men there is no age-related increase in the bone remodeling rate, which is typical of postmenopausal women.

future medicine part of fsg

Overall, these findings suggest that the predominant mechanism responsible for bone loss and increased fracture risk is a decrease of bone formation in the BMUs in men, and this, in turn, produces trabecular thinning. In support of this hypothesis, Khosla *et al.* have recently demonstrated, using high-resolution 3D peripheral quantitative computed tomography imaging, that between the ages of 20 and 90 years, men present a higher degree of trabecular thickness decrease than women (-24 vs -18%) [6].

Together with the reduction in the trabecular density, a smaller femoral neck cortical thickness and a smaller minimal femoral neck cross-sectional area (assessed with computed tomography) were demonstrated to be predictors of hip fracture in a population of more than 3000 men from the Osteoporotic Fractures in Men study [7].

In summary, although much remains unclear regarding the material and structural alterations responsible for fragility fractures in men, recent data suggests different patterns of age-related changes in the skeleton of men and women.

Sex steroids & bone strength

Sexual dimorphism in men and women (e.g., bone size in men being greater than in women) is the result of the differing actions of sex steroids. It has been generally assumed that androgens, by activating the androgen receptor and stimulating periosteal bone expansion, play a key role in the increase of bone size during puberty, and in the preservation of bone mineral density (BMD) in adults [1]. However, recent studies have suggested a significant contribution of estrogens for bone maturation and for maintenance of its biomechanical competence through aromatization of androgens into estrogens and, in turn, activation of the estrogen receptor (α or β) [1,8]. Growing male mice treated with an aromatase inhibitor and estrogen receptor-α disrupted mice demonstrate reduced bone size [8]. Along this line, men with aromatase deficiency, due to inactivating mutations in the *CYP19A1* gene, present common characteristics including tall stature, delayed bone aging, elevated bone resorption markers and reduced bone mass [9]. Treatment with testosterone in these patients produced no benefit, while transdermal estradiol treatment produced skeletal maturation and improved bone mass.

Interestingly, recent evidence suggests that an interaction between estrogens and the GH/IGF-1 axis may indirectly influence bone growth [10]. In this context, androgens and GH/IGF-1 may both have an independent and profound impact on periosteal bone and cortical mass acquisition during puberty.

The role of sex steroids in bone development and maintenance has been further defined in longitudinal and cross-sectional studies in humans. In male siblings, free estradiol levels were found to be positively associated with cortical thickness, with total, cortical and trabecular volumetric BMD (vBMD) at the radius, and with cortical vBMD at the tibia [11]. In addition, a study in elderly men demonstrated a positive correlation between biotestosterone or bioestradiol and BMD, cross-sectional area, section modulus of the hip [11]. Mellström *et al.* found that older Swedish men with low serum E2 and high sex hormone-binding globulin levels have an increased risk of fractures [12].

Overall, these findings improved the understanding of the role of sex steroids (particularly estrogens) in pubertal bone development and age-related bone loss in men.

Treatment of male osteoporosis: present & future

Over the last 10 years, several effective therapies have become available for the management of osteoporosis and the prevention of fractures in postmenopausal women. Treatments for osteoporosis in men are less defined than in women, mainly due to the few randomized, controlled trials performed in male populations, and to the relatively small sample size. However, the key question is whether men are expected to respond differently to osteoporosis therapies than women. The pharmacological properties of bisphosphonates and teriparatide, the most common osteoporosis treatments, make such differentiation unlikely, and available clinical data support their efficacy in males with primary and secondary osteoporosis [1].

Several trials of bisphosphonates in men have shown benefit. Both alendronate and risedronate demonstrated positive effects on bone mass and vertebral fractures risk reduction in men with primary osteoporosis [13,14]. The increase in BMD resulting from those trials appears to be very similar to that previously reported in postmenopausal women. Alendronate and risedronate were also demonstrated to improve BMD in men with secondary causes of osteoporosis (i.e., glucocorticoid-induced osteoporosis, HIV infection, androgen deprivation therapy for prostate cancer, bone loss in states of immobilization and in inflammatory conditions) [1]. In addition, both alendronate and

risedronate were demonstrated to reduce the risk of vertebral fractures in mixed populations of men and women treated with glucocorticoids.

Teriparatide therapy was shown to be effective in increasing BMD and reducing the likelihood of vertebral fractures in men with primary osteoporosis [1,15]. Changes in bone turnover markers and the increase of BMD in men were very similar to those seen in larger antifracture studies in women, suggesting that teriparatide should be useful in both sexes.

Novel antiresorptive and anabolic agents are in development [16]. New antiresorptive drugs are antibodies (denosumab) to the receptor activator of nuclear factor κB ligand (RANKL, a key mediator of osteoclast formation, function and survival), cathepsin K inhibitors (odanacatib) and glucagon-like peptide 2. In postmenopausal women, denosumab demonstrated significantly larger gains in BMD and greater reductions in bone turnover markers compared with alendronate, with a comparable safety profile [17].

Novel anabolic agents include modulators of the calcium-sensing receptors and antibodies that target molecules involved in Wnt signaling (antibodies against sclerostin or Dkk 1), a pathway that regulates gene transcription of proteins important for osteoblast function.

Phase II and III studies in postmenopausal women, using the above-mentioned agents, are ongoing. Randomized, controlled (or comparative) trials will be useful to assess their efficacy, even in males with primary and secondary osteoporosis.

Conclusion

With the aging of the population worldwide, osteoporotic fractures in men are becoming an important public health problem. Osteoporosis in men is a heterogeneous condition. Sex steroids and, in particular, estrogens, appear to play a crucial role in the chain of events leading to bone loss and fractures in aging males. Other hormonal factors, such as secondary hyperparathyroidism due to hypovitaminosis D, may have a role in the pathogenesis of this condition. In addition, several pathological conditions and/or drugs (glucocorticoids, androgen deprivation therapy, HIV and antiretroviral therapy) may contribute to the development of secondary osteoporosis and fractures.

Several agents used to prevent fractures in postmenopausal women with osteoporosis have been demonstrated to be effective in men with primary and secondary osteoporosis. Randomized, controlled trials on larger samples and trials directly assessing fracture risk reduction in men are needed.

Future perspective

It will be useful to gain a better understanding of the role of oxidative stress (reactive oxygen species) in age-related bone loss and strength. Recent research is addressing this as a fundamental and comprehensive pathogenetic mechanism for osteoporosis and fractures [18,19].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Executive summary

Structural basis of bone fragility in men & women

- In men, the predominant mechanism responsible for bone loss and increased fracture risk is a decrease of bone formation in the basic multicellular units.

Sex steroids & bone strength

- Recent studies have suggested a significant contribution of estrogens for bone maturation and for maintenance of bone mass, through aromatization of androgens into estrogens.

Treatment of male osteoporosis: present & future

- Novel therapeutic agents will include: antibodies to the receptor activator of nuclear factor κB ligand; cathepsin K inhibitors; modulators of the calcium sensing receptors; and antibodies that target molecules involved in Wnt signaling.

Conclusion

- Osteoporosis in men is a heterogeneous condition.
- Sex steroids and other hormonal factors play a crucial role in the chain of events leading to bone loss and fractures in aging males.
- Several pathological conditions and/or drugs may contribute to the development of secondary osteoporosis and fractures in men.
- Several agents used to prevent fractures in postmenopausal women have been demonstrated to be effective in men.

Bibliography

Papers of special note have been highlighted as:
- • of interest
- •• of considerable interest

1 Khosla S, Amin S, Orwoll E: Osteoporosis in men. *Endocr. Rev.* 29, 441–464 (2008).

▪▪ **Outstanding review that must be read to fully understand the state-of-the-art in this important and growing field.**

2 Seeman E: Structural basis of growth-related gain and age-related loss of bone strength. *Rheumatology (Oxford)* 47(Suppl. 4), IV2–IV8 (2008).

▪ **Interesting review that clarifies the basis of bone strength and fragility.**

3 Bouxsein ML: Sex differences in bone structure, strength and the factor-of-risk. *Osteoporos. Int.* 19, 1657 (2008).

4 Seeman E: Bone quality: the material and structural basis of bone strength. *J. Bone Miner. Metab.* 26, 1–8 (2008).

5 Compston J: Histomorphometric differences between men and women. *Osteoporos. Int.* 19, 1662 (2008).

6 Khosla S, Riggs BL, Atkinson EJ *et al.*: Effects of sex and age on bone microstructure at the ultradistal radius: a population-based noninvasive *in vivo* assessment. *J. Bone Miner. Res.* 21, 124–131 (2006).

7 Black DM, Bouxsein ML, Marshall LM *et al.*: Proximal femoral structure and the prediction of hip fracture in men: a large prospective study using QCT. *J. Bone Miner. Res.* 23, 1326–1333 (2008).

8 Venken K, Callewaert F, Boonen S, Vanderschueren D: Sex hormones, their receptors and bone health. *Osteoporos. Int.* 19, 1517–1525 (2008).

9 Gennari L, Nuti R, Bilezikian JP: Aromatase activity and bone homeostasis in men. *J. Clin. Endocrinol. Metab.* 89, 5898–5907 (2004).

10 Vanderschueren D, Boonen S, Venken K: Androgens and the periosteum. *Osteoporos. Int.* 19, 1659 (2008).

11 Goemaere S, Lapauw B, Taes Y, Zmierczak H, Kaufman JM: Estrogen as a determinant of femoral bone strength in elderly men. *Osteoporos. Int.* 19, 1659 (2008).

12 Mellström D, Vandenput L, Mallmin H *et al.*: Older men with low serum estradiol and high serum SHBG have an increased risk of fractures. *J. Bone Miner. Res.* 23, 1552–1560 (2008).

13 Giusti A, Palummeri E, Girasole G, Pioli G, Barone A, Bianchi G: Treatment of male osteoporosis with alendronate. *Osteoporos. Int.* 19, 1671–1672 (2008).

14 Boonen S: Risedronate treatment in male osteoporosis. *Osteoporos. Int.* 19, 1671 (2008).

15 Bilezikian JP: PTH as a treatment for male osteoporosis. *Osteoporos. Int.* 19, 1670–1671 (2008).

16 Adami S: New drugs for osteoporosis. *Osteoporos. Int.* 19, 1672–1673 (2008).

17 Brown JP, Prince RL, Deal C *et al.*: Comparison of the effect of denosumab and alendronate on bone mineral density and biochemical markers of bone turnover in postmenopausal women with low bone mass: a randomized, blinded, Phase 3 trial. *J. Bone Miner. Res.* 24(1), 153–161 (2009).

18 Almeida M, Han L, Martin-Millan M *et al.*: Skeletal involution by age-associated oxidative stress and its acceleration by loss of sex steroids. *J. Biol. Chem.* 282, 27285–27297 (2007).

▪▪ **Very interesting paper that clarifies the mechanism by which aging and loss of sex steroids produce bone loss.**

19 Manolagas SC, Almeida M: Gone with the Wnts: β-catenin, T-cell factor, forkhead box O, and oxidative stress in age-dependent diseases of bone, lipid, and glucose metabolism. *Mol. Endocrinol.* 21, 2605–2614 (2007).

▪▪ **Outstanding review regarding common molecular mechanisms contributing to the development of involutional osteoporosis, atherosclerosis, insulin resistance and hyperlipidemia.**