Male osteoporosis

A. Giusti[1], G. Bianchi[2]

[1]*Bone Clinic, Department of Gerontology and Musculoskeletal Sciences, Galliera Hospital, Genova;*
[2]*Department of Rheumatology, "La Colletta" Hospital, ASL3, Arenzano-Genova, Italy*

SUMMARY

As a result of population ageing worldwide, osteoporotic fractures are becoming a serious problem in the western world. Osteoporotic fractures are associated with a significant burden in terms of morbidity, mortality, and economic costs. Although less frequent than in women, male osteoporosis is also a relatively common problem. Since bone loss and fragility fractures in men have been recognized as a serious medical condition, over the last two decades several studies have investigated a number of aspects related to the pathogenesis, diagnosis and assessment, prevention and treatment of male osteoporosis.

A better understanding of factors underlying increased bone fragility in men has led to the definition of appropriate screening and diagnostic strategies, and the development of treatments that have shown to improve bone mineral density and, in some cases, reduce fracture risk in men as well as in women.

This review will summarize recent findings on male osteoporosis with a particular focus on risk factors and causes of bone loss, and available therapeutic options.

Key words: *Male osteoporosis, Fractures, Treatment.*

■ INTRODUCTION

Osteoporosis is defined as an asymptomatic bone disease characterized by a low bone mineral density (BMD) and a deterioration of the micro-architecture of the skeleton, leading to an increased fracture risk (1). Osteoporosis-related fractures are classically recognized as a significant healthcare issue in women.

However osteoporosis is now increasingly viewed also as an important healthcare problem in men (2). Although fewer men sustain osteoporotic fractures than women, it has been estimated that 1 out of 8 men over 50 years of age will sustain an osteoporotic fracture during his lifetime, and that 20-30% of hip fractures occur in men (2, 3).

Studies of osteoporosis in men have contributed to raise awareness of the problem and have improved our understanding of the pathogenesis of osteoporosis and fragility fractures. In addition, a number of small randomized-controlled trials (RCTs) conducted in men with primary and secondary osteoporosis has helped to identify effective evidence-based pharmacological options for the treatment of male osteoporosis (3). However, important pathophysiological and clinical issues still remain unclear.

■ EPIDEMIOLOGY

It is rather challenging to determine the prevalence of osteoporosis mainly due to the lack of consensus on a clear-cut definition. Indeed, the measurement of BMD by dual x-ray absorptiometry in various sites is certainly a useful tool to assess the risk of osteoporotic fractures in the population (2, 3).

In keeping with the World Health Organization criteria based on the T-score for the definition of osteoporosis in men, 2 cut-offs have been proposed starting from normal values for males and females (2-4). Based on bone density measurements, osteoporosis in men was defined as having a BMD value greater than 2.5 standard deviations (SD) below the mean of either men or women aged 20-29 (male and female cutoffs, respectively). Osteopenia was defined as being associated with a

Corresponding author:
Gerolamo Bianchi
Division of Rheumatology
Azienda Sanitaria Genovese 003
Via Bertani, 4 - 16120 Genova, Italy
E-mail: gerolamo_bianchi@tin.it

BMD value between 1 and 2,5 SD below the reference means respectively for young males and females. Looker et al. estimated the prevalence of osteoporosis and osteopenia using these gender-specific cut-offs. On the basis of the male cutoffs, 3-6% of men over the age of 50 presented with osteoporosis, whereas 28-47% had osteopenia. When using female cutoffs, 1-4% was reported to have osteoporosis and 15-33% to have osteopenia (4).

On the basis of these and other data, the use of sex-specific reference ranges appears the most appropriate approach to define osteoporosis and estimate the proportion of men at risk of fragility fracture. However, it should be noted that, even using gender-specific femoral neck T-scores, a significant proportion of males with osteopenia or normal BMD have vertebral, non-vertebral and hip fractures (2).

Since fractures are the primary clinical consequence of osteoporosis, the definition of the incidence and prevalence of fragility fractures in men may represent a better tool to determine the burden of osteoporosis in men.

The fracture incidence in men follows a bimodal distribution with a tendency to peak in adolescence and in elderly age (2, 3). The former peak is mostly related to fractures due to severe trauma, whereas the latter actually reflects the effect of osteoporosis itself. After the age of 75, it has been observed an exponential rise in fracture incidence in men. This exponential increase in older men is as dramatic as in women, although it begins 5-10 years later in life. Overall the absolute incidence of osteoporotic fractures in men is lower compared to women (5, 6). Vertebral and hip fractures predominate in elderly men.

Hip fractures are generally uncommon in men before the age of 75, but they increase exponentially in older men (Fig. 1). The absolute incidence of hip fractures in men varies geographically, however this age-specific significant increase has been documented worldwide (2, 3). The highest incidence of hip fractures in men has been described in northern European countries and in North American whites. The age-adjusted female to male ratio of hip fractures for whites is around 3-4:1.

Until about ten years ago, a secular increase was reported in the age-adjusted incidence
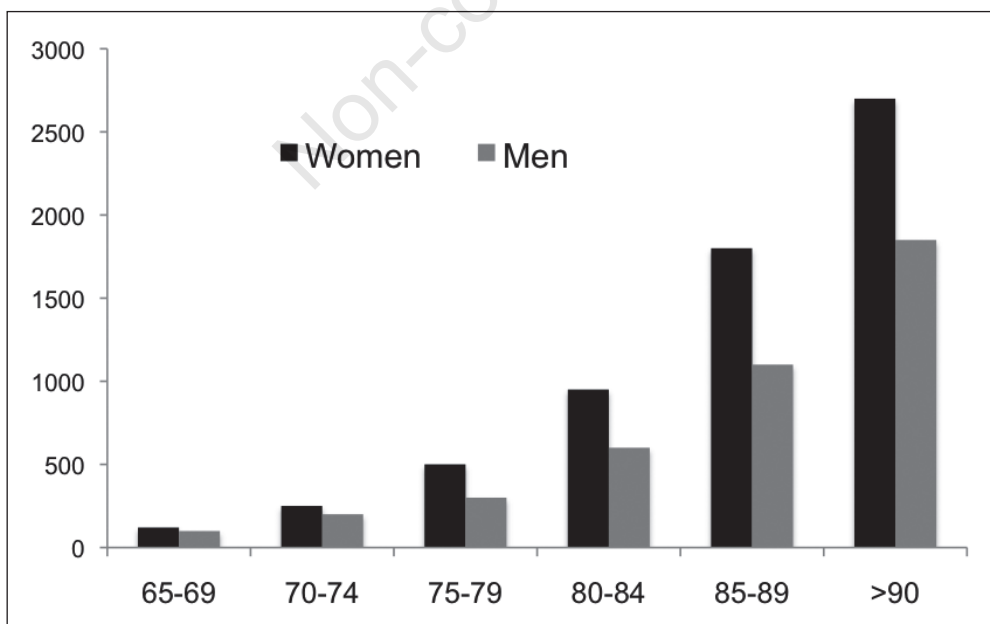
Figure 1 - Age-specific incidence rates (per 100,000 person-years) of hip fracture (excluding subtrochanter) in men and women. Modified from: Nieves et al., 2010 (5).

of hip fractures in men and women (5-7). However, over the last decade, the rates of hip fracture began to decline in the western world, particularly in women, but also in men (7-9). Although the reasons for such change in the secular trend are still unclear, it is highly likely a result of improvements in osteoporosis screening and treatment strategies.

Among all osteoporotic fractures, hip fractures are associated with the greatest mortality and morbidity (9). Also mortality, morbidity and disability associated with hip fractures are greater and more severe in men compared to women. The higher degree of comorbidity and fragility at the time of fracture contributes to a greater incidence of adverse outcomes in men presenting with hip fractures compared to women.

The epidemiology of vertebral fractures is more challenging to define, because patients presenting with vertebral fractures are not usually hospitalized, and sometimes due to the lack of pain they do not even seek clinical attention (2, 9). Therefore, the true incidence of vertebral fractures in men and women, including *silent*

vertebral deformities, is underestimated. Similarly to hip fracture, the incidence of vertebral fractures increases markedly with advancing age (6). A geographic variation in fracture distribution is described also for vertebral fractures, with the highest rates reported in Sweden compared with the rest of Europe.

The European Prospective Osteoporosis Study (EPOS) evaluated the incidence of vertebral fractures in men and women aged 50 years and older from 29 European centers (Fig. 2). A total of 14,011 men and women were recruited (6). The age-standardized incidence of vertebral fractures was two-fold higher in women compared to men (6). For example, the age-standardized incidence of morphometric vertebral fractures was 5,7 per 1000 person years at risk in men versus 10,7 per 1000 person years at risk in women.

In the European Vertebral Osteoporosis Study (EVOS), the age-standardized prevalence of vertebral deformity was estimated to be the same in men and women (10). Below the age of 65, men presented with a higher prevalence of vertebral deformity than women, whereas after this age
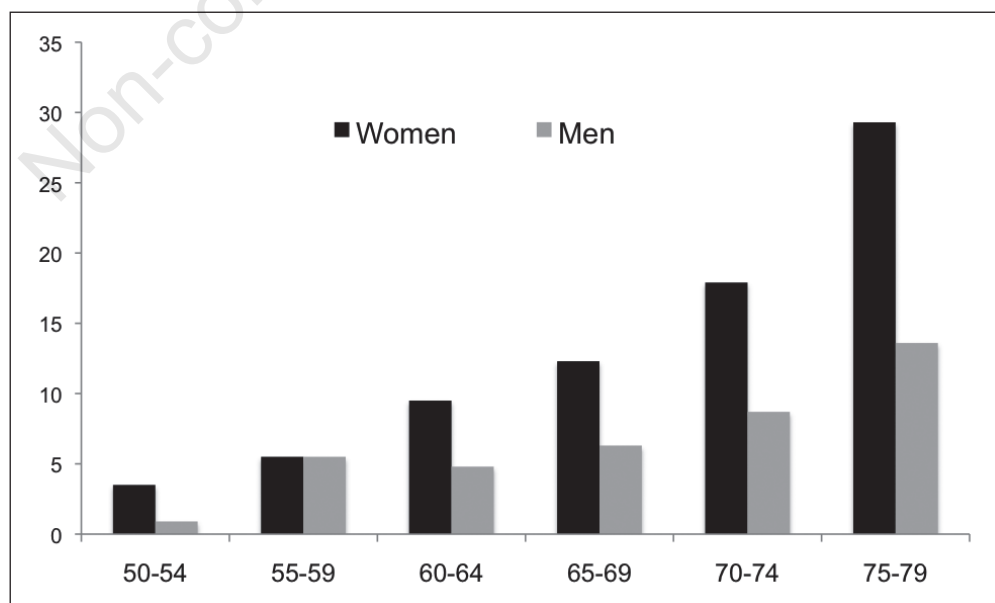
Figure 2 - Age-specific incidence rates (per 1000 person-years at risk) of morphometric vertebral fractures (reduction of at least 20% in at least one vertebral height) in men and women. Modified from: The European Prospective Osteoporosis Study Group, 2002 (6).

the trend was reversed. However, in both genders, the prevalence of vertebral deformity increased with age showing a greater increase in women after age 65.

The data about non-spinal, non-hip fragility fractures is more limited (2). In particular, in contrast with what can be seen in women, the incidence of distal radius fractures in men remains stable with age and shows only a slight increase in very elderly patients (2). A similar trend has also been described for proximal humerus, pelvis, tibial and femoral shaft fractures in men (2). Although, these fractures are probably less frequent in men compared to women (peaking in later life), if combined, they account for a significant cause of morbidity and health care costs in males as well as in females.

■ AGE-RELATED BONE LOSS IN MALE

Men have larger bones compared with women, enjoy greater bone strength and show a reduced fracture risk (11). Unlike women, men have no menopause. Therefore, they do not experience a mid-life loss of sex steroids and consequently an increase in bone loss and fracture risk (12), unless they develop a disorder (hypogonadism) or are prescribed androgen deprivation therapy for prostate cancer.

In men, bone loss proceeds slowly starting in the middle age (late slow phase) (12). With aging, men experience a lower endocortical resorption and a greater periosteal expansion compared to women (2, 11). The periosteal apposition may even counteract the cortical thinning produced by endocortical resorption with an ensuing lower net bone loss compared to women and, more importantly, an absolute increase in bone size (2, 11). The increased bone size together with lower intracortical porosity leads to higher bone strength and lower bone fragility in men compared to women. The trabecular bone loss in aging males is mainly the result of a trabecular thinning due to reduced bone formation (2, 11) rather than to trabecular perforation and loss of

connectivity (characteristic of high bone turnover states). Indeed, the trabecular thinning observed in males does not cause the same loss of strength of the vertebral body produced by the loss of connectivity triggered by the menopause. This further justifies gender differences in bone fragility during aging.

Traditionally, it was believed that the decrease in bio-available or free testosterone was the main cause underlying age-related bone loss in men, because testosterone is the main sex steroid in males (2). However, both cross-sectional and longitudinal evidence indicate that levels of bio-available estradiol rather than testosterone are strongly correlated with bone mineral density and fracture risk (2, 3). In the aging men, a value of bio-available estradiol below the threshold of 40 pM/mL produces a significant increase in bone loss (2, 3). Although evidence suggest that also decreased testosterone levels play a role in the pathogenesis of male osteoporosis, its function in aging men is less clear and may be potentially involved in the maintenance of muscle strength and balance (2, 3, 9).

The primary cause for declining sex steroid levels in men is an age-related increase in sex hormone binding globulin (SHBG) values, which, in turn, limit the biological available sex steroids and produce a decline in bio-available testosterone and estrogen levels (respectively, 64% and 47% during male lifespan) (2, 3).

In conclusion, the relative roles of estrogen, androgen and SHBG in the pathogenesis of male osteoporosis and fragility fractures still need to be clarified just like their use in the clinical practice.

■ CAUSES OF OSTEOPOROSIS IN MEN

Several different conditions may produce osteoporosis and fragility fractures in men (Tab. I). In most cases, osteoporosis is the consequence of several coexisting conditions and lifestyle-related risk factors (*e.g.*, cigarette smoking, alcohol abuse, sedentary lifestyle).

Table I - Primary and secondary causes of osteoporosis and bone loss in men.

Primary Osteoporosis
Age-related Osteoporosis
Idiopathic Osteoporosis
Secondary Osteoporosis
Alcoholism
Glucocorticoid excess
Exogenous
Endogenous
Hypogonadism
Idiopathic
Androgen deprivation therapy for prostate cancer
Chronic obstructive pulmonary disease
Gastrointestinal disorders
Malabsorption syndromes
Celiac sprue
Primary biliary cirrhosis
Inflammatory bowel disease
Bariatric surgery
Postgastrectomy
Hypercalciuria
Hyperthyroidism
Hyperparathyroidism
Medication related
Anticonvulsants
Chemotherapeutics
Thyroid hormone
Neuromuscular disorders
Post-transplant osteoporosis
Systemic illnesses
Mastocytosis
Thalassemia-induced osteoporosis
Monoclonal gammopathy
Other malignancies
Human immunodeficiency virus (HIV) infection
Rheumatoid arthritis

The most frequent causes of osteoporosis in men are alcohol abuse, glucocorticoid excess and hypogonadism (both idiopathic and related to androgen deprivation therapy for prostate cancer).

Over the last decade, the natural history of several lethal diseases, such as the human immunodeficiency virus (HIV) infection, prostate cancer and thalassemia major/intermedia, has significantly changed in the western world, leading to a reduction in mortality and a longer life expectancy. As a direct consequence, patients presenting with these conditions have become more susceptible to aging and chronic diseases (2, 3, 13-15). Therefore, osteoporosis has turned into a frequent complication of these diseases (*e.g.*, thalassemia, HIV infection) and/or the use of some pharmacological

agents (*e.g.*, androgen deprivation therapy) administered to treat them.

Secondary causes of osteoporosis may also add to an underlying age-related bone loss or idiopathic osteoporosis, producing quite dramatic clinical presentations. In some series, secondary causes of osteoporosis account and contribute to up to 40% of cases of osteoporosis in men (16).

A relevant proportion of osteoporotic males, however, have the idiopathic form. Particularly in young men, idiopathic osteoporosis may present quite dramatically. Although its pathogenesis seems still uncertain, some genetic factors appear to play a key role in the pathogenesis of idiopathic osteoporosis.

EVALUATION OF OSTEOPOROSIS IN MEN

A fully and comprehensive assessment of a case of male osteoporosis or fragility fracture should include a detailed family and medical history, including pharmacological treatments, and a physical examination, in order to identify any potential risk factor for osteoporosis/fragility fractures and signs/symptoms suggesting a secondary cause. Particular attention should be focused on the identification of BMD independent clinical risk factors for fragility fractures, due to their relevance for intervention thresholds (17, 18).

Table II - Laboratory tests in the evaluation of male osteoporosis.

Routine laboratory tests
Serum calcium, phosphorus, creatinine, alkaline phosphatase, liver function tests
Complete blood count, protein electrophoresis
Serum 25-hydroxy-vitamin D
Serum testosterone, sex hormone binding globulin and luteinizing hormone
Additional second line tests
Parathyroid hormone, thyroid function
24-h urinary calcium and creatinine
24-h urinary cortisol
Biochemical indices of bone remodeling
Immunological tests for sprue

Targeted diagnostic testing in men with signs, symptoms or other indications of secondary osteoporosis (e.g., mastocytosis)

A bone mineral density measurement by dual-energy x-ray absorptiometry should be performed, since BMD measures are at least as effective in men as in women in predicting fracture risk.

Laboratory testing represents an indispensable part of the diagnostic pathway to identify potential secondary causes of bone loss and/or modifiable conditions (*e.g.*, vitamin D deficiency) (Tab. II).

Lastly, a radiologic evaluation of the thoracic and lumbar spine may be useful to identify prevalent morphometric vertebral fractures.

■ MANAGEMENT OF MALE OSTEOPOROSIS

General measures for fracture prevention in men are similar to those adopted for women: excellent nutrition, appropriate calcium intake, physical exercise, avoid detrimental lifestyle factors (*e.g.*, smoking cessation). Vitamin D supplementation should be always considered in order to attain and maintain an adequate vitamin D level (25-hydroxy-vitamin D >30 ng/mL), due to its implications in terms of bone health and fall prevention (19). Also in patients at risk of falls, intervention to prevent falls by improving balance and strength should be implemented.

In patients presenting with a secondary cause of osteoporosis, the underlying condition causing bone loss must always be treated (*e.g.*, primary hyperparathyroidism, hypogonadism), if possible. In particular hypogonadal men should be treated with testosterone replacement treatment, given the positive effects on BMD, strength and muscle mass (9).

Several pharmacological agents have been tested in randomized-controlled trials undertaken in men with primary or secondary osteoporosis. In general, these were short-term trials, enrolling small samples. In most of them, the primary endpoint was the change in BMD. Therefore they lack the power required to be conclusive about drug effects on fracture risk. Nevertheless, the similarity of effects (on BMD and bone

turnover) seen in men and those reported in larger RCTs in postmenopausal women strongly suggests that these pharmacological agents should be effective both in men and in women (9, 20).

In RCTs, bisphosphonates, strontium ranelate, teriparatide and denosumab demonstrated to improve bone mineral density in men presenting with primary osteoporosis (idiopathic or age-related) or secondary osteoporosis (*e.g*., glucocorticoid-induced, related to androgen deprivation therapy for prostate cancer, thalassemia-associated, post-transplant, HIV-associated) (9, 20-28). In general, the beneficial effects of bisphosphonates and teriparatide on bone mineral density were independent of age and gonadal function, thus suggesting their efficacy in men with idiopathic or age-related osteoporosis regardless of age and testosterone/estradiol status.

In males with idiopathic or age-related osteoporosis (Fig. 3), alendronate, risedronate and zoledronic acid were effective in reducing the risk of new vertebral fractures (20, 22, 24). The zoledronic acid has also demonstrated to reduce the risk of recurrent fractures in men and women following hip fracture (28). Moreover, in a RCT undertaken in a mixed population of men and women with established osteoporosis, also oral pamidronate has demonstrated its beneficial effects on bone mineral density, markers of bone turnover and incidence of new vertebral fractures (20).

In some RCTs of men and women receiving glucocorticoids, bisphosphonates and teriparatide showed significant beneficial effects in preserving and/or improving bone mineral density (20, 23). Although this data refers to small samples alendronate, risedronate and ibandronate have also shown to reduce the risk of vertebral fractures in patients presenting with glucocorticoid-induced osteoporosis (20).

A number of well-designed RCTs undertaken in males with prostate cancer receiving an androgen deprivation therapy assessed the beneficial effects of bisphosphonates and denosumab on bone mineral density and bone turnover, providing evidence of their efficacy in such condition (20, 27).
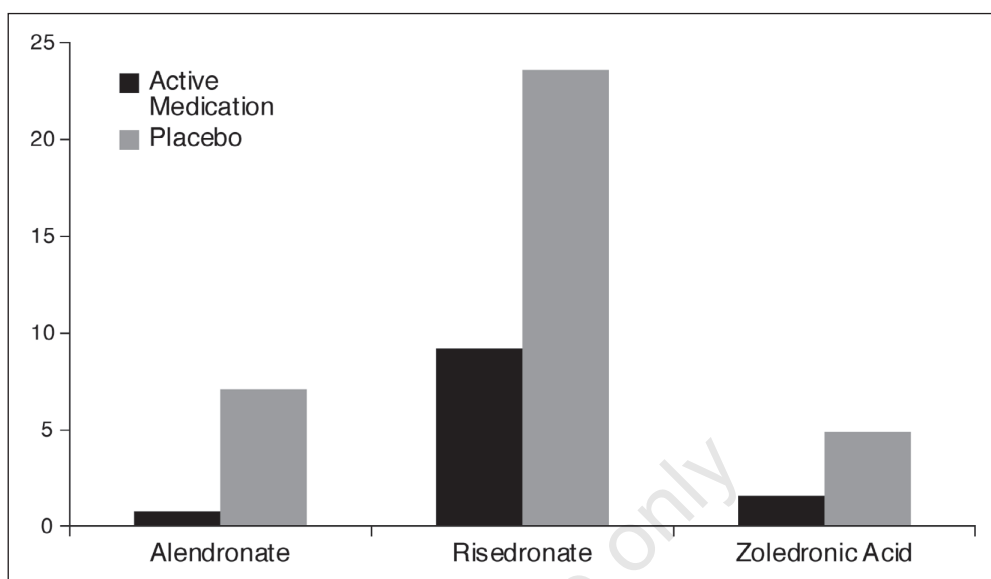
Figure 3 - Incidence of new vertebral fractures (% of patients) with bisphosphonates versus placebo, in randomized controlled trials undertaken in men with primary osteoporosis (20, 24). Duration of follow-up of two years. Differences between active medication and placebo were statistically significant.

Denosumab was also associated with a significant reduction in the incidence of new vertebral fractures among men receiving androgen-deprivation therapy for non-metastatic prostate cancer (27).

■ CONCLUSIONS

Fragility fractures in men are a relevant health care issue worldwide, being associated with significant disability, mortality and reduction of quality of life.

Although awareness about male osteoporosis is raising, this condition is still under-diagnosed and under-treated.

Further studies are needed to better understand the pathogenesis of male osteoporosis, improve case-finding strategies, and further define the potential anti-fracture and long-term efficacy of current and future pharmacological agents.

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