The osteoporotic male: Overlooked and undermanaged?

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Abstract: Age-related bone loss in men is a poorly understood phenomenon, although increasing data on the pathophysiology of bone in men is becoming available. Most of what we know on bone pathophysiology derives from studies on women. The well-known association between menopause and osteoporosis is far from been disproven. However, male osteoporosis is a relatively new phenomenon. Its novelty is in part compensated for by the number of studies on female osteoporosis and bone pathophysiology. On the other hand, the deeper understanding of female osteoporosis could lead to an underestimation of this condition in the male counterpart. The longer life-span exposes a number of men to the risk of mild-to-severe hypogonadism which in turn we know to be one of the pathogenetic steps toward the loss of bone mineral content in men and in women. Hypogonadism might therefore be one among many corrigible risk factors such as cigarette smoking and alcohol abuse against which clinicians should act in order to prevent osteoporosis and its complications. Treatments with calcium plus vitamin D and bisphophonates are widely used in men, when osteoporosis is documented and hypogonadism has been excluded. The poor knowledge on male osteoporosis accounts for the lack of well shared protocols for the clinical management of the disease. This review focuses on the clinical approach and treatment strategy for osteoporosis in men with particular attention to its relationship with male hypogonadism.

Keywords: bone loss, BMD, age-related hypogonadism, sex steroids

The osteoporotic male, perhaps an overlooked and under managed disease

Osteoporosis in men is strictly related to advancing age, the onset being more advanced when compared with females (Rochira et al 2006). The onset of osteoporosis in men is usually at a more advanced age than in women, and is strictly related to aging (Rochira et al 2006).

The measurement of bone mineral density (BMD) is considered the most appropriate clinical tool for the diagnosis of male osteoporosis (osteoporosis when the t-score is lower than 2.5 S.D. and severe osteoporosis when osteoporotic fractures are present) (Consensus Development Conference 1993). Reference values for normal BMD in men are borrowed from women (Rochira et al 2006), based on the assumption that female standards could also be more or less adequate for the male population (Orwoll and Klein 1995; Bilezikian 1999). As a consequence the relationships between BMD measurement and the risk of fractures in men remain controversial. In clinical practice, physicians hold poor tools for the management of male osteoporosis since BMD represents only a surrogate to infer the fracture risk, it does not account for bone quality and bone resistance to fracture, and, lastly, the knowledge of bone pathophysiology is still incomplete in men. In contrast to the treatment of women, osteoporosis in men is often overlooked, and more efforts are needed for both clinical and basic research on this condition in men (Rochira et al 2006).

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Clinical care for male osteoporosis is based on treatments which were first developed for postmenopausal women and only later became available for males. This approach results in uncertainties in the management of the osteoporotic man since evidence-based data is insufficient to state whether men may benefit from treatment found efficacious in women, or whether the dosage used in females is also adequate in men. Again, therapeutic trials have mainly focused on women leaving some drugs untested in men (eg, strontium ranelate). For this reason the number of treatments accessible for male osteoporosis is fewer than in women and differences in the approval of drug use for men are present between some geographic areas (eg, teriparatide is not available for men in Europe). All these controversies merely reflect an underestimation of the real impact of male osteoporosis, which has been disregarded for a long time (Rochira et al 2006). In the past, furthermore, clinicians have focused their attention on female osteoporosis, which has been considered as 'epidemic'. True awareness of the prevalence of osteoporosis in men, of its pathophysiology and of the severity of consequences due to fracture (morbidity and mortality) often remains unnoticed.

This review focuses on bone physiology and pathophysiology in men, but with particular attention to the management of male osteoporosis.

Summary of natural history and clinical presentation of male osteoporosis

Both the onset of osteoporosis (Orwoll and Klein 1995) and the occurrence of fractures are delayed in men (Donaldson et al 1990), the latter rarely occurring before 70 yrs (Bilezikian 1999).

Generally, fractures may have severe implications: a proximal femur or vertebral fracture in an aged man is an event that often leads to permanent disability because of the small chance of recovery. Accordingly the mortality rate, within 5-years of an event, is significantly greater in men than in women (about 3:2) (Center et al 1999).

Bone mineral content preservation is more prolonged in men than in women, accounting for the late-onset of osteoporosis in the human male. It is well known that the same degree of bone loss is associated with a lower risk of fracture in men than in women as a consequence of a higher resistance to fracture of male bone (Bilezikian 1999; Seeman 2002; Seeman and Delmas 2006). This important aspect of the natural history of the disease is due to sexual dimorphic differences in bone structure and stiffness (Seeman 2002; Duan et al 2003). In addition, sex-differences in the natural history of bone accrual (a physiological event) and bone loss (a pathophysiological process) account for the discrepancy between the two sexes due to exposure to different sex steroids, which act in a dimorphic fashion on bone, especially at puberty (Duan et al 2003). The results are differences in bone (micro)structure and bone quality (Seeman 2002; Duan et al 2003). Obviously, in adulthood bone mineral content is the net result of baseline bone mass achieved at the end of puberty (bone accrual), and of the subsequent bone loss (bone resorption).

Despite conflicting results (Riggs et al 2004), a gender difference in bone size, consisting of a greater cortical bone width in men, exists, and is probably related to the greater amount of androgens in men at puberty, and during adulthood as well (Seeman 2002; Duan et al 2003). Thus men develop a greater bone mass during puberty than women do.

Thereafter age-related changes in bone mass lead to progressive loss of the bone mass. This consists of a decrease in BMD with advancing age at both cancellous and cortical sites (Riggs et al 1998). These changes are sexually dimorphic particularly in cancellous bone (rapid accelerated bone loss after menopause only in women). In men bone loss occurs later in life than in women (Rochira et al 2006) and this phenomenon increases progressively with advancing age, particularly in cancellous bone after the age of 70 years (Riggs et al 1998; Rochira et al 2006). Serum testosterone – the bioavailable fraction – declines slowly in men with age, according to the development of a mild age-related hypogonadism (Swerdloff and Wang 2002), whereas the sex-steroid defect is severe in postmenopausal women. Age-related osteoporosis is strictly related to the progressive decline of the hypothalamic – pituitary – gonadal axis function in men (Riggs et al 1998). The continuous slow reduction in circulating androgens, as well as changes in total and bioavailable serum testosterone, are strongly related to bone loss (Bilezikian 1999; Boonen and Vanderschueren 2002). Thus the decrease in BMD depends on age-related hypogonadism and circulating androgens, particularly the bioavailable quota (Slemenda et al 1997; Khosla et al 1998; Kenny et al 2000; Scopacasa et al 2000; Amin et al 2000; Khosla et al 2001a; Khosla et al 2001b).

Recently an increasing body of evidence suggests a key role for relative estrogen deficiency in the pathogenesis of male osteoporosis (Rochira et al 2006). The role of estrogen deficiency in men has been disclosed during the last 10 years (Carani 1997; Faustini-Fustini 1999; Rochira et al 2001;

Rochira et al 2005). In the human male, estrogens, in particular the bioavailable fraction, decline with advancing age (Khosla et al 1998), together with the progressive fall in testosterone (Harman et al 2001; Khosla et al 2001B; Feldman et al 2002). Thus, a condition of relative estrogen deficiency may occur in healthy older men as a consequence of aging, even though it is less severe than in postmenopausal women (Rochira et al 2006).

Nowadays, estrogen deficiency (severe or mild) should be considered one of the key steps in the promotion of bone loss in men (Riggs et al 1998) as well as a major determinant in the pathogenesis of age-related male osteoporosis (Carani et al 1997; Rochira et al 2000; Rochira et al 2006).

A major role of estrogens in bone mass in men has been clearly demonstrated by several case studies performed on rare reports of male congenital estrogen deficiency in which BMD is reduced (Carani et al 1997; Rochira et al 2000; Rochira et al 2001; Rochira et al 2002; Bouillon et al 2004). Several studies (Slemenda et al 1997; Greendale et al 1997; Khosla et al 1998; Barrett-Connor et al 2000; Amin et al 2000; Khosla et al 2001B; Szulc et al 2001; Gennari et al 2003; Goderie-Plomp et al 2004) suggest that relative estrogen deficiency is associated with bone loss in aging men. Thus, relative estrogen deficiency seems to be strongly involved in the pathogenesis of age-related bone loss and osteoporosis in men (Riggs et al 1998; Rochira et al 2006).

Specific risk management and treatment practices for the osteoporotic male

The management of male osteoporosis is based on a clinical approach that may seem easy at first examination, but in fact has several pitfalls. The first step is the attempt to prevent bone loss in the subgroups of subjects considered at higher risk for developing an open clinical osteoporosis. This implies that clinicians should screen subjects, with the aim of recognizing the presence of one or more risk factors. A detailed interview should be conducted in order to gain information on smoking habits, alcohol consumption, physical activities, dietary habitudes, and sun exposure (Orwoll and Klein 1995; Burger et al 1998).

Questions should be designed in order to know whether pubertal development occurred in a normal fashion (ie, delayed puberty is associated with failure in peak bone mass achievement) or whether other concomitant conditions (hypogonadism, impaired thyroid function, hyperparathyroidism, corticosteroid treatments, vitamin-D deficiency, GH deficiency) may contribute to the pathogenesis of osteoporosis (Orwoll and Klein 1995; Rochira et al 2006).

When one or more risk factors and/or concomitant conditions suggest a higher risk, or the presence of osteoporosis, subjects should be carefully monitored in order to establish the degree of bone loss by performing a measurement of BMD (preferably by DEXA). The perfecting of less expensive, and more widely available techniques of BMD measurement, such as calcaneal or phalangeal quantitative ultrasound, is desirable because they would bring an easily available, radiation free, screening test, that could be performed without turning to highly specialized centers. Preliminarly studies suggest that quantitative ultrasound assessment is useful for predicting osteoporotic fractures in men, which represents a complementary procedure to DEXA (Gonnelli et al 2005). The evaluation of BMD by DEXA or ultrasound or both should be coupled to an endocrinological evaluation (hormones, vitamins and parameters of bone turnover). Establishing the degree of bone loss and the degree of androgenization is mandatory in order to choose the best strategy for successive clinical schedules. When a pattern of osteopenia is demonstrated, physicians must prevent further bone loss; a condition of osteoporosis needs pharmacological treatments, according to the age of the subject.

Endocrine management of the older man

A mild age-related hypogonadism is commonly present in elderly males (Boonen and Vanderschueren 2002; Feldman et al 2002). A reduction in bone mineralization, from osteopenia to severe osteoporosis, in men over 55 years should lead the physician to a thorough check of the hypothalamic-pituitary-gonadal axis. Serum testosterone, free testosterone, luteinizing hormone (LH), follicle stimulating hormone (FSH), and prolactin are mandatory in order to exclude hypogonadism. SHBG measurement may also be performed (Legrand et al 2001).

Serum estradiol determination is seldom useful in eugonadic subjects; its assay could be useful in older mildly hypogonadic males because of the possible coexistence of a partial estrogen deficiency (Rochira et al 2006). Relative estrogen deficiency is responsible for some signs and symptoms of hypogonadism (Rochira et al 2005; Rochira et al 2006; Fink et al 2006), and it is held in account as a pathogenetic step towards the development of bone loss, both in men and in women (Riggs et al 1998; Fink et al 2006). Male age-related osteoporosis management should consider estradiol and testosterone, their bioavailable fraction, and sex

hormone-binding globulin (SHBG) (Legrand et al 2001). Unfortunately, commercially available kits for estradiol determination give only partial information. There is no universal consensus on male serum estradiol normal range, and as far as estradiol determination in men is concerned, most estradiol assay kits available do not seem appropriate for the lower end of male ranges, limiting their usefulness to highly specialized centers and within research protocols (Rochira et al 2006). Recently, however, several methods have been compared in order to establish their reliability in the measurement of low serum estradiol suggesting that extraction-based assays correlate better with mass spectrometry than direct assays (Lee et al 2006). Endocrinological evaluation should consider also serum PTH, calcium, phosphorous and markers of bone turnover as first line exams for the diagnosis of osteoporosis. Impaired thyroid function should also be excluded.

Prevention of bone loss

Behavioral counseling is very important in order to prevent bone loss both when bone is unaffected or when osteopenia or osteoporosis are present. Physical activity should be encouraged and dietary suggestions should be provided. A particular consideration is necessary concerning alcoholic beverages: although there is general agreement on the need for a limitation in its consumption for reasons that go beyond bone health, no real definition of *"*moderate*"* use has been given, leaving the matter of quantification open for debate. The ingestion of up to 29 g per day of alcohol (Ganry et al 2000) was positively related to trochanteric BMD. Alcohol not only seems to stimulate aromatization of androgens into estrogens (Gavaler et al 1991), but also appears to inhibit osteoclast activity, and by that bone resorption (Turner et al 2001). Thus a moderate consumption of alcohol, preferably red wine (containing also estrogen-like substances) is advocated, while alcohol abuse should be avoided. Smoking cessation is universally considered necessary (Valimaki et al 1994).

As far as calcium and vitamin D are concerned, a balanced intake of these nutritional components is advocated. Many European adults of both sexes have suboptimal calcium and vitamin D intake (Chapuy et al 1997; Lips 2001). This is of particular importance if we consider that there is evidence of a decreased calcium absorption in the intestinal lumen in response to vitamin D intake, an event which progresses with advancing age (Pattanaungkul et al 2000), thus exposing the elderly to an increased risk of calcium deficiency. Moreover the elderly are also at risk of vitamin D deficiency due to a lack of mobility and to diminished exposure to sunlight; furthermore the capacity of the skin to produce vitamin D_3 decreases with age. Although there is no universal consensus about dietary calcium and vitamin D supplementation, both have proven very important for bone health in every period of life (Shea et al 2002). It is obvious that any reasonable treatment for osteoporosis should correct calcium and vitamin D deficiency first. As a matter of fact these two elements are often used in combination with most of the available antiosteoporotic drugs. Recently a trial on postmenopausal women suggests a beneficial effect of vitamin D and calcium supplementation on BMD, but doubtful efficacy for the reduction of fracture risk (Jackson et al 2006), thus leaving the opportunity of treatment with calcium plus vitamin D somewhat controversial.

Pharmacological treatments for male osteoporosis

Many uncertainties remain about the understanding of the mechanism of bone pathology and the effects of sex steroids therein. This uncertainty is reflected in the various clinical approaches taken by physicians to treat male osteoporosis, that is, strategies for clinical evaluation, prevention, diagnosis and consideration of therapeutic options.

Many different treatments for male osteoporosis have been tested, although most studies are centered on postmenopausal osteoporosis in women (Rochira et al 2006). Apart from counseling and nutrients supplementation, pharmacological treatment may help in preventing bone loss and in reducing the risk of fractures. Cost-benefit analysis of pharmacological treatments mean that these are reserved for subjects with a high risk of developing osteoporosis or fractures. However there is wide consensus on the pharmacological treatment of men with one or more previous fractures, in order to prevent further events.

When men without fractures are taken into account, BMD should be considered, but treatment should be reserved only for severe osteoporosis or mild osteoporosis with more than one of the other risk factors (smoking, alcohol abuse etc).

Calcitonin, a polypeptide hormone which has the effect of decreasing osteoclast activity (DeSantis and Buchman 2002), has also been used as an antiosteoporotic agent, but its efficacy in preventing bone loss is unclear and is less than that of bisphosphonates (McClung 2003). For this reason it is no longer considered a first-line treatment. Calcitonin treatment represents a classical therapy of osteoporosis used in the past and is of historical importance only.

Bisphosphonates are presently the most widespread treatment for osteoporosis available. Alendronate in particular, shown to significantly increase spine, hip, and total-body BMD, thus helping to prevent fractures and height loss in osteoporotic men, (Orwoll et al 2000) has a more significant effect when compared with alfacalcidiol plus calcium supplementation (Ringe et al 2001), or with calcium supplementation alone (Gonnelli et al 2003).

Teriparatide, a recombinant 1–34 human PTH was more recently tested in men, including hypogonadal subjects, showing anabolic effects on bone mineralization especially at lumbar spine level (Orwoll et al 2003), but without substantial difference between hypo- and eugonadal subjects. Other factors, such as smoking, alcohol intake or basal BMD values appeared to diminish its effect. The peculiarity of this drug is that it stimulates bone formation when used discontinuously, while it promotes bone resorption when used for prolonged times (Honeywell et al 2003).

One of the most recent additions to the arsenal of anti-osteoporotic drugs is strontium ranelate. In vitro and in vivo studies, the latter for the most part focused on mice, show promising results: strontium atoms, maybe through the interaction with calcium-sensing receptors, seem to be able to enhance osteoblastic replication and activity, while reducing pre-osteoclast differentiation and osteoclast activity (Canalis et al 1996; Baron and Tsouderos 2002; Takahashi et al 2003; Hott et al 2003; Amman et al 2004). The results in post-menopausal women show a good BMD response together with bioptical evidence of normal bone formation (Meunier et al 2004; Reginster et al 2005).

Other agents used in osteoporosis treatment include recombinant human growth hormone and selective estrogen receptor modulators but they have several limitations, especially in the male.

Use of androgens

Studies on the role of estrogen in human male bone pathophysiology have in part established a lesser role that previously pertained to androgens (Vanderschueren et al 2004; Rochira et al 2006). A direct action of androgens on bone cannot be excluded. Indeed hypogonadism in men is almost constantly associated with an impaired BMD (Finkelstein et al 1992; Finkelstein et al 1996; Benito et al 2003) and hypogonadism represents a frequent cause of secondary osteoporosis in the young man (Orwoll and Klein 1995). Accordingly in elderly men the occurrence of a mild to severe androgen deficiency could lead, directly or indirectly to bone loss (Boonen and Vanderschueren 2002).

Age-related hypogonadism or late onset hypogonadism (LOH) is "a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels" (Nieschlag et al 2005) which can result in a significant detriment to quality of life (Table 1). When osteopenia or osteoporosis is coupled with concomitant hypogonadism the latter should be treated in order to restore normal circulating levels of testosterone (Nieschlag et al 2005). Accordingly, testosterone replacement treatment proved its efficacy in improving the BMD both in the lumbar spine and in the femoral neck in hypogonadal men (Behre et al 1997; Snyder et al 2000), more than other non-aromatizable androgens (Crawford et al 2003). Nevertheless we cannot distinguish between the direct role that testosterone has from the effects carried out by its metabolites: estradiol and 5alpha-dihydrotestosterone (DHT). Bone tissue is known to express type 1 steroid 5alpha-reductase which catalyses the conversion of testosterone to DHT. The activity of the latter on androgen receptor is more potent (Compston 2002), but the pharmacological blockade of 5alpha-reductase with finasteride was not able to produce any notable effects on bone turnover markers, nor on BMD (Tollin et al 1996; Amory et al 2004). This evidence indirectly shifts attention from a direct androgen action on bone homeostasis to an estrogen-mediated mechanism of action (Meier et al 2004), as mentioned earlier (see the paragraph above on natural history and clinical presentation).

The diagnosis of hypogonadism relies mainly on the measurement of total blood testosterone (Bhasin et al 1998;

Table 1 Age-related hypogonadism: definition, diagnosis and treatment

Definition	Late onset hypogonadism (LOH) is "a clinical and biochemical syndrome associated with advancing age and characterized by typical symptoms and a deficiency in serum testosterone levels"
Signs and symptoms	Mood changes with decreased intellectual activity, cognitive functions, sleep disturbances, diminished libido and erectile disfunction, decreased lean body mass with an increase in visceral fat; decrease of bone mineral density associated with osteopenia, osteoporosis, and increased risk of bone fractures
Available preparations	Subdermal, transdermal, intramuscular, oral, buccal
Contraindications absolute	Prostate or breast carcinoma, severe polycythemia, severe heart failure, bladder outflow obstruction or high IPSS scores
Contraindications minor	Moderate obstruction due to a clinically benign, enlarged prostate

Derived from Nieschlag et al 2004, 2005.

Basaria and Dobs 2001; Blum and Harris 2003). Other assays are available, such as free testosterone or bioavailable testosterone measurements, but these methods need further attention to improve their repeatability and availability. Although there is no universal acceptance of the lower limits of normality for serum testosterone, it is generally well accepted that serum testosterone below 8 nmol/L (231 ng/dL), or free testosterone below 180 pmol/l (52 pg/mL) require substitution even in the elderly (Nieschlag et al 2005). Symptoms often appear at a higher threshold, increasing the importance of a careful clinical evaluation to obtain a proper diagnosis and, eventually, for treatment. Accordingly, there is a substantial number of relatively asymptomatic elderly men whose serum testosterone levels fall below the range of values considered to be normal in younger adults. These aspects mean that the condition can often be underestimated, especially in the elderly, and represents the main pitfall for a correct diagnosis. One of the most important aspects involved in the failure of a correct diagnosis in older men is related to the frequent association of other diseases. The consequent need for many different specialists may be detrimental for an adequate approach to hypogonadism, which risks being underdiagnosed. For this reason an endocrinological evaluation is recommended. As a golden rule, testosterone replacement should be considered only in those hypogonadal men who complain about any combination of the signs and symptoms reported in Table 1 (Nieschlag et al 2005), or with markedly decreased testosterone levels (Gruenewald and Matsumoto 2003).

No studies have established the threshold for serum testosterone below which BMD may be affected, or if this value should be related to serum estradiol. Thus, when mild hypogonadism is diagnosed in the absence of any other sign or symptom of hypogonadism except for a reduced BMD, the advisability of treatment is questionable and clinical monitoring remains mandatory. Testosterone substitution should be started when severe osteoporosis is present, or when osteopenia is coupled with severe testosterone deficiency and/or the presence of other signs and symptoms of hypogonadism (Table 1) (Tenover 1999; Swerdloff and Wang 2002; Jockenhovel 2004).

The main contraindications to testosterone replacement therapy include the suspicion of prostate or breast carcinoma, severe polycythemia, pulmonary obstructive diseases, severe heart failure, bladder outflow obstruction or high IPSS scores (Table 1). Moderate obstruction due to a clinically benign, enlarged prostate is not, *per se*, an absolute contraindication (Table 1). Those men successfully treated for prostate carcinoma, after a prudent interval, and with no signs of residual cancer are candidates for substitution.

The traditional form of substitutive therapy is the intramuscular injectable long-acting testosterone esters preparation, but several other formulations are available (Table1). Transdermal testosterone gel (a hydroalcoholic gel) applied to intact, clean, and dry skin proved efficacious in maintaining physiological levels of serum testosterone throughout a day. The gel preparation is usually well tolerated and with fewer side effects compared with the more traditional patch application, thanks to its lower standard daily dosage than those of other preparations; it is preferable for older men whose serum testosterone is only slightly reduced (Swerdloff and Wang 2002; Steidle et al 2003). While all these methods have proven their efficacy in restoring normal testosterone levels, their availability and affordability are not universal.

The many available preparations should be carefully chosen through the adequate understanding of their pharmacokinetics, and possibly selected by a joint decision of the patient and the physician; the most appropriate therapeutic goal is obtaining a serum testosterone level between mid-to-low young male levels. Gel preparations are the best choice for the treatment of older men since they ensure normal circulating testosterone, excluding the risk of over-treatment. Supraphysiological levels should be avoided, and the onset of contraindications during the treatment require its rapid discontinuation (Nieschlag and Behre 1998).

Testosterone supplementation can increase BMD in hypogonadal men, as widely documented in literature (Crawford et al 2003; Amory et al 2004; Benito et al 2005) and as recently confirmed by a well-performed meta-analysis (Isidori et al 2005).

Screening exams can be used to monitor the possible side effects of testosterone treatment. Thus, PSA levels and hematocrit should be checked every 3 or 4 months for the first year of substitution, then annually. Digital rectal examination (DRE) is indicated every 6 to 12 months from the start of treatment. Serum testosterone should be carefully monitored after 3 months since the onset of the replacement treatment, and every six months thereafter.

Conclusion

Age-related osteoporosis in men requires more attention than in the past, both in clinical practice and in research. Better knowledge in the future of both the pathophysiology and natural history of osteoporosis in men will lead to well-established strategies for both clinical management and treatments.

Further efforts are needed to differentiate subjects who do not require frequent medical consultation, from those who need careful monitoring in order to select which are the subgroups of patients who need pharmacological treatment.

In clinical practice, estradiol and testosterone must be considered, particularly with regard to their bioavailable fraction, together with SHBG, for the clinical evaluation of male hypogonadism in the elderly.

Hypogonadism in elderly men should receive greater attention in order to ensure replacement treatment for subjects with pathological levels of circulating androgens.

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