REVIEW

Osteoporosis and male age-related hypogonadism: role of sex steroids on bone (patho)physiology

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Abstract

Male age-related bone loss is caused, at least in part, by hypogonadism that occurs with advancing age. The study of the effects of sex steroids on bone physiology in men has recently highlighted the central role of estrogens on bone pathophysiology. This review focuses on particular aspects of bone physiology and pathophysiology in aging men, noting both the similarities to and the differences from female counterparts. In particular, the role of sex steroids on bone sexual dimorphism in health and disease has been analyzed.

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Introduction

Male age-related osteoporosis is defined as the occurrence of osteoporosis in men over 70 years without any other known cause (1, 2); however, osteoporosis in men can occur at a younger age (3), implying an overlap between male idiopathic and 'senile' osteoporosis.

The diagnosis in men is mainly based on the measurement of bone mineral density (BMD) (osteoporosis when the *t*-score is lower than -2.5 S.D. and severe osteoporosis when osteoporotic fractures are present) (4), but standard parameters for male osteoporosis are still lacking. Thus the definition and diagnosis of osteoporosis in men relies, at least in part, on female standards that have been assumed to be more or less adequate for the male population (1, 2).

Similarly, our knowledge about male osteoporosis derives mostly from studies performed on female osteoporosis, as evaluated since 1995 (1). If we consider the number of published papers during the last 10 and 5 years, the ratio between studies of osteoporosis in men and women is in favor of work on female bone pathophysiology (Table 1). The number of published papers indirectly reflects the number of research programs in the field of osteoporosis, the interest of researchers and finally the quantity of data available in the literature, as well as the results obtained. The prevalence of both

osteopenia and osteoporosis (5) together with the incidence of fractures (6–8) confirms that bone loss is more frequent in women (Table 1) but, on the basis of the amount of the data available in the literature, the difference between the two sexes does not entirely reflect the real extent of the phenomenon, male osteoporosis being less investigated. Accordingly, about 3.5 papers on female osteoporosis have been published for each one on male osteoporosis (Table 1), but epidemiological data support the concept that the diagnosis of female osteoporosis is only 2.5-fold more frequent than in men (Table 1), accounting for the above-mentioned discrepancy of investigations between the sexes. In women, bone physiology, pathophysiology and epidemiology are better defined than in men (Table 2) and nowadays several effective treatments are available. Conversely, bone pathophysiology remains a poorly understood phenomenon in men (Table 2).

Notwithstanding the efforts that have been made in the last 10 years in order to improve our knowledge about bone pathophysiology in men, to identify differences between male and female bone physiology and pathology, and to reduce uncertainties in male osteoporosis, our knowledge about osteoporosis in men is strongly dependent on what we have learned from female osteoporosis. Even treatments available for men have been taken from their female counterparts; furthermore, in contrast to the USA, not all the approved treatments for female osteoporosis are

Table 1 Sex differences in the amount of data available in the literature, the prevalence of osteoporosis and osteopenia, and the incidence of hip fractures in men and women.

	Number of published papers* (Medline)		Epidemiological data on osteopenia, osteoporosis and fractures		
	Last 10 years	Last 5 years	Prevalence of osteopenia (age > 50 years)#	Prevalence of osteoporosis (age > 50 years)#	Incidence (per year) of hip fractures (age > 65 years)§
Osteoporosis in women	6.691 (78%)	3.979 (77%)	~ 43%	~ 16%	8–10/1000
Osteoporosis in men	1.850 (22%)	1.200 (23%)	~ 37%	~ 6%	4–5/1000
Male to female ratio	~ 1:3.6	~ 1:3.3	~ 1:1.6	~ 1:2.6	~ 1:2

* Data obtained from PubMed using 'osteoporosis' and 'man' or 'women' separately as keywords and after having defined a period of time (10 years: from 1 July 1995 to 31 June 2005 or 5 years: from 1 July 2000 to 31 June 2005).

Data from Looker *et al.* (5).

§ Data from Bacon *et al.* (6) and Jacobsen *et al.* (7).

available for men in Europe (e.g. teriparatide) (9), notwithstanding their proven efficacy (Table 2).

Thus the question as to whether male osteoporosis is equal, similar or different with respect to female osteoporosis remains largely unanswered. This review focuses

on particular aspects of bone physiology and pathophysiology in men, noting both the similarities to and the differences from the female counterpart (Table 2). In particular, the role of sex steroids on bone sexual dimorphism in health and disease has been analyzed.

Table 2 Comparison between male and female aspects of bone loss. Many pathophysiological aspects related to bone health in the two sexes highlighting gender differences and similarities are shown.

	Men	Women
(Patho)physiology		
State of the art	Partially defined	Well defined
Peak of bone mass	17–18 years	13–14 years
Increased bone resorption	In advanced age (> 65 yrs)	After menopause
Loss of cancellous bone	Slow and progressive	Rapid soon after menopause, then slow and progressive
Loss of cortical bone	Slow	Slow
Periosteal apposition	Major	Minor
Bone resistance to fractures	Major	Minor
Estrogen deficiency	Reduction of BMD	Reduction of BMD
Role of sex steroids		
Estrogens	Major role	Major role
Androgens	Intermediate role: positive effect on cortical thickness	Minor role (not well investigated)
Aging and sex steroid decline	Testosterone declines progressively and slowly	Dramatic estrogens fall after menopause
Serum estradiol	In adult life 10-fold lower than premenopausal women: In the elderly lower than adult men but higher than postmenopausal women	Higher than adult men Very low levels in aging postmenopausal women
Diagnosis		
Diagnostic criteria	Not available	Well established
Standard parameters, population-based for BMD	Available but only in small populations	Available
Standard cut-off of BMD for fracture risk	Not available	Available
Epidemiology		
Prevalence of osteopenia	No gender differences	
Age-related decline in bone mass		
Prevalence of osteoporosis	> 60 years	After menopause
Occurrence of osteoporosis	Low	High
Incidence of fractures	After 70 years	After menopause
Morbidity after fractures	High (after 70 years)	High (after 60 years)
Mortality after fractures	High	High
Treatments		
Experimental design	Proven in small clinical trials (after trials on women)	Proven in large clinical trials
Treatments available	Few and less studied	Many and well studied

Osteoporosis and osteopenia in men: clinical impact

The prevalence of osteopenia does not differ significantly between men and women aged more than 50 years (Table 1) (5). Conversely, the prevalence of osteoporosis in men is lower than in women (Table 1) (1, 5), even though it may be underestimated when standard female BMD parameters are considered suitable for normal mineralization in men (4, 8), because men generally have a higher BMD than women of the same age (10). Accordingly, the prevalence of male osteoporosis is greater when male-specific ranges are used in men of 50 years or more: ranging from 1% to 4% of elderly men when the diagnosis is based on female cut-off points vs 3% to 6% when based on male cut-off points (5). Unfortunately, no studies have been addressed to finding a standard for BMD parameters in a male population that would be useful in evaluating the risk of fractures according to the degree of bone loss (2, 8). This goal will be achieved only when large cross-sectional prospective studies are performed on large, aged male populations, since 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 major resistance to fracture in the male bone (2, 10).

In men, osteoporosis occurs later than in women (1, 6); as a consequence, men tend to have fractures later in life (11, 12). Fractures often imply severe consequences for life because a proximal femur or vertebral fracture in an aged man is an event that often leads to permanent disability. This is because of the small possibility of recovery with a 5-year mortality which is significantly higher in men than in women (13) (Table 2).

Aging, sex steroids and bone loss in men

Aging in men is associated with modifications of sex steroid production and of bone remodeling. Age-related changes in bone mass occur in both sexes with advancing age and BMD gradually decreases at both cancellous and cortical sites (14, 15), BMD changes being sexually dimorphic particularly in cancellous bone (rapid accelerated bone loss after menopause only in women) (Table 2). In men, however, bone loss occurs later in life than in women (14) and this phenomenon increases progressively with advancing age, particularly in cancellous bone after the age of 70 years (Table 2) (15). The dramatic fall of both sex hormones and bone mass does not occur in men as it does in menopausal women (Table 2). Serum testosterone, particularly the serum bioavailable fraction, declines slowly in men with age, so a mild age-related hypogonadism is often frequent in older men (16). A clear relationship between the decrease in BMD and age-related hypogonadism has been demonstrated since

hip fracture risk is increased in hypogonadal aging men (17) and often serum testosterone is decreased in patients with hip fracture (18). Again, BMD is directly related to bioavailable testosterone (19, 20), while this relationship is not so evident with total testosterone (19, 21–24).

Age-related osteoporosis is now considered to be a consequence of the progressive impairment of the hypothalamic–pituitary–gonadal axis in men (14) and, even though a corresponding dramatic fall of sex hormones as happens in menopause does not occur in men, the continuous slow reduction in circulating androgens, as well as changes in total and bioavailable serum testosterone in men, are strongly related to bone loss (2, 8).

Twenty years ago it was believed that BMD was mainly related to testicular androgens in boys and men and to estrogens in girls and women, but in the last 10 years information about the role of estrogens on bone physiology and pathophysiology in men has been increasing day by day (25–27). Nowadays it is known that bone tissue is able to produce sex steroids (i.e. estrogens and androgen metabolites) locally (28) and bone represents a target tissue for both locally produced and circulating sex steroids, since both androgen and estrogen receptors (α and β) as well as aromatase enzyme, are expressed in bone cells (29). Thus sex steroids may act on bone in an endocrine, paracrine and autocrine fashion.

Estradiol and age-related male osteoporosis

In normal adult men, approximately 30–50 μg estradiol are produced daily from the aromatization of androgens. About 5–10 μg are directly synthesized in the testes (10–20%) and the remaining 40–45 μg (80–90%) comes from the conversion of available circulating androgens, mainly testosterone, in peripheral tissues in which aromatase enzyme is expressed (adipose tissue, muscle, breast, brain, liver and bone) (30). Daily production of estrogen guarantees serum estradiol levels in the range of 66–147 pmol/l (18–40 pg/ml) in normal adult men (30, 31). Thus, in adult normal men, circulating estradiol is tenfold lower when compared with premenopausal women whose estradiol levels range from 73 to 734 pmol/l (20–200 pg/ml) (30, 31). In the human male, estrogens, in particular the bioavailable fraction, decline with advancing age (22) together with the progressive fall in testosterone (32, 33), but estradiol remains twofold higher in normal older men if compared with postmenopausal women whose estradiol levels range from 36 to 73 pmol/l (10–20 pg/ml) (34). Thus, a relative estrogen deficiency also occurs in normal older men as a consequence of aging, but it generally remains less severe than in postmenopausal women since the testes continue to produce a sufficient amount of androgen for peripheral and local conversion into estro-

gens (35, 36), while the cessation of ovarian function in women leaves only a very small quota of circulating androgens coming from adrenal secretion (37). Severe estrogen deficiency occurs in aging men when a severe degree of hypogonadism occurs. In this case, therefore, the amount of circulating estrogens may resemble those of postmenopausal women or may be smaller, since circulating androgen precursors remain higher in aging women than in men as a consequence of both adrenal secretion and residual ovarian function as recently suggested (38).

Recently, congenital estrogen deficiency indicated the consequences of estrogen deprivation in both animals and men. Studies performed on animal models of estrogen deficiency showed that knockout of both the α -estrogen receptor and the aromatase gene in mice leads to lower BMD than in wild-type mice. This is similar to what happens when aromatase inhibitors are used in rodents (39).

A major role of estrogens on bone mass in men has been clearly demonstrated by several studies performed as case studies, observational and interventional series, case control studies and cross-sectional studies.

Studies performed on rare cases of male congenital estrogen deficiency (40) demonstrated that osteopenia or osteoporosis at various degrees together with other bone features (Table 3) are constantly associated with the lack of estrogen activity both in the unique case of a man with estrogen resistance due to an inactivating mutation in the α -estrogen receptor gene (41) and also in four adult men with aromatase deficiency (25, 42–44). In adult men with aromatase deficiency, estrogen treatment improved BMD in a dose-dependent manner even when the treatment was started in adulthood (43, 45). Administration of transdermal estradiol at 50 μ g twice weekly for 6 months, followed by 25 μ g twice weekly for 9 months, in a man with aromatase deficiency, resulted in BMD improvement from 25% to 37% from the baseline (45). A reduction of the dosage resulted in a worsening of BMD together with circulating estradiol lower than normal (45). Accord-

ingly, a dosage of 25 μ g transdermal estradiol twice weekly for 6 months was effective on the BMD in a second man with aromatase deficiency, and further increase of the dosage to 50 μ g twice weekly for the subsequent 18 months did not significantly modify BMD parameters (43). Thus a dosage of transdermal estradiol of 0.24 μ g/kg per day (25 μ g twice weekly) represents the minimal amount of exogenous estrogens useful to obtain and maintain both normal BMD and serum estradiol in the normal range (40) in adult men with aromatase deficiency. An improvement in longitudinal bone growth, bone size and cortical thickness in a 17-year-old boy affected by aromatase deficiency and treated with estrogen has been shown recently (46). Low BMD is mostly due to a lower peak of bone mass rather than to increased bone resorption in aromatase-deficient men, as recently suggested by the lack of efficacy of alendronate (an anti-resorptive drug) in an adult man (43). Accordingly, reduced BMD values at dual-energy X-ray absorptiometry (DXA) in an untreated young aromatase-deficient boy seem to be mainly related to a smaller bone size rather than either trabecular or cortical volumetric BMD (46). In fact, a discrepancy between areal BMD at DXA and volumetric BMD at peripheral quantitative computed tomography (pQCT) was recorded (46). Together these data confirmed that severe estrogen deficiency leads to a failure in the bone accrual normally occurring at puberty. On the other hand, the lowering of the dose of estradiol led to bone loss in an aromatase-deficient man even after an increase in BMD had been achieved (45), suggesting, for estrogens, both an anabolic (achievement of peak bone mass) and an anti-resorptive (BMD decrease when estradiol is lower) role on male bone. In this regard, the bone of young adult estrogen-deficient men resembles that of aging men, being both poorly mineralized and associated with severe or relative estrogen deficiency, respectively. Finally, estrogen treatment in men with aromatase deficiency should be started in order to complete the final phases of skeletal maturation (achievement of peak bone mass and epiphyseal closure) and should be continued throughout life to prevent bone loss and to guarantee bone health (maintenance of bone mass and mineralization) (40).

Additional rare cases show the effects of estrogens on bone mass. Boys with estrogen excess due to gain-of-function mutations of the aromatase gene present with short stature due to precocious epiphyseal closure, gynecomastia and increased BMD (47, 48).

Case series interventional studies have demonstrated that the administration of a high dose of estrogen for more than 2 years to male-to-female transsexuals increased BMD at lumbar and femoral sites (49). Estrogen administration in orchiectomized male-to-female transsexuals showed an increase in BMD after 1 year of treatment, together with a reduction of the markers of bone turnover (50). Recently, high doses

Table 3 Skeletal features and hormonal pattern in men with congenital estrogen deficiency due to aromatase deficiency.

Skeletal features and hormonal pattern

Osteoporosis or severe osteopenia
Bone pain
Low BMD at both lumbar and femoral site
Failure in peak bone mass
Delayed epiphyseal closure
Delayed skeletal maturation and continuous linear growth
Eunuchoid skeleton
Progressive genu valgum
Bilateral osteonecrosis of femoral heads*
Undetectable estradiol
Low, normal or high serum testosterone levels
Normal to high levels of gonadotropins

* Described only in one case.

of estrogen have also been effective in male-to-female transsexuals when gonadotropin hormone-releasing hormone (GnRH) agonists were concomitantly used for the suppression of androgen production (51). These data clearly demonstrated that the positive effect of estrogens on BMD is independent from serum testosterone which is suppressed in male-to-female transsexuals, and that estrogen treatment not only prevents bone loss after androgen deprivation but may cause a gain in bone mass in men. Again, both an anabolic and an anti-resorptive action of estrogens on male bone is supported. An opposite methodological approach confirmed that aromatization is needed for bone health in men since the administration of aromatase inhibitors to normal elderly men increased the markers of bone resorption and lowered serum estradiol (52, 53).

Observational studies performed on osteoporotic males have demonstrated that serum estradiol levels are associated with osteoporosis in men (54) and that BMD is directly related to circulating estrogens rather than to serum testosterone in normal men (55), as well as in young and elderly men (21–23, 34). Even though, in young hypogonadal men, the relationships among bone loss, serum testosterone and circulating estrogens have been poorly investigated, estrogen deficiency also seems to be associated with progressive accelerated bone loss after bilateral orchiectomy in men aged <40 years (56).

Higher rates of bone loss are associated with the lowest free estrogen index (FEI) quartile in 200 elderly men. BMD values at both lumbar and femoral sites and the rate of bone turnover markers were directly and inversely related to FEI respectively. Conversely, bone loss, BMD and markers of bone turnover were not significantly related to the free androgen index or serum testosterone; of more interest is the fact that the estradiol to testosterone ratio was higher in normal men than in osteoporotic elderly subjects (57). Similar results have been reported by Szulc *et al.* (58) who analyzed the relationships between BMD, bone turnover markers and the quartiles of serum bioestradiol at baseline and after 4 years in 596 adult and elderly men.

The analysis of the Rochester, Minnesota study of the genotype of α -estrogen receptor and its relationship with the rate of change in midradius BMD (stratified by bioavailable estradiol levels more or less than 40 pmol/l (<11 pg/ml)) has shown the association with particular genotypes in 119 older men aged 60–90 years (59). Again bioavailable estradiol, aromatase gene polymorphism and changes in BMD were associated with the genotype of the aromatase gene in at least two major studies in men over 70 years (60) and in 500 men over 55 years (61).

Finally, several cross-sectional prospective epidemiological studies performed on a large cohort of men in the last 10 years (Framingham, Rancho Bernardo, Rotterdam Studies) confirmed that estradiol, among

the sex steroids, is the most potent determining factor of BMD in men (23, 62–64).

In conclusion, animal studies and various studies performed on men strongly support the concept that serum estradiol levels have a strong and positive association with BMD in men. This evidence supports a major role of estrogens on the achievement and maintenance of bone mass in men (Table 2) and argue against a main role of androgens on bone as has been suggested in the past. The estrogen to testosterone ratio seems to be a determinant for the occurrence of osteoporosis (57) in men, as happens for other clinical findings related to estrogen deficiency (e.g. insulin resistance) in men (40, 43). Therefore relative estrogen deficiency seems to be strongly involved in the pathogenesis of age-related bone loss and osteoporosis (14).

Androgens and age-related male osteoporosis

Our understanding of the role of estrogen on human male bone physiology has certainly revisited and, in part, reduced the role of androgens on male bone physiology (29), but a direct action of androgens on bone cannot be ruled out even if its mechanism is now too complex to be characterized *in vivo*. Paradoxically, we know more about estrogens and less about androgens (Tables 2 and 4).

Hypogonadism in adult men is associated almost constantly with a BMD lower than normal (65–67) and in adult young men hypogonadism is a frequent cause of secondary osteoporosis (1). In aging men, the occurrence of partial androgen deficiency has been recently directly related to male age-related osteoporosis; thus, a mild to severe decline of circulating androgens occurring with aging could directly or indirectly cause bone loss in men (8).

Testosterone

In hypogonadal men, the positive effects of testosterone administration on bone have been known for a long time (68). Long-term prospective and retrospective studies, in fact, have demonstrated that testosterone replacement is able to improve BMD at both the lumbar spine and the femoral neck (69, 70). In particular, testosterone seems to be more effective in improving BMD than other non-aromatizable androgens like nandrolone (71).

From the data available concerning the relationships between circulating androgens, testosterone treatment and BMD *in vivo*, we cannot distinguish the role of testosterone *per se* from that of its metabolites, estradiol and 5 α -dihydrotestosterone (DHT). The direct role of androgens on bone therefore remains to be established in detail.

DHT

Human bone tissue express functional type 1 steroid 5 α -reductase, the enzyme which transforms testoster-

Table 4 Unsolved issues in the pathophysiology and limits in diagnosis and management of age-related male bone loss.

Pathophysiology
Individual factors involved in bone loss
Genetic
Local aromatase expression and activity
Estrogen receptors functioning
Androgen receptors functioning
Patient's history
Consequences of sex steroids partial deficiency at puberty
Relative role of sex steroids on bone
Detection of threshold values for the action on bone of circulating sex steroids
Relevance of estradiol to testosterone ratio
Relative contribution of circulating steroids or locally produced steroids
Biological direct effects of androgens on bone
Sex steroid interactions with other locally produced hormones, growth factors or cytokines
Limits of the diagnosis:
Age threshold or other parameters useful to discriminate age-related from idiopathic osteoporosis not known
Absence of cut-off values for BMD parameters in men
Absence of data on fracture risk for age-stratified values of male BMD
Limits in clinical evaluation
Need for highly sensitive assays for serum estradiol in clinical practice
Need for diagnostic criteria for a better characterization of mild estrogen deficiency in aging men

one into its metabolite DHT which has a more potent androgen activity on the androgen receptor (28). The opportunity provided by a pharmacological blockade of the enzyme may be useful in disclosing the effects of androgens *per se in vivo* in men. Administration of finasteride (a 5 α -reductase inhibitor) to men with benign prostatic hyperplasia did not influence BMD and serum markers of bone turnover (72). Furthermore, the use of testosterone alone or of testosterone plus finasteride in hypogonadal men did not show any difference between the two treatment schedules, suggesting that the concomitant inhibition of 5 α -reductase does not reduce the beneficial effects of testosterone treatment on BMD (73). Again the use of DHT alone in older men with partial androgen deficiency did not modify BMD parameters notwithstanding a 20-fold increase in serum DHT (74). Thus DHT seems not to be necessary for the beneficial effects of testosterone on BMD in men and this evidence indirectly focuses on the positive effects on bone induced by the aromatization of androgens (74). A possible role of DHT on BMD was previously suggested on the basis of animal studies and *in vitro* research (29), but DHT was able to prevent bone loss in castrated rodents only when used at supraphysiological doses *in vivo* (75). Even though androgens seem to exert a direct action on bone cells (osteoblast, osteoclast, osteocytes), all these effects linked to the activation of androgen receptor (such as apoptosis, modulation and proliferation of osteoblasts and osteo-

clasts) have been proved only *in vitro* or in animal studies (29). The only clinical evidence of a possible direct effect of androgens *in vivo* comes from the finding of significantly higher BMD values in women with ovarian hyperandrogenism compared with normal females (76, 77). Another possible indirect action of androgens on bone may be related to the modulation of locally produced growth factors such as insulin-like growth factor-I (IGF-I) (29). The effects of androgens on cortical bone are better documented, even if not completely defined. Several studies have demonstrated that androgens contribute to periosteal bone accrual in men (78) as well as in male rodents (79) and that androgens induce the differences in bone size between men and women (80). Androgens may act on the periosteal surface by increasing periosteal bone formation. This process seems to continue during adulthood and, at a lower degree, even in aging in a sexually dimorphic manner, characterized by a major amount of periosteal apposition in men compared with women (81). Periosteal apposition gains even in women after menopause, resulting in an increase in both skeletal size and bone strength (82). In addition, Riggs *et al.* (83) failed to find gender differences in periosteal bone formation, thus conflicting results (81) may be due, at least in part, to different methodological approaches (DXA vs pQCT). In our opinion, a gender difference in bone size does exist since men have greater cortical bone width than women (probably because of the effects of androgens at puberty) that are related to the greater amount of androgens in men at puberty and during adulthood and probably to a major continuing pattern of periosteal apposition with advancing age (10, 81). Other recent data suggest that the aromatization of androgens is required for pubertal periosteal bone expansion (46). Estrogen treatment of a young boy with congenital aromatase deficiency induced an increase of both areal BMD and cortical thickness (46) and data from the MINOS study revealed a relationship between low serum estradiol and a decreased cortical thickness (84). Thus the effects of the aromatization of androgens on cortical bone cannot be excluded. In any case, however, some preliminary evidence speaks in favor of a key role for estrogen on cortical bone in men too; several studies have shown a positive correlation between androgens and cortical thickness (10, 78, 79, 81), while the FEI seems not to be associated with cortical bone size in young men during pubertal bone accrual (85). This issue remains poorly understood at the moment and a link to the activity of α - or β -estrogen receptors and their tissue distribution might even be supposed, since periosteal apposition is induced by α -estrogen receptor, while its inhibition is mediated by the β -estrogen receptor (29, 46). Accordingly, the existence of a direct androgen action in adult men with aromatase deficiency is supported by the fact that not only did estrogen treatment result in increased BMD (43)

but also both sexual behavior (86) and BMD (L Maffei, V Rochira & C Carani, preliminary data) further improved when androgen supplementation was added and serum testosterone returned to the normal range (86). In this regard, when Falahati-Nini and coworkers (52) added estrogen alone or testosterone plus an aromatase inhibitor to men treated with a GnRH analogue, they confirmed that estrogens account for only about 70% and androgens for the remaining 30% of the total effects of sex steroids on bone resorption.

Clinical implications

Estrogen deficiency seems to be a pathogenetic step toward bone loss in both men and women (14), notwithstanding the fact that bone pathophysiology and its clinical correlates vary widely between the sexes (Table 2).

Reduced BMD may be present in older men and could be associated with a mild age-related hypogonadism; thus, from a clinical point of view, the hypothalamic–pituitary–gonadal axis should be screened in men aged over 55 years old when severe osteopenia, osteoporosis and/or bone fractures are present. Testosterone, free testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and prolactin should be assayed in order to exclude hypogonadism which is generally characterized by a mild to severe decrease of total and free serum testosterone. In order to establish if a relative estrogen deficiency is present

in men with clinical bone loss, the clinical importance of the assay of serum estradiol remains to be defined. In fact, men with age-related mild hypogonadism may have an impairment of circulating estradiol (54) or serum estradiol in the normal range (31) (Fig. 1). These differences may depend on several factors involving individual differences in aromatase expression and activity (Fig. 1) and in receptor functioning (Table 4) and may account for conflicting results both on unchanged or increased estradiol serum levels in aging (31, 54) as well as having clinical implications (Fig. 1).

Even though the impact of individual local and systemic production of estradiol has not been well investigated, up to now both paracrine and endocrine estrogen actions have been shown to probably play a major role on the degree of estrogenization of human male peripheral tissues (28, 35, 36). Thus the determination of serum estradiol may rarely be useful in older men with normal serum testosterone, but could be important in older men with mild age-related hypogonadism and with a possible concomitant partial estrogen deficiency (Fig. 1). On the one hand, the assay of serum estradiol should be encouraged because relative estrogen deficiency has been considered the major pathogenetic event in the mechanism of age-related bone loss in men since 1998 (14). Thus data on serum estrogen could be useful for a better clinical evaluation of male hypogonadism in men (Fig. 1) and particularly in the elderly, since

Figure 1 Relative estrogen deficiency in age-related male hypogonadism and its clinical implications.

we now know that some sign or symptoms of hypogonadism are due to relative estrogen deficiency rather than androgen (87). On the other hand, this diagnostic procedure in the laboratory should be carefully considered for use in extensive clinical practice for many reasons. First, serum estradiol in men is lower than in premenopausal women and the available kits for the determination of serum estrogen are not sufficiently sensitive for the lower end of the male normal range; secondly, validated normal reference ranges for serum estradiol are still lacking for the aged male population. A powerful tool for the management of male osteoporosis will be available only when a third generation RIA (43, 45) or other highly sensitive methods for serum estrogen determination in men are routinely used in clinical practice after the establishment of normal ranges for aging men. With these sensitive assays it will probably be possible to design, in the near future, some investigation protocols in order to search for and define a plasmatic estradiol threshold useful for identifying the risk of fracture (Table 4).

The management of male age-related osteoporosis should consider serum levels of both estradiol and testosterone, with particular regard to their bioavailable quota as well as sex hormone-binding globulin (SHBG) (88), bearing in mind that commercially available kits for serum estradiol determination are becoming even more sensitive and appropriate also for male ranges and that they give only partial information in clinical practice at this time. In this regard, the determination of serum estradiol should be performed within research protocols with clinical use confined to highly specialized centers on male hypogonadism or osteoporosis after the determination of a trustworthy range for an aged male population, without indiscriminate clinical widespread use.

Some unresolved issues (Table 4) with very important outcomes on clinical practice contribute to the uncertainty about the understanding of the involvement of sex steroids on physiological events, and of mechanisms underlying bone pathology. All these factors reflect the wide and various clinical approaches when physicians operate in the field of male osteoporosis, particularly as far as strategies for clinical evaluation, diagnosis and therapeutical options are concerned.

Conclusions

Both sex steroids, i.e. androgens and estrogens, decline in serum with advancing age in men, the bioavailable fraction being constantly decreased in older men. However, only estrogens seem directly involved in the process of aging in bone tissue, with androgens having a minor role, since some evidence has shown a clear cause–effect relationship between low estrogen levels and bone loss in men. The estrogen to testosterone ratio seems to be the determinant in age-related

hypogonadism, for the occurrence of osteoporosis and the relative decrease of each circulating sex steroid may also interfere negatively on bone homeostasis in an indirect manner, since other endocrine systems (e.g. growth hormone/IGF-I axis) needed for normal bone are affected by sex steroid deficiency. Congenital estrogen deficiency in young men is associated with bone changes similar to those of the aging male.

In clinical practice, estradiol and testosterone must be considered with particular regard to their bioavailable quota as well as SHBG for the clinical evaluation of male hypogonadism in the elderly. Estrogens might be useful for clinical evaluation of male hypogonadism in the elderly. On the basis of all these reflections, a hypothetical possibility for treating male osteoporosis with a small amount of estrogen (89) or with drugs with similar effects, such as selective estrogen receptor modulators (SERMs) (90, 91) or new (future) therapeutic strategies able to promote the aromatization of androgens cannot be completely ruled out; but at this moment we have more to learn about male osteoporosis (Table 4) so this hypothesis will be a real option in the future only after the evidence of placebo-controlled trials whose data will be a determinant in this sense. Surely the aromatase enzyme can be considered a crucial target for new strategies of treatment in the future.

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