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Male Osteoporosis

Gender Differences in Pathophysiology, Clinical Aspects, Diagnosis and Treatment

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Contents

Introduction

Osteoporosis is an increasingly prevalent disease with important clinical, economic, and social consequences, characterized by reduced bone strength, due to altered bone density and quality, which increases the risk of spontaneous and traumatic fractures and related disabilities. Since the bone is an active tissue that constantly remodels itself in response to several factors, such as mechanical stress and hormonal changes, osteoporosis can be regarded as a consequence of exaggerated bone resorption and/or reduced bone formation, due to unbalanced activity between bone forming cells (osteoblasts) and bone resorbing cells (osteoclasts).

Osteoporosis is a chronic multifactorial metabolic disease associated with aging, but with several factors that can contribute to skeletal fragility, including genetics, nutrition, lack of physical activity, smoking, endocrine alterations, and medications. Importantly, osteoporosis is a silent condition, which often manifests itself clinically when bones fracture.

Researches in the last decades clearly indicated strategies for prevention, screening, clinical management, and treatment and, thus, novel drugs have been developed to manage osteoporosis, decrease fracture risk and consequent complications. However, gender disparities exist in this context, and for too much time osteoporosis has been considered a female gender disease, so that our knowledge on male osteoporosis is still not complete. Even if in absolute numbers osteoporosis is indeed more frequent in females, males could also be affected during aging or as consequence of different conditions. Male osteoporosis is a neglected condition, under-considered, under-diagnosed, and under-treated. Guidelines on screening politics do not agree whether and when men should be evaluated, and clinical trials are far less performed in men with respect to women. Furthermore, male osteoporosis is more frequent as secondary to other conditions, in contrast to women in which the most common form is primary osteoporosis. Thus, identification of specific causes of male osteoporosis is essential to drive the correct treatment and specific diagnostic procedures are essential in the management of osteoporosis in men.

Likewise, not only fewer men receive a correct and timely diagnosis of osteoporosis with respect to women, but also fewer men receive adequate treatment.

Of note, relatively few studies assessed the effect of drugs used for osteoporosis in men and very few of them provided data on reduction of fractures.

Hence, male osteoporosis deserves more attention, and it is not correct to directly translate to the male what is known for females. This book highlights some of the more interesting aspects dealing with gender differences in pathophysiology, clinical aspects, diagnosis, and treatment of male osteoporosis.

Part I

Introductory Remarks

Introduction: Gender Differences in Osteoporosis: From Research to Treatment

1

Carlo Foresta

Osteoporosis is a systemic bone disease characterized by a slow but progressive decrease in bone density that results in micro-architecture deterioration, which predisposes to fractures. Fractures are indeed a major concern for the health of individuals, with common fragility fracture sites being found in the hip, spine, and wrist. In 2010 in Europe, there were 22 million women and 5.5 million men with osteoporosis, accounting for 2% of the overall burden of noncommunicable diseases [1]. The mortality associated with major osteoporotic fractures is substantial, with 20% mortality from hip fractures within the first year [2, 3].

Too often, clinicians and the general population believe that the decline in bone density and its complications solely affect postmenopausal women, which may create health disparities. While effectively less common in men than women, over eight million men in the United States have low bone mass or osteoporosis [4, 5], and a study showed a comparable prevalence of osteoporosis for men aged 70 years or older and women aged 65 years [6]. Indeed, osteoporosis and its complications affect both genders, but at different ages and rates [7]. Osteoporosis is four times more common in women than in men, but some evidence indicates that men tend to have more osteoporosis-related complications. The mortality rate associated with hip fractures [8, 9], as well as vertebral and other major fractures [10], is higher in men than in women. In addition, men are even less likely than women to be evaluated or receive antiresorptive therapy after a hip fracture (4.5 versus 49.5%, respectively) [11–13].

Because of the morbid consequences of osteoporosis, the prevention of this disease and its associated fractures is considered essential to the maintenance of health, quality of life, and independence in the elderly population. Despite increasing evidence suggesting the need for reconsidering gender differences in osteoporosis, this

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Table 1.1 Summary of the osteoporosis screening recommendations

Organization	Recommendations	
	Women	Men
National Osteoporosis Foundation	All women >65 years and postmenopausal women with risk factors	All men >70 years or men aged 50–69 years with risk factors
International Society for Clinical Densitometry		
Endocrine Society		
World Health Organization	Women >65 years old	No recommendation
American Association of Clinical Endocrinologist		
United States Preventive Services Task Force		
American Academy of Family Physicians		
Canadian Osteoporosis Society	Women >65 years	Men >65 years
American College of Physicians	Assess the risk factors and consider DXA scan for those at risk for osteoporosis	
UK National Osteoporosis Guideline Group		

disease is still underestimated in men, and screening programs are typically not suited for the male population. Indeed, screening recommendations from health-related scientific societies and organizations vary, and few have clear guidelines for osteoporosis screening in men (Table 1.1). Although screening guidelines vary by organization, most rely on age and the identification of other clinical risk factors to identify males at risk for fracture. In the United States, the NOF [14], the Endocrine Society [5], and the International Society for Clinical Densitometry [15] guidelines are consistent in recommending a DXA scan for men aged 70 years and older and in younger men with prior fractures or other risk factors. In particular, the NOF guidelines recommend screening in men under the age of 70 years if they had glucocorticoid exposure or a prior fracture. The Endocrine Society recommends screening in males younger than 70 years if they have risk factors such as prior fracture, low body weight, and smoking, and the International Society for Clinical Densitometry guidelines include prior fracture or disease or medication associated with bone loss or low BMD. The Osteoporosis Canada recommends BMD screening for males aged 65 years and older and in younger men with risk factors, including prior fracture, use of glucocorticoids or other high-risk medications, high alcohol intake, smoking, and diseases associated with rapid bone loss, fracture, or osteoporosis [16]. The NOGG 2013 guidelines recommend the assessment of the 10-year major osteoporotic fracture probability in men aged 50 years and older using the UK Fracture Risk Assessment Tool (FRAX), an absolute risk assessment tool, with BMD testing suggested based on age and fracture probability using predetermined assessment thresholds [17].

Despite these recommendations, few studies showed what can be best described as disparities for males regarding the osteoporosis screening. In a

study that evaluated 8262 patients who were eligible for osteoporosis screening based on the age criteria, 60% of the women and only 18.4% of the men had undergone DXA. Another study evaluated the osteoporosis screening rate for 310 male patients, aged 70 years or older, in a primary care clinic setting [18]. Only 11% of the eligible men, based on age, had undergone a DXA scan, and the majority of the screened men were 80–89 years of age, while none of the men aged >90 years had undergone a DXA scan. Another retrospective study evaluating the rate of osteoporosis screening in high-risk patients aged 50 years and older reported that only 10% of women and 9% of men had undergone a DXA scan for osteoporosis [19]. A similar study evaluated the screening rate among 363 patients aged 50 years and older who had history of atraumatic hip fracture, and only 11% of men and 27% of women had undergone a DXA scan within 5 years before the fracture [13]. It is still unclear why men tend to be offered less screening than women or whether males tend to be less prone to participate in health screenings. The older age of onset, the high amount of comorbidities that such patients may have, and the physician's and patient's lack of awareness in part may explain this phenomenon [18]. In summary, clinicians need to improve osteoporosis screening among eligible individuals, and in general, men tend to be under-screened for osteoporosis compared with women.

Another issue of paramount importance is osteoporosis diagnosis criteria in the male population. In facts, in clinical practice DXA remains the best diagnostic tool to assess BMD, while peripheral quantitative computed tomography (pQCT) or bone ultrasound still have a role only in a research or screening setting [20]. On the other hand, X-ray is the simplest diagnostic tool to identify vertebral fractures at first-line examination. The criteria for the diagnosis of osteoporosis in men are still controversial. In particular, the site of BMD measurement and reference ranges for male subjects has not been established [21]. According to the US National Osteoposoris Foundation and the Endocrine Society, the recommended site of DXA measurement is the hip and spine [5], while the Osteoporosis Canada recommended to use the lowest *T*-score value for the BMD measured at the lumbar spine, total hip, or femoral neck [16]. A *T*-score equal or < -2.5 SD at the femoral neck is considered as the reference standard in men by the WHO and the UK National Osteoporosis Guideline Group [17, 22, 23]. For the diagnosis of osteoporosis in men, the use of sex-specific references ranges for BMD appears to be the most appropriate approach [5, 24]. However, even using gender-specific femoral *T*-score at femoral neck, a significant number of men with osteopenia or normal BMD suffer from vertebral, non-vertebral, and hip fracture [25]. Actually, it should be kept in mind that BMD measurement only represents a surrogate marker of fracture risk [26]. In this context, the Fracture Risk Assessment Tool (FRAX) can be useful in predicting fracture risk in men. Moreover, it is useful to decide whether to start a treatment [27]. Threshold for starting a specific treatment has not been established yet. To date it has been suggested that a 10-year risk of hip fracture equal or >3% or a 10-year risk of major osteoporotic fracture equal or >20% at FRAX score in men aged 50 or older with low bone mass (osteopenia or osteoporosis) at femoral neck, total hip, or lumbar spine by DXA can represent a proper criteria to start a treatment for

osteoporosis [28] On the other hand, it should be noticed that in men younger than 50 years, there is no evidence to suggest treatment thresholds based on FRAX score.

The main goal of treating men with osteoporosis is to eventually decrease their risk of osteoporotic fractures; however, most studies in men have addressed only surrogate endpoints such as BMD. First-line approach includes general lifestyle measures such as smoking cessation, reduction in alcohol intake, and weight-bearing exercise. These suggestions are pretty much the same as the ones adopted for women for fracture prevention. Nevertheless, lifestyle changes can have a significant impact in the male population given its higher prevalence of smoking habit and alcohol abuse compared with women. As regards antiresorptive treatment, it relies mostly on data obtained from studies on women. Although, several agents have been tested in randomized controlled trials in male subjects with primary or secondary osteoporosis, unfortunately they are usually short-term trials, enrolling small samples, and in most of them, the primary end point is the change in BMD. In general, antiresorptive treatment increase bone density in osteoporotic men, but few data about fracture risk are available [29]. In facts, only zoledronate has been reported to reduce fracture risk in men with low bone density [30].

Taken altogether, there is limited evidence about the effects of therapies for osteoporosis in the male population, and the few studies available cannot be considered conclusive about the drug effect on fracture risk. Thereby, further studies are needed to better understand the pathogenesis of male osteoporosis, define proper diagnostic criteria in male sex, and clarify the long-term anti-fracture potential of pharmacological agents. This is also important because, in contrast to women, osteoporosis in men is more frequently secondary rather than idiopathic, and in such cases rationale treatments could be offered (e.g., testosterone treatment in hypogonadal men). Again, no studies addressed this point especially in terms of fracture prevention.

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Anatomy and Histology of Male Skeletal Tissue: Gender Differences

2

Maria Grano, Giacomina Brunetti, Graziana Colaianni, and Silvia C. Colucci

2.1 Introduction

The skeleton is a rigid and complex structure formed by 206 bones different in shapes and sizes. Based on the shape, bones can be divided into four groups: long bones, which are longer than wide (i.e., femur, humerus, and tibia); short bones, comparable in diameter and length (i.e., the carpal bones of the hand); flat bones, thin and plate-like (i.e., the sternum and the skull); and irregular bones having a peculiar shape which makes them not included in the previous groups (i.e., vertebrae). Many are the functions that skeleton provides: protection of internal organs, levers for muscles during locomotion and mineral reservoir for phosphate, calcium, and carbonate. Although males' and females' skeleton deserve the same function, it has a sexual dimorphic phenotype, because it is larger and more robust in men compared to women. In the following paragraphs, we will describe the different structure of male's and female's skeleton together with the possible mechanisms sustaining the dimorphic phenotype, which are mainly linked to sex hormones.

2.2 General Structure of Bone

Bone tissue is a specialized connective tissue characterized by a mineralized extracellular matrix comprising organic and inorganic components. Bones, covered by the outer fibrous membrane the periosteum, are made by an external layer, the

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cortical bone, and an internal portion, trabecular or spongy bone. Cortical bone, which accounts for about 80% of the skeleton, is solid and compact and includes the shell of the vertebrae, long bones, and the surfaces of flat bones (e.g., cranium or the pelvis). At the microscopic level, cortical bone is organized to form osteons or Haversian systems, shaped by cylindrical concentric layers of lamellae surrounding a central canal, the osteonal (Haversian) canal, which contains the vascular and nerve supply. Trabecular bone, mainly located inside the ends of long bones (the epiphysis), vertebrae, and flat bones, is characterized by interconnected plates and strands of bone tissue, which describes a network of irregular areas surrounding the bone marrow and giving it a spongy appearance [1–3].

The skeleton of mammals grows in three dimensions. The longitudinal growth (*Z*-axis) is mediated by chondrocytes at the epiphyseal growth plates. The appositional growth (*X*- and *Y*-axis), the outward bone expansion, is mediated by osteoblasts, the bone-forming cells, at the periosteal surface, simultaneously with bone resorption mediated by osteoclasts, the resorbing cells, at the endosteal surface. Since bone growth is differently regulated in men and women, it determines sexual dimorphism in bone size and strength, which will have a considerable impact on fracture risk in elderly [4, 5].

2.3 Male Skeletal Tissue Characteristics in Childhood and Adolescence

2.3.1 Differences in Longitudinal Growth and Final Stature

In humans, differences in the skeleton size are well represented by stature, which averages around 7% higher in males [6]. This dimorphism appears more evident during postnatal growth; in fact at birth, male neonates are only 1% taller than females [7]. The key determinant of ultimate height is the later onset of puberty, which occurs 2 years later in men, allowing more time for prepubertal growth [8, 9]. Also, the highest peak of height growth velocity [10] and the delay of growth plate closure [11] are responsible for the higher stature of man compared with women, but their effects are considerably smaller than onset of puberty.

2.3.2 Differences in Peak Bone Mass

Bone strength is determined by the acquisition of peak bone mass in adulthood and the subsequent bone turnover in the cortical and trabecular compartment. Males reach higher peak bone mass that decreases slower during aging compared with females [12, 13] (Fig. 2.1).

Moreover, there are also time- and site-specific differences between sexes. In men, bone mineral content (BMC) peaked at ages 21–22, with respect to ages 23–28 in women, and it is greater at the femoral neck, distal radius, and lateral spine [14].

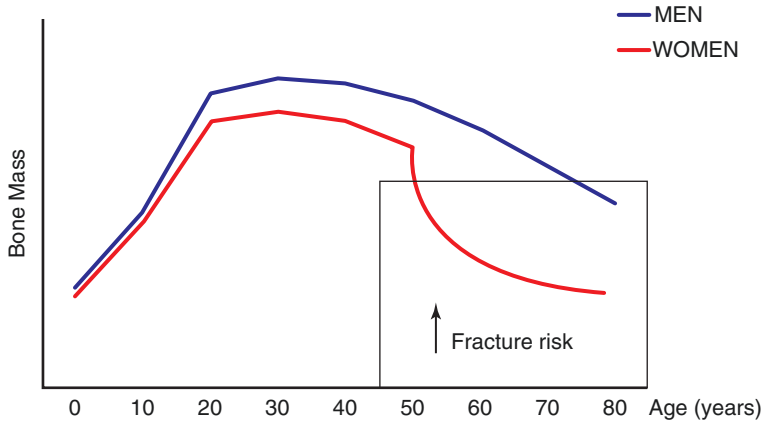

Fig. 2.1 As illustrated in Fig. 2.1, men and women reach their peak bone mass between the ages of 20 and 30. After 45 years of age, there is a gradual decline for men, whereas there is a sharp drop of bone mass in women due to the menopause. Therefore, the fracture risk period can begin at 45 years in women and around 75 years in men

Due to greater periosteal apposition, men have a greater *cortical* bone diameter than women, and this explains why bone in men are more resistant to fracture, given that bone strength is expressed as the fourth power to bone diameter independently of cortical thickness [4]. In addition, the marrow cavity is wider in men, with outward bone expansion and a mild increase in cortical thickness [15]. Endocortical resorption is higher than endosteal apposition in both sexes, but to a lesser extent in females, thus explaining the reduced expansion of their marrow cavity [16]. At the same time, men display lower cortical bone mineral density (BMD) and higher intracortical porosity [4] that coincide with a higher peak incidence of fractures in young men versus women, in particular during the rapid bone growth in childhood and most frequently at the radius [17]. However, despite reduced cortical BMD and higher cortical porosity, the larger cortical bone diameter gives young adult men a greater ultimate failure load compared to women [18].

Regarding *trabecular* bone, men develop greater trabecular bone volume during late puberty, particularly at the distal radius and tibia, mainly due to greater trabecular thickness at the radius and trabecular number at the tibia [19]. However, an opposite situation is observed in the axial skeleton, in which men show a lower trabecular BMD than women in spite of their wider lumbar spine [20, 21].

2.4 Male Skeletal Tissue Characteristics in Adulthood

After reaching peak bone mass, there is a greater periosteal apposition in men than in women, who instead show a greater endosteal resorption [22]. These two opposing, combined actions determine as net effect the higher *cortical* thickness observed in men. Nevertheless, the gender-specific process of thinning cortical bone is also

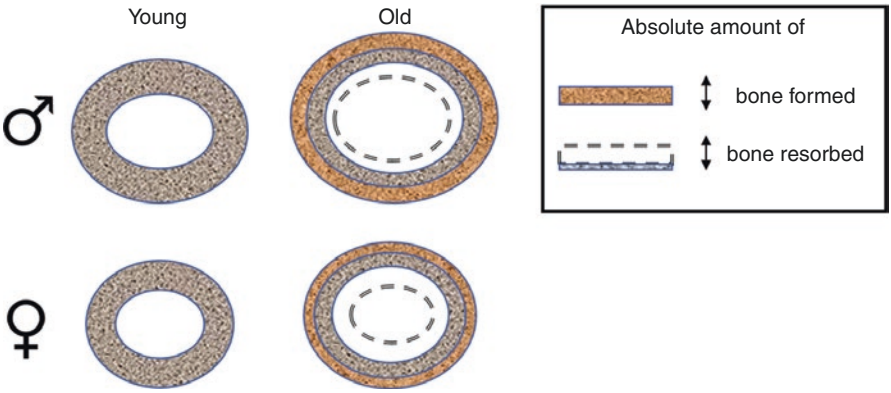

Fig. 2.2 Schematic representation of cortical bone in male and female around the age of peak bone mass (20 years old) and old age, showing that differences between sexes become increasingly greater with aging. The brown circles represent periosteal expansion, and the double dashed line indicates ongoing endosteal bone resorption, in both genders at old age

different depending on the analyzed bone site. At the radius, men aged from 20 to 90 years show 8% decline in cortical area compared with a 17% decrease in women, due to a higher periosteal expansion at the radius in men [21]. At the tibia, men gain more bone mass than women until age 60–70 and continue to increase their cortical bone area. Conversely, women loose cortical bone area from age 50, due to a higher endosteal expansion at the tibia, and after age 70, they have a wider marrow cavity than men, due to the increased endocortical resorption that exceeds periosteal expansion, although the latter is slightly higher in women than in men [23] (Fig. 2.2).

From the fourth to sixth decades of life, *trabecular* bone volume fraction can decline by up to 40–50% for sexes, although there is an exception during lactation, when the skeleton of the mother loses ~120 g of calcium, in favor of the fetal and postnatal bone growth, which corresponds to a reduction of 3–10% in bone mineral content in lumbar spine, hip, femur, and distal radius. This rapid bone loss, at the rate of 1–3% per month, is also mediated by mammary gland-derived parathyroid hormone related-protein (PTHrP) in combination with low estrogen levels to facilitate the maternal hyper-resorption and intergenerational calcium transfer [24]. However, this bone loss is transient, and after a 6-month period, the mother's skeleton is rapidly restored.

2.5 Skeletal Sexual Dimorphism

2.5.1 Sex Steroid Signaling in Bone

Bone geometry, BMD, and bone turnover in men have been related to numerous hormones (e.g., primarily sex steroids, but also GH [25–27], PTH [28], vitamin D

[29, 30], and thyroid hormone [31, 32]), cytokines (e.g., RANK/RANKL/OPG) [33, 34], oxidative stress, as well as classical aging pathways [35].

In general, it has been reported that androgens are essential for skeletal sexual dimorphism in development and aging, even if they possibly show key indirect actions on bone through aromatization, oxidative stress [36], proinflammatory cytokines [37, 38], and growth factors (e.g., transforming growth factor (TGF)-β, IGF-1) [39–41]).

Androgens and estrogens are derived from cholesterol and are synthesized in the gonads and the adrenal glands. In men, about 15% of estradiol (E2) is produced directly from the testes, whereas the other 85% is the result of androgen peripheral aromatization [42]. Interestingly, in old men total E2 levels remain a sufficient level to maintain skeletal homeostasis [43–45]. Testosterone, the main circulating androgen, produced by the Leydig cells of the testicles, works unmodified or following conversion to the more potent dihydrotestosterone (DHT). Testosterone can also be converted to E2 by the aromatase (CYP19A1) enzyme. The serum levels of estrogens and androgens are regulated by follicle-stimulating hormone (FSH) and luteinizing hormone (LH) through hypothalamic-pituitary feedback. In humans, the bioavailability of estrogens or androgens is controlled by the binding to circulating sex hormone-binding globulin (SHBG) [46]. Only 1–5% of circulating free-fraction DHT, testosterone, and E2 is supposed to be biologically active.

The effects of estrogens and androgens on bone developed following the binding to the estrogen receptor (ER) α and β and the androgen receptor (AR), respectively.

Basal sex steroid serum levels are regulated by catabolic enzymes. In the Swedish MrOS study, it has been reported that androgen metabolites correlated with male BMD, but not testosterone levels [47]. Polymorphisms in the enzymes catechol-*O*-methyl-transferase (COMT, an estrogen-degrading enzyme) and uridine diphosphate glucuronosyltransferase 2B7 (which inactivates mainly androgens but also some estrogens) have been linked to high sex steroid levels and bone geometry in young men [48–51]. Other authors found that only in men the COMT polymorphism is related to fracture risk [52]. Although these reports are very interesting, further studies are needed to better explore the role of steroid-metabolizing enzymes on bone.

2.5.2 Sex Steroid-Regulated Longitudinal Bone Size

In men the late estrogen-mediated closure of epiphyseal growth plate cartilage is involved in greater bone length. Testosterone also supports height velocity primarily through the aromatization and estrogen-mediated GH secretion. On the other hand, in boys non-aromatizable androgens augment growth rate without changing the serum levels of GH/IGF-1, perhaps through IGF-1 signaling in the growth plate and the AR in chondrocytes [41, 53]. Consistently, in men with inactivating ERα mutations [54] or aromatase deficiency [55–58], pubertal height velocity acceleration and subsequent growth plate closure seem to disappear, thus favoring the continuous growth.

2.5.3 Estrogen Deficiency: The Primary Reason of Bone Loss in Older Hypogonadal Men

Low testosterone levels in hypogonadal men determined augmented risk of osteoporosis and fractures [59, 60]. Interestingly, in 1998, scientists from the Mayo Clinic suggested the key role of estrogen in the pathogenesis of osteoporosis both in men and women [61]. In fact, in numerous reports, low E2 levels have been linked to bone loss in men [62–64], but not in younger men [65, 66]. Nevertheless, several complimentary lines of evidence [67–71] confirm that estrogens are crucial to restrain bone turnover in aging men.

In general, it seems that estrogens are more important compared with androgens in preserving bone health in aging men. However, low testosterone and high SHBG serum levels may represent supplementary disadvantages. Free or bioavailable testosterone has been linked to the cortical BMD, bone area, as well as to hip, vertebral, and non-vertebral fractures in older men [66, 72–74]. In the same way, increased risk for hip fractures has been described in men with both reduced E2 and testosterone [75]. Furthermore, in mice it has been shown that the best effects of testosterone are linked to a functional AR [76]. Consistently, in a male patient with simultaneous aromatase deficiency and low testosterone, it has been shown an additive effect by testosterone and E2 replacement therapy [77].

2.6 Contributions of Androgen and Estrogen Receptors on Cortical Versus Trabecular Bone

Even if observational studies in humans are essential to establish the role of sex steroids on male bone, the understanding of the respective involvements of AR and ERs is linked to the use of knockout (KO) animal models together with studies on rare human genetic diseases. Information derived from these studies highlighted the great complexity about AR and ER roles in diverse bone compartments.

Both AR and ERα are necessary for a good periosteal bone growth [78, 79]. Otherwise, for optimal trabecular bone development, AR is the only responsible [78, 79]. In fact, trabecular bone mass decreased in androgen receptor knockout (ARKO) and increased in estrogen receptor α knockout (ERαKO) [80, 81], whereas in combined AR/ERαKO, it was similar to ARKO alone [78]. Additionally, with respect to wild-type female mice, male pubertal ARKO animals displayed equivalent length, reduced trabecular bone, and similar cortical bone indexes, implying that androgens are necessary for bone development but not for longitudinal growth [82]. Similar findings were found in humans: Therapy with estrogen in young men with aromatase deficiency positively affects cortical area and thickness, without affecting trabecular vBMD [56]. Additionally, ERα affects trabecular bone formation, ERβ influences female bone health [80, 83, 84], but male ERβKO mice have normal bones and ERαβKO does not show difference to ERαKO alone [85].

2.7 Effects of Sex Hormones on Bone Cells

2.7.1 Androgens Affect Osteoblasts and Osteocytes, and Estrogens also Target Osteoclasts

In vitro experiments from ARKO mice have suggested that AR controls mainly osteoblasts but indirectly also osteoclastogenesis [86]. Otherwise, experimental evidences suggested that ER signaling directly targets osteoclasts. These aspects are detailed below.

2.7.2 Androgen Receptor in the Osteoblast Lineage

AR levels augmented during osteoblast differentiation towards osteocytes [87] with a key direct role in all cells of osteoblast lineage, as suggested by the different rodent models described below. In detail, using osteocalcin-Cre-driven ARKO, it was found that androgens work through the AR in mineralizing osteoblasts to preserve bone by modulating bone resorption and coordinating bone matrix synthesis and mineralization [88]. Col2.3-Cre-driven ARKO displayed that mature osteoblasts are involved in the maintenance of trabecular bone, but not of periosteal apposition [89, 90]. In this murine model, the lack of effects on periosteal apposition is probably because the periosteum contains more pre- and proliferating osteoblasts. Indeed, in another murine model with AR, overexpression in immature osteoblasts increases periosteal and decreases endosteal bone formation [91]. Additionally, in Dmp1-Cre mice lacking AR in osteocytes, it was reported a moderate impairment of trabecular bone maintenance [87].

2.7.3 Androgen Receptor and Estrogen Receptor Alpha in Osteoclasts

Androgens and estrogens inhibit bone resorption in trabecular and endocortical bone by diminishing the number of osteoclasts. This is due to the reduction of osteoclast differentiation and life-span. Interestingly, male mice with targeted ERα deletion in mature osteoclasts (by cathepsinK-Cre) show no variation in osteoclast number or trabecular bone mass, indicating that direct effects of estrogens on osteoclasts play no role in the maintenance of trabecular bone in males [92, 93]. Although the expression of AR in human osteoclasts is widely debated, its expression in rodent osteoclasts is well established [41, 94, 95], and some authors reported that androgens also directly suppress in vitro osteoclastogenesis [41, 94, 96–98]. It has been reported that testosterone and DHT in vitro reduce osteoclast differentiation and increase FasL-mediated apoptosis [92]. However, mice with osteoclast-specific AR deletion display no alterations in osteoclast number or bone mass [93, 99]. Conversely, AR signaling has indirect effects on osteoclasts, such as by regulating cytokine production in bone marrow stromal cells [37]. This indirect effect is

highlighted by different in vivo studies. In detail, mice with target deletion of AR in osteoblasts show increased trabecular osteoclast number but no differences in osteoblasts [93, 100, 101]. In addition, the expression of RANKL and OPG are not changed by AR deletion both in osteoblasts and osteocytes [87], indicating that other cytokines are accountable for the anti-resorptive outcomes of androgens on trabecular bone. In female mice with AR, target deletion in mesenchymal progenitors or mature osteoblasts determines the reduction of trabecular bone mass, but this achievement is less marked than males [93, 100, 101]. On the other hand, transgenic mice overexpressing AR display increased trabecular bone volume [90].

2.7.4 Estrogen Receptor Alpha in Osteoblasts

Numerous studies by different murine models have established that ERα affects osteoblast and osteocyte activity. It has been shown that osteoblast-specific overexpression of aromatase increases bone mass in male mice [102]. Prx1 Cre mice have been used to selectively excise ERα from pluripotent mesenchymal progenitors and osterix-Cre mice to perform Erα deletion in osteoblast progenitors, respectively. These mice mainly showed cortical bone deficits resulting from decreased periosteal bone formation, although cortical bone deficits were overcome during adulthood in Prx1-Cre ERαKO males [103]. Deletion of ERα using the Col1a1 deleter did not affect cortical or trabecular bone. However, this should not be taken as evidence that ERα has no role downstream in osteoblast differentiation. Indeed, osteocalcin-Cre ERαKO decreased trabecular bone in males and both trabecular and cortical bone in females [100, 101]. Dmp1-Cre ERαKO males also showed decreased bone formation and less trabecular bone, but there was no effect on cortical bone, or any effect in females. The authors concluded that the trabecular bone-sparing effects of estrogens are mediated by osteocyte ERα in males and probably by osteoclast ERα in females [104].

Studies on osteocytes, the cells responsible of mechanotransduction in bone, have shown that although both ERαKO [105] and ARKO [106] mice are sensitive to mechanical loading, osteocyte-specific ERαKO and ARKO mice are not sensitive to it, indicating that sex hormones act indirectly on osteocytes in the loading response [87, 104].

In summary, these studies in male mice suggest that both AR and ERα are required for optimal cortical bone expansion via actions in immature osteoblasts and trabecular bone maintenance via actions in more differentiated osteoblasts and osteocytes.

2.8 Indirect Effects of Androgen Receptor and Estrogen Receptors on Bone Via Muscle, Fat, and the Nervous System

The interaction of bone with muscle, adipose, and neural systems is increasingly studied with very interesting findings.

2.8.1 Bone-Muscle Interaction

Male ARKO mice showed altered muscle development [107], and additional ERαKO further reduces muscle mass [78]. It has been shown that muscle-specific ARKO mice did not display impaired bone remodeling, but they showed a small decrease of peripheral skeletal muscle mass. This effect may be because only perineal muscles show high AR levels and androgen modulation in mice [108, 109]. This is in contrast with the well-established anabolic actions of androgens on human muscle.

2.8.2 Bone-Fat Interaction

Clinical data support a positive correlation between bone and fat, primarily in females, probably because adipocyte aromatase activity controls circulating E2 levels [110, 111]. Fat mass is mainly controlled by estrogens as AR-ERα double knockout mice have similar adiposity with respect to ERαKO alone [78], even if androgens also show a lipolytic activity, and male ARKO mice display augmented adiposity [112]. Moreover, a link among insulin, glucose, and bone remodeling has also been proposed in mice, and the impairment of male bone metabolism is observed in the metabolic syndrome and diabetes.

2.8.3 Central Nervous System Control of Bone Mass

Central nervous system affects bone mass. Neuron-specific ERαKO mice display augmented bone formation through leptin [113]. In the nervous system of mice, conditional inactivation of AR alters the somatotropic axis as demonstrated by growth retardation and reduced serum IGF-1, without relative differences in total bone mass or body composition [114]. Thus, the skeletal sexual dimorphism resulting from sex steroids is dependent on indirect effects via growth hormone, IGF-1, and IGF binding proteins in the brain, bone, and liver [39, 40, 115].

2.9 Conclusions

The musculoskeletal system is more vigorous in men, and sex steroid signaling is fundamental for this sexual dimorphism. In particular, in young adulthood, androgens support trabecular bone development and thickness, in midlife cortical consolidation, and in older men the preservation of cortical thickness and trabecular bone volume. Furthermore, albeit in men estrogen deficiency also represents the principal mediator of hypogonadal bone loss, high SHBG and low testosterone possibly represent additional disadvantages. Numerous reports using knockout murine models have developed the knowledge about the role of AR and ERα in osteoclasts, osteoblasts, and osteocytes to cortical and trabecular bone development and

homeostasis. In parallel, they have supported the idea that sex steroids also indirectly affect bone remodeling, i.e., through interaction with the nervous system, IGF-1, and altered response to mechanical loading.

At the end of skeletal maturation, men achieve greater peak bone mass and greater long bone width and cortical diameter. From the mechanical point of view, the increased diameter gives bone a more advantageous spatial distribution, having the cortex placed farthest from its neutral axis. Therefore, these higher peak bone mass and bone strength, together with the lowest amount of bone loss during life, are the reasons why men have a lower incidence of osteoporotic fractures in elderly.

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Physiology of Bone Mass Acquisition and Pathophysiology of Bone Mass Loss: Gender Differences

3

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3.1 Physiology of Bone Mass Acquisition: Gender Differences

Bone is a highly dynamic tissue that responds and adapts to changes in systemic signals, including hormones, as well as mechanical strains. During the intrauterine development and postnatal growth, bones are sculpted to achieve their unique shapes and sizes. In parallel, they adapt the spatial distribution of their mineralized mass to the prevailing loads, in order to maintain the best mechanical performance with as little weight as possible [1]. This is accomplished by the resorption of bone from one site and formation in a different one, a process defined as modeling [2]. During modeling, the cortical bone envelop enlarges and thickens. This is due to the fact that osteoblast-mediated bone apposition at the periosteal envelope exceeds the widening of the medullary cavity by endocortical resorption, mediated by the activity of osteoclasts.

Bone growth accelerates during puberty, in concert with peak height velocity, which corresponds with puberty in males and menarche in females. This is followed by peak total bone mineral content accrual velocity, which coincides with menarche in females and presents a 0.7 year lag in males. The disparity in the timing of bone growth and mineralization may justify the increased risk for fractures described in growing adolescents. The higher fracture rates and the later male incidence rates peak in boys than in girls can be explained by the older puberty age, the lag in the peak of total bone mineral content accrual velocity, and the greater length growth present in males [3].

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Before puberty in both sexes, bone modeling is characterized by long bone length growth. The bone shaft widens due to the periosteal bone apposition and to the endocortical resorption that excavates the medullary canal. Since the periosteal apposition exceeds the endocortical resorption, the long bone cortex becomes thicker. Until puberty there is little difference between the sexes in this process. After puberty, estrogens in females inhibit periosteal bone formation, thereby limiting the diameter of the bone, and increase the endocortical surface. In boys, pubertal androgen production enhanced both the periosteal apposition and the endocortical bone resorption, therefore leading to the development of wider bones with proportionally thicker cortex as compared to girls [3, 4].

This differences in bone size between boys and girls represent the major contributor to the sex differences in bone strength. Indeed, since the bone strength scales as the fourth power to bone diameter, independent of cortical thickness, and men have larger bone than women, the bone strength is higher in men than in women [5]. On the other hand, volumetric bone mineral density (BMD), which is defined as the amount of mineral per unit volume of bone, is not different between the two sexes for both axial and appendicular skeletons [3, 4]. Young adult men have a higher peak of bone mass than women due to an almost 25% greater whole body bone mineral content [6], due to the fact that their bones are longer and wider, but certainly not denser. In keeping, studies by high-resolution peripheral quantitative computed tomography confirmed that the gender differences are minimal or absent in prepubertal children and that men have a greater cortical bone diameter due to greater periosteal apposition, placing the cortex further away from the neutral axis, with a wider medullary cavity [4]. These studies showed that during puberty in both sexes, the endocortical resorption is enhanced, and the marrow cavity increases, but at a lesser degree in females than in males [4]. Moreover, young adult men appear to have slightly but significantly lower cortical volumetric BMD and higher intracortical porosity that, especially during rapid growth, can be associated with the peak incidence of fractures in childhood, typically at the radius and more frequently in boys [7].

Androgens not only act directly on bone through the androgen receptor (AR) but also activate estrogen receptor α (ERα) or β (ERβ) following aromatization into estrogens. Both the AR and ERα pathways are crucial for a normal cortical bone expansion, while AR signaling solely is the dominant pathway for normal male trabecular bone development. Interestingly, some evidences from animal studies suggest that in males the estrogen-mediated effects on bone may, at least partially, depend on the interaction with the insulin-like growth factor 1 (IGF1) [8].

In addition, sex hormones and their receptors may have an impact on the mechanical sensitivity of the growing skeleton. AR and ERβ signaling may limit the osteogenic response to loading in males and females, respectively, while ERα may stimulate the response of bone to mechanical stimulation in the female skeleton [9]. It is important to underlie that these evidences come from animal studies and their relevance for bone health in humans is still to be determined. In general, the current evidences suggest that the sexual dimorphism during bone mass acquisition may be

not determined simply by the differences in sex steroid secretion between the sexes but may also depend on gender differences in growth hormone (GH)-IGF1 and mechanical sensitivity to loading.

3.2 Pathophysiology of Bone Mass Loss: Gender Differences

Until recently, it was thought that after the achievement of the bone mass peak, the bone mass was maintained until the middle age, due to a substantial balance between bone resorption and bone apposition. However, recent studies using quantitative computed tomography (QCT) have shown that trabecular BMD loss begins in the third decade of life in both sexes, with a lifetime losses of the trabecular bone at spine of 55% in women and 45% in men [10, 11]. In women, the main trabecular bone loss occurs at the time of menopause (about 20–30%), while the cortical bone loss during the same period of life is definitely lower (5–10%) [12]. In women, after menopause, the cortical bone loss and the trabecular bone loss rates are lower and similar. Since men do not undergo a condition similar to menopause, they do not experience the accelerated trabecular bone loss typical of females in the menopausal transition. Therefore, during the adult life, men lose less trabecular bone than women.

At variance with trabecular bone, cortical bone is substantially maintained in both sexes until middle age, while, thereafter, in both sexes there is a slow lifetime decline of bone mass that is slightly higher in women (28%) than in men (18%) due to the greater cortical bone loss that occurs in women in the perimenopausal and early postmenopausal period [10].

Beside bone mass, a particularly important aspect of the pathophysiology of bone resistance is linked to bone geometry. Indeed, during adult life, there is a limited periosteal apposition and a continued net endocortical resorption. Therefore, although endocortical resorption reduces cortical thickness and area, the concurrent periosteal apposition (even though of minor entity as compared to endocortical resorption) may partially counteract the negative effect of the endocortical resorption on the cross-sectional area of the cortical bone. Most importantly, this mechanism shifts the thinning cortex farther from the neutral axis, therefore relatively increasing the bone strength against both axial compression and bending forces and, thereby, mitigating the reduction of bone resistance due to the absolute cortical thinning and porosity that occur with advancing age [13].

The amount of endocortical bone that is resorbed is similar in men and in women, but since men have a greater periosteal apposition during aging than women, they have less net bone loss [14, 15]. However, the presence of menopause can be considered the main determining factor for the differences in the entity and in the age-related pattern of fracture risk in males and females. Indeed, in women the risk of vertebral, forearm, and hip fractures begins to increase importantly in the perimenopausal period, even if the marked increase in hip fracture incidence occurs approximately at 65 years of age. At variance, in men the increased rates for both vertebral and hip fractures are delayed by about 10 years [16].

3.2.1 Bone Loss in Women

The menopausal-related ovarian failure is characterized by a rapid decline of serum estradiol by 80–90% as compared with premenopausal status. This decrease of estrogen levels alters the balance between bone formation and bone resorption, which is substantially maintained during the adult life before menopause. Indeed, after menopause there is an increase of both bone apposition and bone formation, with the latter overcoming the former. Indeed, as reflected by the indexes of bone turnover, after menopause the bone resorption increases by about 90% and bone apposition by about 45% as compared with the premenopausal period of adult life [17, 18]. In keeping, the activation frequency of the bone remodeling units increases, and therefore, more sites on the bone surface undergo resorption with the osteoclast resorption time being increased and the osteoblastic bone formation time being relatively decreased [19].

The increased osteoclast activity seems to be due to the lack of the inhibiting effect of the estrogens on bone turnover. Indeed, in the presence of estrogens, the receptor activator of nuclear factor-kB (RANK) ligand (RANKL) is inhibited. This molecule is normally expressed on the cellular membrane of bone marrow stromal cells, T cells, and B cells and promotes osteoclast differentiation, formation, and survival after binding to RANK on the membrane surface of osteoclast lineage cells [20]. Beside the inhibitory effect on the RANKL secretion, estrogens increase the expression of osteoprotegerin (OPG) gene and the OPG secretion by osteoblast. Since OPG is a decoy soluble receptor for RANKL, the increased OPG secretion inhibits the osteoclast development [21]. At menopause, and in any situation of diminished estrogen production, OPG decreases and RANKL increases, thereby enhancing osteoclast differentiation, survival, and activity [22].

Another important mechanism by which estrogen regulates bone resorption is related to the ability of estrogens to regulate the expression of several cytokines, such as monocyte colony-stimulating factor (MCS-F), interleukin (IL)-1 and IL-6, tumor necrosis factor α, and prostaglandins [23–27].

In general, the increase in bone resorption may be also due to an indirect effect of estrogen deficiency. Indeed, the lack of estrogen is associated with an efflux of calcium from the reabsorbed mineral matrix to the blood, with a compensatory decrease of intestinal calcium absorption and of renal reabsorption and an overall negative calcium balance [28, 29]. In keeping with the abovementioned pathophysiological mechanism, several studies have shown that estrogen substitutive therapy is able to correct the reduced intestinal calcium absorption and renal reabsorption [30].

Recent data have suggested that similarly to what happens with advancing age, the loss of estrogens and androgens may increase the reactive oxygen species (ROS) in bone cells [31]. This suggests that sex steroid deficiency may exacerbate the effect of aging on bone tissue. Studies on mice have shown that the increased ROS levels may reduce osteoblastogenesis and increase osteoclastogenesis and that RANKL and MCS-F promote the accumulation of ROS in osteoclasts. However, in mice preventing the ROS accumulation in osteoclasts can protect against the loss of

cortical bone due to estrogen deficiency but cannot preserve bone by the effects of old age, while preventing the ROS accumulation in cells of osteoblast lineage can protect against the effect on cortical bone of both estrogen deficiency and aging. This suggest that the ROS accumulation can be a crucial mechanism of the age-related bone loss, which is typically characterized by the decrease of bone apposition rather than the increase of bone resorption. However, at present, we still do not know if the effect of estrogens on ROS accumulation is direct or indirect via the attenuation of the osteoblastic production of pro-osteoclastogenic cytokines and whether these findings in mice have relevance in humans [1].

Estrogens have also a significant effect on osteoblasts and, thereby, on bone apposition. Indeed, estrogens promote the differentiation of mesenchymal cells toward the osteoblast lineage and the differentiation of osteoblasts from pre-osteoblasts and decrease their apoptosis. These effects are thought to be due to an increased production of insulin-like growth factor 1 (IGF-1) and transforming growth factor-β, directly promoting the Wnt signaling pathway, which is considered a main determinant of osteoblast differentiation and activity. On the other hand, estrogens may decrease the osteocyte production of sclerostin, which is a potent inhibitor of Wnt signaling, thereby further stimulating the Wnt pathway [32, 33].

Some data have shown that the levels of follicle-stimulating-hormone (FSH), which typically increases after menopause, were associated with the changes in bone turnover markers and of hip BMD more strictly than estradiol levels [34]. This finding was supported by data on a mouse model of osteoporosis, and it suggested that FSH may exert a direct effect on bone cells. However, more recent data on postmenopausal women were not able to confirm an important role of FSH levels in postmenopausal-related bone loss [35].

Finally, even though previous data showed that the testosterone concentrations were not associated with the postmenopausal bone loss, more recent evidences suggested that in postmenopausal women the estrogens derived from the aromatization of adrenal androgens are likely to be important for bone health. Indeed, women treated with aromatase inhibitor for breast cancer experience an increase of both bone loss and a relatively BMD-independent risk of vertebral fracture, the latter probably due to a deterioration of bone microarchitecture [18, 36].

3.2.2 Bone Loss in Men

During adulthood and in particular with aging, men lose about 50% less bone than women and have approximately 30% less fragility fractures. As abovementioned, also in men the trabecular bone loss begins in the third decade of life shortly after the achievement of the bone mass peak, therefore independent of gonadal sex steroid levels, which at that time are within the normal range. At variance with women at the menopausal age, during adulthood men do not experience a rapid reduction of sex steroid levels, while they have a progressive increase of sex hormone binding globulin (SHBG) levels double during life-span. The aging-related SHBG reduces the levels of bioavailable testosterone (composed by free and albumin-associated

testosterone) by about 66% during the life-span, and therefore, most importantly for bone health in males, the aromatization-derived estrogen levels decrease by about 50% with aging [37]. Indeed, several studies demonstrated that even in men the estrogen levels, rather than the testosterone ones, are crucial for bone health. For example, in men with estrogen or testosterone or both sex steroid deficiency, the replacement therapy with estrogen but not with testosterone is able to correct the increased bone resorption due to hypogonadism. In addition, in men estrogen replacement can even correct the reduced bone apposition, which is typical in males with both estrogen and testosterone deficiency [38]. In keeping with bone turnover data, several studies have shown that BMD in men correlates more closely with bioavailable estradiol levels than with testosterone levels and that in men trabecular and cortical bone begins to decrease when estradiol levels fell below 15 pg/mL [39, 40].

However, even though also in men estrogens seem to play a major role on skeletal health, and estradiol concentrations are more predictive of the age-related bone loss in men, testosterone levels may anyway have an importance. Indeed, men with both low estradiol and low testosterone levels seem to be at greater risk for hip fracture as compared to men with low estradiol levels and normal testosterone levels or to men with low testosterone levels and normal estradiol levels [40]. In keeping, some data have suggested that similarly to what happens during puberty, even during aging, testosterone can be important for the periosteal cortical bone apposition [15].

3.3 Conclusions

Collectively, data on the physiology of bone mass acquisition show that in men androgens are solely responsible for trabecular bone growth and stimulate periosteal apposition, but estrogens are crucial for cortical bone development. In women estrogens are critical for trabecular bone growth, but inhibit periosteal apposition. The skeletal dimorphism appears at puberty and may be determined by an independent and time-specific effects of sex steroids and GH/IGF-1 levels. Finally, the interaction of sex steroids and their receptors with the adaptive response of bone to mechanical stimulation may potentially play a role.

During adulthood, in both sexes the trabecular bone loss begins in the third decade of life, while cortical bone is substantially maintained until middle age. However, in women the main trabecular bone loss occurs at the time of menopause, while the cortical bone loss during the same period of life is definitely lower. After menopause in women the cortical bone loss and the trabecular bone loss rates are lower and similar. Men do not experience the accelerated bone loss typical of females in the menopausal transition.

The mechanisms underlying the bone loss in women at menopause are mainly related to an increased osteoclast activity due to the lack of the inhibiting effect of the estrogens on bone turnover. The reduction of estrogen levels leads to an increase of pro-osteoclastogenic cytokines, such as RANKL, MCS-F, IL1, and IL6, and to an

increase of ROS accumulation. After menopause, this latter mechanism may impair osteoblast activity, and thereby, it may be crucial for the age-related bone loss, which is typically characterized by the decrease of bone apposition rather than the increase of bone resorption. The effect of the lack of estrogens in diminishing the osteoblast differentiation by influencing the Wnt signaling pathway may be a further mechanism explaining the bone loss in women after the menopausal period.

Even in men estrogens (derived from the androgen aromatization) play a major role in maintaining the bone health during adulthood. In men the age-related bone loss seems to be related to the increase of SHBG levels and to the consequent decrease of bioavailable testosterone that reduces the estrogen levels. However, a direct effect of testosterone on periosteal bone maintenance can be hypothesized.

Finally, in both sexes the mechanisms underlying the pathophysiology of bone loss include even non-sex steroid changes. For example, the decrease of the frequency and amplitude of GH secretion may negatively influence osteoblast differentiation and activity. Due to the reduction of GH levels, the IGF1 concentrations decrease with age. Contemporary, the inhibitory IGF1 binding protein 2 levels increase and seem to be negatively associated with BMD in aged adults [41, 42].

Other mechanisms, independent of sex steroid or other hormonal changes, are likely to be involved in the pathophysiology of bone mass loss and may be related to increased cellular senescence intrinsic within cells of osteoblast and osteoclast lineage [43].

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Male Osteoporosis and Imaging

4

Giuseppe Guglielmi, Maria Mattera,
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4.1 Introduction

Osteoporosis is an important and growing health problem worldwide. Although it has been long considered a disease impacting women, epidemiological studies have shown over the years that the classic age-related increase in fractures seen in women is also evident in men [1].

The World Health Organization (WHO) defines osteoporosis as "a systemic skeletal disease, characterized by low mass and micro architectural deterioration of bone tissue, leading to enhanced bone fragility and a consequent increase in fracture risk" [2]. Patients with osteoporosis are usually clinically silent until they experience a fracture. Fragility fractures occur mainly in the spine and hip, and they result in a significant increase in morbidity and mortality and an exponentially grow of the socioeconomic costs [3]. Due to this, the goal of any osteoporosis therapy is the early diagnosis and the prevention of its complications.

Approximately one in two women and one in four men over 50 years of age will have an osteoporosis-related fracture in her/his lifetime, and, for men in particular, this number tends to increase with increasing age [4, 5]. Men, in fact, suffer osteoporotic fractures about 10 years later in life than women, but life expectancy is

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increasing faster in men, having about twice the 1-year fatality rate after hip fracture, compared to women [6].

Nevertheless, male osteoporosis remains an underdiagnosed and undertreated condition.

Over the past decades, several diagnostic imaging techniques have been developed to characterize pathological changes of osteoporosis, to assess bone weakening and fracture risk to an early stage, and to help monitor disease progression and response to therapy. In addition to dual-energy X-ray absorptiometry (DEXA), which remains the reference method for the diagnosis of osteoporosis, 3D techniques such as quantitative computer tomography (qCT) are increasingly used to provide information about the structural and qualitative features of bone. There was also a growing interest about the possibility of using quantitative ultrasonography (QUS) as a noninvasive and quite inexpensive diagnostic technique for the investigation of bone disease.

4.2 Conventional Radiography

Despite the advent of highly accurate quantitative techniques, conventional radiography remains the first-line investigation for the initial evaluation of osteoporosis. It is a cheap and widely available technique for assessing the quality of bone and for identifying deformities and fractures. But conventional radiography provides a subjective quantification of bone density and microstructural changes only when approximately 30% of bone mass is lost, with a consequent poor sensitivity [7, 8].

Radiographs can be helpful in evaluating the secondary causes of osteoporosis: Up to 50% of the men with osteoporosis have secondary causes of osteoporosis [9], such as glucocorticoid medications, hypogonadism, alcohol abuse, smoking, hyperparathyroidism, thyrotoxicosis, and gastrointestinal disease.

The main radiographic findings of osteoporosis are as follows:

- *Altered Trabecular Pattern*

  Cancellous bone responds to metabolic changes faster than cortical bone. The trabecular pattern is well represented in the axial skeleton and the extremities of long bones [10]. The bone resorption first involves the secondary trabeculae, with a relative accentuation of the primary one (the weight-bearing trabeculae), due to a compensatory mechanism or to callus from microfractures. In the advanced stage, even the primary trabeculae are lost, resulting in the translucent appearance of bone on radiographs [11, 12].
- *Cortical Thinning*

  The microstructural changes seen in cortical bone are due to osseous resorption in the three sites of the cortex (endosteal, intracortical, and periosteal) [13]. Each of these layers responds differently to metabolic stimuli and differs according to the etiology. In senile osteoporosis the endosteal envelope is primarily

affected by bone remodeling, resulting in a widening (scalloping) of the marrow canal and thinning of the cortex.

- *Increased Radiolucency*

  Compared to a normal bone, in the osteoporotic bone, there is a reduced absorption of the X-rays due to the decreased mineralization. This causes an increased radiolucency of the bone, which is evident on radiographs when there is a loss of bone density of approximately 20–40%.

  This findings are mainly evident in the axial skeleton and at the end of the long and tubular bones (hand, proximal femur, and calcaneus). Spinal radiography typically displays an "empty box" or "picture framing," which is a vertebral body with a thin but well-demarcated cortical outline, a verticalization of the trabeculae, and an overall increased radiolucency. (Fig. 4.1a, b) The X-ray of the hip of a man with osteoporosis, similarly, shows an enlarged and indistinct Ward's triangle, the area bounded by the weight-bearing trabeculae. (Fig. 4.2) Conventional radiography is, furthermore, the basic modality to detect and diagnose insufficiency fracture. However, the false negative rate may be very high on routine radiographs, in the range of 29–45% [13–15].

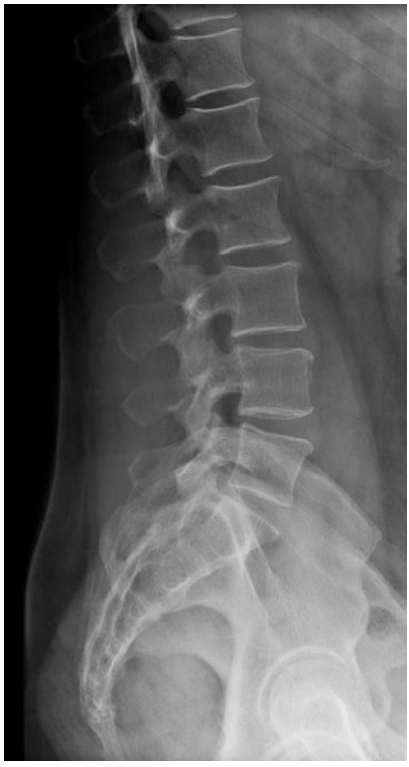


Fig. 4.1 Lateral X-ray of the lumbosacral spine in a 48-year-old man showing the main radiographic findings of osteoporosis

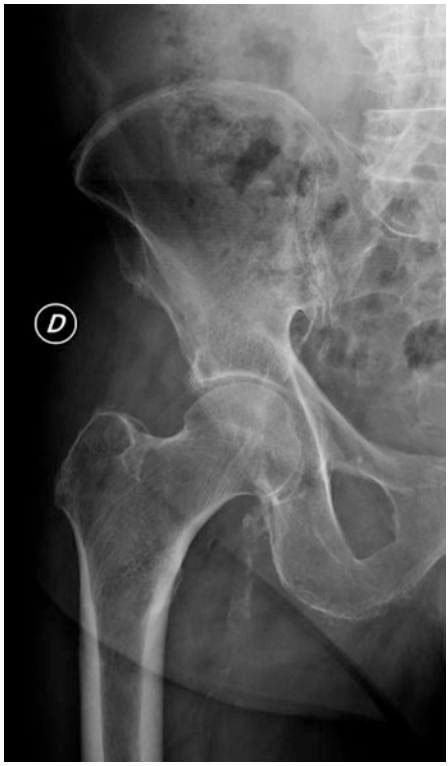


Fig. 4.2 Proximal femur radiograph of an old man patient with osteoporosis

4.3 Dual-Energy X-ray Absorptiometry

Dual-energy X-ray absorptiometry (DEXA) is currently the standardized method for the diagnosis of osteoporosis according to WHO threshold values (Table 4.1) and for the fracture risk assessment.

It consists a low radiation dose (1–6 μSv) rapid scan and provides accurate quantitative measurement of bone mineral density (BMD: g/cm^2), expressed as standard deviation (DS) from the mean of either sex-matched peak bone mass (*T*-score) or age-matched BMD (*Z*-score) [16–18] (Fig. 4.3a–c).

Most frequently DEXA is applied to the lumbar spine (from L1 to L4) and the proximal femur (total hip, femoral neck, trochanter, and Ward's area) but also to other peripheral skeletal sites such as the distal third of the radius and the calcaneus or to the whole body.

DEXA BMD measurements are predictive of fracture: It is shown that decreasing the value of BMD increases the risk of low-trauma fractures. But, BMD is the most important but not the only factor recognized as increasing the fracture risk. Many clinical factors contribute to the occurrence of fragility fracture in non-osteoporotic patients [19].

Table 4.1 WHO criteria for clinical diagnosis of osteoporosis

Diagnosis	BMD *T*-score
Normal bone mass	*T*-score ≥ −1
Low bone mass (osteopenia)	−1 > *T*-score > −2.5
Osteoporosis	*T*-score ≤ −2.5
Severe or established osteoporosis	*T*-score ≤ −2.5 with existing fracture

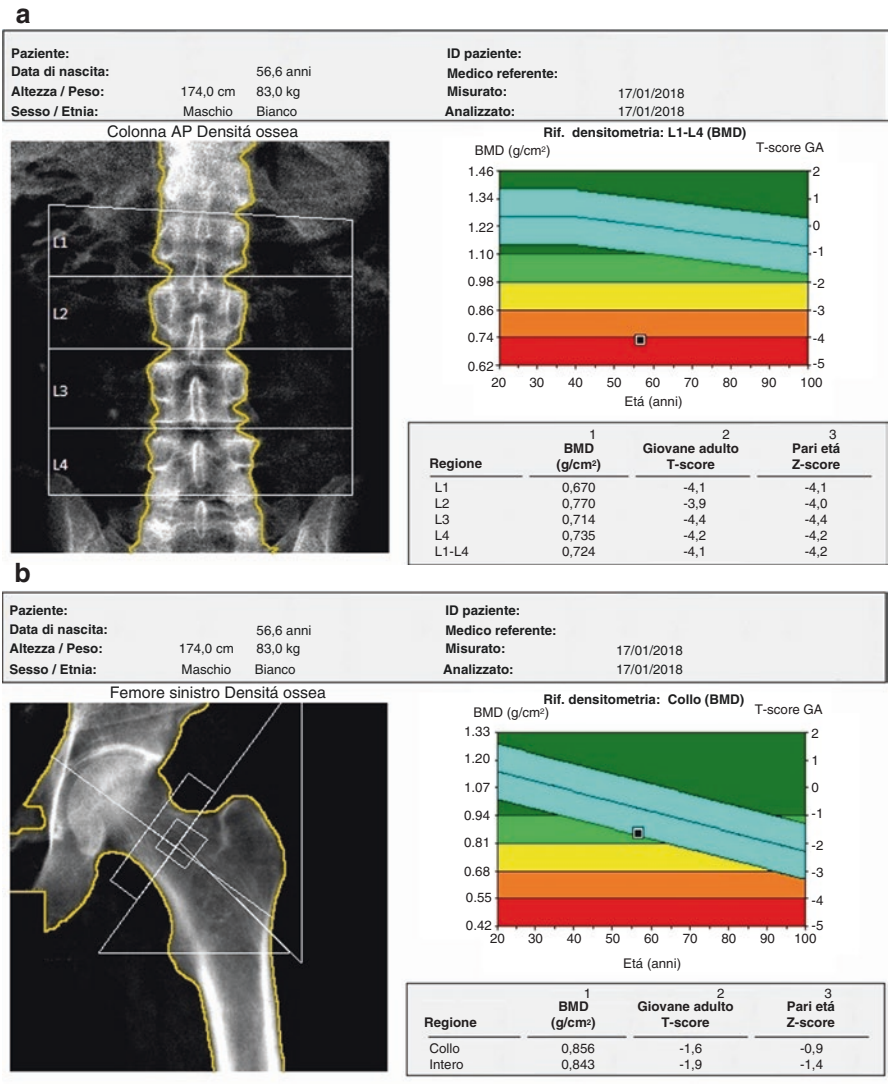


Fig. 4.3 DEXA scan of a 56-year-old male patient showing pathological values (osteoporosis). In the study of the lumbar spine (**a**), the regions of interest (ROIs) are placed on the L1–L4 vertebral bodies; in the left hip study (**b**), the ROI must be placed at the femoral neck, avoiding superimposition of the ischiopubic ramus and the greater trochanter; in the forearm (**c**), the area of analysis is set at the distal radius, with the line of reference at the ulnar styloid process

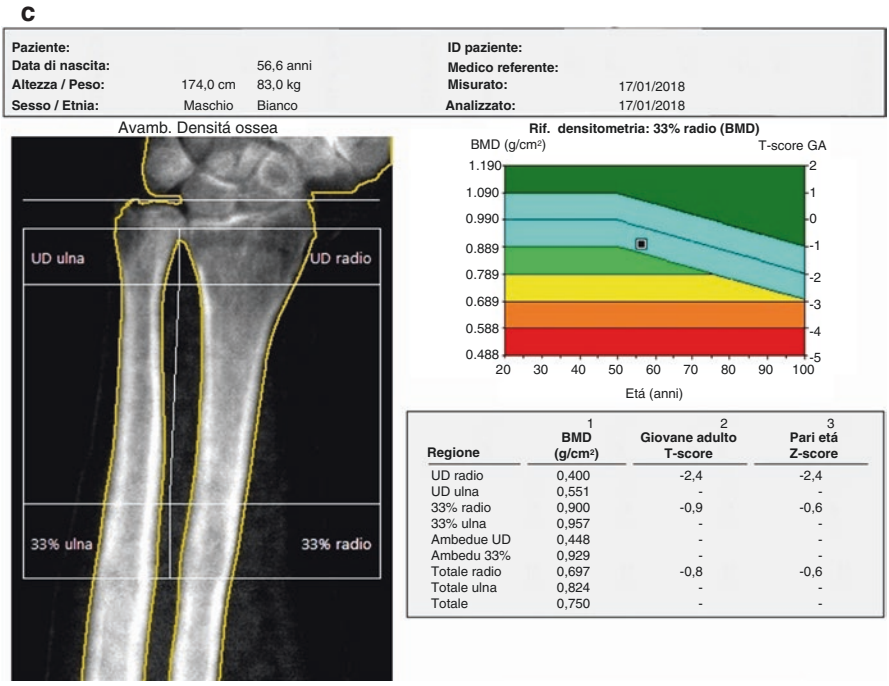


Fig. 4.3 (continued)

According to this, the WHO recently developed the use of a fracture risk algorithm (FRAX) in the DEXA interpretation. This algorithm considers several clinical risk factors (age, gender, ethnic origin and geographic region, smoking, alcohol intake, previous low-trauma fracture, parental hip fracture, oral glucocorticoid therapy, rheumatoid arthritis, and secondary causes of osteoporosis), with or without femoral neck BMD. The result is the patient's 10-year probability of fracture at one of the major osteoporotic sites. The use of FRAX in clinical practice has remodulated the therapeutic approach in particular for patients with suspected osteoporosis but not yet pathological BMD values [20].

The use of femoral neck BMD in the fracture risk algorithm is because the femoral BDM is the best predictor of hip fractures, which are the osteoporotic fractures associated with the worst impact on survival in men [6]. Furthermore age-related degenerative changes of the spine, spinal deformity, and abdominal aortic calcifications [21] may create artifacts and limit the use of lumbar spine BMD.

Currently, the advantages of using DEXA are more than the accurate measuring BMD in central and peripheral sites. Software has been developed to evaluate some geometric parameters related to bone strength, such as the hip structure analysis (HSA) and the trabecular bone score (TBS).

TBS, in particular, is a software that allows DEXA densitometer to process the pixel gray-level variations in DEXA images. This technique is applied to lumbar vertebral bodies and provides indirect information on trabecular microarchitecture [22]. TBS is strongly correlated with the number of trabeculae, with their connectivity and, negatively, with the space between trabeculae. Due to this, high TBS value indicates a dense and strong bone architecture, while a low TBS reflects weak, fracture-prone microarchitecture [23, 24].

Several studies have shown that TBS is a predictor of fracture risk independent of BMD and partly independent of FRAX. Using TBS in association with both BMD and FRAX, therefore, is a very important tool in the diagnosis of osteoporosis and especially in fracture risk assessment.

Moreover, there is a TBS progressive decrease with advancing age (which is more marked in women than in men) [25] and a progressive increase after osteoporosis treatments. The possibility of using the TBS to evaluate the response to treatment is currently being evaluated, such as the probable TBS role in the assessment of fracture risk in some causes of secondary osteoporosis (e.g., diabetes, hyperparathyroidism, and glucocorticoid-induced osteoporosis) [24].

4.4 Vertebral Morphometry

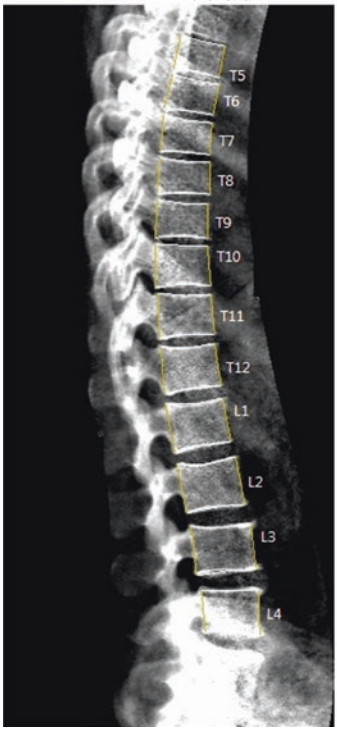
Vertebral body fracture is the most frequent type of low-trauma or atraumatic fractures and, moreover, an independent and significant predictor of increased risk for further fractures [26].

The incidence of vertebral compression fracture have recently shown a trend to rise. It usually occurs earlier compared with hip and wrist factures [27] and in most cases is clinically asymptomatic and may be unrecognized to a conventional lateral radiograph of the thoracolumbar spine [28]. Traditionally, vertebral fractures are identified on conventional radiographs of the thoracolumbar spine in lateral projection with a semiquantitative visual assessment, without a direct measurement. A mild (grade 1) fracture corresponds to a reduction in the anterior, middle, and/or posterior height of approximately 20–25%, a moderate fracture (grade 2) to an approximately 25–40% reduction in height, and a severe one (grade 3) with an approximately 40% or greater reduction in any height [29, 30].

Vertebral morphometry is a quantitative method to identify osteoporotic vertebral fractures based on the direct measurement of vertebral heights. It is mainly performed on images of lateral spine (T4–L4) obtained from DEXA scans and represents the most accurate solution currently used in clinical practice [31, 32] for the assessment of fracture status, also thanks to its lower radiation exposure. (Fig. 4.4).

Paziente:			**ID paziente:**		
Data di nascita:		53,6 anni	**Medico referente:**		
Altezza / Peso:	175,0 cm	75,0 kg	**Misurato:**	24/01/2018	
Sesso / Etnia:	Maschio	Bianco	**Analizzato:**	24/01/2018	

LVA Morfometria



Regione [1]	Alt.media [2] (%)	Rapporto P/A [2] (%)	Rapporto M/P [2] (%)	Rapporto A/P [2] (%)
T5	102	108	92	93
T6	101	113	87	89
T7	101	112	89	90
T8	99	110	87	91
T9	100	106	87	94
T10	110	107	89	94
T11	106	111	89	90
T12	106	110	87	91
L1	104	111	84	90
L2	105	101	89	99
L3	101	107	89	93
L4	93	91	99	110

COMMENT:

Fig. 4.4 Morphometric X-ray absorptiometry of the spine: The examination does not document vertebral fractures

4.5 Quantitative Ultrasound

In the last years, there has been a growing interest among clinicians worldwide on quantitative ultrasound (QUS). It is a noninvasive, low-cost, and radiation-free technique for the investigation of bone disease [33–35]. QUS, in fact, through the analysis of interactions between ultrasound and bone, provides indirect information about not only bone density but even bone quality.

It is performed with two piezoelectric probes, one that emits impulses in the frequency range between 200 kHz and 1.5 MHz (due to the high attenuation values in bone) and the other one that receives them once they have passed through the bone of study. QUS in usually applied to peripheral skeletal sites, in particular to the calcaneus, the distal metaphysis of the phalanx [36, 37], the radius, and the tibia.

This method provides two main parameters:

- *Attenuation of Broadband Ultrasound (BUA: dB/MHz)*
  The attenuation of ultrasound waves is the result of diffraction, scattering, and absorption in the bone and soft tissue. BUA represents the slope of the attenuation curve, which is higher in healthy bone and decreases as the bone mass decreases, as happens in osteoporotic bones.
- *Speed of Sound (SoS: m/s)*
  The transit time velocity is affected by the density and the elasticity of bone.

  The BUA and SoS are useful indicators of bone microstructure and mineral density. Furthermore, from these two parameters, it is possible to obtain more complex index—stiffness index (SI), quantitative ultrasound index (QUI), and amplitude-dependent speed of sound (AD-SoS)—that provide complementary information on bone structural integrity and help to estimate the probability of future fragility fractures [38].

Several studies have documented the ability of QUS to give information on bone structure and to predict osteoporotic fracture risk. Moreover, the versatility of the method makes it a useful tool in children and all the other cases where it is preferable to avoid the use of ionizing radiation.

But, at the moment, QUS cannot be used yet as stand-alone tool for the diagnosis of osteoporosis or for assessing treatment response because it's an operator-employee and scarcely reproducible method which provides just an indirect measurement of bone density.

4.6 Quantitative Computed Tomography (qCT)

DXA is a two-dimensional measurement and cannot distinguish between cortical and trabecular bone. Compared to the DXA, the advantage of quantitative computed tomography (qCT) is the measurement of true volumetric BMD and the selective evaluation of trabecular tissue, providing pertinent information on bone strength.

QCT techniques are used to measure BMD at the lumbar spine and proximal femur (axial qCT) or at the distal radius and tibia (peripheral qCT) [39, 40]. Axial qCT is performed with a standard CT scanner and a phantom, which acts as bone mineral reference standard to calibrate each scan. The regions of interest (ROIs) are positioned in the trabecular portion of the vertebral body, and the obtained vertebral densities are averaged and compared to those of a gender- and race-specific normal population [41, 42]. The results are usually expressed in absolute values and as *Z*-scores and *T*-scores.

QCT has shown a great ability to predict fracture risk and a good sensitivity in the treatment follow-up, [17, 35], but as it delivers high dose of radiation and also several other bone marrow changes may affect the measurements, its application in clinical use has been narrowed.

To obviate axial qCT limitations, it is increasingly used a volumetric QCT (vQCT), which provides separate assessment of cortical and trabecular bone at appendicular sites [40]. The evolution of post-processing software allowed further

analysis on bone geometrical and torsional stability, which correlates to bone strength and consequent susceptibility to fracture [43, 44].

High-resolution quantitative computed tomography (HR-QCT) has been implemented on metabolic bone disease patients for a detailed assessment of bone microarchitecture [45, 46]. With an 80–100 μm resolution, HR-QCT is performed at the radius, tibia, and metacarpal bones and measures, in addition to the parameters classically measured by qCT, bone volume fraction as well as cortical and trabecular parameters including thickness, separation, and number of trabeculae [47]. Nevertheless, high costs and the expertise level required to handle these techniques have limited their application to few research centers.

4.7 Magnetic Resonance Imaging (MRI)

Besides qCT, high-resolution MRI has also proved to be an accurate method to obtain micro-architectural data of trabecular bone, particularly in the peripheral appendicular skeleton (distal radius and calcaneus). MRI also has the capacity to study spinal bone marrow, which is tightly connected with bone strength and turnover.

MRI of bone marrow has a variable appearance because of the distribution of cellular and fatty marrow: with advancing age, the vertebral bone marrow becomes increasingly replaced with fatty marrow, in earliest adulthood in men compared to women [48, 49].

Several studies have shown that to a reduction of bone mineral density corresponds, on MR images, an increase of vertebral marrow fat content with a decreased vertebral marrow perfusion.

MRI is helpful in the diagnosis of vertebral fractures in elderly patients, in particular when conventional radiography, CT, or bone scintigraphy are inadequate for identifying the cause of compression fractures. Distinguishing between benign and malignant fractures is a frequent challenge with growing importance in clinical routine. Both entities tend to occur in elder patients, especially in the thoracic and lumbar spine, and may coexist.

The routine spine evaluation on MRI typically includes T1-weighted, T2-weighted, and short τ inversion recovery (STIR) T2-w images [50] (Fig. 4.5).

In osteoporotic patients, the loss in the trabecular osseous network is usually replaced by fat cells; also bone marrow is infiltrated by a variable amount of edema. In malignant vertebral fractures, the bone marrow is usually replaced by tumor cells [51–54].

Common findings suggestive of osteoporotic vertebral fractures are nonhomogeneous vertebral bone marrow edema and the presence of spared areas of normal bone marrow, especially in the pedicles and posterior elements. In advanced stages of osteoporosis, there are generally multiple vertebral collapses. T2-weighted sequences may feature a vertebral "fluid sign," [55] which is rarely found in malignant fractures. After about 4–6 months, the signal of osteoporotic fractures normalizes to a signal similar to unfractured vertebral bodies.

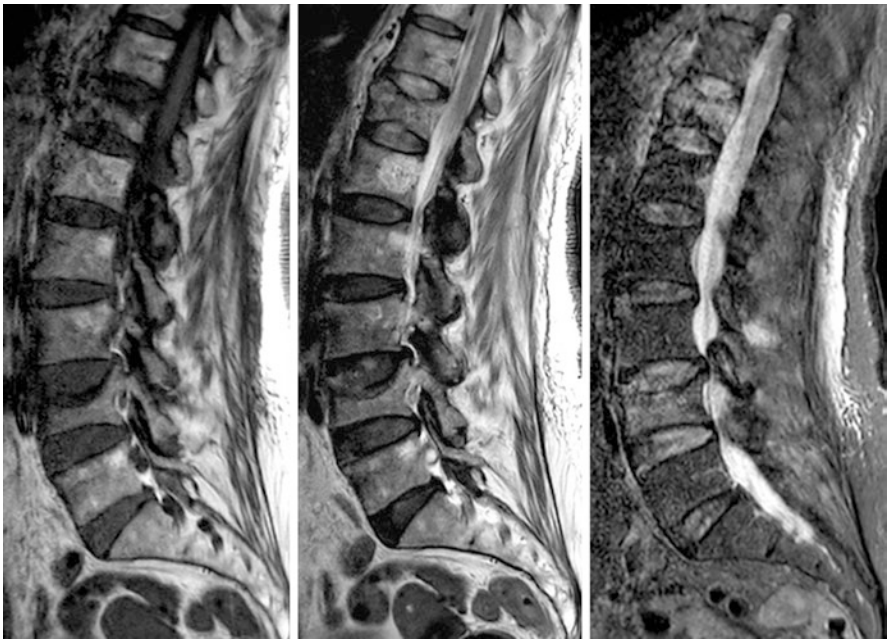


Fig. 4.5 Acute osteoporotic fractures viewed respectively in sagittal T1-weighted, T2-weighted, and T2 short τ inversion recovery (STIR) T2-weighted MR images

In doubtful cases, other functional sequences may be added to the standard MRI protocol to better differentiate osteoporotic vertebral fractures from other causes. Diffusion-weighted imaging (DWI) and apparent diffusion coefficient (ADC) maps evaluate the free mobility rate (Brownian motion) of water molecules—and thus protons—in the extracellular compartment: An increase of interstitial space due to bone marrow edema, as the initial states of osteoporotic fractures, results in an increased motion rate of water molecules [56, 57]. Chemical shift imaging may also play a role in distinguish benign from malignant vertebral fracture, whereas the use of intravenous administration of paramagnetic contrast medium is discussed [58, 59].

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Part II

Causes and Pathophysiology of Osteoporosis in Men

Introduction: Causes and Risk Factors for Male Osteoporosis

5

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Abbreviations

$1,25(OH)_2D$	1,25-Dihydroxyvitamin D
25(OH)D	25-Hydroxyvitamin D
ADT	Androgen deprivation therapy
BMD	Bone mineral density
BMI	Body mass index
CYP19	Cytochrome P450 aromatase
GH	Growth hormone
GnRH	Gonadotropin-releasing hormone
HSC	Hematopoietic stem cell
IgA	Immunoglobulin A
IGF-1	Insulin-like growth factor-1
IGFBP-2	Insulin-like growth factor binding protein-2
LRP5	Low-density lipoprotein receptor-related protein 5
M-CSF	Macrophage colony-stimulating factor
PTH	Parathyroid hormone
QCT	Quantitative computed tomography
RANKL	Receptor activator of nuclear factor kappa B ligand
ROS	Reactive oxygen species

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SHBG	Sex hormone-binding globulin
UV	Ultraviolet

5.1 Introduction

Osteoporosis is the most common form of metabolic bone disease, characterized by reduced bone mass and qualitative impairments in bone properties, associated with a reduction in bone strength, an increased risk of fragility fractures, and high morbidity and mortality rates, especially in men [1]. Rapid increases in the number of elderly people, with concomitant use of certain drugs (i.e., glucocorticoids), have markedly raised the number of men suffering from osteoporosis. Hence, during the last years the importance of osteoporosis in men has been reconsidered, although it still remains often unrecognized and untreated [2]. In fact, osteoporosis represents a silent disease until fragility fractures occur, resulting in relevant secondary health problems and even death [3].

Thus, an appropriate understanding of the most common risk factors and causes of bone loss and skeletal impairment is essential for an early diagnosis and a correct management of male osteoporosis in clinical settings. Herein we will briefly describe the main pathophysiological mechanisms responsible for bone loss and increased fracture risk in men throughout the life.

5.2 Pathophysiology of Male Osteoporosis

Osteoporosis has long been considered as a women's disease, with less clinical relevance among men. In fact, the male sex itself represents one of the strongest protective factors against bone loss and osteoporosis fractures. This significant advantage in bone strength observed in men mainly depends on higher cortical bone expansion during pubertal peak bone mass acquisition [4]. Of note, there is a 10-year difference in age before men show signs of an age-related bone loss [5]. During aging men show less bone loss than women, since they undergo higher periosteal bone accretion to compensate the endosteal bone loss [6]. Moreover, elderly men have more stable plasma levels of sex steroids compared to women and do not experience an accelerated phase of bone loss as observed with menopause in women, when a rapid decrease in estrogen levels occurs; this results in a better maintenance of skeletal integrity in aging men [7]. Nonetheless, during the last decades, it has been widely recognized that also male osteoporosis represents a significant public health and economic burden [8, 9]. First of all, rapid increases in the number of elderly people have considerably raised the incidence of osteoporosis among men. Furthermore, even if osteoporosis still remains four times more common in women [10], evidence supports that men tend to exhibit more osteoporosis-related complications, along with higher mortality after fragility fractures [11, 12]. Several lifestyle habits and/or pathological conditions specifically increase the risk for bone

Table 5.1 Primary and secondary causes of male osteoporosis

Primary osteoporosis
Age-related osteoporosis
Idiopathic osteoporosis
Secondary osteoporosis
Drugs: Corticosteroids, anticonvulsants, thyroid hormone, heparin, chemotherapeutics, thiazolidinediones
Endocrine diseases: Hypogonadism (Klinefelter syndrome, Kallmann syndrome, hypopituitarism, androgen deprivation therapy, hemochromatosis), hyperthyroidism, hyperparathyroidism, hypercortisolism, hyperprolactinemia, acromegaly, GH deficiency, diabetes mellitus (type 1 and type 2)
Gastrointestinal diseases: Celiac disease, gastrectomy/gastric bypass, chronic liver diseases, primary biliary cirrhosis, chronic inflammatory bowel disease, pancreatic insufficiency
Systemic illnesses: Rheumatoid arthritis, lupus erythematosus, ankylosing spondyloarthritis, myelo- and lymphoproliferative diseases, multiple myeloma, systemic mastocytosis
Conditions associated with immobilization: Parkinson's disease, paraplegia, poliomyelitis, cerebral palsy, muscular dystrophies
Kidney diseases: Idiopathic renal hypercalciuria, renal tubular acidosis, chronic kidney disease
Other diseases: Chronic obstructive pulmonary disease, anorexia nervosa, AIDS/HIV, amyloidosis, sarcoidosis, depression
Miscellaneous and lifestyle choices: Sedentary lifestyle, alcoholism, smoking, caffeine

loss and osteoporosis in men, thus resulting in substantial increases in morbidity and mortality rates, mainly as a consequence of hip and vertebral fractures [13].

The risk factors for osteoporosis and/or bone fragility fractures in men can be distinguished in two main groups, (a) non-modifiable risk factors and (b) modifiable risk factors, defined as those that can be treated or modified by an adequate intervention. The former group includes age, genotype, race, previous fragility fractures, and familial history of hip/vertebral fracture, whereas the latter encompasses low bone mineral density (BMD), low muscle mass, alcoholism, smoking, low body mass index (BMI < 20 kg/m^2), low physical activity, reduced calcium intake and/or malabsorption, vitamin D deficiency, excessive sodium intake, the presence of osteoporosis-associated diseases, and the use of bone-resorbing drugs (i.e., glucocorticoids) [14]. Indeed, male osteoporosis is a heterogeneous condition, including a large variety of etiologies. Table 5.1 lists the major causes of osteoporosis in men, separating these into primary causes (age-related and idiopathic osteoporosis) and secondary causes (those related to specific diseases or drugs). Even if it is useful to consider the possible causes individually for didactic purposes, in most patients more causes often coexist.

5.3 Age-Related Osteoporosis

Significant bone loss gradually occurs with aging in men, representing a crucial feature of osteoporosis which could be sufficient to cause fragility fractures, regardless of the presence of other causes of skeletal impairment. It has been established that aging men lose BMD at a rate of 1% per year [15]. Nevertheless, specific causes

of senile bone loss in men are still partially unknown. However, the observation of increased markers of bone remodeling raised the hypothesis that the acceleration in bone turnover contributes to the age-related bone loss [16]. In fact, QCT (*quantitative computed tomography*) analysis demonstrated that a substantial cortical bone loss in men begins mainly after the age of 75. Moreover, in older men higher rates of cortical and trabecular bone loss have been associated with lower levels of biologically active sex steroids and higher levels of bone turnover markers [17]. Indeed, several hormonal changes occur with aging. Aging in men is associated with relevant changes in the hypothalamic-pituitary-gonadal axis, resulting in reduced serum levels of testosterone and estradiol (including their free fractions), with a concomitant rise (over twofold) in SHBG (*sex hormone-binding globulin*) concentrations [18–20]. SHBG binds to testosterone and further decreases free or bioavailable testosterone [21, 22]. Overall, both androgens and estrogens, as well as SHBG, are crucial for skeletal maintenance in males, probably playing an independent and coordinated role [7, 23]. The exact role of androgens on male bone is still partially unclear, but a compelling body of evidence suggests that these hormones could play a direct role in bone metabolism and maintenance. Of note, observational studies demonstrated that patients with androgen insensitivity syndrome, where there is a partial or total lack of androgen receptor signaling [24], exhibit reduced BMD regardless of estrogen replacement [25, 26]. Nevertheless, testosterone also contributes to indirect effects on the bone through its aromatase-mediated conversion to estrogen [7], as demonstrated by osteopenia or osteoporosis observed among males with aromatase deficiency [27, 28] or undergoing selective blockade of aromatase activity [29].

Reduction in testosterone levels has been suggested to be responsible for the decline in muscle strength and bone mass observed in the aging male [30]. Low free testosterone levels are associated with frailty, sarcopenia, and increased falls in elderly men [31–33]. However, low bioavailable estradiol levels and high SHBG levels were also associated with lower BMD and faster hip BMD loss in a cohort of almost 6000 men at least 65 years old. The combination of low bioavailable estradiol, low bioavailable testosterone, and high SHBG has been related to faster rates of BMD loss [34]. Furthermore, specific polymorphisms of aromatase (CYP19), which promotes the conversion of androgens to estrogens in the testis and in peripheral tissues, have also been described as a potential cause of low estradiol serum levels and increased rates of bone loss in elderly men, irrespective of serum androgen or SHBG levels. Interestingly, the association between aromatase polymorphisms and serum estradiol levels was attenuated in the subgroup of overweight men (BMI > 25 kg/m^2), suggesting that adipose tissue contributes to circulating estrogen levels and mitigates the impact of genetic variations in CYP19 through increased activity of the enzyme at peripheral level [35].

Nonetheless, there are a number of other hormonal factors potentially involved in skeletal impairment of elderly men. For instance, aging is characterized by decreases in the amplitude and frequency of growth hormone (GH) secretion [36], with low liver production of insulin-like growth factor-1 (IGF-1). IGF-1 is a key determinant of bone mass whose concentrations are positively associated with

BMD and inversely related to the fracture risk in older men [37, 38]; indeed, serum IGF-1 levels markedly decline with age [39]. Furthermore, serum levels of insulin-like growth factor binding protein-2 (IGFBP-2), which is considered as an inhibitory binding protein, increase significantly with age and are predictive of lower BMD and increased markers of bone resorption [40]. Given that IGF-1 has been shown to inhibit SHBG production by hepatocytes in vitro [41] and serum SHBG concentrations are inversely correlated with IGF-1 levels in men [42], age-related changes in the GH/IGF system may contribute to impaired bone formation even through modulation of sex steroids activity.

In addition to these mechanisms, many other processes could promote age-related bone loss, such as reduced physical activity and nutritional/hormonal factors. Mechanical forces, lean body mass, and muscle strength exert major effects on bone mass in men, as demonstrated by the higher BMD observed at both regional and systemic level in physically active men [43, 44]. In light of the obvious age-related decline in physical activity and muscle mass/strength [45], senile bone loss as well as increased risk of falls and fractures in men may be linked, at least in part, to decreased mechanical forces on skeletal tissues. According to this, Frost suggested that the loss of muscle mass/strength occurring with aging is likely to be the main cause of age-related osteoporosis in both sexes [46].

A crucial role in age-related bone loss is also played by various nutritional factors, such as inadequate calcium intake and poor vitamin D status. In fact, an adequate dietary calcium intake has been positively related to higher lumbar spine and femoral neck BMD in elderly men, potentially resulting in a reduction in the risk of osteoporosis during late decades of life [47]. The average level of dietary calcium essential for the maintenance of mineral homeostasis in young men is quite low (400–600 mg/day), even though there are data suggesting a higher requirement in older men [48], thus explaining the frequent alterations in calcium handling observed in these individuals [49]. In addition, reduced levels of 25(OH)D (25-hydroxyvitamin D < 75 nmol/L) are often observed among elderly for different reasons, such as inadequate exposure to ultraviolet (UV) radiation (especially in countries with higher latitudes), poor vitamin D dietary intake, chronic kidney disease, etc. [50]. Hypovitaminosis D further contributes to age-related bone loss and fall/fracture risk through various mechanisms, including impairment in calcium/phosphate homeostasis, increase in serum PTH levels (secondary hyperparathyroidism), and reduced muscle mass/strength [51, 52]. Indeed, lower 25(OH)D levels have been associated with lower BMD values, bone loss (particularly evident with 25-hydroxyvitamin D levels below 50 nmol/L), and higher fracture risk [53, 54].

Finally, it has also been hypothesized that increase in oxidative stress could represent an important mechanism underlying the age-related bone loss. The levels of reactive oxygen species (ROS) increase in the bone with age [55]. In turn, ROS are able to promote osteoblast apoptosis and osteoclast differentiation, leading to reduced bone formation and increased bone resorption [56]. Sex steroid deficiency may also accelerate the detrimental effects of aging on the bone by reducing antioxidant defenses [57]. Accordingly, antioxidants have been shown to prevent bone loss caused by gonadectomy in mice [57, 58].

5.4 Idiopathic Osteoporosis

Idiopathic osteoporosis in men is defined as the onset of osteoporosis and fragility fractures occurring before the age of 60 years, when the aforementioned age-related bone changes are not usually observed. However, a remarkable heterogeneity of causes may explain the pathogenesis of the disease. Some cases could represent defects in peak bone mass acquisition due to environmental or genetic factors [59]. Although several genes have been suggested to explain the genetic component of idiopathic osteoporosis (i.e., *IGF-1*, *LRP5*, *CYP19*) [60–62], future studies are needed to better understand the association between genetic factors and idiopathic osteoporosis in men. Up to 10% of men suffering from idiopathic osteoporosis displays hypercalciuria with or without increased bone resorption [63]. Moreover, reduced intestinal calcium absorption has been reported with lowered levels of $1,25(OH)_2D$ (1,25-dihydroxyvitamin D) [64].

Men with idiopathic osteoporosis may have an osteoblast dysfunction that leads to decreased osteocalcin production and increased production of factors stimulating osteoclast activation, such as macrophage colony-stimulating factor (M-CSF). This results in a catabolic cellular balance responsible for negative bone turnover [65]. Even if the specific causes of such cellular dysfunction needs further evaluation, different explanations can be proposed. For example, these patients could have lower serum IGF-1 concentrations despite a normal GH secretory capacity [66, 67], which may reduce bone formation. The reduction in IGF-1 levels appears to be related to a simple sequence repeat in the *IGF-1* gene, which is present at an increased frequency among these men [60]. As observed during aging, reduced IGF-1 levels in such patients could simultaneously contribute to impaired bone formation and increase in SHBG levels, the latter responsible for a decreased availability of sex steroids [62, 68].

Abnormalities in cortisol rhythm have also been considered as a potential cause of bone loss in idiopathic osteoporosis [69]. Furthermore, low circulating total estradiol levels have been observed despite normal testosterone levels, consistent with possible aromatase defective activity in at least a subset of these patients [70, 71]. Accordingly, low estrogen levels have been related to deficits in bone formation and bone mass [72].

In conclusion, strong similarities are evident between the hormonal abnormalities frequently observed in younger men affected by idiopathic osteoporosis and those underlying the age-related bone loss, thus warranting further investigations in this field [13].

5.5 Secondary Osteoporosis

A large number of factors can induce osteoporosis, including several diseases and drugs (see Table 5.1). Secondary causes account for almost 40% of cases of male osteoporosis [49]. The three main causes of secondary osteoporosis in men are represented by glucocorticoid excess (especially during long-term glucocorticoid

therapy), hypogonadism, and alcohol abuse [13]. Since the removal of the specific cause could be curative in such cases, primary osteoporosis should always be distinguished from secondary forms. Herein we will only focus on the most typical and frequent forms of secondary osteoporosis in men, even though the other secondary causes listed in Table 5.1 should always be considered and excluded in the appropriate clinical setting.

5.5.1 Glucocorticoid-Induced Osteoporosis

Chronic exposure to glucocorticoids, either due to exogenous use or increased endogenous production (Cushing's syndrome), is the most common cause of secondary osteoporosis in men [13]. Notably, men are more likely to have inflammatory bowel disease as well as chronic obstructive pulmonary disease and organ transplantations as reasons for use of oral glucocorticoids [73].

The pathophysiology of glucocorticoid-induced osteoporosis is complex and not still completely understood. It is well-known that glucocorticoids directly promote osteoclast-mediated bone resorption and reduce bone formation by inducing osteoblast and osteocyte apoptosis as well as by inhibiting osteoblast proliferation and differentiation. However, the detrimental actions of excessive levels of glucocorticoids on the skeleton may be also mediated by their indirect effects on bone metabolism, including reduction in muscle mass and strength, and secondary hyperparathyroidism due to impaired intestinal calcium absorption and/or increased renal calcium excretion [74, 75]. In addition, exogenous glucocorticoids strongly reduce testosterone levels in men by different potential mechanisms not still fully defined, but which may include inhibition of gonadotropin secretion and direct antagonism of testicular steroidogenesis [74, 76, 77]. As such, glucocorticoid-induced hypogonadism could significantly contribute to bone loss in men undergoing long-term glucocorticoid therapy and should be early recognized by the clinicians as an important cause of glucocorticoid-mediated osteoporosis.

Glucocorticoid-induced bone loss is an early event under long-term glucocorticoid therapy, more evident during the first 6–12 months of treatment. Following this period, there is a reduction in osteoclast-mediated bone resorption although inhibition of bone formation is maintained, with a slower but constant bone loss that also affects the cortical bone. The incidence of fractures is mainly related to dose and duration of glucocorticoid therapy: in fact, fragility fractures occur in 30–50% of patients during the first 5 years of therapy, especially at sites with predominant trabecular bone (spine, rib, and proximal femur). Moreover, fracture risk is increased in the presence of other risk factors (i.e., advanced age, history of previous fractures), is much higher as compared to that expected based on BMD values, and rapidly decreases after treatment discontinuation [74, 78]. This suggests that an appropriate prevention of glucocorticoid-mediated bone loss should be started as early as possible, irrespective of BMD values, in order to avoid the onset of irreversible alterations of bone microarchitecture.

5.5.2 Male Hypogonadism

Sex steroids are major regulators of bone metabolism and both estrogens and androgens are crucial for the maintenance of male bone health, through their action on osteoblast lineage cells. Furthermore, androgens exert additional beneficial effects on extraskeletal parameters, such as muscle mass and strength as well as propensity to fall [7]. Hence, hypogonadism in men represents a prominent cause of bone loss and secondary osteoporosis throughout life [13, 79–81].

Bone mass accumulation in adolescence is strictly related to gonadal maturation during puberty [82]. In fact, disorders of puberty can impair pubertal bone expansion, leading to failure to acquire peak bone mass and affecting bone health during adulthood [83]. In particular, men who experienced an abnormal puberty (i.e., Klinefelter and Kallmann syndromes) show decreased bone mass [84]. Moreover, sex steroids are essential for the maintenance of bone mass in adulthood. Therefore, the onset of acquired hypogonadism in mature men is associated with low BMD and osteoporosis [79]. Reduced bone mass and fragility fractures are observed in many forms of hypogonadism, such as anorexia, hyperprolactinemia, and hemochromatosis [85, 86]. In addition, reduction in gonadal function secondary to other conditions (i.e., renal insufficiency, glucocorticoid excess) is suspected to contribute to the development of bone loss [74, 87].

Finally, an increasing number of cases of hypogonadism have been described among men undergoing androgen deprivation therapy (ADT) based on GnRH agonists and/or antiandrogens for prostate cancer [88]. ADT leads to an accelerated bone loss, along with a rapid increase in fracture risk [89]. As a result, BMD is more frequently low in these patients, and the onset of osteoporosis at an accelerated rate can easily occur [90]. Bisphosphonates and monoclonal antibody denosumab represent the first-line drugs for the management of bone health in such condition. These drugs should be started at initiation of ADT and reasonably continued throughout the duration of the treatment [14]. Interestingly, biannual administration of denosumab has led to an increase in BMD at the lumbar spine, along with a reduced incidence of new vertebral fractures among men receiving ADT for non-metastatic prostate cancer [91]. A further potential benefit deriving from the use of denosumab in men with non-metastatic prostate cancer consists in the prevention of metastatic bone disease. In fact, it is well-known that prostate malignant cells have a peculiar affinity for the bone, and the bone marrow may act as a reservoir for cancer cells; in particular, the hematopoietic stem cell (HSC) niche represents the site for dormant malignant cells that result in relapse many years after the diagnosis [92]. Tumor cells are able to produce a large variety of cytokines and growth factors that can increase the production of receptor activator of nuclear factor kappa B ligand (RANKL) by osteoblast lineage cells. This will cause activation of osteoclasts and impairment of the complex balance between new bone formation and bone resorption, resulting in a vicious cycle characterized by multiple interactions between cancer cells, osteoclasts, osteoblasts, and bone microenvironment that may enhance tumor growth and promote local and systemic invasion [93]. Moreover, monthly high-dose denosumab administration has recently been shown to significantly

increase bone metastasis-free survival and delay time to symptomatic first bone metastases in men with non-metastatic castration-resistant prostate cancer at high risk of bone metastasis [94].

5.5.3 Alcohol Abuse, Celiac Disease, and Other Conditions Associated with Male Osteoporosis

Alcohol abuse is a major cause of secondary osteoporosis in men [13], representing a significant determinant of bone loss, as demonstrated in longitudinal studies [95]. The detrimental skeletal consequences of chronic alcohol abuse seem to be multifactorial. In addition to the well-known alcohol-related gonadal and nutritional changes (i.e., poor calcium and vitamin D status, reduced serum free testosterone concentrations), which negatively affect bone health [96–98], in vivo and in vitro studies indicate that alcohol can exert a direct effect on the bone by suppressing osteoblast activity and bone formation [99, 100].

Gastrointestinal diseases represent another extremely common cause of secondary osteoporosis. In particular, celiac disease is the paradigm of malabsorption syndrome, which frequently leads to important extraintestinal clinical manifestations, including impairment in bone mineralization, osteoporosis, and increased fracture risk. Notably, fracture risk appears to be higher in symptomatic cases and in male patients [101]. The pathogenesis of bone damage in celiac disease is likely to be multifactorial, involving both local and systemic mechanisms. First, atrophy of intestinal mucosal is responsible for altered calcium absorption; as a consequence, to avoid hypocalcemia, PTH levels increase substantially, thus leading to a high osteoclast-mediated bone resorption which in turn impairs bone microarchitecture, especially at trabecular sites. Interestingly, hypersecretion of pro-inflammatory cytokines (i.e., tumor necrosis factor-alpha, interleukin-1, interleukin-6) significantly contributes to increased osteoclast activation [102]. Last, there are evidences for a direct role of IgA-type circulating autoantibodies in the pathogenesis of celiac disease-associated bone complications (osteopenia, osteoporosis). Specifically, these antibodies recognize bone tissue transglutaminase, which seems to be a crucial enzyme even in bone mineralization processes [103].

Finally, a variety of other pathological conditions or drugs have been associated with bone loss and osteoporosis in men, such as liver and kidney disease, anticonvulsant use, hyperthyroidism, immobilization, etc. (see Table 5.1) [14]. However, there is poor evidence to conclude that the skeletal abnormalities caused by such conditions affect men any differently (qualitatively or quantitatively) than women.

5.6 Conclusions

Osteoporosis in men is not a rare condition, representing a remarkable clinical issue and a public health burden, especially with the growing aging of the population. Although male osteoporosis is a heterogeneous clinical entity, declining sex

steroids levels (both testosterone and estradiol) appear to play a pivotal role in promoting age-related bone loss. Furthermore, other hormonal and nutritional changes occurring with aging (i.e., increases in serum SHBG and PTH levels, decreased IGF-1 levels, reduced calcium intake, vitamin D deficiency) may also have an additional role in the pathogenesis of the disease. Several secondary causes of osteoporosis also significantly contribute to bone loss and fragility fractures in men, with the most frequent represented by long-term glucocorticoid therapy, hypogonadism, and alcohol abuse. Of note, a growing reason for concern is the increasing number of cases of osteoporosis observed among men undergoing androgen deprivation therapy for prostate cancer.

Therefore, given the silent nature of osteoporosis, often undiagnosed until a fracture occurs, awareness regarding the disease and its different etiologies is critical to prevent morbidity and mortality and to maintain quality of men's lives.

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Estrogens and Male Osteoporosis

6

Vincenzo Rochira and Bruno Madeo

Abbreviations

BMD	Bone mineral density
CHH	Congenital hypogonadotropic hypogonadism
EMAS	European Male Aging Study
ER	Estrogen receptor
GH	Growth hormone
GPER30	Transmembrane G protein-coupled receptor GPR30
IGF-1	Insulin growth factor-1
MrOS	Osteoporotic Fractures in Men Study
PTH	Parathyroid hormone
RANK	Receptor activator of nuclear factor kappa-B
RANKL	Receptor activator of nuclear factor kappa-B ligand
RBS	Rancho Bernardo Study
SERMs	Selective estrogen receptors modulators
TRT	Testosterone replacement treatment

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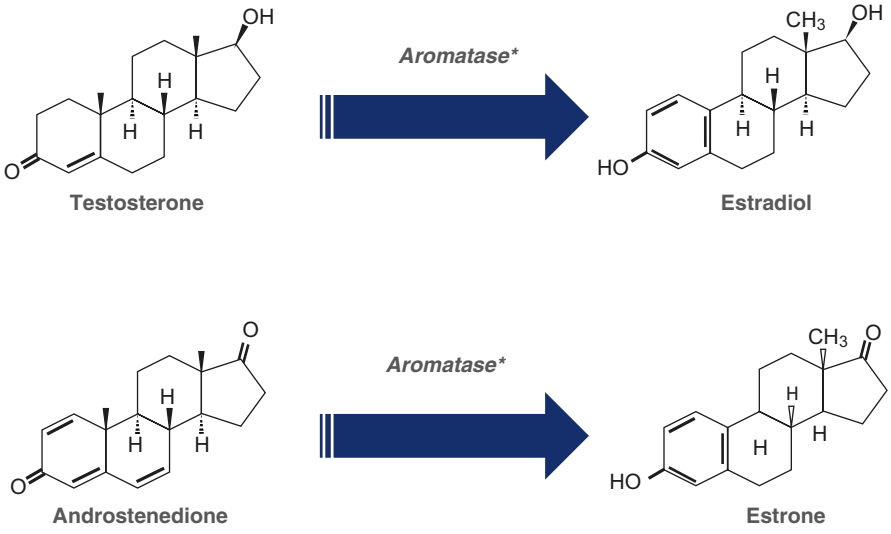
6.1 Introduction

The pivotal role exerted by estrogens on several physiological functions in men is a relatively new issue since traditionally the physiological effects of circulating sex steroids in the male had been all ascribed to androgens, particularly testosterone [1–3]. At the end of the 1990s, the description of the first cases of men with congenital estrogen deficiency—i.e., estrogen resistance [4] and aromatase deficiency [5, 6]—pointed out the importance of estrogens for the male skeleton and other physiological aspects. These rare diseases, in fact, demonstrated that a condition of severe estrogen deficiency is constantly associated with the lack of skeletal maturation and both severe bone loss and osteopenia/osteoporosis in adult men [7, 8]. Starting from this evidence, several other actions of estrogens in men have been progressively disclosed and better characterized leading to fix the concept that estrogens play an important role on some male physiological processes [9–11] even though their concentrations are much more lower than in women [12]. In men estrogens derive from androgens after their aromatization through the activity of the CYP19A1 enzyme, named aromatase, which is expressed in many tissues in men and catalyzes the biochemical reaction of aromatization of the A ring of androgens [2, 13, 14] (Fig. 6.1). Estrogens in men exert their action through the binding to the estrogen receptor (ER). Nuclear ER-alpha and ER-beta and the transmembrane G protein-coupled receptor GPR30 (GPER30) are expressed in human male tissue. The nuclear receptors account for genomic effects of estrogens, while the GPR30 transmembrane receptor accounts for non-genomic, rapid effects of estrogens [2, 13, 14].



*the enzyme is expressed in various tissues including the testes, adipose tissue, muscle, brain, liver, breast, skin, and the endothelium

Fig. 6.1 Biochemical pathway of estrogen synthesis in men summarizing the reaction of aromatization of androgens to estrogens

6.2 Mechanisms of Estrogen Actions on Bone

In men aromatase is expressed in fibroblasts as well as in other cells within the bone (i.e., osteoblasts and osteoclasts) [13, 15]; furthermore, other tissues such as the adipose tissue and the bone marrow, which are located near the bone tissue, express aromatase and are able to locally produce estrogens [14]. Circulating estrogens as well as locally produced estrogens exert their effect on bone through the binding to the ERs in bone cells. ERs are widely expressed in bone cells [16]. In particular ER-alpha and ER-beta are both expressed in osteoblasts, osteoclasts, and osteocytes [16]; furthermore evidence suggests that also the GPR30 is expressed in the bone [17, 18]. Apart from direct effects of estrogens on bone mediated by ERs (*direct effects*), estrogens are also able to modulate the activity of other hormones involved in bone physiology (*indirect effects*); thus they act on bone through a dual way by modulating bone cells and a complex hormonal network, including other hormones and substances able to induce changes within the bone tissue.

6.2.1 Direct Action of Estrogen on Bone

The direct action of estrogens on bone is mainly due to the activation of the biochemical pathway led by ER-alpha [17–21]. In particular, the ligand between estrogens and the ERs leads to various biological effects depending on the different bone cell line [16]. Estrogens are able to support and promote osteocyte vitality, and estrogen deficiency leads to apoptosis of osteocytes [22]. Furthermore, estrogens positively modulate the bone response to mechanical strain through their binding to the ER-alpha, thus supporting a complex interaction among osteocytes and mechanical loading and bone. This complex interaction involves the receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL) [23], a pathway on which estrogens act by facilitating the anabolic bone response to mechanical load [24].

The binding of estrogens to ERs leads to the activation of different pathways also in osteoclasts resulting in (i) the induction of apoptosis [25, 26] and (ii) the negative modulation of the signaling of the receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) and the consequent inhibition of osteoclast differentiation [16, 27, 28]. Overall estrogen action on osteoclasts results in the decrease of bone resorption mainly due to the decrease of the number of osteoclasts recruited and of the modulation of cytokines toward an anti-osteoclastic activity [29]. Vice versa, estrogens act on osteoblasts by promoting/maintaining bone formation. Accordingly, estrogens lead to an anti-apoptotic effect on osteoblasts [30] and promote osteoblast adhesion and differentiation [31].

In summary, estrogens act on bone remodeling by promoting bone formation and inhibiting bone resorption, while estrogen deficiency leads to an imbalance of bone remodeling in favor of a net prevalence of bone loss in men [29].

6.2.2 Indirect Actions of Estrogens on Bone: The Endocrine Network

6.2.2.1 Estrogens and GH/IGF-1 Axis

Sex steroids stimulate the pituitary leading to an increase of growth hormone (GH) secretion [32, 33]. The increase of gonadal steroids at puberty in boys is able to modify also the secretory pattern of GH. At puberty, in fact, the rise in serum testosterone results in a positive enhancement on the secretion of GH [33–35]. As a consequence, the increased GH secretion leads to very high levels of circulating insulin growth factor-1 (IGF-1) [34–36] when the amount of serum IGF-1 in the serum is similar to that of acromegalic patients [37]. It is now textbook knowledge that the rise of GH secretion is mainly due to a direct effect of estrogens rather than testosterone in males [32, 38, 39] and that serum estrogens account for the impressive increase of IGF-1 at the time of puberty in boys [37, 39]. Besides, the crosstalk between gonadal steroids and GH/IGF-1 axis at puberty is more complex and seems to be bidirectional in boys, with GH exerting also a positive modulation of reproductive functions [37].

The concomitant increase of testosterone, estradiol, GH, and IGF-1 at puberty represents a peculiar condition in terms of hormonal *milieu* for bone anabolism. Accordingly, all these hormones concur to the achievement of optimal peak of bone mass during puberty [17, 21]. Sex steroids and GH/IGF-1 contribute to the progression of bone maturation and to the massive increase of bone mineralization in boys at puberty [35]. Among gonadal steroids, estrogens together with GH and IGF-1 play a major role on bone by acting in a synergic way, all promoting both bone mineralization and maturation [8, 19, 37, 40–42].

In men with congenital estrogen deficiency, the lack of circulating estrogens leads to a condition of GH deficiency [43, 44], and both estrogen and GH deficiency result in the lack of pubertal spurt and in suboptimal peak of bone mass [7, 8, 19, 40, 45, 46].

6.2.2.2 Estrogens and Calcium Metabolism

Estrogens may increase calcium absorption in the gut not only in women but also in boys and men [47]. Both testosterone and estradiol seem also to reduce bone sensitivity to parathyroid hormone (PTH), thus protecting the bone from the PTH-related bone resorption [48].

6.3 Pathophysiology of Estrogen Deficiency on Human Male Bone

6.3.1 Congenital Estrogen Deficiency as a Cause of Osteoporosis in Men

Severe estrogen deficiency due to congenital aromatase deficiency and/or mutations of the gene encoding for the ER-alpha directly cause bone loss and finally lead to osteopenia or osteoporosis in these patients [45]. An osteoporotic lumbar fracture

has been described in a young man with aromatase deficiency, thus suggesting that these patients have an increased risk of fractures [49]. The mechanism through which severe estrogen deficiency leads to the reduction of bone mineral density (BMD) is dual. Firstly, in these patients, estrogen deficiency occurs early during the first pubertal stages due to the inability of the aromatase enzyme to convert androgens into estrogens [40]. Early estrogen deficiency blocks bone maturation including bone mass accrual with the consequent failure in achieving the peak of bone mass [7, 8, 19, 40, 42]. Thus, the adult skeleton enters adult life with a lower than normal bone mass, and this gap cannot be filled due to the persistence of estrogen deficiency during adulthood [5, 6]. Secondly, estrogen deficiency interferes with the well-known role of estrogen on the maintenance of bone mass in adulthood [42, 46]. BMD increases in a dose-dependent fashion in adult men with aromatase deficiency when they are treated with increasing doses of exogenous estradiol [45, 46], further confirming that estrogen deficiency is the cause of bone loss in these patients.

All the abovementioned consequences of estrogen deficiency on BMD have been demonstrated both in rare models of estrogen deficiency and in study population (see below for details) [42, 50].

6.3.2 Estrogens and the Achievement of Peak Bone Mass

Peak bone mass is reached soon after the final phases of pubertal development and takes place on average around the age of 20–22 years in men [51]. The main factors involved in the determination of peak bone mass are nutrients, health status, vitamin D, physical exercise, and the rise of sex steroids at puberty [51, 52]. Sex steroids are known to be extremely important for bone mass accrual at puberty since longtime [53], but only recently the main role of estrogens in both sexes has been clarified [7, 8, 19, 42]. Since the end of the 1990s, the current endocrinological knowledge was based on the assumption that estrogens led to bone accrual in females [54, 55] while androgens in males [56]. The observation that men with congenital estrogen deficiency fail in the achievement of peak bone mass [4–6, 40] provided evidence of a major role of estrogens in this physiological process also in men [7, 8, 19, 57]. Outside the context of these rare diseases of complete congenital estrogen deficiency, the role of estrogens on the achievement of peak of bone mass has been unequivocally demonstrated in normal pubertal boys [58]. As a matter of course, it is well-known that abnormal peak of bone mass is a strong risk factor for the development of osteoporosis later in life [59]. The finding of a direct correlation between serum estradiol and BMD in boys [60–62] together with the association of some polymorphisms of ER-alpha with increased peak bone mass [63] strengthened the evidence of a direct major role of estradiol on the achievement of peak bone mass [17, 52]. Even in longitudinal studies, the annual percent change in BMD is directly correlated to serum total and bioavailable estradiol but not with serum testosterone in young men aged 22–39 years [64]. In particular, estrogens promote bone accrual at the level of cortical bone, but have no effect on the endosteal circumference, the latter being mainly under the control of androgens [17, 40, 61].

Data coming from male patients with congenital hypogonadotropic hypogonadism (CHH) show that testosterone replacement treatment (TRT) fails in normalizing BMD that remains in the osteopenic/osteoporotic range suggesting that failure in obtaining optimal peak of bone mass at puberty avoids restoration of normal BMD after TRT in CHH [65]. Furthermore, female patients with complete androgen insensitivity have a peak of bone mass and bone size that is only slightly reduced compared to control men, showing values that are in between compared to those of male and female subjects [66]. These data suggest that the peak of bone mass is under the main control of estrogens in boys and that androgens are also required for optimal peak of bone mass and that both androgens and estrogens are required at the right time during puberty, remaining partially ineffective if administered in adulthood.

6.3.3 Estrogens and Bone Mass Maintenance

Once the peak bone mass has been achieved, the bone mass remains the same for several years in men and starts to slowly decline in concomitance with advancing age after the years of 50, the highest rate of bone loss being registered after the age of 70 [17, 50, 51]. The decline in serum testosterone progressively increases with aging, and serum estradiol declines in parallel [12]. Changes in sex steroids lead to an unbalance between rates of bone formation and bone formation negatively affecting bone maintenance. Accordingly, the hormonal control of BMD maintenance in adult to older men is mainly under the guide of estrogens and to a lesser extent of androgens [17, 42]. Lesson from rare cases of men with aromatase deficiency indicates that the lowering of the dose of exogenous estradiol constantly results in a decrease of both serum estradiol and BMD in adult men [46]. Both cross-sectional [67–70] and longitudinal studies have demonstrated that serum estradiol is directly related to BMD in men and that its decline is responsible for bone loss in older men [17, 42, 50]. In particular, cross-sectional studies performed on large cohort of aging men have investigated the relationships among sex steroids (both testosterone and estradiol) and BMD [12]. The results of these studies are almost all in line with the finding of a direct correlation between serum estradiol and BMD [12, 71], such as in studies like the European Male Aging Study (EMAS) [72] and the Rancho Bernardo Study (RBS) [73, 74] or the Osteoporotic Fractures in Men Study (MrOS) in which BMD was positively and significantly correlated with bioavailable serum estradiol [75]. Besides, free serum estradiol was directly related to BMD measured at different sites in the MrOS and RBS [73, 75] and to calcaneus BMD in the EMAS [72]. The methodological approach of most of these studies is of great relevance since serum estradiol was measured by the gold standard liquid chromatography-tandem mass spectrometry (LC-MS/MS) as in the case of the MrOS [76] and the EMAS [77, 78]. Finally, a direct role of serum estradiol on fracture risk has been demonstrated in men by the outcomes of the MrOS [71].

All these studies have confirmed pioneer studies which pointed out on the relationships between estradiol and bone in men and that were performed in parallel

with the first descriptions of men with congenital aromatase deficiency [7, 19, 42]. In these studies, preliminary data on the role of estrogens on bone in men were provided. Serum E2 especially the bioavailable fraction resulted directly related to BMD in men by both cross-sectional [73, 79] and longitudinal [64, 80] studies. Several studies investigated the impact of the genotype of ER and of the gene encoding for the aromatase enzyme on BMD. Overall these studies demonstrated that polymorphisms of the ER-alpha gene are associated with bone loss in men [69, 81]. Similarly, other studies investigated the role of polymorphisms of the gene encoding for the aromatase enzyme on male bone demonstrating an association between some polymorphisms and bone loss [82, 83].

The most important limit of the studies performed at the end of the 1990s is that serum E2 was assayed with immunometric assays in clinical studies and that genetic studies were performed by means of traditional gene sequencing. These methodological flaws have been now overcome by the use of LC-MS/MS and next-generation sequencing, and the results of all these seminal studies have been largely replicated by using LC-MS/MS for the measurement of sex steroids (see above the results of large cohort studies for details) and next-generation sequencing for the genetic studies (see below for genome-wide association studies).

6.4 Estrogen Deficiency and Osteoporosis in Men

Estrogen deficiency in vivo is constantly associated with bone loss, which is the result of increased bone resorption and decreased bone formation. In men estrogen deficiency may occur as a consequence of congenital diseases resulting in a reduced production of estrogens (Fig. 6.2) or due to iatrogenic treatments blocking estrogen synthesis; in all these cases, serum testosterone is unaffected or may be slightly increased (Table 6.1). Furthermore, a condition of relative estrogen deficiency may develop in men with hypogonadism (Table 6.1) as a consequence of reduced levels of testosterone (the precursor of estradiol) depending on the efficiency (expression and activity) of the aromatase enzyme; in all these cases, relative estrogen deficiency is constantly associated with testosterone deficiency (Table 6.1). The decrease of serum estradiol as well as the severity of estrogen deficiency in men is related to several factors including hypogonadism, obesity, and individual genetic differences influencing the expression and activity of the aromatase enzyme (Fig. 6.2) [82–86]. In male hypogonadism the reduction of serum testosterone leads to a concomitant decrease of serum estradiol due to the reduction of androgen precursor to be aromatized (Fig. 6.1). Accordingly, Finkelstein et al. demonstrated by an elegant study design that the reduction of testosterone below 200 ng/dL is constantly associated with a corresponding decrease of serum estradiol below 10 pg/mL and with a significant change of bone turnover markers and a decrease of BMD [10]. Thus, relative estrogen deficiency in hypogonadal men is responsible to a great extent for bone loss, testosterone deficiency having a minor but contributing role to further decrease of bone mineral density [42]. The degree of relative estrogen deficiency depends on several factors. The amount of adipose tissue may

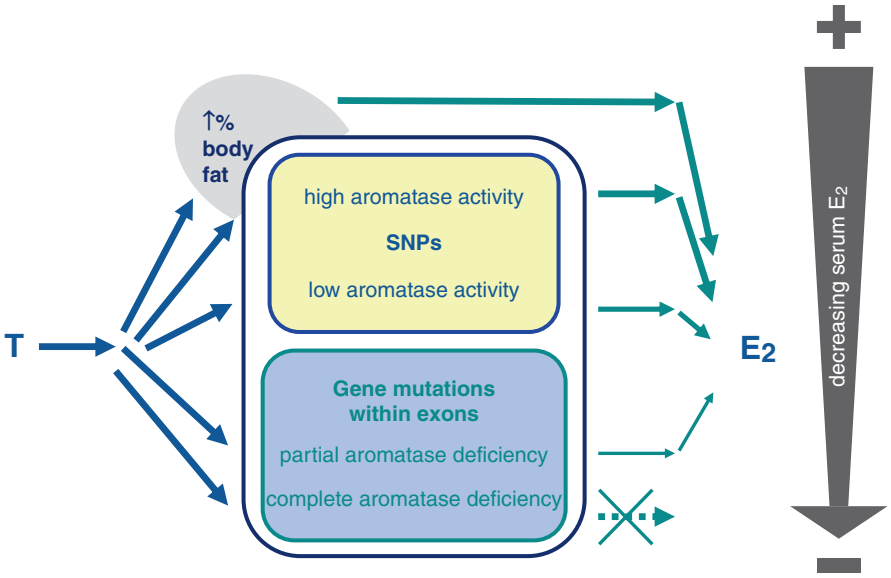


Fig. 6.2 Individual factors involved in the determination of the amount of circulating estrogens in men

Table 6.1 Cause of estrogen deficiency in men

Disease	Grade of ED	Type of estrogen deficiency
Acquired male hypogonadism in childhood	Mild to severe	Relative estrogen deficiency[a]
Acquired male hypogonadism in adulthood	Mild to severe	Relative estrogen deficiency[a]
Adult-onset male hypogonadism	Mild	Relative estrogen deficiency[a]
Congenital male hypogonadism *Isolated hypogonadotropic hypogonadism* *17 alpha-hydroxylase deficiency* *17,20-lyase deficiency* *P450 oxydoreductase deficiency*	Mild to severe	Relative estrogen deficiency[a]
Congenital male estrogen deficiency *Aromatase deficiency* *Estrogen resistance*	Severe	Estrogen deficiency in the presence of normal (or high) serum testosterone
Iatrogenic male hypogonadism *Androgen deprivation therapy* *Orchiectomy*	Severe	Relative estrogen deficiency[a]
Iatrogenic male estrogen deficiency *Aromatase inhibitors*	Mild to severe	Estrogen deficiency in the presence of normal (or high) serum testosterone

[a]Depending on the degree of hypogonadism (very low, low, or low to normal serum testosterone levels) and on the aromatase activity in terms of conversion rate of serum testosterone into estradiol

counterbalance the reduction of estradiol in serum, thanks to the increase of aromatase activity, which at the end ensures a high rate of androgen transformation into estrogens even in the presence of low serum testosterone notwithstanding hypogonadism (Fig. 6.2); this results in bone mass preservation and in prevention of bone loss [84]. Recently, several genetic variants of the aromatase enzyme resulted to be directly related to the amount of circulating estradiol (Fig. 6.2) and to BMD in a genome-wide association study including a large number of men (*n* 11,097) through Mendelian randomization analysis [87]. This study demonstrated that every genetically determined 1 pg/mL of estradiol results in a BMD increase of 0.048 standard deviation at lumbar spine [87]. The same group of research established that serum estradiol, but not testosterone, has a causal effect on bone fractures by studying 175,583 men using a Mendelian randomization approach [88].

In men estrogens lead to bone loss especially when they are very low in serum, a mechanism similar to that operating in women at the time of menopause [12]. Even though serum estradiol declines more slowly in aging men compared to women and does not reach very low values as in postmenopausal women [12], the amount of serum estradiol in men with hypogonadism or in older men may reach low levels below 20 pg/mL [89]. Evidence support a threshold for serum estradiol below which the loss of BMD becomes significant leading to an increased risk of osteoporosis and osteoporotic fractures. By using different methodological approaches, several studies pointed out a threshold which is comprised between 15 and 20 pg/mL below which BMD is severely impaired in men [10, 29, 42, 64, 89–95].

6.5 Unresolved Issues

At present, several cases of severe aromatase deficiency have been described in men [45, 49], but no data are available in men on the phenotype of partial aromatase deficiency, a clinical condition that has been already described in women [45, 96]. Theoretically, men with partial aromatase deficiency should present with a mild phenotype including detectable but lower than normal serum estradiol and osteopenia or osteoporosis [45, 86] (Fig. 6.2).

With the exception of rare cases of men with aromatase deficiency [45, 46], there are no data coming from interventional studies using estrogens in men with osteoporosis and concomitant relative estrogen deficiency. Furthermore, evidence about a possible role of selective estrogen receptor modulators (SERMs) in men needs to be investigated. At present, few data suggest that raloxifene have no effect on BMD in men [97].

6.6 Clinical Implications

Data coming from research setting have provided evidence about the major role estrogens play on the pathophysiology of bone in men. However, all these data have little impact in the clinical setting due to the fact that the measurement of serum estradiol by commercially available kits in clinical laboratories is inaccurate [86].

At present, the approach to male patients with osteopenia or osteoporosis is mainly based on the measurement of serum testosterone in order to rule in/rule out male hypogonadism. This empirical approach allows identifying all patients with low serum testosterone who may benefit from testosterone replacement treatment aiming to restore normal serum testosterone and normal serum estradiol. This approach, however, does not consider the possibility of tailoring the treatment using serum estradiol as a possible therapeutic target of testosterone replacement treatment thanks to the monitoring of serum estradiol changes from baseline. In clinical practice we know that there are many conditions for which the amount of serum testosterone and estradiol is not predictable. Accordingly, hypogonadal men having similar values of serum testosterone may differ in terms of serum estradiol depending on several factors (e.g., aromatase activity, aromatase expression, the percentage amount of tissues able to convert testosterone into estradiol) [50, 85, 89] (Fig. 6.3). On the other hand, men with normal serum testosterone may be estrogen-deficient if aromatization and the conversion rate of testosterone are downgraded [86]. Theoretically, the measurement of serum estradiol is needed to establish if a condition of relative estrogen deficiency (that is based on the finding of serum estradiol below the lowest limit of the normal range) is present [42, 86] (Fig. 6.3), but this diagnosis in men remains still challenging since the value of serum estradiol measured by means of commercially available immunometric kits is not accurate [3]. At present the measurement of serum estradiol is indicated to confirm the diagnosis in case of severe, congenital estrogen deficiency (i.e., aromatase deficiency and estrogen resistance) [45] (Table 6.1). Conversely, the measurement of serum estradiol is not recommended in the diagnostic work-up of men with osteoporosis [98, 99] and

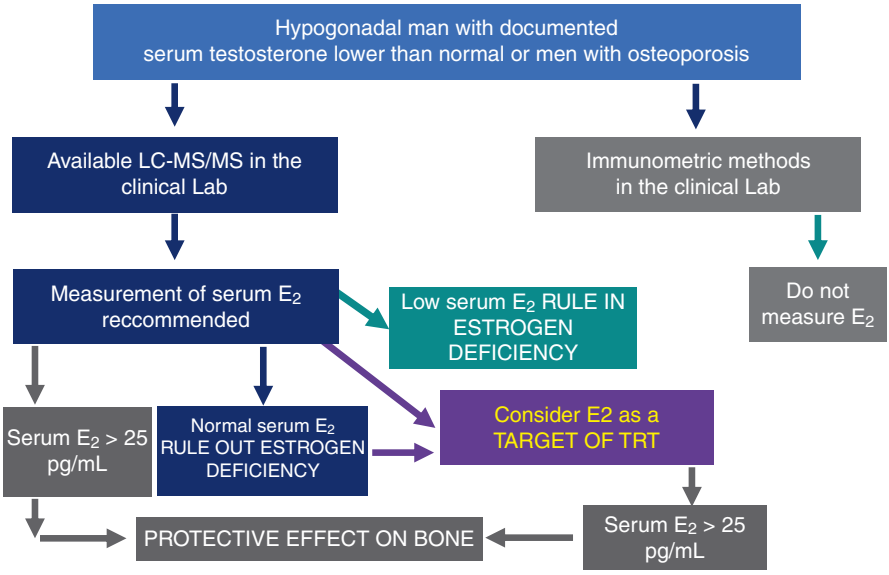


Fig. 6.3 Usefulness of the determination of serum estradiol in the work-up of male osteoporosis

of men with hypogonadism [98, 100, 101] as well as in the routine, clinical assessment of the male patient [86]. In the clinical setting, the measurement of estrogens is performed in clinical laboratories that usually use immunometric assays for the determination of circulating estrogens [86]. The immunometric assays provide measurements that are not accurate and are not reproducible when the amount of estrogens is low as it is in the normal male range [102, 103]. The immunometric assays are overall not reliable since they are less accurate and less reproducible than LC-MS/MS, which represents the gold standard method for the measurement of serum estrogens [102, 103]. Accordingly, the use of LC-MS/MS allows measuring serum estrogens with a high degree of accuracy even when they are very low as it happens in men [104, 105]. Thus, in *real life*, serum estradiol is not routinely assessed in men [86]. In the presence of accurate methods for the measurement of serum estradiol, however, the determination of circulating estrogens may be of help for the diagnosis of relative estrogen deficiency and for establishing if testosterone treatment is able to restore also normal serum estradiol [86] (Fig. 6.3). Accordingly, the dosage of testosterone needed to restore normal serum estradiol in hypogonadal men under TRT may vary individually due to several factors, and the normalization of serum testosterone not necessarily implies the achievement of normal values of serum estradiol (Fig. 6.2). Recently, Aguirre et al. pointed out the importance of targeting TRT considering also serum estradiol measured by LC-MS/MS as a target in men with hypogonadism since the response to TRT in terms of conversion to estradiol may change according to patient's genetic profile of aromatase, as we had previously hypothesized [50]. At present, a serum estradiol above 25 pg/mL may be considered protective for bone loss in men [29, 42, 86], and the more serum estradiol is higher within the normal range for men, the more bone mass maintenance is ensured [84]. Furthermore, the increasing number of laboratories that use the LC-MS/MS also for clinical purposes together with the advancement in the knowledge of normative values in the healthy men obtained by LC-MS/MS [104, 106] is changing the approach to the measurement of sex steroids in clinical laboratories. Since LC-MS/MS is cost-effective and time-consuming especially in clinical laboratories that manage a great number of sex steroid measurements per day, LC-MS/MS will probably replace immunometric assays in the near future [106]. At present, the measurement of serum estradiol must be included in the clinical work-up of the man with osteoporosis, especially when also hypogonadism is documented in all clinical setting where the measurement of gonadal steroids is obtained by means of LC-MS/MS (Fig. 6.3). The availability of accurate measurement of serum estradiol is of help for ruling in/ruling out the diagnosis of relative estrogen deficiency, for stratifying the risk of osteoporosis, and for monitoring the effects of TRT on serum estradiol, bearing in mind that a serum estradiol above 25 pg/mL exerts a protective role on bone [42, 50, 84–86] (Fig. 6.3).

In summary, the assessment of serum estradiol is recommended in clinical settings that are able to provide this measurement through LC-MS/MS; the goals of serum estradiol measurements are the diagnosis of the presence of relative estrogen deficiency other than low testosterone and the use of serum estradiol as a reliable target of testosterone replacement treatment (Fig. 6.3).

6.7 Conclusions

Estrogens are key hormones in the pathophysiology of bone in men. Estrogen deficiency is a clinical condition leading to bone loss and the development of osteoporosis, but is rarely considered in clinical practice as a consequence of imprecise methods for the measurement of serum estradiol within the normal male range. The advent of mass spectrometry for research investigation and its increasing use in the clinic will probably allow the endocrinologist to better define and treat all clinical conditions of estrogen deficiency in men in the next future.

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Vitamin D and Male Osteoporosis

7

Andrea Di Nisio and Carlo Foresta

7.1 Introduction

Vitamin D is a lipophilic hormone playing a key role in bone metabolism and calcium homeostasis [1], mainly acting by binding the vitamin D receptor (VDR), whose distribution involves almost all human tissues and cells. Interestingly, recent data have also demonstrated potential modulation of extraskeletal effects such as immune system, cardiovascular diseases, insulin resistance, type 2 diabetes and cancer [2], conditions commonly linked with obesity. Vitamin D derives from two sources: the most important is exposure to sunlight, accounting for approximately 80% of circulating vitamin D. During exposure to solar ultraviolet B (UVB) radiation (wavelength, 290 to 315 nm), 7-dehydrocholesterol in the skin is converted to pre-vitamin D3, which is immediately converted to vitamin D3 in a heat-dependent process [3]. Whereas vitamin D2 is manufactured through the ultraviolet irradiation of ergosterol from yeast, vitamin D3 is synthetized through the ultraviolet irradiation of 7-dehydrocholesterol from lanolin. Both are used in vitamin D supplements. Vitamin D can also be acquired from the diet [2]. Few foods naturally contain (i.e. oily fish) vitamin D [4]. Vitamin D2 and vitamin D3 from dietary sources are incorporated into chylomicrons and transported by the lymphatic system into the venous circulation. Vitamin D in the circulation is bound to the vitamin D-binding protein, which transports it to the liver, where vitamin D is converted by vitamin D-25-hydroxylase to 25-hydroxyvitamin D [25(OH)D], the major circulating form of vitamin D used by clinicians to determine vitamin D status [2] (Table 7.1). This form of vitamin D is biologically inactive and must be converted in the kidneys by 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1) to the biologically active form—1,25-dihydroxyvitamin D [1,25(OH)D] [3]. The renal production of

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Table 7.1 Vitamin D optimal serum levels (ng/mL)

	Institute of Medicine	Endocrine Society
Deficiency	0–30	0–20
Insufficiency	31–39	21–29
Sufficiency	40–80	30–100
Toxicity	>150	–

1,25-dihydroxyvitamin D is tightly regulated by plasma parathyroid hormone levels and serum calcium and phosphorus levels. The efficiency of the absorption of renal calcium and of intestinal calcium and phosphorus is increased in the presence of 1,25(OH)D [5]. In a negative feedback, the expression of 25-hydroxyvitamin D-24-hydroxylase (CYP24) is increased by 1,25(OH)D, which is excreted in the bile. 1,25(OH)D also enhances intestinal calcium absorption in the small intestine by interacting with the vitamin D receptor—retinoic acid x-receptor complex (VDR-RXR).

Nowadays, vitamin D biological effects are divided in skeletal and extraskeletal, the latter not tied to its role in the calcium and phosphorus metabolism [6]. It is well-known that vitamin D plays a pivotal role for normal bone development both in utero and in childhood, leading to optimal skeletal health in adults [3, 7]. Vitamin D fulfils its skeletal function acting directly on three target organs: the intestine, stimulating dietary calcium and phosphorus absorption in a parathormone (PTH) independent manner; the kidneys, where calcitriol with PTH increases the renal distal tubule reabsorption of calcium; and the bone, where both calcitriol and PTH stimulate osteoblasts to mobilize skeletal calcium stores [6, 7].

1,25(OH)D exerts its biological function on the bone by binding its receptor in osteoblasts, causing an increase in the expression of the receptor activator of nuclear factor-κB ligand (RANKL); RANK, the receptor for RANKL on preosteoclasts, binds RANKL, which induces preosteoclasts to become mature osteoclasts [8]. Mature osteoclasts remove calcium and phosphorus from the bone, maintaining calcium and phosphorus levels in the blood [8]. Adequate calcium (Ca^{2+}) and phosphorus (HPO_4^{2-}) levels promote the mineralization of the skeleton. Severe vitamin D deficiency causes two clinical syndromes: rickets in children and osteomalacia in adults [2].

The absorption of dietary calcium and phosphorus is reduced by 90% and 40%, respectively, when vitamin D is missing [9]. The interaction of 1,25(OH)D with VDR increases the efficiency of intestinal calcium absorption to 30–40% and phosphorus absorption to approximately 80% [9, 10]. In one study, serum levels of 25(OH)D were directly related to bone mineral density in white, black, and Mexican-American men and women, with a maximum density achieved when the 25-hydroxyvitamin D level reached 40 ng/mL or more [11]. When the level was 30 ng/mL or less, there was a significant decrease in intestinal calcium absorption [10] that was associated with increased parathyroid hormone. The deposition of calcium in the skeleton is also altered during foetal development if low levels of calcium and vitamin D are present in utero [12]. If vitamin D deficiency persists, the parathyroid glands are maximally stimulated, leading to secondary

hyperparathyroidism [2]. In particular, a study showed that 93% of subjects 10–65 years of age admitted to a hospital emergency department with muscle aches and bone pain, who had a wide variety of diagnoses, including fibromyalgia, chronic fatigue syndrome, and depression, were deficient in vitamin D [13], suggesting that vitamin D actions are not only limited to bone metabolism.

7.2 Vitamin D and Male Hypogonadism

Until a few years ago, the only connection between the testis and bone was the well-known action of testosterone on skeletal growth and bone mass accrual and, consequently, the role of hypogonadism in causing low bone mass and osteoporosis [14]. Testosterone replacement therapy alone in men with hypogonadism and osteoporosis is not sufficient to completely restore BMD, which suggests that alternative therapeutic approaches should be evaluated, such as the use of vitamin D supplements.

Population studies show an association between the levels of testosterone and 25-hydroxyvitamin D in men and highlight that men with primary and secondary hypogonadism, as well as those with compensated (subclinical) hypogonadism, are frequently deficient in vitamin D [15–17]. It has been demonstrated that the male reproductive tract expresses most of the enzymes involved in vitamin D metabolism. In particular, the testis is featured by the highest expression of CYP2R1, a member of cytochrome P450 family [18], considered to be a key enzyme of vitamin D activation through its 25-hydroxylase activity [19]. The physiological importance of CYP2R1 expression in the testis has been highlighted in the past few years in studies that suggested a pathophysiological link between testicular damage, reduced levels of 25-hydroxyvitamin D, and reduced bone mass [14]. Although definitive data are not available, there is an increasing evidence suggesting that an impairment of testicular function leads to low levels of 25-hydroxyvitamin D and consequently to an increased risk of osteopenia and osteoporosis [14]. Low vitamin D is frequent in this condition and seems to be more important than testosterone in inducing low bone mineral density (BMD) and osteoporosis. Supplementation with vitamin D restores BMD after 2 years of treatment, whereas testosterone alone seems to be ineffective. These data highlight that low 25-hydroxyvitamin D levels seem to have a more critical role than low T levels in inducing low BMD in KS subjects. Furthermore, vitamin D supplementation seems to be more effective than T replacement therapy alone in increasing BMD.

7.3 Vitamin D Supplementation

Vitamin D and calcium supplementation are often recommended for women, especially postmenopausal women, to prevent fractures, although actual use is uncertain. In order to prevent osteoporosis-related fractures, vitamin D 700–800 IU/day should be complemented with calcium, using a dose of 1000–1200 mg/day of

elemental calcium [20, 21]. Based on 2011–2012 data from the National Health and Nutrition Examination Survey, an estimated 27% of men and 35% of women older than 20 years take a vitamin D supplement, and 26% of men and 33% of women take a calcium supplement. The exact dosage of supplementation is not known [22]. Research is needed to determine whether daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium reduces fracture incidence in postmenopausal women and in older men. Prospective studies should assess the potential benefits of vitamin D and calcium supplementation in premenopausal women on fracture incidence later in life. Studies need to be adequately powered and should evaluate consistent fracture outcomes. Studies are also needed to evaluate the effects of vitamin supplementation on diverse populations. In a recent meta-analysis, vitamin D, with or without calcium, had no statistically significant effect on all-cause mortality or incident cardiovascular disease compared with placebo [22].

The Institute of Medicine (now the National Academy of Medicine) (2011) and the World Health Organization (2004) [24] recommend standards for adequate daily intake of calcium and vitamin D as a part of overall health. Neither organization has recommendations specific to fracture prevention. The Institute of Medicine notes the challenge of determining dietary reference intakes given the complex interrelationship between calcium and vitamin D, the inconsistency of studies examining bone health outcomes, and the need to limit sun exposure to minimize skin cancer risk. The National Osteoporosis Foundation supports the Institute of Medicine's recommendations regarding calcium consumption and recommends that adults 50 years or older consume 800–1000 IU of vitamin D daily [25]. The Endocrine Society recommends that adults 65 years or older consume 800 IU of vitamin D daily for the prevention of falls and fractures [26] (Table 7.2). The American Geriatric Society recommends that adults 65 years or older take daily vitamin D supplementation of at least 1000 IU as well as calcium to reduce the risk for fractures and falls [27].

In a recent paper published on *JAMA*, the US Preventive Services Task Force (USPSTF) concludes that the current evidence is insufficient to assess the balance of the benefits and harms of vitamin D and calcium supplementation, alone or combined, for the primary prevention of fractures in community-dwelling, asymptomatic men and premenopausal women [22]. However, these recommendations do not apply to persons with a history of osteoporotic fractures, increased risk for falls, or a diagnosis of osteoporosis or vitamin D deficiency.

Table 7.2 Recommended vitamin D daily intake

	Recommended vitamin D intake (IU/day)			
	Institute of Medicine		Endocrine Society	
Age	RDA	Upper limit	RDA	Upper limit
0–12 months	–	1000–1500	400–1000	2000
1–18 years	600	2500–4000	600–1000	4000
19–70 years	600	4000	1500–2000	10,000
>70 years	800	4000	1500–2000	10,000

In a recent meta-analysis of randomized clinical trials, the use of supplements that included calcium, vitamin D, or both compared with placebo or no treatment was not associated with a lower risk of fractures among community-dwelling older adults [28]. These findings did not support the routine use of these supplements in community-dwelling older people. A meta-analysis by Tang et al. [29] reported that calcium supplementation was significantly associated with the prevention of osteoporosis-related fractures. Prior analyses also reported favourable associations of high dose (≥800 IU daily) vitamin D supplementation and fracture incidence [30, 31]. Bischoff-Ferrari and colleagues [31] found that supplementation with 800 IU or more of vitamin D per day was associated with lower rates of hip fracture and nonvertebral fractures in adults 65 years or older. However, although the meta-analysis by Zaho and colleagues [28] reports no evidence of a protective role of vitamin D supplements on facture risk in non-hospitalized adults aged >50 years, it should be noted that this analysis has focused on healthy subjects. Consequently, the results of this study cannot be applied to people either already affected by osteoporosis or other pathologies of bone metabolism or to those already in therapy with bone-protective drugs. For these subjects, an adequate calcium intake and optimal vitamin D levels are crucial, in order to sustain the efficacy of anti-osteoporotic drugs. Moreover, some of the studies considered are low quality and show consistent differences in terms of dosage, formulation, and mode of administration of vitamin D supplements, and the concomitant use of calcium in association with vitamin D is inconsistent across studies. Despite these limits, Zhao and colleagues suggested that supplementation with vitamin D and calcium is not necessary in the general population, in which prevention campaigns should be pursued in order to sustain an adequate intake of calcium and vitamin D by the means of a correct nutrition and sun exposure. However, these preventive strategies are not always sufficient to achieve normal vitamin D levels in risk populations, in which cases pharmacological supplementation is necessary.

Finally, more in-depth analyses are required to study the impact of vitamin D deficiency on bone health during infancy [32]. Indeed, epidemiological studies from Europe [33–37], the Middle East [38], North America [39], and Oceania [40, 41] suggest that low vitamin D in children should be a health concern worldwide. In 2011, the Institute of Medicine defined that the adequate nutritional vitamin D intake in newborns (0–12 months) should be 400 IU and the daily dose in children (1–18 years) should be 600 IU [23].

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Testicular Function and Skeletal Alterations

8

Alberto Ferlin

8.1 Introduction

Testicular function is essential for bone metabolism during the entire life of a man. Sex hormones, and in particular testosterone produced by the Leydig cells of the testis, are fundamental during development and puberty for skeletal growth and bone mass accrual and during adulthood to maintain bone metabolism. Indeed, the role of hypogonadism in causing low bone mass and osteoporosis is well-known, low testosterone levels being among the most frequent causes of secondary male osteoporosis [1, 2]. In fact, clinical guidelines [3–5] suggest that the diagnosis of male hypogonadism in general and in men with osteoporosis in particular can be made biochemically by the determination of testosterone levels. Nevertheless, testosterone replacement therapy alone does not completely restore bone mass in men with hypogonadism and osteoporosis [4, 5].

Basic and clinical researches in the past few years now provide new information on the crosstalk between the testis and bone, highlighting in particular different functions of the Leydig cells of the testis, other than steroidogenesis and testosterone production, able to maintain the bone health.

First, Leydig cells produce insulin-like 3 (INSL3), which has a role in osteoblast function [6–8]. INSL3 is a peptide hormone produced under the long-term regulatory effects of luteinizing hormone (LH), and it is increasingly used as a marker of Leydig cell function, as an alternative to testosterone [9–16]. Reduced plasma levels of INSL3 are observed in many conditions characterized by disturbed Leydig cell function, such as infertility, obesity, and Klinefelter syndrome, as well as in aging [9–16]. Second, Leydig cells express the *CYP2R1* gene [17, 18], which encodes the major enzyme involved in 25-hydroxylation of vitamin D. Testosterone and 25-hydroxyvitamin D levels are associated, and

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hypogonadal men (primary, secondary, and subclinical hypogonadism) have frequently vitamin D deficiency [18–21].

A reciprocal effect from the skeletal system to the testis has also been demonstrated. In fact, osteocalcin, a major product of osteoblasts and a marker of bone formation, is released from the bone matrix during the resorption phase and has a role in steroidogenesis and testosterone production by binding to the G-protein-coupled receptor GPRC6A on Leydig cells [22, 23]. Osteocalcin-deficient mice and Gprc6a-deficient mice have reduced testis size and fertility and markedly decreased testosterone levels [22, 24]. The discovery of the endocrine effects of osteocalcin has important consequences in the andrological setting [25]. Indeed, not only a positive association between serum levels of testosterone and osteocalcin exists [26], but also GPRC6A has been identified as the putative membrane-associated receptor for androgens [27], revealing a complex testis to bone crosstalk unconceivable until a few years ago (Fig. 8.1).

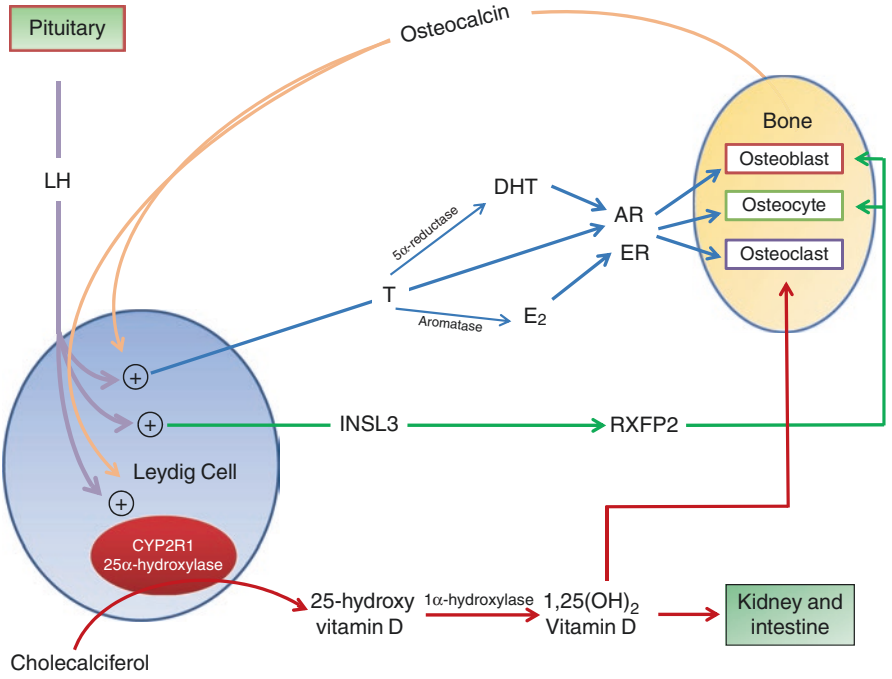

Fig. 8.1 The crosstalk between the testis and bone. The Leydig cell, under the effect of LH, acts on bone metabolism by producing testosterone (T) and INSL3 and expressing the CYP2R1 enzyme that hydroxylates cholecalciferol to 25-hydroxyvitamin D. T, directly or after conversion to DHT and estradiol (E_2), acts on bone cells through the androgen receptor (AR) and estrogen receptor (ER), respectively, whereas INSL3 acts through its receptor RXFP2. 1,25-dihydroxyvitamin D regulates calcium homeostasis and bone metabolism by acting on the kidney, intestine, and osteoblasts. The osteoblast protein, osteocalcin, promotes testosterone production in the Leydig cell by activating steroidogenesis enzymes and stimulates CYP2R1

8.2 Testosterone, Hypogonadism, and Bone

As discussed in other chapters of this book, bone mass and metabolism are regulated by sex steroid hormones. Both testosterone and estrogens are necessary for bone growth and for the maintenance of skeletal integrity [1, 28], by genomic and genomic effects of their respective receptors [28–32].

The increase in the production of sex steroids at the start of puberty is clearly linked to an increase of bone mineral acquisition during this period and contributes to the establishment of sex differences in bone growth. From mid-puberty onward, boys develop a larger periosteal perimeter than girls, while girls have more endocortical apposition [30]. Moreover, men gain more bone mass during growth and lose less of it during aging than women [32]. The traditional hypothesis is that in males, androgens stimulate periosteal bone formation, whereas estrogens in females inhibit periosteal bone formation [32]. Androgens, through the AR pathway, are particularly effective stimulators of trabecular bone, where they preserve or increase trabecular numbers via suppression of trabecular reabsorption, which reduces trabecular spaces and, therefore, increases trabecular number [33]. The role of testosterone is, therefore, fundamental in bone maturation at the end of puberty for bones to reach their peak mass and during adult life to maintain it.

Although studies performed in elderly men found that bone mineral density (BMD) is more tightly correlated to estradiol levels than to testosterone levels [34–37], testosterone undoubtedly has a role in maintaining bone integrity, and male hypogonadism is a well-characterized risk factor for osteoporosis [2]. The prevalence of hypogonadism among men with osteoporosis is not clearly known but is present in 20% of men with vertebral fractures and 50% of men with hip fractures [38]. Furthermore, men with hypogonadism have a significantly lower BMD than age-matched men without hypogonadism [39]. Furthermore, testosterone exerts its beneficial effect on skeletal growth and homeostasis by increasing mechanical loading [31]. In fact, testosterone increases muscle mass and strength, which are fundamental for bone health.

8.3 Leydig Cell Function and Bone Health Beyond Testosterone

Other than testosterone production, the Leydig cells influence bone metabolism by at least two other functions: the production of INSL3 and the expression of *CYP2R1,* which leads to low levels of 25-hydroxyvitamin D. Interestingly, INSL3 and 25-hydroxyvitamin D levels are lower than normal not only in cases of overt hypogonadism but also in cases of subclinical hypogonadism (normal testosterone, high LH) [19, 40], a condition that is also associated with the risk of low BMD.

INSL3 is a testis-specific hormone secreted by Leydig cells with a role in testicular descent [41, 42] and other less clear roles adulthood. The molecular mechanisms by which INSL3 acts on human osteoblasts to have an anabolic effect have been clarified [7, 8]. The activation of the G-protein-coupled receptor RXFP2 by INSL3

induces an increase in levels of cAMP, activation of the MAP kinase cascade, expression of key osteoblast genes involved in osteoblast differentiation, matrix deposition and osteoclastogenesis, and finally stimulation of mineralization.

A possible role for INSL3 in bone metabolism was first suggested 10 years ago [6]. Subsequent researches, clearly defined that INSL3, in addition to testosterone, represent a further male-specific factor that regulates bone metabolism in men and mice [8]. Osteoblasts and osteocytes [43] are the main INSL3-responsive cell. Mutations in *RXFP2* are associated with reduced BMD [6, 44] and reduced INSL3 levels are observed in cases of male hypogonadism. Interestingly, levels of INSL3, similar to levels of testosterone, increase during puberty, and therefore, pubertal changes and sex-specific differences in bone development might be attributed to both hormones [14].

It is well-known that vitamin D is a fundamental regulator of bone mineralization and calcium homeostasis [45]. In order to be biologically active, vitamin D must be converted to its active form, 1,25-dihydroxyvitamin D_3, by two sequential hydroxylation steps catalyzed by 25-hydroxylase and 1α-hydroxylase, respectively. Different P450 vitamin D 25-hydroxylases exist, the one encoded by *CYP2R1* being considered the most important. In fact, inactivating mutations in *CYP2R1* result in selective 25-hydroxyvitamin D deficiency, defective calcium homeostasis, and rickets [46–49], and genome-wide association studies showed that common variants at the *CYP2R1* locus are associated with variations in circulating levels of 25-hydroxyvitamin D_3 [50]. Interestingly, the expression of CYP2R1 is highest in the testis [18, 47, 51, 52].

In the last few years, it has been demonstrated the pathophysiological role of testicular CYP2R1. In very summary, a link between testiculopathy, reduced levels of 25-hydroxyvitamin D_3, and alteration of the bone status has been shown [17, 53, 54]. In particular, it has been estimated that the testis accounts for ~60% of 25-hydroxylation and it is now well accepted that testiculopathy of any cause could have a role in the pathogenesis of vitamin D insufficiency, through impaired 25-hydroxylase activity [53, 55].

The expression of CYP2R1 has been detected in Leydig and spermatogenic cells, and mRNA expression of CYP2R1 is reduced in the testes that have a complete absence of germ cell (Sertoli cell-only, SCO) histology [18, 56, 57]. In general, about half of the patients with SCO and severe hypospermatogenesis have insufficient levels of 25-hydroxyvitamin D (<50 nmol/L) and osteopenia or osteoporosis. Importantly, vitamin D levels are lower than normal not only in cases of overt hypogonadism but also in cases of subclinical hypogonadism, suggesting that low 25-hydroxyvitamin D levels might be regarded as a novel and sensitive marker of testicular function. On the other hand, patients with testiculopathy seem to represent a group of men at risk of low BMD, despite conserved bone-sparing effects of androgens and estrogens [5, 17, 53].

Interestingly, CYP2R1, similar to other cytochrome P450 enzymes [58], is stimulated in the Leydig cell by LH and human chorionic gonadotropin (hCG). In fact, the expression of CYP2R1 is increased in a dose-dependent manner by hCG in a Leydig cell line (MA-10), and 25-hydroxyvitamin D levels increase in patients with

hypogonadotropic hypogonadism after treatment with hCG [54]. A further complete loop between the testis and bone derived furthermore from the demonstration that also osteocalcin stimulates CYP2R1 [59].

Indeed, from a clinical point of view, it is important to note that several studies have demonstrated a relationship between plasma levels of testosterone and 25-hydroxyvitamin D [19–21]. Notably, primary and secondary hypogonadism, as well as compensated hypogonadism, seem to be associated with suboptimal and deficient vitamin D levels with similar high prevalence, about 30% and 50%, respectively [19]. Studies also suggested a role for vitamin D in stimulating testosterone production [60], further complicating the complex interplay between testis function and calcium-phosphorus metabolism.

8.4 INSL3 and 25-Hydroxyvitamin D as Biomarkers of Leydig Function

Evidence is accumulating to suggest that in male hypogonadism, bone metabolism might be altered by a combination of low testosterone and low levels of INSL3 and 25-hydroxyvitamin D. However, INSL3 production and 25-hydroxylation of vitamin D are more susceptible than steroidogenesis to Leydig cell impairment. Therefore, also forms of subclinical hypogonadism (normal testosterone and elevated LH) might be associated with reduced levels of INSL3 and 25-hydroxyvitamin D. In other words, when testosterone is normal but LH levels are higher than normal, INSL3 and 25-hydroxyvitamin D might be used as early markers of the functional state of the Leydig cell [8, 40, 55].

International guidelines on male hypogonadism suggest determination of testosterone levels, in association with specific signs and symptoms, as the main parameter for the diagnosis and treatment choice of men with hypogonadism. In most cases, reduced testosterone levels will be sufficient to biochemically diagnose hypogonadism in general and in men with osteoporosis. However, patients with mild testicular dysfunction are also at risk of bone alteration, owing to low INSL3 production and CYP2R1 expression. These men have normal testosterone levels, so they would be missed if only testosterone levels are assessed. In this light, in addition to patients with overt hypogonadism, “new” categories of individuals, affected by mild Leydig cell impairment (e.g., those with infertility, obesity, testicular cancer, cryptorchidism, or aging) should be considered at risk of bone alterations.

8.5 Conclusion

The crosstalk between the testis and bone is much more complicated than just one directional mediated by testosterone. Leydig cell function has been demonstrated to be fundamental for bone health at least in other two ways, INSL3 production, which has a role on osteoblast and osteocyte function, and 25-hydroxylation of vitamin D by the CYP2R1 enzyme.

Implications also for treatment are derived from these novel physiologic axes. Testosterone replacement therapy in men with hypogonadism and osteoporosis is not sufficient to completely restore BMD, suggesting that alternative therapeutic approaches should be evaluated in future studies, such as the use of vitamin D supplements. Similarly, the best therapeutic strategy of osteopenia and osteoporosis in men with subclinical hypogonadism is unknown. Testosterone therapy, by suppressing LH, does not maintain the full actions of the Leydig cells, further reducing INSL3 and 25-hydroxyvitamin D levels. Therefore, at least patients with hypogonadotropic hypogonadism and normogonadotropic hypogonadism should benefit from the stimulation of the Leydig cell function by hCG, thus allowing to maintain testosterone, INSL3, and 25-hydroxyvitamin D levels. Studies dealing with these aspects are welcome.

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Osteoporosis in Klinefelter Syndrome

9

Riccardo Selice

Patients with Klinefelter syndrome (KS) have a high risk of developing osteoporosis and osteopenia and an increased risk of fractures [1, 2]. KS is associated with decreased bone mass in 25–48% of cases [3] and with osteoporosis in 6–15% [4] and is due to both reduced bone formation and higher bone resorption [5]. The annual decrease in bone mass rate in KS has been calculated in 1.18 ± 0.53% at the lumbar level and 1.03 ± 0.43% at the femoral neck level [6].

It is generally accepted that a bone density *T*-score at or below 2.5 standard deviations (SD) below normal peak values for young adults defines osteoporosis, whereas a *T*-score between −1 and −2.5 SD defines osteopenia (Table 9.1). For younger men both *T*-score and *Z*-score could be used for the diagnosis of low BMD, with a *Z*-score < 2 SD below the gender- and age-specific population mean identifying osteoporosis.

Young KS subjects have normal bone density in childhood and at the beginning of pubertal development [2]. During the later stages of puberty KS subjects develop a progressive testicular failure leading to primary hypogonadism. Such a deficiency in testosterone production during puberty represents the most important risk factor for reduced bone mass and osteoporosis in KS, although there are other possible hormonal modulators of bone metabolism (Table 9.2).

Decreased bone mass in KS has usually been attributed to hypogonadism, and supporting this hypothesis testosterone plasma levels has been shown to positively correlate with BMD in these subjects [6–9]. Similarly to that observed in hypogonadal non-KS patients, bone histology of KS subjects demonstrated loss of cancellous tissue, profound depression of osteoblast activity, decreased osteoid seam width, and slowing of the apposition rate [10]. These findings have not been documented in KS subjects with normal testosterone levels who have a normal cortical bone mass [7].

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Table 9.1 Diagnostic criteria for osteoporosis in men

Age	Criteria
<50	The diagnosis should be made on the basis of both *T*-score and *Z*-score. Some authors recommend to using only the *Z*-score (low BMD when *Z*-score < −2 SD, osteopenia if *Z*-score < −1 SD)
50–64	*T*-score ≤ 2.5 SD at both spine and hip plus risk factors for fracture
≥65	*T*-score ≤ 2.5 SD
Any age + secondary causes of low BMD	*T*-score ≤ 1 SD

Table 9.2 Possible mechanisms contributing to osteoporosis in KS

Low testosterone levels
Low vitamin D levels
Low AR expression
Non-random X chromosome inactivation and AR CAG length
Low INSL3 levels
Unfavorable fat/muscle ratio

However, several studies showed that testosterone replacement in KS men with low testosterone levels and low BMD does not reverse the decreased bone mass [11, 12]. This was more evident when testosterone replacement therapy was started after puberty, also after many years of therapy [4]. On the contrary, other studies showed that androgen replacement therapy starting in young age (i.e., before 20 years) can lead to normal BMD [8]. Of particular interest is the finding of reduced bone mass also in KS subjects with normal testosterone levels [9] and of similar prevalence of low BMD in KS men with low and normal T levels [12], suggesting that bone loss in KS might be, at least in part, independent from the presence of hypogonadism.

On this basis other possible mechanisms contributing to osteoporosis in KS must be considered.

Even if estradiol levels are generally normal or high in this syndrome, low estrogen levels have been related to decreased bone mass in these patients in some studies [13, 14], and estradiol levels are inversely related to the rate of bone loss [6]. However, these data have not been replicated, and conclusions on this possible pathogenic mechanism cannot be made.

Another possible mechanism involved in the development of bone loss in KS might be related to the unfavorable fat/muscle ratio caused by increased fat mass and reduced muscle mass [1, 15]. However, it is not clear whether such an altered ratio is caused exclusively by the low testosterone levels or by other mechanisms related to the genetic defect. In fact, studies suggested that the unfavorable fat/muscle ratio is already present in young adolescents, whereas bone mass defects appear in late puberty or later [2].

Recent research suggested other possible pathogenic mechanisms of reduced BMD in KS, related in particular to the AR function, to insulin-like factor 3 (INSL3) and 25-hydroxyvitamin D levels.

The first exon of the AR gene encodes for the transactivation domain of the AR protein. It contains the highly polymorphic CAG repeat, the length of which is inversely correlated with androgen sensitivity [16]. Although the length of CAG repeat has been associated with different disorders (male hypogonadism, cryptorchidism, prostate cancer, testicular cancer), conflicting data have been published on the relation between it and bone metabolism. The CAG polymorphism of the AR has been reported to be negatively and independently associated with BMD, in particular in young men [17, 18]. On the contrary, another study found on the contrary a positive relation, explained with the negative feedback of CAG-related AR sensitivity on testosterone concentrations and thus on higher estrogen levels, with a global positive effect on BMD [19].

A certain degree of androgen resistance has previously been reported in KS [3, 20], with a decreased activity of bone 5-α-reductase [21] and a lower peripheral AR expression on lymphocytes [22], testis [23], and smooth muscle cells [24]. However, the AR expression in the bone has never been studied in KS.

Another important aspect of AR is that the AR gene is located on the X chromosome (and therefore present in double copy in KS) and there is evidence of non-random X inactivation in men with more than one X chromosome [25]. In KS the CAG polymorphism length depends on the inactivation rate of the two X chromosomes by methylation. Therefore, the effective CAG repeat value in heterozygous KS men for the CAG polymorphism of the AR gene is calculated after the analysis of the methylation rate in the two X chromosomes in order to obtain a X-weighted biallelic mean, not an arithmetic mean [26]. In this way, a relation with different clinical outcome and response to testosterone therapy was found, with a statistically significant negative correlation between bone density evaluated by phalangeal ultrasound and the X-weighted biallelic mean of CAG repeats [26], as previously shown in normal men [17]. Moreover, a higher inactivation rate of shorter alleles has been described, thus determining a less functional AR [26].

This was the first important finding, suggesting that reduced testosterone levels are not the only cause of decreased bone mass in KS subjects and that additional factors related to the androgenic status might contribute to the altered bone metabolism in subjects with KS. A non-random X inactivation and lower androgen function could therefore be, at least in part, responsible for or contribute to decreased bone mass in KS, particularly evident in those patients with normal testosterone concentration. Thus, this mechanism could explain not only the high prevalence of decreased BMD in eugonadal KS patients but also the frequent ineffectiveness of testosterone replacement therapy in improving BMD in KS.

Another important aspect related to testicular failure and bone metabolism in KS is the circulating levels of INSL3. INSL3 is a protein hormone produced almost exclusively by pre- and post-natal Leydig cells of the testis [27–29]. The major known endocrine role of INSL3 is related to the regulation of testicular descent during fetal development by acting on gubernaculum via its specific receptor RXFP2 (relaxin family peptide 2) [30, 31]. In addition to the prenatal role for INSL3, further possible endocrine and paracrine actions in adult males have recently gained particular attention [27, 32, 33]. These studies showed that INSL3 is produced

constitutively but in a differentiation-dependent manner by the Leydig cells under the long-term Leydig cell differentiation effect of LH. On this basis INSL3 has been proposed as a specific marker of Leydig cell differentiation status [27, 29, 32].

The dynamic of circulating levels of INSL3 is very similar to that of testosterone. After birth, INSL3 increases at about 3 months of age under the increased levels of LH (minipuberty) [34]. Soon after, INSL3 declines to undetectable levels and remains low during infancy [34] and then progressively increases throughout puberty [35]. Finally, INSL3 levels in adulthood decline steadily throughout life, and at 75–80 years INSL3 concentrations are reduced by about 40% with respect to levels found at 35–40 years [36]. Reduced plasma concentrations of INSL3 are seen in situations of undifferentiated or altered Leydig cell status or reduced Leydig cell number, such as in anorchid men and men with hypogonadism, infertility, or obesity [27, 32, 36].

Although the exact role of post-natal INSL3 is not fully understood, the general hypothesis is that reduced INSL3 activity (caused by altered testicular function, *INSL3* or *RXFP2* gene mutations) could cause or contribute to some symptoms and signs of hypogonadism, such as reduced BMD. RXFP2 is expressed in many tissues besides the gubernaculum, including the kidney, skeletal muscle, thyroid, pituitary gland, brain, and bone marrow [27, 37, 38], and paracrine roles for INSL3 have been suggested in the testis, ovary [39], thyroid [40], and mammary gland [41]. Most importantly, it has been shown that human and mouse osteoblasts express the INSL3 receptor and that young adult men carrying the T222P mutation of the *RXFP2* gene and with normal testosterone levels are at significant risk of reduced bone mass and osteoporosis [42]. Consistent with the human phenotype, bone histomorphometric and μCT analyses at the lumbar and femoral sites of *Rxfp2*$^{-/-}$ mice showed decreased bone volume, alterations at the trabecular bone, reduced mineralizing surface, bone formation, and osteoclast surface [42]. These data suggested a functional osteoblast impairment causing a negative balance between bone formation and bone resorption in mice knockout for *Rxfp2* and in humans with mutations in *RXFP2*.

Only one study examined INSL3 levels during puberty in boys with KS, showing a normal increase in serum INSL3 at initial stages of puberty and then a leveling off [43]. Few studies examined INSL3 in adult men with KS, reporting that adult KS with reduced testosterone levels had also very low levels of INSL3 [27]. These preliminary data suggested that INSL3 could be a valuable marker of Leydig cell function in KS. Taken together these findings, although preliminary, would suggest that the low INSL3 levels observed from mid-puberty onward in KS could have a role in the reduced bone density and osteoporosis in these subjects.

Vitamin D levels might be another possible modulator of bone metabolism in KS. Vitamin D is a key regulatory factor of bone mineralization and calcium homeostasis in both men and women [44]. In order to be biologically active, vitamin D must be converted to its active form, 1,25-dihydroxyvitamin D3, by two sequential hydroxylation steps catalyzed by 25-hydroxylase and 1α-hydroxylase. In the presence of inadequate vitamin D status, calcium absorption is lower than optimal, and there is a compensatory increase in PTH levels (secondary hyperparathyroidism),

with a subsequent stimulation of bone reabsorption and accelerated bone loss. The high bone turnover associated with elevated PTH levels is characterized by a lower degree of mineralization [45].

It has been demonstrated that the male reproductive tract expresses most of the enzymes involved in vitamin D metabolism. In particular, the testis is featured by the highest expression of CYP2R1, a member of cytochrome P450 family [46], considered to be a key enzyme of vitamin D activation through its 25-hydroxylase activity [47].

The physiological importance of CYP2R1 expression in the testis has been highlighted in the past few years in studies that suggested a pathophysiological link between testicular damage, reduced levels of 25-hydroxyvitamin D, and reduced bone mass [48]. Impairment of testicular function leads to low levels of 25-hydroxyvitamin D and consequently to an increased risk of osteopenia and osteoporosis [48].

Few recent reports determined 25-hydroxyvitamin D levels in KS [12, 49, 50], demonstrating that KS subjects have 25-hydroxyvitamin D levels lower than healthy controls, with mean levels of 50–55 nmol/L.

It has been hypothesized that low 25-hydroxyvitamin D levels in KS subjects seem to be related to the severe testicular hypotrophy and Leydig cell impairment, which are characteristic signs of these subjects. A recent study has demonstrated that lumbar and femoral BMD in KS were positively associated with 25-hydroxyvitamin D and patients with 25-hydroxyvitamin D deficiency had lumbar and femoral BMD significantly reduced with respect to KS subject with 25-hydroxyvitamin D ≥50 nmol/L. These findings are supported by the significantly higher percentage of patients with osteopenia or osteoporosis among men with 25-hydroxyvitamin D deficiency with respect to KS patients with vitamin D ≥50 nmol/L [12].

Decreased bone mass in men with KS is of course multifactorial. Reduced testosterone levels play undoubtedly an important role, but genetically determined reduced androgen action on the bone by a non-random X chromosome inactivation and different CAG length polymorphism of the AR gene as well as low INSL3 and 25-hydroxyvitamin D levels might cooperate and modulate the effect of testosterone. The combined effect of all these factors at the end of puberty and during young adulthood could therefore represent the pathogenic mechanisms leading to the precocious decrease in bone mass in KS patients.

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Lifestyle and Osteoporosis Risk in Men (Physical Activity, Diet, Alcohol Abuse)

10

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10.1 Diet

Historically, an adequate diet, with a correct intake of vitamin D and balanced intake of proteins, carbohydrates, and fats, may be useful to achieve optimal peak bone mass even at a young age. Studies have also gone beyond single nutrient associations and linked foods, food groups, and dietary patterns with bone health. It is important to synthesize this body of work to determine which dietary approaches can be maximized for optimal bone health and osteoporosis prevention.

Fruits and vegetables provide a multitude of micronutrients such as vitamin K, folate, magnesium, potassium as well as antioxidants such as vitamin C and carotenoids. Higher fruit and vegetable intakes have been associated with higher BMD and less BMD loss over time [1]. A more recent study in middle-aged and older men linked fruit and vegetable intake less than the recommended 5 servings/day with higher risk of hip fracture [2].

An amount of evidence suggests the role of selected nutrients in male bone health. Antioxidants such as vitamin C suppress osteoclast activity through their antioxidant action and promote bone formation by mean of osteoblastic cells [3]. Nowadays, a complex association involves interaction of nutritional factors such as vitamin C, vitamin E, and calcium intake [4] and

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non-nutritional factors such as smoking [5]. Among male smokers, higher dietary vitamin C intake was associated with less femoral neck BMD loss [6]. While in male non-smokers, total vitamin C intake was positively associated with femoral neck BMD and a lower hip fracture risk [7].

Several studies show a protective role of carotenoids for BMD and fracture risk in older adults with most consistent results for lycopene intake. In men, intakes of total carotenoids, β-carotene, lycopene, and lutein+ zeaxanthin were protective against trochanter [8] and hip bone loss [9]. Evidence-based medicine suggests a controversial role of vitamin K, and there are weak evidence supporting low vitamin K status as a risk factor for poor bone health [10]. Several studies suggest folate may not be important for bone health, while low vitamin B12 status may be a modest risk factor for fracture. Supplementation with vitamin B12 and folic acid has shown mixed results [11, 12]. Thus, little evidence supports folate or vitamin B12 supplementation to prevent fracture. In addition to protein, certain seafoods (>3 serving per week) are higher in polyunsaturated fatty acids (PUFA) and specifically the *n*-3 fatty acid (FA) family, which have been positively linked with bone health due to their anti-inflammatory properties [13]. The association between PUFA and risk of hip fracture remains uncertain. In the Framingham Original Cohort, dietary alpha-linolenic acid (ALA; *n*-3 FA) was protective against hip fracture over 11 years of follow-up [14]. In men, those in the highest quartiles of arachidonic acid intakes (*n*-6 FA) had an 80% lower risk of hip fracture than those in the lowest quartile of intake. Well-designed clinical trials are needed to elucidate whether bone health can be improved by greater fish intake and test whether certain individual PUFA are driving these effects. Nowadays, it is well recognized that olives, olive oil, or olive polyphenols have the potential to be developed as bone protective agents. This is supported by evidence derived from preclinical studies using animal models and a limited number of human studies. The bone protective effects of olive and its products are attributed to their ability to increase bone formation and inhibit bone reabsorption, by suppressing oxidative stress and inflammation. However, the exact pathways are still elusive and await future validation [15]. Other nutritional factors, such as inadequate protein intake, may also play a role in accelerating age-related bone loss in men [16]. Protein intake has been implicated in previous studies as being both detrimental and beneficial to bone health [17]. Recent studies suggest that the influence of protein on bone health may differ according to calcium intake. Greater protein intake benefits BMD and protects against risk of fracture among adults with adequate calcium intake. Thus, calcium intake modifies the association of dietary protein with bone measures [18]. The presence of calcium mineral as a major constituent of bone clearly suggests the importance of adequate calcium and vitamin D status for skeletal health. Dietary calcium intake and endogenous vitamin D synthesis are sufficient for most individuals in many populations. However, there are evidence that supplemental approaches [19–21], particularly targeted to individuals with inadequate calcium and vitamin D status, may benefit bone mass and reduce fracture risk [22]. The average daily intake of calcium in the general population is insufficient, especially in the elderly. This dietary deficiency may contribute to a negative calcium balance and induce secondary hyperparathyroidism, with

detrimental consequences. The recommended dietary allowance of calcium varies depending on age and specific conditions [23]. It is recommended, whenever possible, to increase calcium intake through diet. The dose of calcium supplements should be selected based on the dietary deficiency. Therefore, it is recommended to achieve an adequate calcium intake through diet, limiting the use of calcium supplements to situations where this is not feasible and only until the daily allowance has been achieved [24]. Additionally, most of medications for osteoporosis treatment, such as bisphosphonates, are licensed in the context of calcium and vitamin D repletion [25]. Thus, the knowledge of dairy foods can be a good tool for physician. Dairy foods are an essential resource of bone-building nutrients; numerous studies have examined whether dairy food intake (mainly milk) confers protection against osteoporosis. Daily milk and milk+ yogurt intake may lower risk for hip fracture in older adults through mechanisms that are partially, but not entirely, attributable to effects on BMD [26]. Lately, preliminary data show a positive correlation between bone health status and adherence to Mediterranean diet (MD), suggesting that a high adherence to MD promotes bone health [27].

10.2 Alcohol Abuse

Alcoholism is a disease characterized by a dependency on alcohol. Since alcohol affects almost every organ in the body, chronic heavy drinking is associated with many serious health problems, including pancreatitis, liver disease, heart disease, cancer, and osteoporosis. Alcohol negatively influences bone health for several reasons. Past findings agree with in vitro studies that demonstrate diminished osteoblast numbers and osteoblast function in humans, suggesting a direct effect of alcohol on osteoblast by mean of a reduction of biosynthesis of osteocalcin [28]. Microscopic studies of bone tissue from rats demonstrated decreased trabecular bone volume, decreased numbers of osteoblasts, and decreased rate of bone formation. These experimental evidence suggests impaired bone formation and mineralization, along with other characteristics indicative of osteoporosis [29]. These effects on the bone may be exerted indirectly through the many cell types such as hormones and growth factors that regulate bone metabolism. Men with alcoholism have a reduction of biosynthesis of several hormones such as testosterone and IGF-1 and cortisol; these hormonal changes have a negative impact on osteoblastogenesis [30]. Excessive alcohol interferes with the balance of calcium. Calcium balance is further disrupted by the alcohol's ability to interfere with the production of vitamin D essential for calcium absorption [31], with a secondary normal-elevated levels of parathyroid hormone (PTH) [32].

Clinical studies investigating alcohol intake and bone health suggest a "J"-shaped curve, where moderate ingestion of alcohol may offer maximum protection; however, intakes beyond this level show negative effects on the skeleton [33]. Chronic heavy alcohol consumption is associated with decreased BMD [34–36] and increased fracture risk [37–39], but there have been notable discrepancies. In contrast moderate drinkers (for men ≥3 day per week with a

consumption ≤28 g/day ethanol) appear to have neutral or beneficial effects. Differences may be related to dose, pattern, and duration of drinking and skeletal site(s) evaluated. For example, Pumarino and colleagues evaluated the skeleton in male continuous and intermittent heavy drinkers [40]. Osteopenia was noted in the femur neck but not in the spine, suggesting site specificity, and the type of alcohol abuse was found to be less important than duration. However, a recent study evaluated the relationship between current alcohol consumption and the bone in the distal radius and tibia in aged men and women using high resolution computed tomography [41]. In contrast to the above analyzed studies, moderate to heavy alcohol consumption was associated with minimal changes in bone geometry, density, and microarchitecture. Inexplicably, light drinking was associated with generally negative effects on indices of bone quality in males but not females. It should be noted, alcoholics differed among studies in age and duration of alcohol abuse and ranged from healthy to having cirrhosis, pancreatitis, diabetes, and other conditions that may influence bone metabolism.

10.3 Physical Activity

The mechanisms by which the skeleton responds to activity remain incompletely understood. Overwhelming evidence indicates that bone mass increases in response to the cyclic administration of mechanical loads [42]. Not only the bone density is higher in physically active people, but exercise also reduces the rate of age-related bone loss [43]. Osteocytes and osteoblasts sense mechanical strain, and exercise stimulates osteocyte activity and survival [44]. Weight-bearing impact-loading activities, such as jumping, appear to be particularly osteogenic [45], yet only a limited number of impact-loading studies have been trialed in men. A recent review of trials examined the effect of exercise on the BMD in middle-aged and older men without osteoporosis. Two different programs involving resistance training alone or in combination with impact-loading exercise appeared to be most beneficial for skeletal health [46]. Thus, a single modality of impact-loading exercise is effective for improving BMD in older men, but the optimal individual impact-loading exercise prescription is unclear. Lately, a recent trial in postmenopausal women with osteoporosis shows that high-intensity resistance and impact training (HiRIT) can enhance indices of bone strength and functional performance [47]. However, there are no conclusive data in males with bone loss. Nowadays, HiRIT is not traditionally recommended for individuals with osteoporosis because of a perceived high risk of fracture.

Recent international guidelines recommend maintaining a minimum level of physical activity because of its useful role in the prevention of osteoporosis. The impact of physical activity depends on frequency, duration, intensity, and subjects' age at the beginning of the training. Individualized physical activity, to improve muscle strength, balance, and walking, has been shown to reduce the risk of both falls and fall-related traumas. It has been demonstrated that, fall risk self-assessment tests, and recommendations on the prevention of falls, have also a positive effect on bone health and quality of life [48].

10.4 Conclusion

Non-pharmacological interventions (individualized physical activity and balanced diet with also an adequate calcium and vitamin D intake) and correction of modifiable risk factors (alcohol abuse, environmental risk factors for falls) are recommended to prevent osteoporosis risk for all subjects and may be useful to achieve optimal peak bone mass even at a young age.

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Drug-Induced Male Osteoporosis

11

Valentina Camozzi

Osteoporotic fractures are the main cause of morbidity and mortality among elderly men. The risk of having at least one fragility fracture in a 50-year-old male is around 13%, compared with 40% of women. X-ray studies suggest that up to a third of men over 65 years old have at least one vertebral fracture [1].

The risk of hip fracture in men is 5–6% compared to 16–18% in women, but the mortality resulting from fragility fractures is significantly higher in men than in women [2–4].

While the menopause is the main cause of bone loss in women, in more than 50% of men the bone loss is linked with secondary cases, including hypovitaminosis D, increased excretion of calcium with urine, and drugs.

Although it has been known for more than 30 years that the same drug can have different effects in the two sexes, there are very few studies that separately consider males and females in establishing drug-induced bone damage. Generally, in many population studies, in which some thousands of patients of both sexes have been examined, the multivariate statistical analysis did not show substantial differences between the two sexes, with very few exceptions.

The medications that have been shown to induce bone damage as well as an increased risk of fractures are essentially glucocorticoids, proton pump inhibitors, antiepileptics, androgen deprivation therapy, anticoagulants, some antidiabetics, selective reuptake of serotonin inhibitors, calcineurin inhibitors, and diuretics. Their actions are summarized in Table 11.1.

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Table 11.1 Mechanism of action and effect on bone metabolism, bone mineral density (BMD), and risk of fractures of principal drugs potentially harmful to bone

Medication	Mechanism of action	Effect	BMD	Fracture risk
Glucocorticoids	Stimulate osteoclast activity Increase osteocyte apoptosis Decrease osteoblast recruitment and activity Decrease intestinal Ca absorption Increase urinary Ca excretion Suppress GH secretion	Increased bone resorption Decreased bone formation Delayed repair of micro-fractures	↓	↑↑↑
Protein pump inhibitors	Decrease intestinal Ca absorption	Increased PTH secretion Increased bone resorption	↓ =	↑
Antiepileptic drugs	Accelerate vitamin D catabolism Accelerate sex hormone catabolism Inhibit osteoblast proliferation	Decreased intestinal Ca absorption Hypogonadism Reduced bone formation	↓	↑↑
Androgenic deprivation therapy	Inhibit testosterone and estradiol secretion Enhance RANKL production Decrease OPG production	Increased bone resorption Decreased bone formation	↓↓↓	↑↑↑
Thiazolidinediones	Antagonize PPAR γ expression in bone marrow stromal cells reducing osteoblast differentiation Promote osteoclast differentiation	Decreased bone formation Increased bone resorption	↓	↑
Anticoagulants	Inhibit osteoblast differentiation Enhance RANKL production Decrease OPG production	Decreased bone formation Increased bone resorption	↓↓	↑
Calcineurin Inhibitors	Unknown	Increased bone resorption	↓ =	↑
Selective serotonin reuptake inhibitors	Unknown	Uncertain effect on bone remodeling processes	=	↑↑ Independent of BMD and higher for non-vertebral fractures
Diuretics	Increase urinary Ca excretion Hyponatremia	Increased PTH secretion Increased bone resorption Increased propension to fall	↓ =	↑

11.1 Glucocorticoids (GC)

GC are currently used to treat a wide variety of diseases, including autoimmune, inflammatory, and dermatological diseases, respiratory disorders, malignancies, and solid organ transplants.

Approximately 30–50% of patients receiving GC, even at relatively low doses of about 3–10 mg/day of prednisone, have fractures [5–7].

GC have direct and indirect effects on the bone. In the initial phase of therapy, GC act directly on osteoclasts. The stimulation of osteoclasts by GC determines a prolonged survival of these cells, allowing an enhanced prolonged bone resorption which occurs mainly in the regions where the trabecular bone is prevalent, such as the spine. GC also induce apoptosis of the osteocytes, contributing to the delayed healing of micro-fractures and increasing the risk of major fracture [8, 9]. Finally, GC reduce the recruitment of osteoblast precursors, leading to a reduction of osteoblastic differentiation and activity, with consequent impairment of bone formation. Generally, atraumatic fractures occur in patients receiving GC at a higher bone density than that observed in postmenopausal osteoporosis.

GC also indirectly affect bone loss: such actions include decreased intestinal calcium absorption, suppression of growth hormone, alteration of sex hormones, and increased calciuria [7, 10].

The daily dose of GC predicts the fracture more than the cumulative dose. While doses higher than 7.5 mg/day of prednisone have a fivefold higher risk of hip and column fractures, even lower doses, for example, 2.5 mg/day, appear to significantly increase the risk of vertebral fracture [11].

The administration of 10 mg/day for more than 3 months leads to a 17-fold increase in vertebral fractures and to a sevenfold increase in hip fractures with respect to normal population.

At the suspension of GC treatment, the risk of atraumatic fractures gradually decreases, reaching basal levels within 2–3 years [12, 13].

11.2 Proton Pump Inhibitors (PPI)

PPI were introduced at the end of the 1980s for the treatment of gastroesophageal diseases.

Several large observational studies suggest that PPI use is associated with a modest increase in the risk of fragility fractures [14–16].

The mechanism by which PPI increase the risk of fracture is not known. By suppressing acid secretion, PPIs could reduce intestinal calcium absorption, leading to a reduction in serum calcium, increased parathormone secretion, and increased bone resorption [17].

The existence of an association between BMD and the use of PPI is doubtful, suggesting that the increased risk of fracture is probably due to qualitative rather than quantitative changes in the bone [18, 19].

Many, but not all, studies on the prolonged use of PPI over a year have shown a 20–62% increased risk of hip fractures and a 40–60% increased risk of vertebral fractures. This effect seems to be related to the duration of their administration: in fact, the short-term use of PPI is not associated with any increase in the risk of fracture, while the use of these drugs over 1 year increases the fracture risk to about 50% and use over more than 7 years increases the fracture risk to about 400% [20–22].

A recent meta-analysis found that hip fractures were associated with both high- and low-dose PPI, but the cumulative dose seems to be more important than the daily dose in increasing the risk of fracture of both the spine and hip [23].

The risk of fracture is rapidly decreasing at the suspension of PPI therapy [21, 24].

Numerous studies suggest that patients taking bisphosphonates who also take PPI have an increased risk of fracture than those who take bisphosphonates alone [25, 26]. In a population-based Korean study on elderly patients, the OR for hip fracture related to PPI use was 34% higher than the normal population (OR 1.34; 1.24–1.44) and increased to 1.7 (95% CI: 1.31–2.23) in patients taking both bisphosphonates and PPIs. In this study the males were more numerous than the females (65% vs. 35%); however the multivariate analysis did not reveal any difference between the two sexes [27]. Higher cumulative doses of PPI (>30 mg) given in combination with bisphosphonates resulted in a higher risk of hip fracture. In another cohort study, based on a Spanish population of over 5 million people, it was found that the use of PPI associated with bisphosphonates significantly increased the risk of fracture by 22% (OR 1.22; CI 95% 1.02–1.46) with respect to population taking bisphosphonates alone [28].

Based on these data, the use of H2 antagonists rather than PPI should be considered in patients who are already taking a bisphosphonate. In fact, even if there is no unanimous agreement, H2 antagonists seem to have lower or no impact on fracture risk [29]. If PPI is necessary, then to shorten therapy as much as possible should be considered.

11.3 Antiepileptic Drugs (AED)

AED are used for treatment of epilepsy, migraine, psychiatric disorders, and chronic and neuropathic pain.

In epilepsy, AED are associated with a reduction in bone density in men over 65 years old; however some reports indicate an osteopenizing effect of phenytoin even in younger patients [30, 31].

In comparison with the general population, epileptic patients have themselves a risk of fracture 2–6 times greater than normal population [32].

In a population-based Danish study, the use of AED was associated with a significant increase in the risk of spine and hip fractures, as well as other fractures [33].

Not all AED appear to have the same impact on fractures: in a recent meta-analysis, a high risk of fracture was evidenced in patients taking phenobarbital,

phenytoin, and topiramate, while valproic acid, gabapentin, lamotrigine, and carbamazepine did not increase the risk of fracture [34, 35].

In other studies, gabapentin was associated with increased bone loss and increased risk of fracture [32].

Koo et al. have found that levetiracetam is not associated with an increase in biochemical markers of bone turnover or bone loss after 1 year of therapy, suggesting that the new AED drugs are probably more protective for the skeleton than the old ones [36].

The causes of bone loss and increased fracture risk in patients taking AED are not yet fully elucidated. A number of evidence indicate that bone loss is associated with accelerated catabolism of vitamin D and its active metabolites, due to increased activity of the cytochrome p450 system. This would result in hypovitaminosis D, reduced intestinal absorption of calcium, and secondary hyperparathyroidism which would ultimately determine decreased BMD and increased risk of fracture [35, 37].

Several antiepileptic drugs, including phenytoin, carbamazepine, and valproic acid appear to have a direct effect on bone cells, which would lead to an increase in bone turnover [34, 35, 38]. Interaction with vitamin K has also been proposed as a possible mechanism for osteoporosis: vitamin K is an important cofactor in the synthesis of osteocalcin, a marker of bone formation [39].

Furthermore, AED appear to increase the metabolism of sex steroids, resulting in decreasing both testosterone and estradiol levels [37, 39].

Animal studies suggest that phenytoin has a direct inhibitory effect on osteoblast proliferation and decreases osteocalcin production, leading to reduced bone formation.

Finally, other mechanisms of action could indirectly influence bone metabolism, including increased leptin, increased homocysteine, and reduced IGF1 [40–42].

11.4 Androgenic Deprivation Therapy (ADT)

The importance of sex steroids, especially estrogen, for the maintenance of bone mass in adult and elderly men has now been established by numerous transversal and prospective studies showing a strong association between serum total estradiol levels and bone loss. ADT reduces serum testosterone levels in patients with prostate cancer to less than 5% and serum estradiol to less than 20% of the normal levels [43–49].

From a molecular point of view, the key mechanism of ADT in reducing bone mass is represented by the activation of RANKL and by the inhibition of OPG, with a consequent increase in bone resorption and bone loss [50].

In the first months of therapy, the decrease of BMD is approximately 2–5% per year, while the increase of vertebral and hip fractures is approximately 20–50% after 5 years of treatment.

ADT determines a rate of bone loss in elderly people of about 4–4.6% per year, significantly higher than that observed in normal aging men and in postmenopausal women. The rate of bone loss is approximatively twice than that observed in women with breast cancer treated with aromatase inhibitors [51, 52].

The prevalence of osteoporosis or osteopenia in patients with prostate cancer varies from 4 to 38%. The addition of ADT rapidly worsens pre-existing osteoporosis.

Associated with the rapid reduction of BMD, there is also an increased risk of fracture: in the various epidemiological studies, the increased risk of vertebral fracture is 23–39% higher than that of the normal population. Patients who received combination therapy with ADT and antiandrogens have a higher risk of fracture than those who received monotherapy [51, 53–55].

Mortality after fragility fractures is 38% higher in men with prostate cancer and fracture than in those with prostate cancer without fracture (OR 1.38; CI: 1.34–1.43) [54, 56].

11.5 The Thiazolidinediones (TZD)

TZD are widely used for the treatment of type 2 diabetes mellitus. These drugs antagonize the activated proliferator peroxisome receptor γ (PPAR γ) expressed in bone marrow stromal cells, osteoblasts, and osteoclasts, which plays an essential role in the differentiation of precursor cells to osteoblasts. TZD also act on bone remodeling by increasing bone marrow adiposity, decreasing the aromatase activity, and promoting osteoclast differentiation, thus also inducing an increase in bone resorption [57].

In humans, TZD decrease BMD at the lumbar spine and hip and increase the risk of fracture. Rosiglitazone and pioglitazone are associated with a significant increase in the fracture risk (OR 1.45, CI 95% 1.18–1.79). Some studies indicate a gender difference in the osteopenizing action of TZD: Loke et al. showed a significant increase in the risk of fractures in women (OR 2.23, 95% CI 1.65–3.01, $p < 0.001$), but not in men (OR 1.00, 95% CI 0.73–1.39, $p = 0.98$) [58].

Other studies have confirmed the finding, showing a fracture increase of 20–50% in women, but not in men [59, 60]. In contrast, Douglas et al., in an observational study of the UK population, found that TZD significantly increased the risk of non-vertebral fractures regardless of age and gender [61].

11.6 Anticoagulants

Heparin has been used for the prevention and treatment of venous thromboembolism for over 50 years. Its prolonged use causes reduction of BMD and increase of fractures. The main effect of unfractionated heparin is the inhibition of osteoblast differentiation and activity, resulting in reduced bone formation. In addition, bone resorption is also increased, favoring osteoclast differentiation by reducing OPG and increasing RANKL [62].

Heparin-induced bone loss is dose-dependent and reversible with its discontinuation [63, 64].

Some studies, taking into account a limited population, suggest that low molecular weight heparin (LMWH) is associated with a lower incidence and prevalence of

fragility fractures than unfractionated heparin [65, 66]. However, a large prospective study in pregnant patients found no differences between unfractionated heparin and LMWH [67].

The most recent heparins, including fondaparinux, do not appear to have any effect on osteoblast differentiation or function in vitro and are expected to be neutral in bone metabolism [68, 69].

The various studies on the effect of warfarin on bone density and on the incidence of fractures did not lead to univocal results. Many small cross-sectional studies and retrospective studies indicate that warfarin is associated with reduction of BMD and increased vertebral and costal fractures [70–72]. However, other studies do not seem to have any significant effect on BMD or fracture [73–75].

11.7 Calcineurin Inhibitors

Calcineurin inhibitors, including cyclosporin (CsA) and tacrolimus (FK506), have been widely used as immunosuppressants to prevent transplant rejection or to treat autoimmune diseases. Both are associated with bone loss and increased fracture risk, although the exact mechanisms are still unknown. In vitro, calcineurin inhibitors inhibit osteoclastogenesis and osteoclast activity by reducing the nuclear factor of acute T cells, cytoplasmic 1 (NFATc1) [76, 77].

In animal models and in humans, these drugs cause both duration- and dose-dependent bone loss, mainly due to an increased bone resorption [78–83].

Bone damage caused by calcineurin inhibitors in men is difficult to assess due to the simultaneous damaging effect of confounding factors, such as underlying disease and the use of post-transplant glucocorticoids. However, when CsA or FK506 is administered as monotherapy or with low doses of glucocorticoids (<10 mg daily), there is not significant reductions in BMD [84, 85]. The use of CsA or FK506 in autoimmune diseases at doses below 5 mg/kg/day does not appear to be associated with significant bone loss [86].

11.8 Selective Serotonin Reuptake Inhibitors (SSRI)

SSRI, including fluoxetine, sertraline, paroxetine, fluvoxamine, and citalopram, as well as duloxetine (norepinephrine reuptake inhibitor), are widely used in the treatment of depression, anxiety, premenstrual syndrome, peripheral neuropathy, fibromyalgia, and chronic musculoskeletal pain.

In several population-based studies, there was a close association between depression and low bone density in young and old men, with an increased relative risk of developing osteoporosis threefold higher than that of the normal population [87–91].

Because the presence of osteoporosis is common in depressed individuals, it is difficult to establish the role of SSRI in the development of the disease. Several studies have shown that SSRI are associated with bone loss and increased risk of fracture [92–95].

Recent meta-analyses confirm this association with an increased risk of fracture of about 1.5–2 times compared to normal population [96–98]. The increased fracture risk is expected to be higher within 1 month after initiation for tricyclics, and after 8 months for SSRI, and diminishes in few years following discontinuation [96].

Fracture risk is higher for femoral and non-vertebral fractures than for vertebral ones [98]: the adjusted probability ratio for hip fracture was 2.4 (95% CI: 2.0–2.7) for exposure to SSRI, 2.2 (95%CI: 1.8–2.8) for exposure to secondary amine tricyclic antidepressant, and 1.5 (95% CI: 1.3–1.7) for exposure to tertiary amine tricyclic antidepressant [93, 95].

Depending on the dose used, the increased risk of fracture may appear early, within 6 weeks of starting therapy, or after prolonged use at lower doses, after 3–5 years of treatment [95, 97, 99], with a prevalence which is about twice that of the normal population, and tends to disappear after about 1 year from the discontinuation of therapy.

The daily use of SSRI is also associated, in a dose-dependent manner, with higher probability of fall (OR 2.2; 95% CI: 1.4–3.5) and with lower bone mineral density at the hip and spine [100, 101].

Surprisingly, SSRI-associated fractures seem to be independent of BMD, indicating a possible effect on the qualitative, rather than quantitative, characteristics of skeletal tissue [96].

11.9 Diuretics

Different classes of diuretics can lead to different effects on calcium metabolism. Loop diuretics inhibit the Na-K-2Cl transporter and increase renal calcium excretion. They are often used in the treatment of hypercalcemia, congestive heart disease, and chronic renal failure.

Carbonic anhydrase inhibitors decrease bicarbonate absorption, so the resultant metabolic acidosis can increase renal calcium excretion. These drugs are now used for the treatment of glaucoma and can promote nephrocalcinosis and nephrolithiasis.

The increased urinary calcium excretion would lead to hyperparathyroidism and, ultimately, to increased bone resorption, enhanced bone loss, and higher risk of fracture.

In contrast, thiazide diuretics block the thiazide-sensitive Na-Cl transporter in the distal convoluted tubule and decrease calcium excretion. They are often used in the treatment of nephrolithiasis and are associated with a reduction in the risk of fracture [102–105]. Medications used to treat heart failure, including spironolactone and thiazide, may protect against osteoporosis. In contrast, loop diuretics may worsen osteoporosis [106, 107]. Arampatzis et al., in a large observational study, found that elderly patients with fragility fractures had a significant higher consumption of loop diuretics, spironolactone, and amiloride, but not thiazide, than those without fractures [108].

The action on the renal handling of calcium does not seem to be the unique explanation of the influence of diuretics on osteoporosis and risk of fracture. Some evidences attribute the increased risk of fracture to hyponatremia, which is easily found during the prolonged use of various types of diuretics. Severe hyponatremia may cause dizziness and increase the propensity to falls and has been associated with increased bone loss and incidence of fracture, independently of BMD [109–112].

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Obesity and Male Osteoporosis: Protective Factor?

12

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12.1 Introduction

In an increasingly obese and aging population, metabolic chronic diseases, low bone mass, and osteoporotic fractures are major public health concerns. In fact, during the last decades, obesity and osteoporosis have become important global health problems with an increasing prevalence worldwide [1–4]. Furthermore, the belief that obesity is protective against osteoporosis has come into question as demonstrated by recent epidemiologic and clinical studies, which show that high level of fat mass might be a risk factor for osteoporosis and fragility fractures, both in men and women [5–8]. In particular, we have demonstrated that TF negatively correlates with BMD independently from vitamin D levels, reduced IGF-1, and increased inflammatory markers [7].

Several potential mechanisms have been proposed to explain the complex relationship between adipose tissue and bone, and understanding how obesity determines low bone mass and modulates fracture risk is important to identify and treat people in order to prevent fractures. Most available evidences indicate that a significant number of fractures occur in obese men. Body mass index (BMI) is positively associated with bone mineral density (BMD), and the mechanisms of this association in vivo might include increased loading and higher aromatase activity [9].

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Indeed, fat tissue is one of the major sources of aromatase, an enzyme also expressed in the gonads, which from androgen precursors synthesizes estrogens, steroid hormones which play a pivotal role in the maintenance of skeletal homeostasis and protecting against osteoporosis by reducing bone resorption and stimulating bone formation [9]. However, some fat depots, as visceral fat, might have negative effects on the bone by producing cytokines, molecules able to modulate bone metabolism as pro-resorptive factors [10–12]. Adipose tissue, in fact, secretes various inflammatory cytokines, including interleukin (IL)-6, tumor necrosis factor-alpha (TNF-α), resistin, leptin, and adiponectin, which affect human energy and metabolic homeostasis but are also involved in bone metabolism [13–16]. Moreover, high intramuscular fat content is associated with poorer muscle function, attenuating loading effects and increasing the risk of falls [9]. A recent study has demonstrated that in older men, the condition of sarcopenic obesity is associated with increased fall rates compared with non-sarcopenic obese subjects [10].

On the other hand, since the demonstration that bone cells express several specific hormone receptors [14–17], and since recent observations have shown that osteocalcin (OCN) and osteopontin (OPN), bone-derived factors, affect body weight control and glucose homeostasis [18–20], the bone has come to be considered an endocrine target organ and an endocrine organ itself [21]. These considerations suggest a possible role of bone as a player of a potential feedback mechanism between the skeleton and the other endocrine organs [21]. Thus, the cross talk between fat and bone likely constitutes a homoeostatic feedback system in which adipokines and bone-derived molecules represent the link of an active bone-adipose axis.

Moreover, adipocytes and osteoblasts originate from a common progenitor, a pluripotent mesenchymal stem cell (MSC) [22], which has an equal propensity for differentiation into adipocytes or osteoblasts (or other lines) upon the influence of several cell-derived transcription factors. This process is complex, suggesting significant plasticity and multifaceted mechanism(s) of regulation within different cell lineages, among which are adipocytes and osteoblasts [23, 24].

Finally, obesity is associated with gonadal dysfunction: in women, obesity is associated with androgen excess disorders, mostly the polycystic ovary syndrome, whereas androgen deficiency is frequently present in obese men [25].

12.2 Fat, Bone, and Fat Bone Marrow Interplay

Obesity has always been recognized as a risk factor for cardiovascular and metabolic chronic diseases [2]. Nevertheless, it has been considered a protective factor for bone loss and osteoporosis, which is defined as a bone metabolic disease, characterized by a decrease in bone strength leading to an increased risk of developing spontaneous and traumatic fractures. Even though body fat and lean mass have been positively correlated with BMD, since obesity apparently exerts protection against bone loss, during the last decades, numerous evidences have described an opposite event, suggesting an inverse relationship between obesity and osteoporosis and showing that an increased abdominal fat tissue might be considered a risk factor for osteoporosis and fragility fractures [5, 7, 8] (Fig. 12.1).

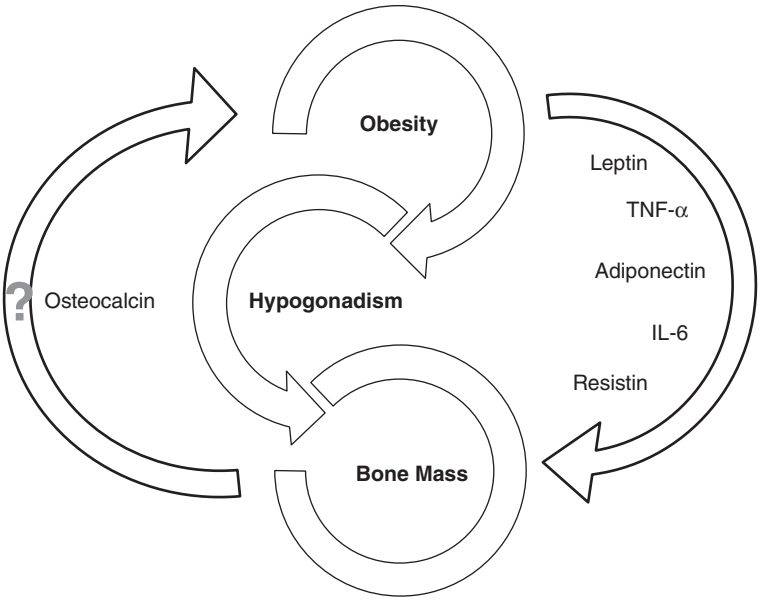

Fig. 12.1 Interplay between bone, fat, and gonads

The mechanisms whereby increased central adiposity leads to metabolic alterations, cardiovascular morbidity, and bone loss have been largely based on the demonstration that adipose tissue secretes a number of cytokines and bioactive compounds, named adipokines.

The adipokines, which include a variety of pro-inflammatory peptides, are involved in many physiological or pathological processes, and their dysregulation is a strong determinant of the low-grade inflammatory state of obesity, which promotes a cascade of metabolic alterations leading to cardiovascular complications, insulin resistance (or diabetes mellitus), and bone loss [11, 13].

Leptin, the first identified adipose tissue-derived factor, is an anorexigenic hormone secreted by adipocytes in proportion to body fat content, and its levels are typically elevated in obesity, which is considered a leptin-resistant state [26]. Interestingly, in obese subjects hyperleptinemia has been widely recognized as an independent cardiovascular risk factor associated with hyperinsulinemia and insulin resistance [27], whereas its effect on the bone appears composite, since both negative and positive actions have been reported on BMD, both in men and women [28, 29]. Leptin-deficient ob/ob mice and leptin receptor-deficient db/db mice are extremely obese, with increased vertebral trabecular bone volume due to increased bone formation [30], while intra-cerebroventricular infusion of leptin in both ob/ob and wild-type mice has shown to decrease vertebral trabecular bone mass [30]. In vivo studies indicate that the effect of leptin might depend on its site and mode of action [31], and it has been proposed that peripheral administration of leptin could increase bone mass

by inhibiting bone resorption and increasing bone formation, while inhibiting bone formation through a central nervous system effect [28]. In vitro studies also indicate that leptin can act directly on bone marrow-derived mesenchymal stem cells (BMSCs) to enhance their differentiation into osteoblasts and to inhibit their differentiation into adipocytes [32]. Finally, leptin inhibits the expression of neuropeptide Y (NPY), a hypothalamus-derived peptide, essential for the regulation of food consumption, energy homeostasis, and bone remodeling [33]. Specific NPY-knockout mice display a significant decrease in body weight, a significant increase in food intake, and two-fold increase in trabecular bone volume compared with wild-type animals [34].

Adiponectin exerts a protective role on cardiovascular system and glucose metabolism, and in contrast with leptin, its serum levels are reduced in obese and diabetic subjects and increase after weight loss [35]. Indeed, low levels of adiponectin are a common feature of obesity and correlate with insulin resistance [36]. Moreover, adiponectin levels are inversely related to the circulating levels of C-reactive protein (CRP), TNF-α and IL-6, powerful inhibitors of adiponectin expression, and secretion in cultured human adipose cells [37]. Interestingly, human osteoblasts express adiponectin and its receptors, and in vivo and in vitro studies show that adiponectin increases bone mass by suppressing osteoclastogenesis and activating osteoblastogenesis [38], likely indicating that a rise in adiponectin, upon fat reduction, could beneficially affect BMD.

Resistin is produced by macrophages and visceral adipocytes. Resistin is elevated in obesity and regulates insulin sensitivity in skeletal muscle and liver, and it is positively associated with insulin resistance and glucose tolerance in both human and animal models [39]. Resistin might also play a role in bone remodeling, increasing osteoblast proliferation, cytokine release, and osteoclast differentiation [40] (Table 12.1).

Table 12.1 Adipokines and bone remodeling

Leptin	– Inhibition of bone resorption and increasing bone formation, while inhibiting bone formation through a central nervous system effect, through peripheral administration [28] – Direct action on marrow-derived mesenchymal stem cells (BMSCs) to enhance their differentiation into osteoblasts and to inhibit their differentiation into adipocytes [32] – Inhibition of the expression of neuropeptide Y (NPY), a hypothalamus-derived peptide, essential for the regulation of food consumption, energy homeostasis, and bone remodeling [32]
Adiponectin	– Increase in bone mass by suppressing osteoclastogenesis and activating osteoblastogenesis [38]
Resistin	– Might play a role in bone remodeling, increasing osteoblast proliferation, cytokine release, and osteoclast differentiation [40]
TNF-α	– Effect on bone remodeling, with a potent effect on osteoclastogenesis, not only promoting RANKL production but synergizing with RANKL to amplify osteoclastogenesis and to intensify osteoclastic resorption by directly modulating RANKL-induced signal transduction pathways [47]
IL-6	– Stimulation of osteoclastogenesis and bone resorption – Stimulation of the increase of mesenchymal progenitor differentiation toward the osteoblastic lineage [50]

TNF-α is a pro-inflammatory cytokine which plays important regulatory effects on lipid metabolism, adipocyte function, insulin signaling, and bone remodeling [41]. Its expression correlates with percent body fat, insulin resistance, and osteoclast activity in humans [42, 43]. Osteoclasts are cells tasked with resorbing bone and the identification of three different molecules: the receptor activator of NF-kB ligand (RANKL), an osteoclastogenic cytokine, its receptor (RANK), and its inhibitor osteoprotegerin (OPG) built the bases of the modern bone biology [44]. RANKL is the key osteoclastogenic cytokine effector, inducing osteoclast formation and promoting osteoclast resorptive activity [45]. TNF-α promotes RANKL production by BMSCs and mature osteoblasts, reduces OPG production, and upregulates the receptor RANK on osteoclast precursors, increasing their sensitivity to prevailing RANKL concentrations [46]. Additionally, TNF-α turns out to have another property that is relatively unique among the inflammatory cytokines; it has potent effects on osteoclastogenesis as it not only promotes RANKL production but synergizes with RANKL to amplify osteoclastogenesis and to intensify osteoclastic resorption by directly modulating RANKL-induced signal transduction pathways [47].

IL-6 is a cytokine which has a wide range of actions; it is secreted by several cell types, including fibroblast, endothelial cells, and adipocytes; and its plasma levels are significantly upregulated in human obesity and insulin resistance [48]. As TNF-α also IL-6 is a well-recognized stimulator of osteoclastogenesis and bone resorption. Several data show that IL-6 mRNA is expressed in preosteoblasts and osteoblasts [49] and that it stimulates osteoblast proliferation and differentiation by controlling the production of local factor [50, 51].

Mature bone cells secrete factors that modulate insulin sensitivity and glucose metabolism, such as OCN, by which the skeleton could function as an endocrine organ itself [50, 52]. OCN is an osteoblast-specific protein and a major non-collagenous protein in the extracellular matrix. Karsenty and colleagues demonstrated that uncarboxylated OCN, acting as a pro-hormone, can increase β-cell proliferation, insulin secretion, insulin sensitivity, and adiponectin expression [53]. Thus, osteoblasts might be able to regulate glucose metabolism by modulating the bioactivity of OCN. In addition, more recent studies showed that OCN bioactivity is modulated by enhanced sympathetic tone driven by leptin, which has been shown to suppress insulin secretion by β-cells [54], and three recent studies have demonstrated an inverse correlation between serum OCN and plasma glucose levels, supporting a role for this pathway in humans [55]. Thus, a novel picture has emerged linking glucose metabolism, adipose stores, and skeletal activity.

OPN is an active player in many physiological and pathological processes, including biomineralization, tissue remodeling, and inflammation. Modulation of immune cell response by OPN has been associated with various inflammatory diseases and might play a pivotal role in the development of adipose tissue inflammation, insulin resistance, and diabetes [56]. OPN expression is drastically upregulated by 40- and 80-fold in adipose tissue from diet-induced and genetically obese mice, respectively [57], and it has been demonstrated that OPN expression in adipose tissue and circulating OPN levels were substantially elevated in obese, diabetic, and insulin-resistant patients compared with lean subjects and conversely that dietary weight loss significantly decreased OPN concentrations [58, 59].

Emerging evidence points to a critical role for the skeleton in several homeostatic processes including energy balance and adipose metabolism, and the connection between fuel utilization and skeletal remodeling seems to begin in the bone marrow with lineage allocation of MSCs into adipocytes or osteoblasts. Adipocytes and osteoblasts, in fact, originate from a common progenitor, a pluripotent mesenchymal stem cell [60], which has an equal propensity for differentiation into adipocytes or osteoblasts or other lines, such as chondrocytes, fibroblast, and endothelial cells, under the influence of several cell-derived transcription factors. This process is complex, suggesting significant plasticity and multifaceted mechanism(s) of regulation within different cell lineages, among which are adipocytes and osteoblasts [22, 61].

Transdifferentiation is the switching of differentiated cells that sometimes occurs during disease [62], and it interests partially differentiated cells (e.g., pre-osteoblasts) that switch to another lineage (e.g., adipocytes) [63]. Fat bone marrow is indicative of aging, and it is frequently observed in the presence of osteoporosis [64]. One possible cause of bone marrow fat deposition is the aberrant commitment of BMMSCs into adipocytes because of their inability to differentiate into other cell lineages, such as osteoblasts. There exists an inverse relationship between bone marrow fat production and bone formation during osteoporosis; in fact an inhibited adipogenesis in subjects with a high bone mass has been observed [65]. Recently, a correlation between the osteo-adipogenic transdifferentiation of bone marrow cells and numerous bone metabolism diseases has been established. Human BMMSC-derived osteoblasts, adipocytes, and chondrocytes had the potential to transdifferentiate to each lineage, and these findings provided new insights on the pathogenesis of skeletal diseases such as osteoporosis in both sexes [66].

Estrogens can regulate several molecular signals within bone metabolism and play a pivotal role in the development of bone marrow fat [67–69]. Recent studies have shown that estrogens suppress osteo-adipogenic transdifferentiation via canonical Wnt signaling, which regulates bone development, adipogenic differentiation, and gene expression in the whole process of bone metabolism [65, 70]. Specifically, canonical Wnt/beta-catenin signaling is highly expressed in mesenchymal precursor cells and pluripotent cells, especially toward the osteoblast lineage, while inhibiting adipogenic differentiation [71]. Canonical Wnt signaling stabilizes and promotes cellular and nuclear beta-catenin levels, which inhibit adipogenesis [72], and the suppression of Wnt signaling is crucial for PPAR gamma induction and preadipocyte differentiation [73].

PPARγ plays a central role in initiating adipogenesis, and mutations of the PPARγ gene are associated with an altered balance between bone and fat formation in the bone marrow [61]. PPARγ insufficiency led to increased osteoblastogenesis in vitro and higher trabecular bone volume in vivo, confirming the key role of mesenchymal stem cell lineage allocation in the skeleton [60]. Interestingly, aged mice exhibit fat infiltration into the bone marrow, and enhanced expression of PPARγ-2, along with reduced mRNA expression of bone differentiation factors [73], and mice with premature aging (the SAM-P/6 model) show nearly identical patterns of adipocyte infiltration, with impaired osteoblastogenesis [74], indicating that aging, or

events that accelerate aging, results in significant bone marrow adiposity and in defect in osteoblastogenesis in mice [75].

Estrogens and androgens can both modulate several molecular signals within bone metabolism and play a role in the development of bone marrow fat. Moreover, BMMSCs express androgen receptor (AR), and a recent study shows that androgens, independently of their aromatization, are able to prevent rosiglitazone-induced adipogenesis in human mesenchymal stem cells [76].

12.3 Obesity, Androgen Deficiency, and Bone Metabolism

Estrogens and androgens modulate bone remodeling by regulating the activity of the abovementioned molecules, thus protecting against bone loss by regulating the activity of genes responsible for osteoclastogenesis and mesenchymal cell replication, exerting pro-apoptotic effects on osteoclasts and anti-apoptotic effects on osteoblasts and osteocytes. Conversely, hypogonadism leads to increased bone resorption, both in men and women [77].

Testosterone deficiency syndrome is becoming recognized as an increasingly frequent problem in the aging male population [78], and low serum testosterone is more common in men with type 2 diabetes mellitus, metabolic syndrome, cardiovascular disease, and obesity than in the general population [79–81]. Interestingly, it is known that obesity in men is associated with low testosterone and reduced sex hormone-binding globulin (SHBG) levels. An increased BMI is associated with a low measured, or calculated, free and bioavailable testosterone. Specific pathogenetic mechanisms involved in this phenomenon are complex and not completely understood, but evidence indicates that testosterone deficiency induces increased adiposity, while increased adiposity induces hypogonadism [82].

The prevalence of secondary hypogonadism in adult male subjects affected by type 2 diabetes has been estimated to be 29% (range 25–40%), with a higher prevalence of 50% when obesity and type 2 diabetes coexist. Indeed, several studies indicate that men who are obese at baseline and at follow-up, either if fat tissue excess is measured by BMI or by central obesity prevalence (waist/hip ratio or waist circumference), exhibit a greater decline of total and free testosterone compared to men who were never classified as obese [83], mainly due to higher amounts of visceral fat [84]. Visceral adiposity is associated with elevated concentrations of insulin, C-peptide, and glucose intolerance, which are negatively correlated to total and free testosterone levels [85, 86]. The link between obesity and (decreased) SHBG is mainly explained by the effects of obesity-induced insulin resistance, resulting in higher insulin levels that subsequently suppress hepatic production of SHBG that would then result in reduced delivery of testosterone to the peripheral tissues and increased availability of free testosterone as a substrate for aromatase to convert into estradiol [87, 88].

Male obesity is associated with increased aromatase activity within adipocytes [89], and estradiol in turn exerts a negative feedback effect on LH secretion from the pituitary [90]. This may worsen obesity and promote increased fat mass that

represents a vicious circle perpetuating the hypogonadal state, thus resulting in a reduction in muscle mass and an increase in the volume of visceral fat [91]. Another mechanism that mediates obesity-related effects on the male hypothalamic-pituitary-testicular axis is mediated by increased plasma leptin levels that exert a direct negative action on LH-/hCG-stimulated testicular androgen production and decrease Leydig cell responsiveness to gonadotropin stimulation [92]. Finally, inflammatory mediators, such as C-reactive protein, have been demonstrated to contribute to the suppression of the hypothalamic-pituitary-testicular axis function and to the development of male secondary hypogonadism [93].

Emerging data suggest that bone mass, energy metabolism, and reproductive function might be coordinately regulated. The main mediator of this axis is undercarboxylated osteocalcin (uOCN), a bone-derived hormone, which has recognized effects as the improvement of insulin secretion from the pancreas; the amelioration of systemic insulin sensitivity, in particular in skeletal muscle; and the stimulation of the global endocrine activity of the Leydig cell, including vitamin D 25-hydroxylation and testosterone production [94]. A rising interest toward the non-classical effects of 25-hydroxycholecalciferol 25(OH)D (vitamin D) exists, based on the presence of its receptors in tissues other than the bone, gut, and kidneys [95]. Several studies have suggested the involvement of vitamin D in the pathogenesis of CVD, cancer, and metabolic syndrome [96–98]. The association of low vitamin D levels and metabolic syndrome is more pronounced in overweight and obese than in normal-weight individuals [99]. A recent study confirmed the lowest vitamin D concentrations and the highest prevalence of vitamin D deficiency in type 2 diabetes patients with hypogonadism, particularly in those with secondary hypogonadism [100]. Several mechanisms have been proposed to explain the role of vitamin D in the pathogenesis of insulin resistance, and adiponectin has been proposed as a major player with its strong association with impaired glucose tolerance, independent from adiposity [101]. Adiponectin and glucose homeostasis are both correlated to OCN levels, an osteoblast hormone linked to vitamin D metabolism, as mentioned above [94, 102]. Interestingly, animal studies suggest that bone might be a positive regulator of male fertility and that this action might be mediated through OCN, via binding to a specific receptor present on Leydig cells that favors testosterone biosynthesis. OCN-deficient mice show a decrease in testicular, epididymal, and seminal vesicle weights and sperm count, and Leydig cell maturation appears to be halted in the absence of OCN [103]. Androgens favor periosteal bone formation in men and maintain trabecular bone mass and integrity by inhibiting IL-6 production [104]. Also, androgens stimulate the proliferation of osteoblast progenitors and the differentiation of mature osteoblasts by decreasing osteoclast formation and bone resorption, via increased production of OPG by osteoblasts [77]. The net result of these functions leads to an accrual in bone formation [105]. Finally, our group has recently demonstrated an association between visceral fat mass, altered insulin sensitivity, OCN, and testosterone levels in aging obese male subjects that are significantly correlated with skeletal health [106]. In this view, OCN might be considered a new important marker of metabolic and gonadic function in obese men, other than the well-established function as a marker of bone remodeling.

12.4 Conclusions

Body fat and bone interplay through several adipokines and bone-derived molecules, such as OCN, which modulate bone remodeling, adipogenesis, body weight control, and glucose homeostasis. Thus, the existence of a cross talk between fat and bone tissue suggests a homoeostatic feedback system in which adipokines and bone-derived molecules form part of an active bone-adipose axis.

In conditions such as aging, hypogonadism, obesity, or metabolic alterations, an osteo-adipogenic transdifferentiation and an aberrant commitment of BMMSCs into adipocytes might occur. In particular, since BMMSCs express androgen receptor, androgens can modulate several molecular signals within bone metabolism and might play a role in the development of bone marrow fat, which might explain several mechanisms linking obesity to an increase of male skeletal alterations as compared to subjects with normal body weight.

Finally, obesity is associated with gonadal dysfunction, leading to androgen deficiency. Since androgens promote bone formation, and bone tissue might be a positive regulator of male fertility, through OCN, and since an association between visceral fat mass, insulin sensitivity, OCN, and testosterone levels in obese men has been observed, OCN might be considered a new important marker of metabolic and gonadic functions in adult obese men, other than the well-established function as a marker of bone remodeling.

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HIV and Osteoporosis

13

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13.1 Introduction

The advent of highly active antiretroviral therapy (HAART) has significantly improved the survival of people living with human immunodeficiency virus (HIV) infection [1].

Together with increased survival, several serious co-morbidities have appeared, which may compromise both the duration and the quality of life of these patients. The main concern of infectious disease specialists is, at present, the prevention of heart disease, diabetes, hyperlipidemia, chronic renal insufficiency, malignancies, cognitive disorders, and osteoporosis [2].

A high prevalence of osteopenia and osteoporosis has been reported in people living with HIV (PLWHIV) [3–7]. Osteoporosis is a systemic skeletal disease characterized by decreased bone mass and microarchitectural deterioration of bone tissue; these conditions cause increased bone fragility, which in turn increases the risk of fracture.

Several studies have found a higher incidence of fragility fractures in PLWHIV than in the general population. For PLWHIV the odds ratio for fracture may rise up to 2.17 (95% CI 1.29–3.66). It is interesting to note that a large part of the studied patients were young males (age range 36–56 years) [8]. Due to the very low risk of fracture shown by young age-matched healthy subjects, PLWHIV appear to be a high-risk population. The incidence of osteoporotic fractures is significantly higher in HIV-infected patients, both males and females, compared to serum-negative controls; it is estimated that the prevalence of subclinical vertebral fractures is approximately 25% [9]. It is well known that PLWHIV are facing a premature aging, and,

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as a matter of fact, fracture onset occurs earlier in these patients than the general population [10, 11].

Aging is one of the most important determinants of bone loss in humans; thus the increased survival of PLWHIV in the HAART era, together with the premature aging, may represent a risk factor for osteoporosis. Nevertheless aging cannot explain the whole burden of this co-morbidity as there are clear demonstrations that both the HIV virus and the HAART play an important role in the pathogenesis of this particular bone disease [7].

Furthermore, other risk factors for osteoporosis, such as low body weight, drug abuse, smoking, and alcohol consumption [9] together with an increased rate of vitamin D deficiency, are frequently present in PLWHIV [12].

Considering only males, hypogonadism should be regarded as an additional risk factor for osteoporosis and fractures, as it may be present in almost 25% of HIV-infected men [13, 14]. Testosterone has a clear direct effect on bone health as it stimulates osteoblasts to form new bone and helps osteocytes to prevent bone loss [15]. Low testosterone levels, therefore, contribute to reduce bone mineral density (BMD) in HIV-infected men. However, recent data have shown that the lack of estradiol, rather than testosterone, is responsible for bone loss in these patients; estradiol plasma levels lower than 27 pg/mL were clearly associated with reduced BMD, thus representing a threshold beneath which bone loss may occur [16]. Testosterone replacement therapy should be always offered to hypogonadal men with HIV as it may slow down the declining BMD [13]. Finally, some authors have also reported that in men living with HIV the response to the anti-osteoporotic drug risedronate may be blunted by hypogonadism [17].

The etiology of osteoporosis in PLWHIV is multifactorial [18, 19]. HIV-infected bones constantly show an imbalance of bone remodeling, with both increased bone resorption and inhibited bone formation (Fig. 13.1). The virus, as well as the

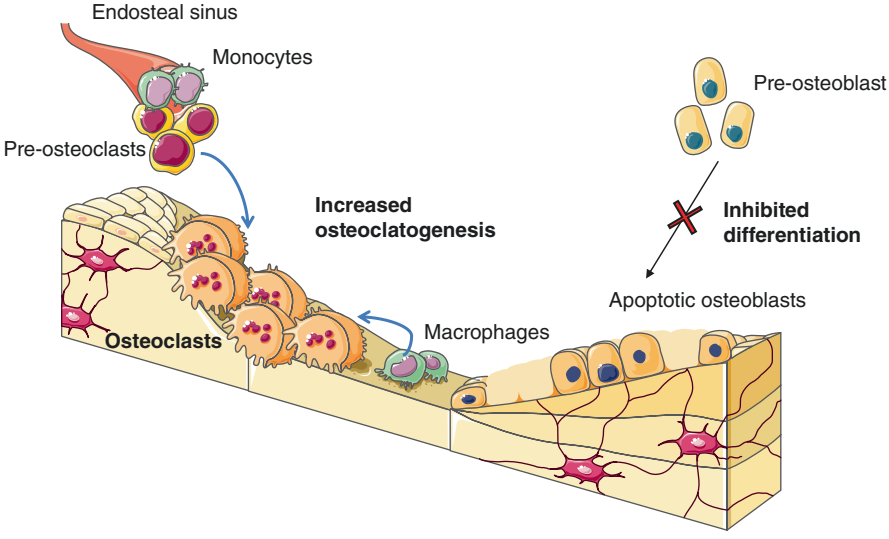

Fig. 13.1 HIV-infected bones show an imbalance of bone remodeling, with both increased osteoclast bone resorption and inhibited osteoblast bone formation

HAART, plays a key role in enhancing osteoclastogenesis and in reducing osteoblast differentiation [7].

13.2 Pathogenic Mechanisms of Bone Damage

13.2.1 The Virus

Mesenchymal bone marrow stem cells are able to differentiate into osteoblasts. Several studies have demonstrated that these cells can be infected by HIV and may even constitute a reservoir for virus replication. The viral proteins switch mesenchymal stem cell differentiation toward the production of adipocytes, via an overexpression of PPARγ, at the expense of osteoblasts, whose formation is slowed down by a reduced expression of the transcription factor RUNX-2 [7]. In vitro studies have shown that viral proteins may induce the apoptosis of cultured osteoblast and reduce their activity. In fact, infected cells show a decreased ability in calcifying the bone matrix, a reduced production of alkaline phosphatase, and a low expression of RUNX-2 [7]. Finally, in vivo histomorphometric studies have confirmed a reduction both in the number and activity of osteoblasts, which are associated with low plasma osteocalcin levels [7].

The HIV can also increase bone resorption by stimulating osteoclast differentiation. Both the increased production of RANKL/M-CSF and the reduced synthesis of osteoprotegerin boost monocyte/macrophage cells toward mature osteoclasts. These cytokine alterations maintain an accelerated osteoclastogenesis that ultimately increases the number of osteoclasts involved in bone resorption. Finally the excess of RANKL and M-CSF may also upregulate HIV replication, thus enhancing viral infection [7].

In conclusion, HIV causes an imbalance of cellular activity at the bone level, both by decreasing osteoblast bone formation and by increasing osteoclast-mediated bone resorption.

13.2.2 The HAART

The antiretroviral drugs play an important role in reducing bone mass in PLWHIV. Traditionally the HAART has been made up by a combination of three different drugs: two nucleoside reverse transcriptase inhibitors (NRTI), the so-called backbone, and a protease inhibitor (PI) or, alternatively, a non-nucleoside reverse transcriptase inhibitor (NNRTI). Other classes of drugs have been recently discovered (i.e., integrase inhibitors and entry inhibitors), which have much lower bone toxicity than the former drugs. Despite these improvements, the HAART is still eminently based on the use of NRTIs, NNRTIs, and PIs, at least as a first line of treatment [7, 9].

A fundamental meta-analysis has shown that the odds ratio of osteoporosis in PI-treated patients was 1.6 times greater than that of not-on-PI patients [20]. The PIs accelerate the osteoclastogenesis process by reducing the degradation of

RANKL. The mechanism, involving interferon-γ, is extremely complex, and not all the PIs show the same power in activating osteoclasts. Nonetheless the result is an increased osteoclast-mediated bone resorption. In addition, the PIs are able to inhibit the cytochromes P450 and, among these, the hepatic 25-hydroxylase and the renal 1-alpha-hydroxylase. The result of these actions leads to a significant reduction of circulating active vitamin D and an increase of inactive forms, in particular 24,25-(OH)2-cholecalciferol [7]. Given the high prevalence of hypovitaminosis D in HIV-infected patients, the use of PIs may increase the risk of osteomalacia in PLWHIV [12]. The NRTIs exert a marked inhibition on the mitochondrial DNA polymerase-γ. As this enzyme is crucial in the replication of mitochondrial DNA (mtDNA), NRTIs may induce mitochondrial dysfunction, with a reduced energy production and an increased conversion of pyruvate into lactic acid. Hyperlactatemia (15–20% of patients) and the more rare lactic acidosis (0.4% of patients) have been clearly correlated with a progressive bone demineralization, as the alkaline salts of bones are used as buffers of endogenous acidity [7] (Fig. 13.2). Tenofovir (TDF), a nucleotide reverse transcriptase inhibitor, commonly placed in the NRTI class, which is the world's most prescribed drug, deserves a special mention. TDF is highly effective in controlling HIV infection, and it shows very low mitochondrial toxicity. Several studies have correlated TDF use with a reduction of bone mineral density (BMD) that cannot be attributed to the inhibition of mitochondrial DNA polymerase-γ. TDF exerts its negative action on bone via two different mechanisms. In fact it causes renal glomerular toxicity, characterized by a progressive glomerular filtration rate reduction and a consequent increase of parathyroid hormone (PTH) that, in turn, may enhance bone turnover and bone demineralization. Nevertheless the most negative effect of TDF is exerted on the renal proximal tubule. The

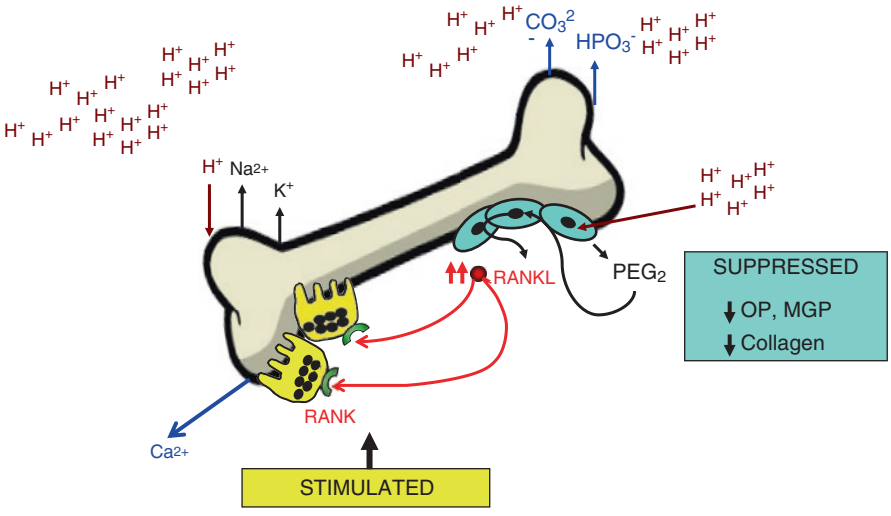

Fig. 13.2 Mechanism by which H+ lead to the release of bone calcium and are buffered by the bone mineral during metabolic acidosis

progressive accumulation of the drug inside the tubular cells may reach a concentration level that determines mitochondrial toxicity and therefore a deregulation of cellular activity. The result is a severe reduction of the proximal tubular reabsorption of ions that may even cause, in some rare cases, the onset of Fanconi syndrome. More frequently, however, TDF impairs the metabolism of phosphate, resulting both in a severe depletion of plasma phosphate and in an increased urinary phosphate excretion [7]. The severe hypophosphatemia, together with the vitamin D deficiency, dramatically reduces the degree of bone mineralization, causing therefore a real osteomalacia [7, 9]. Recently, a new molecule has been released, called tenofovir alafenamide (TAF), which has lower renal toxicity than TDF. TAF serum half-life, in fact, is higher than that of TDF, and it allows the administration of lower doses of the drug that consequently exert a reduced renal toxicity. Randomized double-blind studies have shown that the bone mass reduction induced by TAF is significantly lower than that caused by TDF [21].

13.3 Diagnosis and Therapy

The diagnosis of osteoporosis in PLWHIV is mainly based on the measurement of bone mineral density and on the evaluation of risk factors for fracture. A recent consensus has proposed an algorithm that may easily drive the actions of physicians in the process of diagnosis and treatment [9]. The authors have proposed four steps: the screening, the assessment, the management, and the monitoring. Infectious disease (ID) physicians should investigate the presence of risk factors for fracture (RFF) as well as they should take into consideration patients' age. As a matter of fact, PLWHIV younger than 40 and without RFF should not undergo any further screening. Older patients, particularly if they have important RFF (i.e., a previous history of fragility fracture, glucocorticoid treatment for >3 months, or a high risk for falls), should be evaluated both with FRAX algorithm and with dual-energy X-ray absorptiometry (DXA). After this assessment, patients have to be managed by lifestyle advices (i.e., adequate daily intake of calcium, giving up smoking and drinking, regular physical exercise) and by the administration of vitamin D. In order to reach the suggested target for plasma 25-(OH)-vitamin D (above 30 ng/mL), high doses of cholecalciferol are required in PLWHIV as vitamin D metabolism may be altered both by the virus and the HAART. Moreover vitamin D deficiency must be corrected before starting any anti-osteoporosis therapy. Before beginning any treatment, secondary forms of osteoporosis must be excluded by means of adequate blood and urine tests. The proper management of HIV relies on the synergistic action between an endocrinologist (or another bone specialist) and an ID physician, with the latter doing all those HAART changes that are necessary to reduce bone toxicity, without any return of viral replication. Among the drugs that can be used by the bone specialist, alendronate and zoledronate are the most studied in this particular form of osteoporosis [9]. Even risedronate has been used with good results in a subgroup of HIV-infected hypogonadal males [17]. All the published studies, however, had BMD as primary endpoint, since the number of patients enrolled did

not provide an adequate sample size to evaluate the effects on fractures. A weekly dose of oral alendronate, associated with calcium and vitamin D, has been effective in increasing BMD in treated patients [9]. As far as it is well known that PLWHIV usually have a reduced adherence to therapies, a treatment with weekly tablets is a therapy at high risk of being abandoned. The same problem has been described in the seronegative population with osteoporosis [22]. Zoledronate resulted as effective as alendronate in increasing BMD in PLWHIV. As far as zoledronate is given intravenously once a year, it may guarantee a higher adherence to therapy than oral bisphosphonates. Moreover recent studies have shown that the administration of zoledronate every 2 years ensures an increase in BMD that is substantially equal to that obtained with a yearly schedule [23]. In case of very severe osteoporosis, the use of teriparatide may be taken into account, even though the available literature data on its safety are scarce. Safety and effectiveness of denosumab were never tested in HIV-positive population with osteoporosis [9].

13.4 Conclusions

The advent of HAART has dramatically increased the lifetime expectancy of PLWHIV, but it has also raised the burden of co-morbidities associated with the disease. Osteoporosis is very frequent in PLWHIV, and due to the aging of this population, it is reasonable to expect an increase of osteoporotic fractures in the next future. Since the integrated management of osteoporosis is a crucial aspect of the future treatment of HIV infection, the cooperation of ID physicians and bone specialists will be essential for ensuring to PLWHIV both a good virus control and a low risk of fracture.

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Cardiovascular Risk and Osteoporosis: Is There a Link?

14

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Abbreviations

IL-1, 6	Interleukin-1, 6
RANKL	Receptor activator of nuclear factor kappa-B ligand
TNF-α	Tumor necrosis factor-α

14.1 Introduction

The incidence of both osteoporosis and cardiovascular disease (CVD) is rising due to the aging of the population. These two diseases were long viewed as independent chronic pathologies. However, for over than 30 years, attention has considered the potential for people with low bone mineral density (BMD) being at increased risk of developing CVD, and vice versa, the individuals with CVD have a higher risk of experiencing bone loss and thus greater predisposition to risk of fracture. A number of potential reasons might explain the possible link between poor bone health and CVD.

Given that CVD is a leading cause of premature mortality, understanding whether low BMD is a potential CVD risk factor is of high importance. Since CVD events could accelerate the transition of people with bone disease to greater disability and mortality, it may be important to consider cardiovascular health in people with osteoporosis and fractures.

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14.2 Relationship Between Bone Mineral Density, Fractures, and Cardiovascular Disease

The relationship between bone mineral density, fractures, and cardiovascular disease was evaluated in a large number of studies which had either retrospective cross-sectional and prospective longitudinal design.

14.2.1 Retrospective Studies

Several retrospective studies showed a correlation between vessel wall alteration and low BMD.

Increased coronary calcium burden was found in postmenopausal women with osteopenia and osteoporosis in comparison to those with normal BMD [1, 2]. In another cross-sectional study, BMD correlated negatively with intimal medial thickness (IMT) [1, 3]. Similarly, carotid IMT or plaque thickness and BMD were measured in 155 patients within 7 days after an acute ischemic stroke [1, 4]. Osteoporosis (*T*-score <−2.5) was significantly and independently associated with IMT/plaque thickness in females but not in males. A retrospective study in 209 patient looked for an association between osteoporosis (BMD *T*-score <−2.5) and coronary angiography findings. The risk of coronary artery stenosis >50% was higher in the group with osteoporosis. BMD was more strongly associated with coronary artery disease than were the conventional cardiovascular risk factors (smoking, hypertension, diabetes, and family history) [1, 5].

Other retrospective studies showed an excess risk of CVD in patients with osteoporosis.

Studies, evaluating volumetric BMD and bone microarchitecture at the distal radius and distal tibia of 350 patients, have found that cortical volumetric BMD at the distal radius was significantly lower and cortical porosity significantly higher in the group with ischemic heart disease. When men were analyzed separately, only distal radius cortical volumetric BMD was significantly lower in the group with ischemic heart disease. In females, none of the differences were statistically significant [1, 6]. In a cross-sectional study [1, 7], in both males and females, the presence of silent brain infarction correlated significantly with osteopenia and osteoporosis. A retrospective review of data from 101 postmenopausal women living in a nursing home showed that a history of myocardial infarction, stroke, or peripheral arterial disease was found in 51% of women with osteopenia or osteoporosis compared to only 38% of those with normal BMD values [1, 8]. Similarly, in another retrospective study of postmenopausal women, the prevalence of cardiovascular disease was 69% in the group with osteoporosis (hip *T*-score <−2.5) and only 22% in the group with normal BMD [1, 9]. A cross-sectional study of 5050 males and females found a significant association between a history of myocardial infarction and low BMD after adjustment for risk factors [1, 10]. An examination of data from a nationwide Korean database showed that the 10-year risk of coronary artery disease (Framingham risk score) was significantly associated with

BMD. In males, after adjustments for covariates, the Framingham risk score was significantly associated with BMD at the femoral neck or lumbar spine. No significant associations were found in females [1, 11].

14.2.2 Prospective Studies

Recent systematic review and meta-analysis by Veronese et al. [12] collected 28 prospective studies (1,107,885 participants followed for average 5 years) which evaluated the relationship between osteoporosis and CVD. The primary outcome of the review was the risk of any type of CVD according to BMD status or the presence of fractures. The authors found out that patients with lower BMD, especially at lower limbs, had modestly increased risk of CVD (coronary heart disease, cerebrovascular conditions, and death due to CVD reasons). Each 1-SD decrease of BMD corresponded to an increased risk of CVD at follow-up at 16%. As regards fractures, the presence of vertebral and hip fractures at baseline was associated with an increased risk of CVD, in particular cerebrovascular conditions and death due to CVD reasons, but not coronary heart disease.

In conclusion, both retrospective and prospective studies confirmed the reciprocal association between osteoporosis and/or fractures and CVD.

14.3 Pathophysiological Links Between Osteoporosis and Cardiovascular Disease

The exact pathogenic mechanism that may explain the association between altered bone metabolism and atherosclerosis as the main underlined cause of CVD is not fully understood. This phenomenon cannot be explained by the presence of one specific factor but by the influence of multiple factors and common pathways shared between osteoporosis and atherosclerosis (see Fig. 14.1).

Vascular calcification is highly associated with CVD and mortality. In blood vessels, intimal calcification is associated with atherosclerosis, whereas medial calcification is a non-occlusive process which leads to increased vascular stiffness and reduced vascular compliance. For many decades, vascular calcification has been noted as a consequence of aging. Studies now confirm that it is a rather actively regulated process which shares many features with bone development and metabolism [13].

Vascular calcification is an active process that starts from the phenomenon of transformation of vascular smooth muscle cells into osteoblast-like cells. Osteoblast-like cells express several factors involved in the osteogenesis, such as bone morphogenetic proteins (BMP), alkaline phosphatase (ALP), osteopontin, Gla protein of matrix, osteoprotegerin (OPG), and receptor activator of nuclear factor kappa-B ligand (RANKL) which promote the production of hydroxyapatite and bone formation in vessels [14].

The BMP is a powerful growth factor of osteoblast differentiation and also seems to be an important mediator of vascular calcification. In the atheromatous plaques,

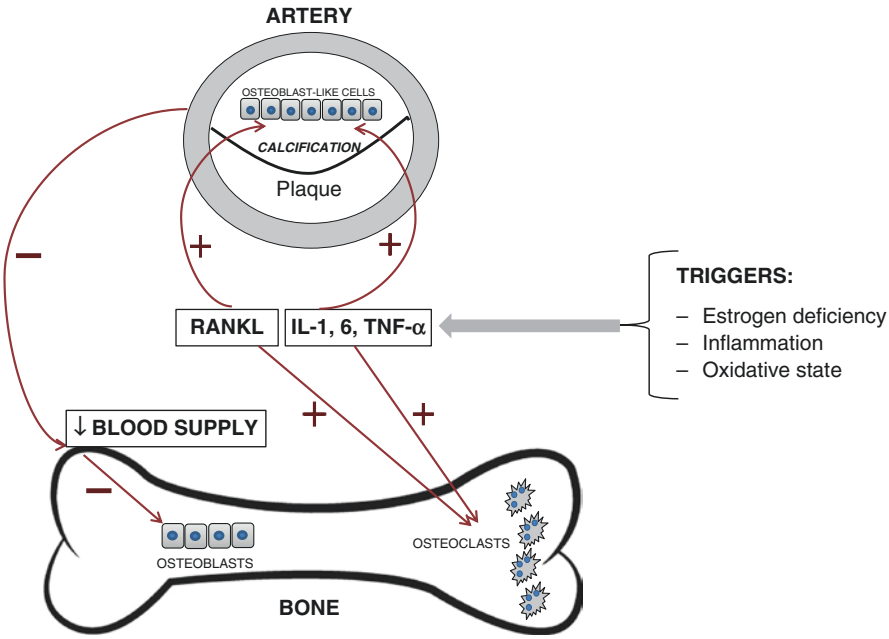

Fig. 14.1 Pathophysiological links between osteoporosis and cardiovascular disease Osteoporosis and cardiovascular disease share common pathways which are triggered by the same pathological factors such as estrogen deficiency and inflammatory and oxidative stress. Estrogen decline production causes secretion of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α. Inflammatory and oxidative states, increased with age and under certain conditions, promote vascular smooth muscle cell differentiation into osteoblasts leading to the progression of vascular calcification and, at the same time, induce osteoclast and inhibit osteoblast differentiation in bone. Additionally, RANKL released by infiltrating T cells and endothelial cells in the arteries affected by atheromatous plaques stimulates vascular calcification by transformation of vascular smooth muscle cells into osteoblast-like cells and, at the same time, induces osteoclastogenesis in bone. Finally, the progression of vascular calcification reduces blood supply to bone, further impairing bone metabolism

endothelial cells, foam cells, and smooth muscle cells exhibit greater BMP2 and BMP4. In vitro studies have demonstrated that this process is upregulated by oxidative stress, oxidized LDL, and tumor necrosis factor alpha (TNFα) [14–16]. In the same manner, oxidative stress and inflammation induce an increase of ALP and osteopontin in smooth muscle cells which further participate in mineralization [14–16].

A growing evidence suggests that the triad of OPG/RANKL/RANK, key proteins involved in bone metabolism, may be important in vascular calcification. In general, OPG produced by osteoblasts binds to RANKL, preventing in this way the connection of RANKL to its receptor RANK causing inhibition of osteoclastogenesis. In normal conditions, OPG is expressed not only by osteoblasts but also in several tissues, including vessels (endothelial and vascular smooth muscle cells).

OPG is released under basal conditions by endothelial cells upon stimulation with inflammatory cytokines (interleukin-1, IL-1, and TNFα) [17]. OPG seems to be protective against vascular calcification since OPG knockout mice developed spontaneous arterial calcification [13, 18]. While OPG is expressed in normal arteries, RANKL, being normally produced by osteoblasts and T cells, is undetected in non-diseased human vessels. However, RANKL may be released by infiltrating T cells and endothelial cells in the arteries affected by atheromatous plaques [17]. RANKL stimulates vascular calcification by transformation of vascular smooth muscle cells into osteoblast-like cells and by increasing production of BMP through the alternative NF-κB pathway [13, 19].

The phenomenon of transformation of vascular smooth muscle cells into osteoblast-like cells represents the crucial step in vascular calcification and is induced by numerous factors such as BMP, RANKL, oxidative stress, inflammation, and estrogen deficiency. These triggers participate not only in vascular calcification but also in bone loss.

Estrogen deficiency is a major risk factor for osteoporosis and CVD. After menopause, estrogen levels decrease dramatically, resulting in the formation of osteoclasts and bone turnover increase with subsequent rapid bone loss. In addition, the decline in estrogen production causes secretion of pro-inflammatory cytokines such as IL-6, IL-1, and TNF-α [14, 20, 21]. *Inflammatory state* influences vascular calcification/atherosclerosis and bone metabolism by increasing bone resorption through an induction of osteoclastogenesis [14]. Moreover, *oxidative stress and production of oxidized LDL*, increased with age and under certain conditions, promote vascular smooth muscle cell differentiation into osteoblasts, at the same time inducing osteoclast and inhibiting osteoblast differentiation in bone [1, 14].

Finally, another factor that links osteoporosis and CVD is vascular-related intraosseous ischemia. The progression of vascular calcification and atherosclerosis may predispose to a reduced blood flow into bone. Since oxygen consumption is coupled with bone formation, a reduced blood supply may impair bone metabolism, resulting in bone loss and osteoporosis. Such, in case of asymmetrical peripheral arterial disease, the hip bone mineral content in the affected limb is lower than that of the contralateral limb [1, 14].

14.4 Osteoprotegerin as a Biomarker of Cardiovascular Disease

In recent years, new approaches are being used to search for novel biomarkers for CVD. A biomarker is a characteristic that objectively measures and is evaluated as an indication of normal biological processes, pathological processes, or pharmacological responses to a therapeutic intervention. Measurements of biomarkers are frequently used in cardio-metabolic medicine and are recognized for the value they add to the diagnosis and prognosis of various diseases [17, 22].

Serum OPG has been proposed as a biomarker of vascular risk and prognosis in a variety of CVD. However, the results in this field are inconsistent.

OPG is highly expressed in various tissues such as the heart, lung, kidney, liver, bone marrow and immune system (dendritic cells), osteoblasts, and vascular cells (endothelial and vascular smooth muscle cells). As it is well known, OPG exerts a protective role in bone inhibiting osteoclastogenesis via binding the RANKL which prevents the coupling of RANKL with its receptor RANK on pre-osteoclasts [17, 23].

The role of OPG in vascular system is much more complicated. OPG is released under normal conditions by endothelial cells. OPG plays a significant role in the physiology of endothelial and vascular smooth muscle cells enhancing its survival, proliferation, and migration. OPG acts as antiapoptotic factor for endothelial cells. Sustained release of OPG from vascular cells has been demonstrated in response to inflammatory cytokines, thus suggesting that OPG might have a new function as a potential biomarker of early endothelial dysfunction [17]. Additionally, OPG seems to be protective against vascular calcification since OPG knockout mice developed spontaneous arterial calcification [13, 18]. OPG neutralizes the effect of RANKL on the induction of activity of vascular smooth muscle cells by inhibiting its binding in vessels, thus preventing excessive vascular calcification [17].

On the other hand, controversially, there is evidence that OPG might exert pro-atherogenic effect, participating in the pathogenesis of atherosclerosis and CVD by amplifying the adverse effects of inflammation. Additionally, in experimental studies on animals, human OPG induced signs of fibrosis and upregulated the arterial expression of transforming growth factor-β1 (TGF-β1), thus supporting the pathogenic role of OPG in the initiation of atherosclerotic lesions [17, 24].

While the experimental studies on animals showed a "dual" role of OPG in the vascular system (protection from vascular calcification and initiation of atherosclerotic process), clinical studies have demonstrated consistent data that higher serum OPG levels are associated with poorer cardiovascular outcomes in the context of coronary disease, abdominal aortic aneurysms, and cardiovascular mortality. In a 10-year follow-up survey, serum OPG levels were an independent risk factor for the progression of atherosclerosis as well as the incidence of and mortality from CVD [17, 25]. Additionally, OPG has been identified as an independent predictor of heart failure development [17, 26], and it correlates with severity of peripheral artery disease [17, 27].

Taken together these data, the physiological and pathological roles of OPG in the vascular system are rather complex. Released from endothelial cells, it might be a biomarker of early endothelial dysfunction, participating further at initial steps of inflammation-induced atherosclerotic lesions. With progression of arterial calcification, OPG may exert a protective role. Thus, higher serum OPG is a sign of progression of vascular injury and a sign of compensatory mechanism against vascular calcification. Therefore, OPG could be a new promising marker of risk prediction of CVD.

14.5 Conclusion

Huge clinical evidence consistently shows a link between osteoporosis and CVD: patients with osteoporosis are at higher risk of ischemic heart disease and stroke, and vice versa, patients with ischemic heart disease or peripheral arterial disease are at higher risk of osteoporosis and fragility fractures. The possibility of a reciprocal cross talk might open the possibility to develop new strategies for multiple-purpose preventive and therapeutic interventions targeted at reducing both bone loss and atherosclerosis progression. In this holistic view, it is conceivable that patients with osteoporosis would take advantage from the evaluation of cardiovascular risk, whereas patients with CVD would benefit from the assessment of bone health.

Many pathophysiological hypotheses have been suggested to explain this link. The process of vascular calcification (the main underlying cause of CVD) and bone loss share the same biological regulators (OPG/RANKL/RANK system) which are triggered by the same factors (estrogen loss, inflammation, and oxidative stress), promoting both the development of calcified vascular plaque and increased bone turnover. If the current hypothesis is confirmed, then assays of these factors might help to predict both CVD and osteoporosis. Finally, although the role of OPG in vascular system is still controversial, however, it could be a promising biomarker of progression and prognosis of CVD.

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Osteoporosis: May Doping Cause It?

15

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15.1 Introduction

Doping is a broadly spread phenomenon, and a social problem, concerning sport at both recreational and competitive levels, and is defined as the use of a substance, or a technique, to illegally improve athletic performance [1]. Depending on the mechanism of action, doping agents may exert direct or indirect ergogenic effects, including enhanced strength, enhanced energy production and better recovery, and/or anabolic actions, including increased protein synthesis, particularly in muscles, and/or stimulating actions, including increased attention and loss of fear. The wide spectrum of effects exerted by doping agents provides a competitive advantage during sport activity; therefore, their use has been prohibited prior to or during competitions. A "Prohibited List" comprising doping substances and methods banned prior to or during competitions is published yearly by a dedicated international agency, the World Anti-Doping Agency (WADA). WADA "Prohibited List" includes substances and methods fulfilling at least two of the following criteria: enhancement of sports performance, and/or threat for the health of the athlete, and/or violation of the spirit of sports [2]. WADA "Prohibited List" includes, at present, anabolic androgenic agents (AAS), hormone and metabolic modulators, peptide hormones and growth factors, β2-adrenergic receptor agonists, and glucocorticoids, all of which represent the most widely used performance-enhancing substances, as well as additional less used drugs. Considering the relatively high prevalence of doping agents' usage among athletes, and besides any consideration

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in regard to the unethical and anti-sportive aspects of doping, the potentially associated undesired side effects and doping-related health risks are undoubtedly worth of investigation. Chronic exposure to high doses of performance-enhancing substances, which often exert pleiotropic actions on multiple anatomical/functional targets, raises the risk of potential long-term complications; osteoporosis might represent one of most serious and long-lasting complication associated with doping, nevertheless, few and sparse studies addressing this topic have been performed so far. The current chapter describes the relationship between selected doping agents and general bone health impairment, with particular reference to the risk of developing osteoporosis, and to the early occurring and the long-term consequences of doping on bone metabolism; in particular, the chapter focuses on the effects of AAS, aromatase inhibitors (AIs), growth hormone (GH), β2-adrenergic receptor agonists and glucocorticoids, which belong to the classes of most commonly used doping agents.

15.2 Anabolic Androgenic Steroids

AAS are used to improve competitive sport performance, as well as for recreational purposes, to achieve desirable body image and to increase muscle mass and strength [3]. In particular, AAS have been hypothesized to exert several effects that may enhance performance, such as antagonism of the catabolic effect of glucocorticoids, direct stimulation of protein synthesis, increased red blood cell production, and central nervous system effects, which increase motivation and decrease fatigue [4]. Among AAS, gonadal steroids, including both androgens and estrogens, are known to exert positive effects on bone mineral density (BMD), at physiological concentrations; moreover, androgen receptors (AR) and estrogen receptors are expressed in osteoblasts, osteoclasts, and osteocytes, as well as mononuclear and endothelial cells in the bone marrow [5]. A general overview of the effects of gonadal steroids on osteoblast and osteoclast activity is depicted in Fig. 15.1. The effect of androgens, mainly testosterone, on bone homeostasis is directly mediated by activation of AR and, indirectly, by the estrogens, converted from testosterone by aromatase enzyme, which stimulate bone formation and inhibit bone resorption [6, 7]. Androgens directly control periosteal bone formation, which contributes to the greater width of cortex in men, stimulate bone formation activity of osteoblasts, and inhibit bone resorption activity of osteoclasts [8]. Estrogens exert a bone anti-resorptive action mainly by attenuating osteoclasts differentiation, activity and survival [8]. The molecular mechanisms mediating the anabolic effects of androgens and estrogens on bone comprise the suppression of receptor activator of nuclear factor kappa B ligand (RANK-L) expression by osteoblasts, resulting in an inhibition of RANKL-RANK pathway, which ultimately reduces bone resorption by osteoclasts and induces osteoclasts apoptosis [9]. Furthermore, an increased production of anti-resorptive cytokines, mainly represented by osteoprotegerin [10], is also mediated by estrogens, but not by androgens, which, conversely, seem to suppress osteoprotegerin production, therefore probably explaining the greater anti-resorptive effects of estrogens, as

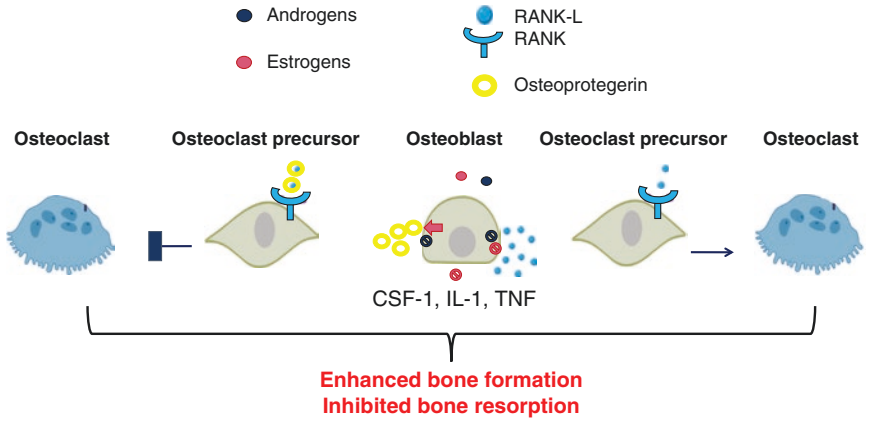

Fig. 15.1 General overview of the effects of gonadal steroids on bone metabolism

compared to androgens [9]. Lastly, a decreased osteoblastic production of several resorptive cytokines, which include colony-stimulating factor-1, interleukin-1 (IL-1), and tumor necrosis factor-alpha (TNF-α), is also induced by estrogens [8, 10]. Consistently with the anabolic effects of testosterone on bone in men, hypogonadism, characterized by testosterone deficiency, represents one of the most important endocrinological disorders associated to a significant risk for osteoporosis together with impairment of muscle mass and strength, and testosterone replacement therapy increases bone mass as well as muscle mass and strength, in hypogonadal men [8]. Athletes using AAS display increased bone mass, in paticular bone mineral content (BMC) and BMD, and extremely low fracture rate, compared to athletes not using AAS [5]; by contrast, after AAS withdrawal, athletes may develop osteoporosis and experience a higher hip or vertebral fracture rate, promoted by both quick loss of the muscle mass gained during doping [5] and hypogonadotropic hypogonadism secondary to the suppression of hypothalamus-pituitary-testis axis consequent to the abuse of AAS [11].

In particular, this specific form of male hypogonadism has been demonstrated to be reversed by short-term administration of clomiphene citrate or human chorionic gonadotropin, with a different recovery time on the basis of AAS abuse duration, although some evidences also reported a partially irreversible damage along the hypothalamus-pituitary-testis axis, targeting, by means of unclear molecular mechanisms, the hypothalamic and/or pituitary and/or Leydig cell function [11, 12].

15.3 Aromatase Inhibitors

AIs are a class of compounds which inhibit the aromatase enzyme, responsible for the peripheral conversion of androgens to estrogens [13]. AIs are used by male athletes as a corrective treatment for gynecomastia occurring after administration of

androgens and to restore endogenous testicular activity following a doping cycle, based on induction of LH increase driven by blockade of estrogen synthesis [14]. Although there seem to be no studies available, specifically focusing on the effects of AIs on bone metabolism in athletes, information on their effect on male athletes might be extrapolated from evidences in male adolescents affected by early puberty and constitutional delay of puberty, in elderly men with late-onset hypogonadism and in women suffering from breast cancer. In male adolescents affected by early puberty and constitutional delay of puberty, AIs delay epiphyseal maturation and increase the predicted adult height [5]; therefore, AI abuse during adolescence may stimulate bone formation and muscle strength, through increased circulating levels of testosterone, whereas AI abuse during adulthood, after the epiphyseal maturation completion, may only increase muscle strength [5]. AIs use in elderly men for late-onset hypogonadism might represent a further useful model to better understand the potential adverse effects on bone of AIs used as performance-enhancing drugs, although contrasting evidences are available. Indeed, some studies have demonstrated a significant decrease of BMD together with a reduction of estrogen levels, whereas different studies did not report bone impairment in elderly men treated with AIs, probably due to the moderate decrease in estrogen levels, associated with a contemporaneous increase in androgen levels [15–17]. These contrasting evidences might be explained by the complex balance existing between estrogens and androgens in the regulation of bone metabolism: indeed, estrogens have been demonstrated to be the main sex hormones involved into development and maintainance of male skeleton homeostasis, but androgens also play an important role in promoting periosteal apposition and increasing bone size in men [18]. Although no clear evidences are available concerning the risk of osteoporosis in men treated with AIs, interestingly, more consistent evidences exist in women; in particular, early studies showed that women with breast cancer treated with AIs had increased bone resorption, decreased BMD at the femoral neck and lumbar spine, and increased risk of fractures [19, 20]. Moreover, the ATAC (Anastrozole, Tamoxifen, Alone or in Combination) trial, the largest randomized trial comparing anastrozole and tamoxifen therapy, demonstrated that the annual incidence of fractures was higher in women receiving anastrozole, compared to those treated with tamoxifen, throughout 5 years of treatment [21]; nevertheless, during follow-up and discontinuation of therapy, fracture incidence decreased in the anastrozole treatment arm, by reaching similar rates as compared to tamoxifen [21], suggesting that the effect of AIs on bone, and the AI-related predisposition to fractures could be reversible.

15.4 Growth Hormone

GH is used by athletes as a doping agent due to its lipolytic activity, as well as for the positive effects on protein synthesis and muscle growth, although the realistic association between these biological effects and an improvement in sport performance has not been clearly demonstrated so far [2, 5]. Several studies are available concerning

the effects of GH on bone homeostasis; in particular, acromegalic patients, which are characterized by excessive circulating GH levels, represent a suitable model of GH abuse. Indeed, acromegalic patients suffer from osteoporosis, together with bone overgrowth, and damage to joints, which ranges from arthralgia to osteoarthritis, induced not only by bone overgrowth but also by soft tissue swelling [22–24]. More specifically, it has been demonstrated that acromegalic patients have a significant impairment of bone health and a consequent high risk of vertebral fractures, occuring in up to 60% of patients with a 3–8 fold higher prevalence than in general population and a slight predominance in men [25–27]. The possible mechanism underlying bone impairment induced by GH excess is represented by the alteration of the trabecular microstructure, occurring irrespective of unchanged or increased trabecular density, which, in turn, may affect the micro-mechanical properties of bone trabeculae [28]. Moreover, the evidence of a direct action of GH/IGF-1 axis on bone turnover is confirmed by the fact that bone formation markers, specifically procollagen type III N-terminal propeptide and osteocalcin, have been demonstrated to be significantly higher in healthy volunteers treated with GH, compared with those treated with placebo, and are efficiently measured in blood samples during doping tests for GH abuse in athletes [29, 30].

Lastly, the existence of a direct effect of GH on bone metabolism is further confirmed by the impact of GH replacement therapy in patients with GH deficiency (GHD) [31]. In particular, a recent metanalysis on a hge number of patients with GHD demonstrated an increase of BMD in lumbar spine and femoral neck, in studies with replacement of more than 1 year [32]. Consistently, in a 15-year prospective study of GH replacement therapy in patients with adult-onset GHD, GH treatment gradually increased total body BMC during the study period [33]. These evidences overall suggest that, in GHD patients, replacement with GH is able to progressively improve bone mass and bone status. In conclusion, the aforementioned pathological models well demonstrate the dual role of GH on bone status: restoration of normal GH levels might contribute to improve bone mass in GHD patients, whereas an excess of GH levels, typical of acromegalic patients and GH-abusing atheletes, might promote detrimental effects including bone overgrowth, osteoporosis and damage to joints.

15.5 β2-Adrenergic Receptor Agonists

β2-adrenergic receptor agonists are used by athletes for the anabolic effects on skeletal muscle [34], as well as for additional actions, which may collectively enhance performance, including bronchodilation, anti-inflammatory actions, together with the increased functional capacity and strength of skeletal muscle [35]. Little evidence exists, in humans, concerning the effects of β2-adrenergic receptor agonists on bone metabolism even if it has not specifically focus on doping use of these substances in athletes [5]. Despite some authors speculated that the increase of muscle mass caused by β2-adrenergic receptor agonists would be accompanied by an anabolic effect on bone, due to the mechanostat system regulating bone mass

[36], data from the literature highlighted that the use of β2-adrenergic receptor agonists might be a risk factor for osteoporosis [37]. Indeed, β2-adrenergic receptors are expressed in osteoblasts and osteoclasts [38], and β2-adrenergic receptor agonists use has been suggested to decrease osteoblastic activity and bone formation [39] and increase osteoclastic activity and bone resorption [40]. In particular, animal studies highlighted that rats treated with clenbuterol and salbutamol had increased plasma levels of C-terminal collagen cross-links, a bone resorption marker [41]. Moreover, different *in vivo* studies in female rats demonstrated that 2 mg/kg/day clenbuterol administered for 4 weeks inhibited longitudinal bone growth at femoral metaphysis and decreased BMC in growing rats [42], whereas treatment for 6 weeks reduced BMD as well as femoral and lumbar spine trabecular microarchitecture [43]. The observed microarchitectural changes induced by clenbuterol treatment resembled those observed in postmenopausal osteoporosis [44]. Human studies reported an increased risk for hip fractures in subjects affected by respiratory pathologies using β2-adrenergic receptor agonists [37]; conversely, subjects using β-adrenergic receptor antagonists, compounds employed as treatment for cardiovascular diseases, had a reduced risk for hip and spine fractures [45], therefore suggesting that β2-adrenergic receptors activation, rather than inhibition, might be associated to an increased risk of bone impairment, also in athletes which eventually abuse of β2-adrenergic receptor agonists as performance-enhancing drugs.

15.6 Glucocorticoids

Glucocorticoids are used by athletes mainly for their metabolic effects, which include stimulation of gluconeogenesis and mobilization of amino acids and fatty acids, but also to alleviate pain and reduce tiredness [46]. No specific studies strictly focusing on glucocorticoid doping impact on bone status seem to be available in literature nevertheless, glucocorticoid-induced osteoporosis is the first cause of secondary osteoporosis, and vertebral fractures are typical of glucocorticoid-induced osteoporosis, although the risk of non-vertebral fractures, including hip fractures, is also increased [47]. Different studies highlighted that bone impairment is associated with the use of glucocorticoid as anti-inflammatory and immunosuppressive therapies [5]. More significantly, Cushing's syndrome (CS), which is characterized by chronic endogenous hypercortisolism, provides relevant insights into the effects of glucocorticoid excess on bone metabolism and general bone health; indeed, BMD is reduced, in patients with CS, and osteopenia, osteoporosis, and skeletal fractures have been reported in up to 78%, 57%, and 76% of patients, respectively [48, 49], and increased frequency of osteoporosis has been reported also in subclinical CS [50]. Relative gender differences have been reported in bone impairment; in particular, male patients have a higher prevalence of osteoporosis and vertebral fractures, compared to female patients [51, 52], whereas amenorrhoeic and eumenorrhoeic women display similar BMD and prevalence of fractures [53, 54], suggesting that in the presence of hypercortisolism, testosterone deficiency might exacerbate the impairment of bone status and that glucocorticoid excess overcomes estrogenic bone protection

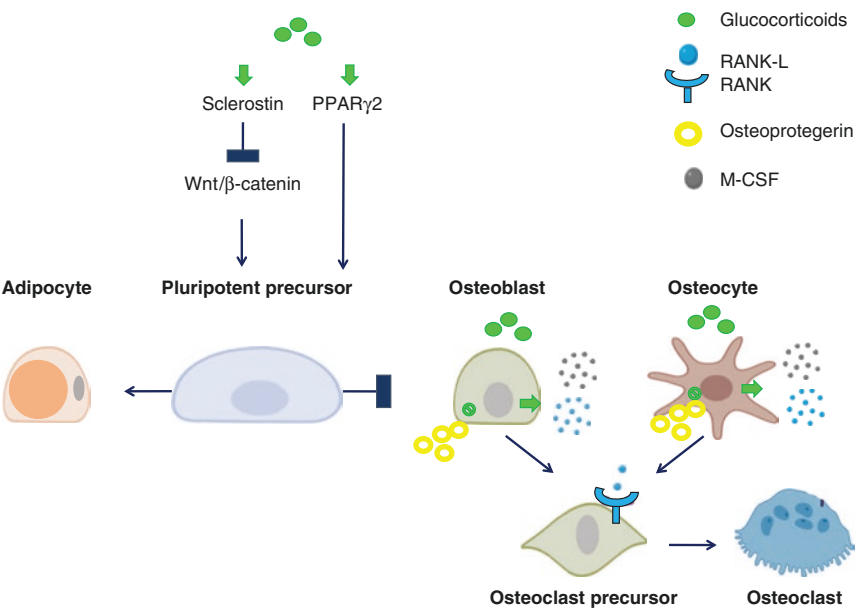

Fig. 15.2 General overview on the effects of glucocorticoids on bone metabolism

[49]. Moreover, a progressive improvement of BMD has been reported by prospective studies in patients followed up for at least 1 year after remission from hypercortisolism [55–57], with a greater increase in BMD after remission in male than female patients [58], highlighting that bone damage might be potentially reversed with control of glucocorticoid excess [49, 59]. Glucocorticoid-induced osteoporosis is characterized by increased bone turnover, with decreased bone formation and increased bone resorption [47]. A general overview on the effects of glucocorticoid excess on bone metablism is depicted in Fig. 15.2. Glucocorticoids push the differentiation of pluripotent precursor cells toward adipocytes, rather than osteoblasts, which determines a reduction in the number of osteoblasts, by upregulating peroxisome proliferator-activated receptor gamma receptor 2 (PPARγ2) [60] and by affecting the Wnt/β-catenin signalling pathway [61, 62]. In particular, glucocorticoids increase sclerostin expression, which results in the inhibition of Wnt signalling, leading to reduced differentiation of osteoblast precursors to mature osteoblasts and increased osteoblast and osteocyte apoptosis [47]. Moreover, glucocorticoids increase the production of macrophage colony stimulating factor (M-CSF) and RANKL and decrease the production of osteoprotegerin by osteoblasts and osteocytes, resulting in an increased number and enhanced activity of osteoclasts [63, 64]. In conclusion, on the basis of these molecular evidences, and on the basis of side effects of glucocorticoids as anti-inflammatory and immunosuppressive therapy and of CS-related bone comorbidities, it can be speculated that also athletes abusing glucocorticoids as performance-enhancing drugs might experience a long-term bone impairment and might have a significantly increased risk of osteoporosis.

15.7 Conclusions

Osteoporosis is a frequent adverse effect of drugs, which are also used as doping agents, suggesting that osteoporosis is likely to represent a side effect of doping. Although few and incomplete studies exist, specifically performed in athletes, concerning doping agent effects on bone status, the most commonly used doping substances have been proven to negatively influence bone status. It might be speculated that doping occurring during pubertal and post pubertal age, a timeframe coinciding with achieving peak bone mass, might be of relevance to the development of osteoporosis later in life; nevertheless, further investigation should be performed to address this hypothesis, and to determine the eventual reversibility of negative effects, and the global long-term consequences on bone health might also add strength or disprove this hypothesis. Moreover, specific studies performed in athletes, and, in particular, comparative studies in elderly athletes with and without past history of doping, would be required to address remaining questions concerning the entity and mechanisms of doping-related bone impairment.

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Part III

Treatment of Male Osteoporosis

Androgen Therapy

16

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16.1 Indications to Testosterone Treatment (TT) of Male Osteoporosis

Increased bone loss and resorption rates are evident in the adult androgen deficiency syndrome (or Late Onset Hypogonadism, LOH), as a morbid condition associated to other comorbidities [1] such as metabolic syndrome, obesity [2], and type 2 diabetes mellitus [3, 4]. In addition, many andrological disorders, i.e., Kallmann syndrome, Klinefelter syndrome, hypophyseal or hypothalamic tumors, and androgenic deprivation for prostate cancer, are often associated with bone mineral density (BMD) reduction and increased risk of fracture.

In males, the evaluation of BMD by X-ray densitometry (DEXA) is the method of choice for defining the risk of fracture, and it is indicated, according to the Essential Levels of Care, at any age in the presence of major risk factors (e.g. unbalanced diet, low level of physical activity, hypovitaminosis D, fragility fracture, prolonged corticosteroid therapy) or in the presence of three or more of the following minor risk factors for men over the age of 65:

1. Familiar history of severe osteoporosis
2. Body mass index <19 kg/m^2
3. Inadequate calcium intake (<1200 mg/day)
4. Smoke >20 cigarettes/day
5. Alcohol abuse (>60 g/day)

Currently, densitometry criteria for the diagnosis of male osteoporosis are not based on evidence levels compared to female, and *T*-score <−2.5 DS is used as a diagnostic cut-off with respect to the young adult male subject [5, 6]. An additional

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diagnostic tool chart (FRAX) can be used by clinicians to assess real-life fracture risk. Actually, bone turnover markers are not considered useful during follow-up because of their high costs [6]. Actually, the Endocrine Society Guidelines recommend to begin periodic osteoporosis risk assessment (by DEXA) in men at increased risk of osteoporosis, in men with late-onset hypogonadism (LOH), or under androgen deprivation therapy for prostate cancer [5] but to avoid testosterone treatment (TT) for osteoporosis in men who have normal T levels or who are at high risk of bone fracture, regardless of T levels.

Thus, measurements of serum testosterone levels are useful to identify men who have androgen deficiency and who may be candidates for TT other than specific anti-osteoporotic treatments. For example, in the European Male Aging Study only sexual symptoms (poor morning erections, decreased libido, and erectile dysfunction) showed an association with total testosterone levels below 320 ng/dL (11 nmol/L) and free testosterone levels below 64 pg/mL (220 pmol/L), after adjusted for age [1]. Testosterone alone is important to maintain lean mass and muscle size and strength, while estradiol is necessary to prevent increases in fat mass and vasomotor symptoms; both testosterone and estradiol are required to maintain appropriate sexual function and BMD [7, 8].

Several studies have tried to find a threshold value of testosterone as a bone health marker. In the Osteoporotic Fractures in Men study, the odds of having osteoporosis at the hip tripled, as did the odds of experiencing rapid hip bone loss in men with baseline testosterone levels below 200 ng/dL (6.9 nmol/L) vs. men with testosterone levels above 200 ng/dL (6.9 nmol/L) [9]. Additionally, in the Dubbo Osteoporosis Epidemiology Study, the risk of low-trauma fracture was higher in men with baseline testosterone levels in the lowest quartile [median level of 227 ng/dL (7.9 nmol/L) [10]. Thus, men whose serum testosterone level is 200–300 ng/dL (6.9 –10.4 nmol/L) or below appear to be at higher risk for bone loss and fracture and are more likely to have a favorable response to TT. Other studies have shown that BMD in the aging male population is positively associated with endogenous androgen levels [11]. Indeed, testosterone levels in young men have been shown to correlate with bone size, strongly suggesting a role in the achievement of peak bone mass and protection from future osteoporosis [12]. In particular, several studies have documented that testosterone plays a crucial role in the maintenance of male bone health mainly through its aromatization to estradiol (E2), while dihydrotestosterone seems to be not essential for the beneficial effects of testosterone on BMD [13]. Two recent studies have reported an association between serum-free or bioavailable testosterone levels and the risk of bone fractures suggesting a possible direct role of testosterone in increasing bone health [14, 15].

16.2 Evidence-Based Medicine for Testosterone Therapy

Before starting TT, an accurate evaluation of absolute *contraindications* is mandatory (Table 16.1), and regular *follow-up* is needed in patients receiving TRT, as potentially androgen-dependent adverse events may occur suddenly (Table 16.2) [5].

Table 16.1 Absolute contraindications against testosterone treatment

Diagnostic suspect or diagnosis of prostatic carcinoma
PSA level > 4 ng/mL (or > 3 ng/mL Afro-Americans)
Breast cancer
Severe obstructive apnea
Male infertility
Hematocrit (Hct) >52% or/and high risk of venous thromboembolism
Severe lower urinary tract symptoms associated with benign prostate hyperplasia

Table 16.2 Monitoring of patients receiving testosterone treatment (TT)

The clinical-biochemical response to TT should be assessed after 3, 6, and 12 months and thereafter annually (according to different method of administration of TT)
In men with abnormal mineral density, DEXA measurements should be repeated 12–24 months after the beginning of TT and thereafter annually
Hematocrit: At 3, 6 and 12 months and thereafter annualy. Testosterone dosage should be decreased or therapy discontinued if hematocrit increases above level of 52%
Prostate exploration by digital rectal examination and plasmatic PSA levels should be assessed before commencing TT. PSA evaluation at 3, 6, and 12 months and thereafter annually is recommended
Monitoring of potential cardiovascular side effects and the risk of venous thromboembolism is indicated in men receiving TT
Men with cardiovascular comorbidity should be assessed by a cardiologist before TT is initiated, and there should be close cardiovascular monitoring during TT

It is now clear that normalization of testosterone levels increases BMD in men with hypogonadism due to GnRH deficiency and a prolonged TT normalize BMD in these men [16]. Normalization of testosterone increases BMD in men with acquired hypogonadism due to prolactin-secreting adenomas [17], other pituitary-hypothalamic disorders, or primary testicular disorders [18]. Also, TT can increase BMD in elderly men whose baseline testosterone levels were 200–300 ng/dL (6.9–10.4 nmol/L) but not in men with higher baseline levels [19]. In men with acquired hypogonadism, TT reduces bone turnover markers, suggesting that the testosterone-induced increase in BMD is due to anti-resorptive effects possibly mediated through the conversion of estradiol [20]. Because of the decline of sex steroids in aging men, it has been suggested that this may be paralleled by a decrease in BMD that occurs in aging men. The effects of testosterone on BMD of hypogonadal men with disorders of the hypothalamic-pituitary-gonadal axis are time-dependent and appear to be related to baseline levels and to cut-off below 200 ng/dL (6.9 nmol/L), while TT fails to increase BMD in men whose testosterone levels are within the reference range. Three placebo-controlled trials have examined the effect of testosterone administration on BMD in older men with low baseline testosterone levels. In men aged 60 or older with baseline testosterone levels below 320 ng/dL, 12 months of testosterone increased spine and total hip BMD, but there was no significant change at the femoral neck, and prevented a decline in femoral neck BMD [21].

In middle-aged men, Isidori et al. meta-analyzed different parameters related to TT and bone parameters, reporting a reduction of bone resorption markers as well as with an increase at the lumbar spine by +3.7% (CI: 1.0–6.4%) compared to placebo, but not at the femoral neck, and a consistent reduction in bone resorption markers (pooled effect size = −0.6 SMD, CI: −1.0 to −0.2) [22]. Another meta-analysis of 8 trials involving 365 patients reported similar results [23]. Conversely, insufficient data have been published so far to calculate the effect of TT on the risk of bone fractures [24]. Interventional studies showed that long-acting testosterone preparation in young adults with hypogonadism of adult age (testosterone <320 ng/dL) increases femoral and vertebral BMD after 3 [25] and 10 years of continuous therapy, respectively [26]. These preparations were also able to ameliorate metabolic syndrome components, male obesity secondary hypogonadism, and cardiovascular risk [27] without prostate adverse events [28]. These data allow speculating that T may exert a specific action on osteoblast likely through a direct activation of androgen receptor (AR) [29, 30]. In addition, the response to therapy would also depend on the length of the CAG receptor triplet for AR androgen [31]. This improvement shows a timetable effect of TT on the bone starting after 12 months with a progressive increase of 5% per year until 36 months [32]. An increasing number of studies have demonstrated that TT in healthy hypogonadal men increases areal vertebral bone density, volumetric vertebral and femoral BMD, and bone strength, although no data on fracture prevention is available [33].

16.3 Conclusions

Aging affects the remodelling balance in a sex-specific manner and in men , it is associated with decreased bone formation and turnover. The influence of hormones on bone metabolism is not limited to sex steroid hormones, but there are several hormones (such as FSH, IGF-1, TSH, PTH and other) which are able to affect it [34]. Thus, an exhaustive hormonal assessment, after a proper medical history collection, should be completed for men during bone loss evaluation. After 65 years of age, the presence of sexual symptoms may be a sign of possible androgen deficiency, and therefore the evaluation of testosterone levels associated with a BMD may be helpful in order to detect treatable LOH associated with osteoporosis. The clinicians can offer TT on an individualized basis after explicit discussion of the potential risks and benefits [5]. Lifestyle changes (adequate level of physical activity, healthy diet, etc.) and other available interventions (such as vitamin D supplementation and adequate calcium intake) are recommended prior to TT is commenced. Furthermore, it is mandatory to perform the evaluation of the overall cardiovascular risk and prostate health before starting TT and during it. In agreement with guidelines, we recommend combination therapy with anti-absorbent agents (bisphosphonates or teriparatide or denosumab) in men who require (symptomatic hypogonadal men) TT and which have a high risk of fracture repeating BMD tests of the lumbar spine, femoral neck, and hip after 1–2 years of T therapy [5].

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Pharmacological Therapy

17

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17.1 Introduction

Osteoporosis is an asymptomatic bone metabolic disease, characterized by a decrease of bone mass and deterioration of the micro-architecture of the skeleton, which leads to an increased fracture risk [1]. It is a multifactorial disease potentially caused by genetic mutations, endocrine disorders, and lifestyle alterations. Hormones, such as estrogen, calcitonin, parathyroid hormone (PTH), and vitamin D, modulate bone remodeling, thus maintaining bone homeostasis [2]. Osteoporosis in men is a relatively common problem [3], although less frequent than in women, with a prevalence of 17% versus 34%, respectively, but it is underestimated, underdiagnosed, and undertreated. In the last decade, studies of male osteoporosis have increased the awareness of the problem and have improved our understanding of the pathogenesis of osteoporosis and fragility fractures in men. Approximately 25–30% of all hip fractures occur in men [4], and indeed many men suffer vertebral deformities [5]. Hip and vertebral fractures are associated with significant mortality and disability. By 2050, the worldwide incidence of hip fracture is expected to rise by 240% in women and 310% in men compared to 1990 involving approximately 1.66 million in 1990 to 6.26 million in 2050 [6].

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17.2 Etiology

It is well known that male osteoporosis has a multifactorial etiology and osteoporosis in men is often secondary. The causes of osteoporosis in men include an excess of glucocorticoids, hypogonadism and a variety of other systemic conditions, gastrointestinal diseases, vitamin D deficiency, medications (such as anticonvulsant), and lifestyle factors, such as smoking, alcohol consumption, and physical inactivity, but often there is no obvious causes (Table 17.1). Osteoporotic fragility fractures are the leading cause of morbidity and mortality among aging men [7, 8], and 30% of all hip fractures occur in men, which often result in mortality.

In men, bone loss proceeds slowly, starting at middle age. As in women, hypogonadism is a well-documented risk factor for developing osteoporosis in men and in older decades, testosterone levels are negatively correlated with the risk of fractures, and it seems that this age-related testosterone deficiency should not be considered as one of the many causes of secondary osteoporosis, rather one of the major and most important mechanisms of senile osteoporosis. Indeed, androgens play a pivotal role in bone tissue homeostasis: they directly stimulate the proliferation, differentiation, and function of osteoblasts; inhibit osteoclast recruitment; and influence interactions between osteoclasts and osteoblasts. They stimulate growth hormone secretion (GH), increase the sensitivity of bone cells to IGF-1, and stimulate the production of bone matrix [9]. Androgen receptors are present in both osteoblasts and osteoclasts [10]; however, several data suggest that estrogens play a significant role in the pathogenesis of osteoporosis in men as demonstrated in women [11, 12]. In fact, a positive correlation between serum estradiol concentrations and bone mineral density in men has also been described. Severe osteoporosis has been reported in men with deletion of estrogen receptor gene and aromatase-deficient males. Acute hypogonadism induced by ablation treatment for prostate

Table 17.1 Causes of primary and secondary osteoporosis and bone loss in men

Primary osteoporosis (~35%)
Age-related osteoporosis
Idiopathic osteoporosis
Secondary osteoporosis (~65%)
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 osteoporosis (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)

cancer (surgical or pharmacological castration, antiandrogen therapy) is associated with an extremely high risk of fragility fractures. Other well-recognized causes of bone loss in men are cigarette smoking and alcohol abuse, as well as corticosteroid treatment.

In contrast to the rapid decrease in estrogen levels in postmenopausal women, the decrease of testosterone secretion in aging men is much more extended in time. Consequently, men rarely experience rapid acceleration of bone loss. As a consequence, the exponential increase in frequency of osteoporotic fractures with age is approximately 5–7 years delayed in men, compared to women [13–15].

17.3 Treatment

Treatment of osteoporosis in men at increased risk of fragility fractures was first included in the latest revision of the European guidelines on the evaluation of medicinal products in the treatment of osteoporosis [16]. Pharmacological agents are classified into two groups, antiresorptive and anabolic agents. The main mechanism of action of antiresorptive agents, such as calcitonin, bisphosphonates, estrogen, selective estrogen-receptor modulators, and denosumab, is the reduction of bone resorption through the inhibition of the activity of osteoclasts, while anabolic drugs act by stimulating bone formation (Table 17.2).

Pharmacological approach of osteoporosis should be recommended to all men with a diagnosed osteoporotic fracture and men with a high 10-year absolute fracture risk (FRAX). Treatments for osteoporosis in men are less defined than in women, mainly due to the fact that there are fewer randomized clinical trials (RCTs) performed in male populations, relatively smaller sample sizes, and lack of long-term extension studies. Available clinical data on drugs used to treat osteoporosis support their efficacy in men with primary osteoporosis as well as in women [17].

Only a minority of men are screened and treated for osteoporosis and fracture prevention, even after first fracture. Bisphosphonates are generally recommended as first-line pharmacotherapy in men. Future drugs for osteoporosis in men might include more selective antiresorptive compounds which do not markedly inhibit bone formation as well as newer osteoanabolic agents that appear to more selectively stimulate bone formation. Drugs now approved for the treatment of osteoporosis in men include the antiresorptive bisphosphonates alendronate, residronate and zoledronic acid, the antiresorptive monoclonal antibody denosumab, and the bone-forming agent teriparatide.

Table 17.2 Drugs for treatment of male osteoporosis

Testosterone
Bisphosphonates (alendronate, risedronate, zoledronic acid)
Teriparatide
Denosumab
Strontium ranelate

Treatment effects in men are analogous to what is observed in the treatment of postmenopausal osteoporotic women. Bisphosphonates are the treatment of choice in idiopathic osteoporosis. Denosumab is also approved for treatment in men receiving androgen deprivation therapy for non-metastatic prostate cancer; further, bisphosphonates and teriparatide are also available to clinicians for the treatment of glucocorticoid-induced osteoporosis in men. Testosterone treatment may be indicated in men with documented symptomatic hypogonadism, but, to date, osteoporosis is neither a sufficient nor a specific indication for testosterone treatment. Testosterone treatment increases BMD in hypogonadal men and is most effective in those whose epiphyses have not closed completely. New compounds with well-advanced clinical development include romosozumab, a monoclonal antibody against sclerostin.

The aim of the treatment in osteoporosis is to prevent all-life fractures in those who have not yet suffered and to reduce the risk of fractures in patients with advanced osteoporosis. Comprehensive fracture prevention should address all men over the age of 65 years and should be aware of the risks, modifications of lifestyle, and nutrition, and, as far as possible, the elimination of risk factors for fracture and prevention of falls.

17.4 Bisphosphonates

Bisphosphonates inhibit osteoclastic bone resorption and are the most widely used drugs in male osteoporosis. Studies of male osteoporosis include the evaluation of alendronate, risedronate, and zoledronic acid. These agents are indicated to increase bone mass in men with osteoporosis.

17.5 Alendronate

Alendronate is a potent bisphosphonate that inhibits osteoclast-mediated bone resorption [18] which has high affinity to bone with long-term effects. In postmenopausal women with osteoporosis and in patients with glucocorticoid-induced osteoporosis, alendronate significantly increases bone mineral density; it also reduces the incidence of major osteoporotic fractures, including those of the spine and hip, in postmenopausal women [19].

Oral alendronate has been tested against placebo or alfacalcidol in two RCTs undertaken in men with primary or hypogonadism-associated osteoporosis. In a 2-year double-blind study, Orwoll et al. investigated the efficacy of alendronate (10 mg/day) or placebo in 241 men with osteoporosis aged 31–87 years. The study included men with femoral neck BMD at least 2 SD and lumbar spine BMD at least 1 SD below the male reference, or with femoral neck BMD at least 1 SD below male reference and at least one vertebral deformity or a history of an osteoporotic fracture [20]. Alendronate-treated men showed a similar increase in BMD as previously reported in postmenopausal women [21], and the changes in BMD with alendronate

were not affected by circulating levels of sex steroids (testosterone and estradiol). Therefore, treatment and anti-fracture efficacy of bisphosphonate may potentially be similar in both hypogonadal men and eugonadal men. Moreover Ringe et al. evaluated the efficacy of oral alendronate 10 mg versus alfacalcidol 1 μg daily in a 3-year open-label RCT of 134 men. Alendronate-treated patients experienced a significantly lower incidence of new vertebral fracture compared to placebo-treated subjects (OR = 0.36, 95% CI: 0.14–0.94), and a non-significant lower incidence of new nonvertebral fracture with alendronate was also reported [22]. The benefits of alendronate therapy in men with osteoporosis were very similar to those in postmenopausal women.

17.6 Risedronate

A similar 2-year BMD endpoint study was performed with risedronate 35 mg once a week in 284 men with osteoporosis aged 36–84 years and effectively increased bone mineral density in comparison with placebo, but no significant effect on the risk of fractures was found [23].

The study reported a significant increase from baseline to endpoint in lumbar spine BMD and significant increases in hip BMD compared with placebo. This study also showed that the positive effects on bone density and on NTX, a marker of bone resorption, were not affected by circulating testosterone. The positive effects of risedronate in men with osteoporosis were confirmed in an open-label, prospective, match-control trial [24]. The aim of this study was to assess the effect of treatment with risedronate 5 mg daily relative to control in men with primary or secondary osteoporosis over 2 years. Risedronate significantly reduced the risk of vertebral and nonvertebral fractures, improved BMD, decreased height loss, and reduced back pain in men with osteoporosis, and efficacy was sustained over 2 years since a consistent 60–61% risk reduction in vertebral fractures was observed at 1 and 2 years, respectively, demonstrating that daily risedronate is an effective therapy for men with primary or secondary osteoporosis (Table 17.1).

17.7 Zoledronic Acid

Zoledronic acid is a bisphosphonate, administered intravenously, that at a dose of 5 mg once a year, has anti-fracture efficacy in postmenopausal women with osteoporosis and positive effects on bone mineral density in men. Three RCTs investigated the beneficial effects of intravenous zoledronic acid 5 mg once yearly versus placebo or alendronate. Zoledronic acid has significantly improved bone mineral density and reduced bone turnover markers, with changes from baseline similar to those reported for other bisphosphonates in men with osteoporosis and were consistent with those seen in postmenopausal women with osteoporosis receiving bisphosphonates.

More recently, a 2-year fracture endpoint study in male osteoporosis investigated once-yearly intravenous zoledronic acid treatment in a randomized, multicenter, double-blind, placebo-controlled. The primary efficacy endpoint was the reduction in vertebral fracture risk at the 2-year endpoint of the trial. In further detail, 1199 men with osteoporosis were randomized to an annual infusion of either zoledronic acid (5 mg) or placebo and supplemented with calcium (1–1.5 g) and vitamin D (800–1200 mg) daily. The treatment with zoledronic acid resulted in a significant reduction in the risk of new vertebral fractures, by 67% (RR: 0.33; 95% CI: 0.16–0.70) [25]. Similar results were observed for moderate-to-severe and worsening morphometric vertebral fractures, while no significant difference was observed between groups in the incidence of new clinical fractures. Zoledronic acid also significantly increased the BMD at the lumbar spine, total hip, and femoral neck over 24 months, as compared to placebo. Total testosterone level did not affect the antifracture efficacy of zoledronic acid or its beneficial effects on the BMD. Further, a 2-year head-to-head RCT comparing once-yearly zoledronic acid with once-weekly alendronate in men with primary or hypogonadism-associated osteoporosis demonstrated the non-inferiority of zoledronic acid compared to alendronate in improving the BMD at the lumbar spine, femoral neck, and total hip [26]. The 302 patients were randomized to receive either once-yearly ZOL 5 mg IV or weekly oral ALN 70 mg for 24 months. Changes in BMD and bone marker levels were assessed. ZOL increased BMD at the lumbar spine, total hip, femoral neck, and trochanter and was not inferior to ALN at 24 months (Table 17.2).

In summary, findings from RCTs with alendronate, risedronate, and zoledronic acid demonstrated their efficacy in reducing the risk of new vertebral fractures in men with primary and hypogonadism-associated osteoporosis. Evidence for a significant effect on non-vertebral fractures is still insufficient, mainly due to the small numbers of patients included in clinical trials. Oral and intravenous bisphosphonates were also shown to significantly reduce markers of bone turnover and to increase the BMD compared to baseline and to placebo. Bisphosphonates were well tolerated, producing only expected and self-limiting specific adverse effects including upper gastrointestinal toxicity associated with oral use and symptoms related to an acute-phase reaction after the first exposure to intravenous zoledronic acid.

17.8 Teriparatide

Teriparatide is a parathyroid hormone analogue (PTH1-34) that has an identical sequence to the 34 N-terminal amino acids (the biologically active region) of the 84-amino acid human parathyroid hormone. It is indicated as treatment in men with primary or hypogonadal osteoporosis at high risk for fracture and in the treatment of osteoporosis associated with sustained systemic glucocorticoid therapy in men at high risk of fracture. Teriparatide treatment for the management of primary osteoporosis in men has been evaluated in two well-designed RCTs as monotherapy or combination therapy [27–29]. In a placebo-controlled, double-blind trial, 437 men with primary osteoporosis (hip or spine *T*-score <−2.0 SD) were randomized into

three groups and either received teriparatide 20 μg, teriparatide 40 μg, or placebo injection daily, respectively. The patients were supplemented with calcium (1000 mg/day) and vitamin D (400–1200 IU) [30]. During the study, indices of bone formation increased early upon therapy with teriparatide, followed by increase of markers of osteoclastic activity, while markers of bone turnover were stable or declined slightly in the placebo group. Daily treatment with teriparatide at both doses increased, in a dose-dependent manner; lumbar spine and femoral neck BMD and changes were significantly greater in the teriparatide groups compared to the placebo group, beginning after 3 months. The BMD response to treatment was independent of baseline free testosterone, age, body mass index, baseline lumbar spine BMD, smoking, and alcohol intake. Thus, teriparatide is effective in the management of osteoporosis in men as well as in women. Indeed, teriparatide was well tolerated, producing only expected and rare self-limiting specific adverse effects, including transient post-dose increase of serum calcium and 24-h urinary calcium excretion, nausea, and headache. The overall safety and tolerability of teriparatide in men and women have also been highlighted by over a decade of experience that has not revealed relevant safety issues [31].

Teriparatide (1–34 rhPTH) has been registered for the treatment of "severe" osteoporosis in men with fragility fractures, multiple risk factors, or ineffective prior therapy. The use of teriparatide was evaluated also in combination with other therapies. In particular, 83 men with low BMD were randomized to receive 10 mg/day alendronate or 40 μg/day teriparatide subcutaneously or both. Alendronate was administered for 30 months, and teriparatide was started after 6 months. Lumbar spine and femoral neck BMD increased significantly more in men on teriparatide monotherapy compared with the other groups. A second study showed that alendronate impaired the action of teriparatide to increase bone turnover in men [32, 33]. Teriparatide appears to be an effective therapy in men with osteoporosis, yet maintenance of its effects after treatment cessation is not fully understood and may require subsequent initiation of anti-resorptive treatment.

17.9 Strontium Ranelate

Strontium ranelate is an antiresorptive agent approved in Italy for the treatment of severe osteoporosis in postmenopausal women at high risk of vertebral and/or hip fractures and in men at high risk of fracture when other pharmacological treatments are not indicated. Mechanisms of action of this molecule are not fully understood, even though preclinical studies suggested that it might have a dual action by inhibiting bone resorption and stimulating bone formation [34, 35].

A 2-year, controlled, double-blind study has been performed in osteoporotic men. The objective was to analyze men with a similar risk profile as the postmenopausal women previously included in the pivotal phase 3 trial. In a preliminary communication of the results at 1 year, the authors reported that the same dosage of strontium ranelate, with calcium and vitamin D supplementation, resulted in similar significant BMD gain at the spine and hip in osteoporotic men compared with

osteoporotic postmenopausal women [36]. RCTs have investigated the effects of oral strontium ranelate 2 g daily compared to placebo or alendronate (70 mg weekly) in men with established primary osteoporosis [37]. Studies revealed efficacy of this molecule [38, 39] since new radiographic vertebral fractures occurred in 5.8% of men receiving strontium ranelate and 7.8% of men receiving placebo. However, the safety analyses revealed an imbalance in the occurrence of coronary artery disorders (angina pectoris and coronary artery disease) in the strontium ranelate group as compared to placebo group, with a significant higher incidence of adverse events in the strontium ranelate group (strontium ranelate 8.7% versus placebo 4.6%). Thus, these safety effects strongly limited the use of this drug in subjects with cardiovascular risk.

17.10 Denosumab

Denosumab is a human monoclonal antibody which, antagonizing the binding of RANKL to RANK, reduces osteoclast differentiation and activation, increase apoptosis, and, thus, inhibit bone resorption. The anti-fracture efficacy of denosumab has been clearly established in RCTs performed in postmenopausal women and men receiving androgen deprivation therapy for non-metastatic prostate cancer. The "Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months" (FREEDOM) trial showed the efficacy of denosumab on fracture-risk reduction at different skeletal sites among osteoporotic women [40]. The efficacy and safety of denosumab in men with low BMD (primary or hypogonadism-associated) have been consequently investigated in a 2-year RCT performed in 242 patients (ADAMO study). Denosumab increased lumbar spine BMD by 5.7% after 12 months compared with an increase of 0.9% in the placebo group ($P < 0.0001$). Denosumab treatment also significantly increased the BMD at the total hip and femoral neck compared to placebo. Treatment with denosumab produced a significant (versus baseline and placebo) decrease of serum CTX.

Moreover, in patients at high fracture risk, its beneficial effects were shown in older men under androgen deprivation therapy for prostate cancer. A double-blind, randomized, multicenter study investigated the efficacy of denosumab (60 mg subcutaneously every 6 months) vs placebo in men receiving androgen deprivation therapy for non-metastatic prostate cancer (734 patients in each group). After 24 months, lumbar spine BMD increased by 5.6% in the denosumab group as compared to a loss of 1.0% in the placebo group ($p < 0.001$). The amount of bone mineral density obtained is comparable to the increased observed in postmenopausal women [41]. Denosumab was well tolerated in subjects affected by osteoporosis, and no account of jaw osteonecrosis, arterial fibrillation, and symptomatic hypocalcaemia was reported. The most common adverse reported effects were musculoskeletal pain, hypercholesterolemia, and cystitis as previously described in women [42].

Thus, all these studies demonstrated the efficacy of anti-osteoporotic treatments in men revealing the need to further increase their use to prevent fragility fracture in men affected by osteoporosis.

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Femur Fragility Fracture in Men and Surgical Therapy Risks

18

Umberto Tarantino, Monica Celi, Alessandro Provenza, and Giuseppina Resmini

18.1 Introduction

A fragility fracture is a low-energy fracture that occurs when a patient falls from standing height or less [1, 2]. Fragility fractures represent an epidemic problem worldwide, the most common and serious fragility fractures occur in the hip, and the majority of these patients have osteoporosis. It is known as osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration, and strength impairment, which increase the risk of fragility fractures, leading to high morbidity and reducing patient' s quality of life [3]. Gender and age influence the risk of fragility fracture [4]. Osteoporosis is four times more common in women than in men, but some evidence indicates that men tend to have more osteoporosis-related complications. Osteoporosis in men is an important health issue. Men account for approximately 20% of all cases of osteoporosis and contribute substantially to the fracture burden. The number of persons with hip fragility fracture has increased during the last decades worldwide. The total number of incident fragility fractures is estimated to be 9 million annually worldwide, of which 1.6 million were at the hip [1]. In Europe, the number of fragility hip fractures was estimated to be as high as 900,000. In Italy, osteoporosis potentially affects 5,000,000 people, of which 80% are women of postmenopausal age. In particular, one out of three women and one out of eight men in the over 50s population are estimated to be affected by osteoporosis [5]. In Italy, about 160,000 hospital admissions for fragility fractures are recorded per year, of which nearly 100,000 involve

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the femur fragility fracture. Every year we register in Italy approximately 21,496 femur fragility fractures [6]. With aging, the incidence of fragility fracture increases in both sexes; the peak number of hip fractures occurs at 75–79 years of age for both sexes. However, the hip fracture risk increases in women after 40 years, but only after 65 years in men and one-third of these fractures occur in males. Compared with women, after a hip fracture, men have higher rates of 1-year mortality (31–38% for men versus 12–28% for women), persist 10 years post fracture [7], and are twice as likely to be institutionalized [8]. Secondary fractures occur rapidly after the first fracture. The risk of subsequent fractures seems to be higher just after a fracture, especially in the first year. Many studies have shown that after a femoral fragility fracture there is a 30% risk of having a new controlateral fracture of femur in the same year and 10% within 5 years [9]. There are factors associated with an increased risk of osteoporosis-related fractures. These include general factors that relate to aging and sex steroid deficiency, as well as specific risk factors such as the use of glucocorticoids therapy for some chronic disease and androgen deprivation therapy (ADT) for prostate cancer, reduced bone quality, and disruption of microarchitectural integrity. Fragility fractures result when weakened bone is overloaded, often by falls or certain daily chores.

Bone loss in men, similar to women, is related to aging. Changes in bone structure and geometry induced by aging contribute to decreased bone strength and increased fragility fracture risk in the elderly population [4]. However, differences in skeletal size, mechanical loading, and muscle mass may also play a role in the patterns of bone loss between genders [10]. In fact, when peak bone mass is achieved, bone density in men is one-fourth to one-third greater than in women, and male bones reach a larger diameter and cortical thickness than female bones. Additionally, the pattern of bone loss is different between genders. Bone mass rapidly decreases in women at menopause, around 50 years old, in contrast with men of the same age [11]. Nevertheless, bone loss takes place in both trabecular and cortical compartments with increased cortical porosity with age [12]. Hip fragility fractures are primarily caused by falls, and the prospect of falling becomes much more prevalent with aging [13]. In addition to aging, characteristics common to patients who fell and fractured their femur included an impairment, stroke or medications that decrease mental alertness, nonuse of eyeglasses that were prescribed, and inappropriate footwear. Most of hip fractures occur equally inside or outside the home, but above all older people fall at home [14].

Beyond age and sex, several other factors increase the risk of fragility fractures such as body mass index (BMI), personal history of fragility fracture, parental history of hip fracture, smoking, glucocorticoid use, rheumatoid arthritis (or other chronic autoimmune inflammatory diseases), secondary causes of osteoporosis (type 1 diabetes, low vitamin D levels, hyperthyroidism, hyperparathyroidism, hypogonadism, chronic malnutrition, malabsorption, eating disorders, chronic liver disease, chronic kidney disease, HIV infection, or treatments with medications that can cause any of the abovementioned issues), or daily alcohol intake >3 units [15]. Hip fragility fractures can be divided into femoral neck, intertrochanteric and subtrocantheric fractures. All of them should be treated surgically. The type of surgery

needed to manage a hip fracture is determined by the fracture type and the individual needs of the patient. Surgery typically involves fixation with 2–3 cannulated screws (most typically, 3), with the patient with a fracture stable. If the fracture is unstable, the basic choices are reduction and internal fixation, hemiarthroplasty, or total hip arthroplasty. Guidelines recommend surgery within 48 h of hospitalization, arguing that early surgery better functional results, reduced mortality, hospital stay, and postoperative complications [16, 17].

In the face of considerable advances in surgical techniques, which now enable the treatment and functional recovery of femur fragility fractures, postsurgical management of these patients is often inadequate for preventing new fracturing events. All fractured subjects should be immediately considered at high risk for further fractures and must be included in a monitoring and treatment program. However, although fragility fracture is one of the major risk factors for further fractures, only a minority of these patients are currently initiated to an appropriate diagnostic and therapeutic route after acute surgical treatment of the hip fracture.

Men with hip fragility fracture should have additional laboratory testing to assess for these osteoporosis secondary causes. Serum calcium, estimated GFR, 25-hydroxy vitamin D, intact PTH, TSH, and testosterone levels should be a part of the osteoporosis assessment.

The orthopedist is the specialist who can and must assume the burden of managing the femur fragility fracture in elderly and osteoporotic subjects, curing it acutely, respecting the correct importance of surgical timing, taking into account the poor quality of the bone, using all the dedicated synthetic media, following the repair and healing process, promoting early mobilization to improve functional recovery, administering vitamin D, and setting up a drug therapy aimed at reducing the risk of refracture.

Finding men with known fracture risks, such as those on androgen deprivation therapy, or on oral glucocorticoid therapy should lead to evaluation, treatment, and fewer fractures. Secondary prevention is important as well. If a man has survived one fracture, he is at high risk for another. It is not too late to evaluate and treat.

18.2 Classification and Pathophysiology of Femur Fragility Fracture in Men

Fragility fractures are some of the most severe complications associated with primary and secondary osteoporosis in male. Primary osteoporosis includes hypogonadal osteoporosis and senile osteoporosis. Secondary osteoporosis is associated with long-term drug treatments (e.g., corticosteroids). Primary male osteoporosis includes age-related osteoporosis and idiopathic male osteoporosis. Age-related osteoporosis in men, like in women, is more likely to occur as age increases and is typically seen in males older than 70 years. Instead, idiopathic male osteoporosis is generally defined as one or more fractures and a low BMD in men before the age of 65–70 years old [18]. There are multiple theories as to the etiology of idiopathic male osteoporosis, such as genetic factors or a familial history [19]. Several

epidemiological and clinical observations have shown that osteoporosis in men has an important genetic component, as well as in women. Genetic causes of primary osteoporosis in men may involve genes for IGF-I or estrogen metabolism. Multiple genes have shown effects on bone development, strength, density, etc. Van Pottelbergh et al. showed that men whose fathers had osteoporosis tended to also have reduced bone size and reduced volumetric BMD [20]. It has been generally accepted that sex hormones play an important role in primary osteoporosis. Men do not have a dramatic loss of androgens with aging, unlike what happens with loss of estrogen at the menopause in women, but most reports have shown that serum testosterone levels decline with aging. Traditionally, bioavailable or free testosterone deficiency was a stronger predictor of rapid hip bone loss [21]. However, several studies indicate that levels of bioavailable estradiol rather than testosterone are strongly correlated with the fracture risk [22], while estradiol deficiency or higher sex hormone binding globulin (SHBG) related to greater hip bone loss but also for fracture. These results suggest that estradiol, but not testosterone, may be the major sex hormone with an impact on fragility fracture risk in older men [23]. Men with low testosterone levels had worse of muscle strength and balance with a greater risk of falls resulting in increased risk of fragility fracture [24]. In fact, large most fragility fractures occur in men older than 70 years, with the incidence rising with further aging.

Male osteoporosis that can be linked to or explained by causes other than aging is generally classified as secondary male osteoporosis. Secondary osteoporosis is more common in men than in women [25] and is the reason that patients need a thorough evaluation consisting of medical history, physical examination, and laboratory testing. Chronic diseases that have been associated with secondary osteoporosis include diseases such as chronic obstructive pulmonary disease (COPD), cardiovascular disease, rheumatoid arthritis, osteoarthritis, general frailty, diabetes mellitus, hypercalciuria, hyperparathyroidism, hyperthyroidism, inflammatory bowel disease, bariatric surgery and mobility disorders such as Parkinson's disease, multiple sclerosis, cerebrovascular accidents, and spinal cord injury. Other causes of secondary osteoporosis in men include age, weight or body mass index, current smoking, alcohol abuse, previous fracture, parental history of fracture and recent fall history, and low serum levels of 25-hydroxyvitamin D.

It is important to pay attention to men undergoing glucocorticoid therapy for some chronic disease and androgen deprivation therapy (ADT) for prostate cancer. Glucocorticoid therapy is especially important because increased fracture risk can be demonstrated as early as 3 months after starting oral glucocorticoid therapy [26]. In the ADT fracture risk is elevated (as high as 20% fracture risk in 5 years) because of their very low serum levels of both testosterone and estradiol.

The severity of the bone loss and dramatically increased fracture risk are underappreciated, and only a minority of men are evaluated and/or treated for glucocorticoide- and ADT-induced osteoporosis. In addition to glucocorticoide therapy and ADT, the following drugs may be associated with increased fracture risk: proton pump inhibitors, antidepressants, dopamine antagonists, thiazolidinediones, immunosuppressives (e.g., cyclosporine), enzyme-inducing antiseizure medications

(e.g., phenytoin), opiate analgesics, and some cancer chemotherapy (e.g., cyclophosphamide).

Although the incidence of hip fracture is known to increase with age, knowledge about risk factors for hip fracture among very old people is limited. Recently, Wiklund et al. studied risk factors for hip fracture for very old people and has documented how the following seven factors were associated with increased risk of incident hip fracture: walking indoors with help from ≤1 person, Parkinson's disease, currently smoking, delirium in the previous month, underweight, and age. They concluded like these factors could have important clinical implications in identifying persons at high risk of hip fracture, as well as in the development of effective preventive strategies [27].

Osteoporosis is a multidisciplinary pathology that can be treated by several specialists, but becomes an orthopedic problem when it is the cause of femur fragility fracture. It is necessary for the orthopedic specialist to have a correct approach to men with fractured femur to ascertain and quantify the presence of underlying osteoporotic disease as well as to establish the appropriate pharmacological therapy aimed at reducing the risk of further fractures. Management of hip fragility fracture in men should also take into account possible comorbidities associated with concomitant therapy whose presence could alter the quality of bone tissue resulting in increased susceptibility to fractures but also modify healing processes and predisposing any complications of fracture, or lead to more complicated patient management during and post-hospitalization. Once the presence of osteoporosis with hip fragility fracture has been established with imaging techniques, laboratory tests can be a valuable help for further in-depth research. It is a mistake to undertake osteoporosis therapy without having investigated etiology. Laboratory examinations are indispensable in the diagnostic test and should be performed in all patients with proximal femoral fracture. The laboratory allows you to discriminate between primitive forms and secondary forms of osteoporosis, diagnosis differential with other pathologies that may result in a clinical picture similar to osteoporosis.

The fundamental goal of pharmacological therapy for fragility fractures is to increase skeletal resistance and consequently decrease the risk of further fractures. After each event of fracturing by low energy trauma, the risk of subsequent fractures is increased by 2–4 times, especially within 1 year of the previous one, regardless of the presence of other risk factors. Various drugs are currently available which, with different action mechanisms, have been shown to be effective in determining not only an increase in bone mass but also a qualitative improvement in skeletal tissue. For the different characteristics of the studies performed, comparisons between the various drugs are not easy, and therefore one cannot currently determine with certainty in terms of efficacy the priority of a drug compared to another. It is important to remember how these drugs have always been active in association with calcium and vitamin D. The therapeutic choice for osteoporosis should therefore be personalized based on the patient's metabolic profile and fracture risk, as well as evaluated on the basis of antifractorial efficacy, safety, cost, and different ways of administering the various therapies. In any case, osteoporosis therapy is the best benefit if taken regularly, for an adequate period of time, generally for years, and especially

when the risk of fragility fracture is particularly high, i.e., in the presence of negative predictors such as previous fracture, low bone mass, advanced age, and other conditions unfavorable to the bone.

18.3 Fragility Fracture and Falls in Men

Falls and fragility fractures become much more prevalent with advancing age [13]. The most serious fragility fractures occur in the hip; in fact an estimated 95% of hip fractures are due to falls [28]. However, only 1% of falls in older adults result in a hip fracture, suggesting that the likelihood of hip fracture depends on the circumstance and biomechanics of falling such as orientation of the fall; characteristics of the faller such as height, reaction time, muscle mass, and amount of soft tissue padding over the hip; energy of the fall; and characteristics of the impact surface [29]. Hip fractures occur equally inside or outside the home, but above all older people fall at home, maybe because they spend most of their time there and, feeling more confident, are more careless. Falls are a critical factor in the etiology of fracture in men. The risk of falling is often multifactorial, increases with age due to physiological age-related changes with reduced physical function, or more properly pathological factors, or due to the environment. One-third of generally healthy individuals aged 65 or above and a half of those aged 80 or above will fall at least once a year. Patients with falls have more problems in walking than those without a history of falls. Rubenstein et al. in extensive longitudinal study showed that 10% of the people over 65 need assistance in walking across a room, 20% need help in climbing stairs, and 40% are unable to walk more than 500 m [30]. An important explanation for the increased risk of falling with older age is muscle weakness. This is caused not only by decreased muscle mass but also by reduced muscle strength and power, as a consequence of loss of muscle fibers, fatty degeneration and fibrotic changes, and a decreased number of functioning motor units [31]. It has been documented that distal muscle weakness of lower limb, in 48% of non-institutionalized patients and in 80% of patients in nursing homes, leads to significant postural instability and that the proximal muscle weakness reduces the compensatory movement of the arms [32]. Although the reduction of muscle strength is part of the physiological aging process, much of this reduction is probably attributable to the presence of comorbidity and to physical inactivity. Older and frail persons and those who have had a stroke or are taking medications that decrease mental alertness are particularly predisposed toward falls. In a large observational longitudinal osteoporotic fractures in men study (MrOS), Cawthon et al. identified numerous risk factors for falls and hip or nonvertebral fractures. MrOS showed the relation between BMI and fracture risk. After accounting for BMD, men with higher BMI are at a higher risk of hip fracture. Falls were higher in men who slept 5 h or less than for those who slept 7–8 h. Also, hypoxia during sleep was associated with a 40% increased risk of recurrent falls and a 30–40% increased risk of nonvertebral fractures. Low measured activity levels were associated with a higher risk of nonvertebral fracture. Poor physical performance, in particular inability to rise from a chair, is a strong risk factor for falls and hip fractures. Yet, MrOS evaluated the relation between numerous

medical conditions and medications with falls and fractures. Nonbenzodiazepine sedative hypnotics used in the treatment of sleep disturbances or anxiety-related disorders were associated with increased risk of falls, and benzodiazepines were related to increased falls by increased disability, depressive symptoms, and poorer physical performance. Yet, MrOS showed that abdominal aortic calcification (AAC), assessed on lateral spine radiographs, was associated with increased risk of hip fracture. Older men with Parkinson's disease have a threefold higher risk of multiple falls and higher bone loss and fracture. Chronic obstructive pulmonary disease (COPD) was associated with an increased risk of nonspine. MrOS showed that diabetics have an increased risk of nonvertebral fractures. Men with moderate to severe lower urinary tract symptoms had a greater risk of falls. In MrOS, the association of testosterone level to the risk of falling persisted regardless of physical performance. Also, low vitamin D levels are associated with higher rates of fracture risk, suggesting potential use of serum 25(OH)D in identifying men at high risk of hip fracture. It is important to note how low vitamin D with low bioavailable estradiol and high SHBG were associated with greater bone loss and higher fracture risk, suggesting that men with this combination may be at particular risk of fragility fracture. Higher parathyroid hormone (PTH) can contribute to the relationship between 25(OH)D and bone loss or hip fracture. Only TSH, but not FT4 or categories of thyroid function, was associated with hip fracture risk [33].

Environmental barriers are responsible for 30–50% of the falls; the external environment contains many risks, but above all older people fall at home. At home, barriers are represented by thresholds, stairs, carpets, slippery surfaces, inadequate lighting, or, on the contrary, excessive or dazzling illumination, which are possible causes, too [34].

18.4 Surgical Risks in Femoral Fragility Fracture Treatment

The treatment of hip fractures due to osteoporosis tends to move toward surgery, with the use of implants which, through recomposition of the fragments or their prosthetic substitution, allow early mobilization of the patient. The type of surgery needed to manage a hip fracture is determined by the fracture type (femoral neck, intertrochanteric, and subtrochanteric) and the individual needs of the patient. Femoral neck fractures may be classified as stable or unstable, depending on the fracture pattern, displacement, and angulation. Garden classified the femoral neck fractures in four types, according to the displacement, relating it to a possible vascular damage and, ultimately, to the healing of the fracture and to the survival of the femoral head (Fig. 18.1). The appropriate surgical treatment is usually fixation in situ with percutaneous, partially threaded, cannulated screws, for Garden type 1 and 2 fractures, approximately 20% of the cases, and hip joint replacement (hemiarthroplasty or arthroplasty) for Garden type 3 and 4 fractures [35]. The choice of the operative treatment is based on the displaced femoral neck fractures. However, the debate as to whether the femoral head should be retained or replaced continues. In their meta-analysis, published in 1996, Rogmark and Johnell [36] showed that,

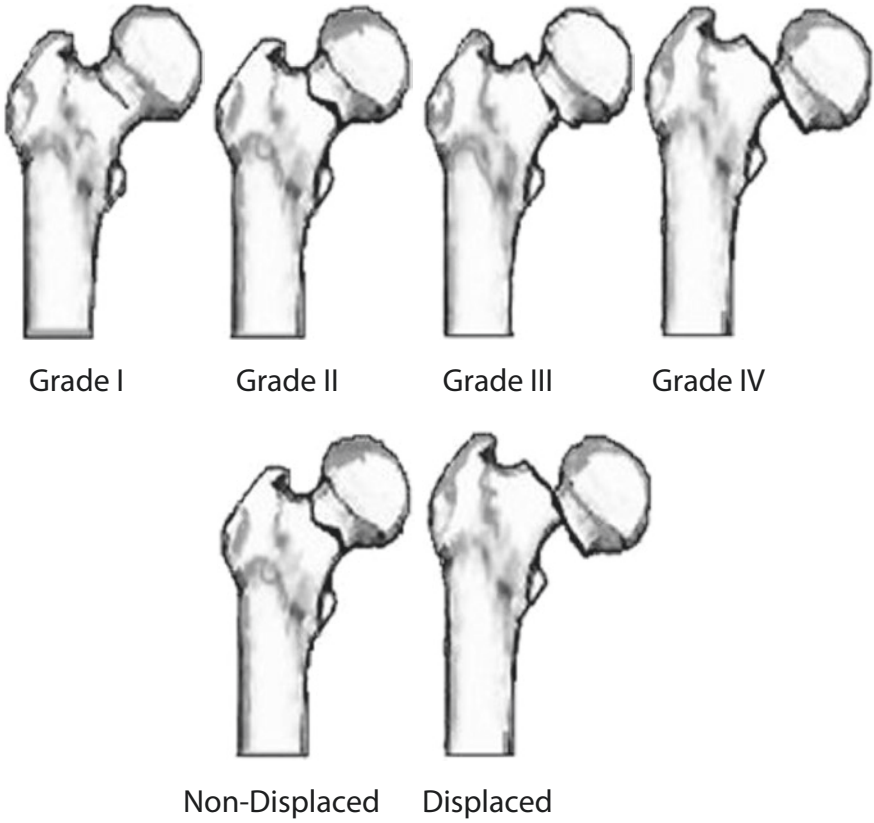

Fig. 18.1 The Garden classification consists of four subtypes: Garden grade I is an incomplete femoral neck fracture, with valgus impaction; Garden grade II is a complete but non-displaced fracture; Garden grade III fracture is a complete and partially displaced fracture with alignment of the femoral neck relative to the neck in varus deformity; and Garden grade IV is a complete fracture with complete displacement [Garden RS. Low-angle fixation in fractures of the femoral neck. J Bone Joint Surg (Br) 1961;43:647—63; Van Embden D, Rhemrev SJ, Genelin F, Meylaerts SA, Roukema GR. Orthop Traumatol Surg Res. 2012 Jun;98(4):405–8. Epub 2012 May 3]

regardless of the type of internal fixation, the failure rate was 21–57%, and reoperation was required in 14–53% of all their cases. In contrast, the reoperation rate after arthroplasty was 7%, confirming analogous results of any previous meta-analysis. Moreover, in a recent prospective randomized study, Frihagen et al. [37] reported that, among people over 60 years old, arthroplasty was associated with better functional outcome, higher health-related quality of life, and more independence compared with internal fixation. These fractures are rare among young individuals, and there is consensus that any such cases should be treated with closed reduction and internal fixation in an attempt to preserve the femoral head. It has been shown that young adults achieve higher rates of fracture union, and it is believed to be due to the healing potential and good bone quality of the upper femur in this age group [38]. Fractures of proximal femur are divided in intracapsular and extracapsular. This second category comprises almost 50% of hip

fractures and includes the intertrochanteric and the subtrochanteric (up to 5 cm below the lesser trochanter) ones (Fig. 18.2). The first type comprehends undisplaced, displaced, and displaced unstable (with reverse obliquity or displacement of the lesser trochanter) kind of fracture. This kind of fracture presents less risk of

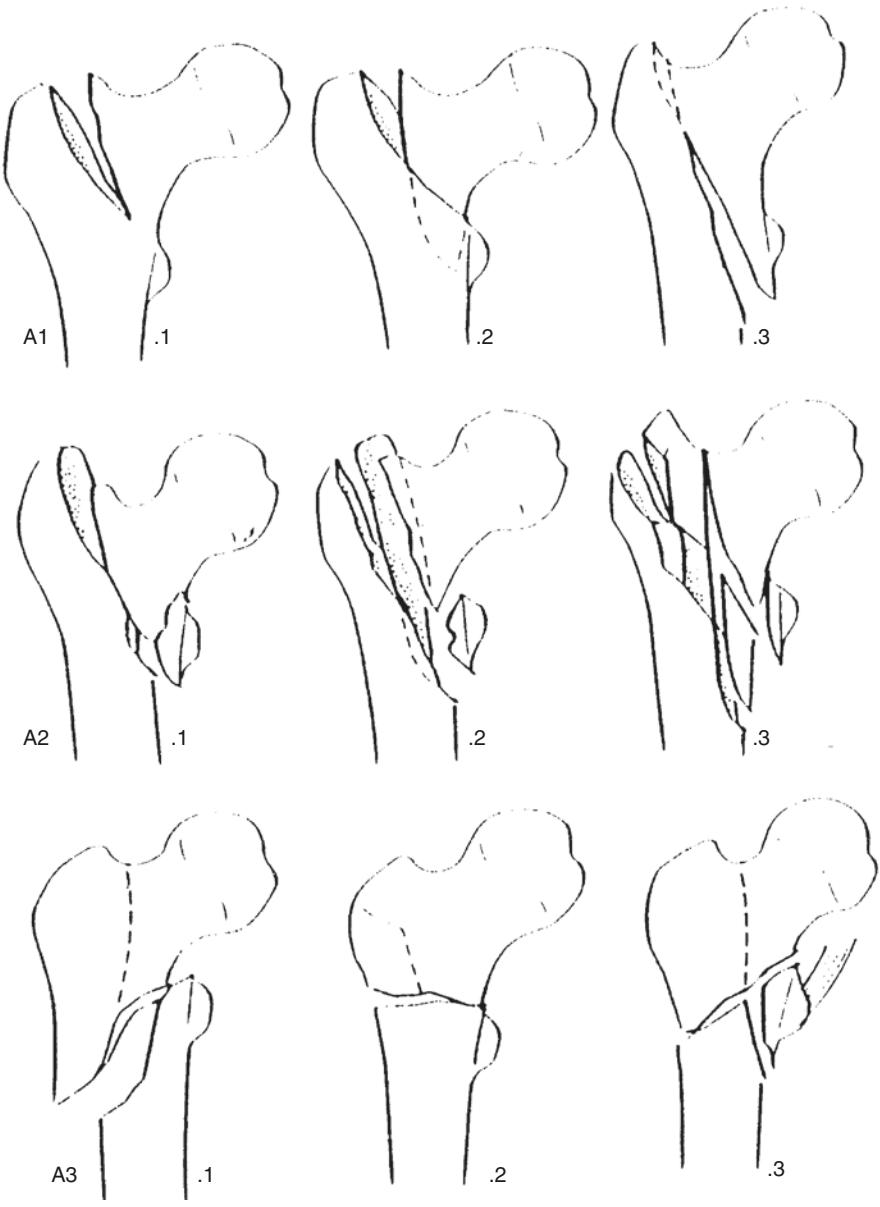

Fig. 18.2 AO classification groups (31A1, 31A2, 31A3) for extracapsular fractures. These three groups be may be termed as stable trochanteric, unstable trochanteric, and trans-trochanteric [Humayon Pervez, Martyn J. Parker, Glyn A. Pryor, Lennel Lutchman, Nishan Chirodian Injury, Int. J. Care Injured 33 (2002) 713–715]

femoral head necrosis but more risk of blood loss and is complicated by higher low-term mortality. When surgical treatment is needed (it is almost the rule for femoral fractures), successful internal fixation may be challenging, because they occur in osteopenic bone that has thin trabeculae and decreased capacity to support internal fixation devices. The main matter of debate is how to obtain the stability and consequently a rapid mobilization of the patients, particularly in cases of unstable intertrochanteric fracture, as, for example, when fragmented corticale bone. Sliding hip screw and plate systems have provided satisfactory results in the treatment of intertrochanteric fractures over the past decades [39]. Nonetheless, they have been associated with a failure plate of up to 23%. Intramedullary sliding hip screw devices were introduced in the late 1980s (Gamma nail, Howmedica) [40]. The main advantage was good stability with minimal surgical exposure. Historically, the first generation of intramedullary hip screws were developed in order to improve clinical results and minimize complications [41]. At the same time, a variety of trials have been published, comparing new and older designs of intramedullary implants with sliding hip screws.

About the intracapsular fractures, impacted and non-dislocated femoral neck fractures with good interfragmentary contact of the fragment can be treated successfully with a dynamic osteosynthesis, as three cancellous bone screws. As to extracapsular fractures, throchanteric plate and intramedullary nails are commonly used. The use of plate is indicated in stable and unstable fractures with the integrity of the sidewall, to allow the correct placement. The advantages of the plate are a less invasive surgery with reduced blood loss, rotational stability through two cephalic screws, the low risks of collapse and subsequent deformity. Besides, a trochanteric plate prevents medialization of the femoral shaft and comminution of the neck-head fragment, as well as its varus angulation. Possible disadvantages of the plate are screw cutout or head penetrations. Intramedullary nails are preferred by many surgeons for patients with intertrochanteric fractures, subtrochanteric extensions, and isolated subtrochanteric fractures [42]. The nail permits a reduction of the bending moment in the plant, a limited periosteal lesion, and a rotational stability with large-sized locked cephalic, divergent, or helical screws. The nail does not respect the neutralization principle of tensile force on the lateral part of the proximal femur, causing pain in older patients during mobilization. The nail leads to displacement into varus and not uncommonly retroversion of the head-neck fragment.

Despite substantial evidence that a prior fracture results in an increased risk of subsequent fracture, less than 30% of postmenopausal women and less than 10% of men with prior fracture are treated [43]. Although some of this deficiency in clinical care is due to the overall lack of awareness of osteoporosis by the public and primary caregivers, the relative importance of prior fracture in relation to subsequent fracture risk does not appear to be fully appreciated, particularly in men. The proximal femur fractures are life-threatening due to the long period of bed immobilization and the high risk of complications. For these fractures open reduction and internal fixation in the first days from trauma is a life-saving action.

A stable reduction is the basis for success of the surgical procedure. Closed reduction must be preferred, but, if anatomical reduction is not achieved, a gentle open reduction must be performed avoiding excessive periosteal splitting by indirect maneuvers (Schanz screws as joystick, Kirschner wires for temporary fixation and trans-articular too) [44]. Nonanatomical reduction must be avoided because it eventually exposes to the risk of secondary displacement. A demanding closed reduction that employs excessive traction may cause vascular impairment. If gentle maneuvers are not effective, open reduction must be preferred [45]. For the surgeon the technical problems are obtaining and maintaining a proper reduction and stabilization of unstable fractures in a mechanically low-resistant bone with the tendency to a slow healing process. The peri- and postoperative complication rates in the older group of patients are higher than in the younger population. A proper reduction can be more important than the type of hardware used to treat the fracture [46]. A nonaccurate reduction can increase the failure rate of the operation threefold and can delay the healing time of the fracture [47]. The surgical experience is very important to minimize the rate of complications [48]. The choice of the hardware is very important too. The osteoporotic bone, having lower mechanical properties, presents more complex fracture patterns and reduced resistance to the holding power of the thread of the screws of the hardware. Many studies have shown that a low BMD is related to a lower holding power of the screws on the bone [49]. The force needed for the pullout of the implant is so ever inferior with the possibility of microfractures and bone resorption at the bone-hardware interface and secondary failure of the construct [50]. In the osteoporotic bone, the most common failure pattern of internal fixation is bone failure rather than implant failure. They are related to poor bone quality, because of the weakening of the bone structure, and are the result of low-energy injuries and often involve the metaphyseal segments of the bone. The fracture of the upper extremity of the femur is one of the most typical fractures of the elderly patients. They may be intracapsular (femoral neck fractures) or extracapsular (intertrochanteric and subtrochanteric fractures). Each kind of fracture can be treated in several ways: the intracapsular fracture can be treated with screws, unipolar or bipolar hemiarthroplasty, or even with total arthroplasty. The extracapsular fractures instead can be treated with sliding hip screw, intramedullary nail, femoral neck screws, helical blade, or primary arthroplasty. What must be remembered is that osteoporotic bone has distinct morphologic characteristics that influence its biomechanical properties and therefore the choices and techniques for internal fixation. Therefore only a complete understanding of the biology of the osteoporotic bone will lead to a good quality of the treatment of the fragility fractures [51]. The early postoperative mobilization is also of capital importance in preventing skin and soft tissue complications. The patient also needs to be carefully assessed from internal medicine specialist before and after the operation in order to assess the previous pathology and the eventual new ones. The rehabilitation protocol is often difficult to be carried out by the older patients that are depressed or unable to act or understand the medical orders.

18.5 Discussion and Conclusion

Traditionally, osteoporosis was considered a disease that affects only women. However, a little over two decades ago, osteoporosis came to be recognized as a disease that is also prevalent in elderly men and with bleak survival outcomes following fracture. Despite their growing importance, however, there is little information on the outcomes of hip fractures in men. Several studies have noted higher mortality following hip fracture among men than women, but there are few data on the influence of comorbid diseases, treatment strategy, or complications on the short-term death rate in men. There is almost no information concerning functional outcomes in these patients [52].

Most studies have concentrated almost exclusively on osteoporotic fractures in women. With increasing longevity in males, osteoporosis will become of increasing importance in both males and females. There are few published long-term data on absolute risk of subsequent fracture following initial low-trauma fracture in women and fewer in men. For men, an initial fracture conferred a higher relative refracture risk (2.8- to 4.3-fold) that yielded a similar absolute refracture risk to that of women of the same age with an initial fracture. Thus, the reduced risk of initial fracture associated with male sex was lost once a single low-trauma fracture occurred. In multivariate analyses, femoral neck bone mineral density, age, and smoking were predictors of subsequent fracture in women, and femoral neck bone mineral density, physical activity, and calcium intake were predictors in men [53]. Fragility fractures are a challenging problem both for patients and orthopedic surgeons. The elderly is disabled and may present a reactivation of a previous illness or new medical problems related to the fracture, the surgical treatment, or the period of immobilization. This is particularly true for the patients affected by a vertebral or a proximal femur fracture. The orthopedic surgeon is sometimes the first doctor that diagnoses osteoporosis in the ER department after the fracture and is supposed to follow up the patient. His role, therefore, is not only the treatment of the present condition but also the prevention of future fractures. This can be done by studying the patient clinically, with the education to lifestyle modifications, prescribing a proper medical therapy, or referring the patient to the metabolic disease specialist. Patients affected by hip fracture have got eightfold more possibility to fracture the contralateral hip with respect to the general population, but, today, less than 50% receive an adequate treatment for osteoporosis [49, 54]. The orthopedic surgeon needs to have a personalized therapeutic algorithm to use in primary and secondary fracture prevention. In general, a moderate physical activity and a diet rich in calcium, proteins, and vitamin D are strongly suggested. The prevention of domestic accidental falls is of paramount importance. The older patients living in nursing houses should wear hip protectors that have been shown to be very useful for hip fracture prevention [55].

Fragility fractures should be managed in the context of a multidisciplinary clinical system, guaranteeing adequate preoperative assessment and preparation of patients including adequate pain relief, appropriate fluid management, and surgery within 48 h of injury. Operative treatment is the treatment of choice for the majority

of the displaced femoral neck fractures. However, the debate as to whether the femoral head should be retained or replaced continues. The concept that the most of the efforts must be reserved to the acknowledgment of the biologic properties of the bone is a new conception that surgeons must consider, and so the surgical technique has to follow and to respect these advancements. In conclusion, we have demonstrated a similar increased of absolute risk of subsequent fracture in both women and men following virtually all low-trauma fractures except ankle fractures in women and rib fractures in men. For both sexes, absolute subsequent fracture risk was equal to or greater than the risk of an initial fracture for a woman in a 10-year-older age bracket or for a man 20 years older. The increased risk persisted for up to 10 years depending on age and sex, with about 50% of surviving men and women having another fracture. The critical clinical relevance of these findings is that incident low-trauma fracture is a signal for increased risk of all types of subsequent osteoporotic fracture, particularly in the next 5–10 years. Thus, virtually all low-trauma fractures indicate the clinical need for fracture preventive therapy, and given the early peak of refracture, such preventive treatment should not be delayed. The lack of consideration of osteoporosis and treatment initiatives by the medical profession and the public, particularly in relation to men, should be the focus of education initiatives. The treatment of fragility femoral fractures has now reached very important findings allowing not only to achieve rapid healing with few failures but also an early rehabilitation therapy, a good quality of life, a longer survival, and better maintenance of the conditions of self-sufficiency. The choice of the osteosynthesis must be based on specific indications, experience of the surgeon, and patient's needs.

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Principles of Rehabilitation in Male Osteoporosis

19

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19.1 Introduction

Osteoporosis is a common disease in postmenopausal women, but it also represents a major issue for men with a growing burden for public health system. In 2000, about 39% of new fragility fractures occurred in men, with a female-to-male ratio of 1.6 for vertebral fractures, 2.3 for hip fractures, 3.0 for humerus fractures, and 4.0 for forearm fractures [1].

Moreover, hip and vertebral fractures are the most painful and disabling fracture types, resulting in important clinical scenarios, ranging from chronic pain and loss of mobility and functional independence to an increased risk of institutionalization and death [2]. In Europe, all fragility fractures account for more deaths and morbidity than any cancer type, except for lung cancer [2].

It should be emphasized that both disability and mortality as consequences of hip fractures are significantly higher in men than those reported in women. Among male patients with hip fractures, about 80% will not return to functional independence, and 50% needs to be managed in an institutionalized setting, meanwhile about 25% remains in nursing home or other assisted care [3]. These unfavorable rates are probably due to higher comorbidity burden in men compared to women at the time of fracture, adversely influencing functional recovery, even though they are generally younger [4]. On the other hand, some studies did not report any difference according to gender in terms of disability, because this latter is underestimated, as a consequence of higher rate of mortality in men [5, 6]. At 1 year after hip fracture,

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mortality rate is 37% in men compared to 25% in women [7–9], whereas at 2 years, this rate reaches 42% in men and 33% in women, showing a slight reduction of difference in mortality rate according to gender.

Furthermore, spine is another typical site of fragility fractures that might induce back pain, disability, and poor health-related quality of life (HRQoL). Interestingly, it was reported that clinical vertebral fractures have a higher age-adjusted relative risk (RR) of dying than hip fractures (8.64 vs. 6.68) (Table 19.1) [10].

Considering these epidemiological issues, preventive strategies and rehabilitation are cornerstones of the management of osteoporotic patients, particularly in men with fragility fractures.

19.2 Physical Activity as Strategy of Primary Prevention in Male Osteoporosis

The best comprehensive approach to the prevention of fragility fractures includes nutrition, physical activity, and behavioral interventions for subjects at higher risk.

The first step is to identify risk factors for osteoporosis and fragility fractures, such as poor sun exposure, smoking habits, high alcohol intake, other nutritional alterations, diseases or drugs influencing bone health, and history of falls that lead to a higher risk of fracture regardless of bone mineral density (BMD).

In order to prevent fragility fractures, an adequate assessment of risk of falls is mandatory, taking into account personal and environmental risk factors.

Personal risk factors of falls include low muscle strength, impaired balance, and poor physical function that should be evaluated by specific tests with an adequate accuracy [11].

The *hand grip strength* (HGS) *test*, performed using a Jamar dynamometer (Sammons Preston Rolyan, Bolingbrook, IL), considered the maximum value (in kilograms) of three consecutive measurements of the dominant upper limb strength (with an interval of 1 min after each measurement) [12, 13]. HGS is positively related to lower extremity muscle strength and negatively related to incident disability [14].

Similarly, men unable to properly perform the HGS have about four times increased risk of hip fracture [15].

Table 19.1 Gender differences in terms of incidence of fragility fractures and mortality rates after hip fractures worldwide

	Male	Female
Hip fractures (*n*)	490,000	1,137,000
Vertebral fractures (*n*)	554,000	862,000
Forearm fractures (*n*)	332,000	1,328,000
Humerus fractures (*n*)	178,000	528,000
Mortality at 1 year after hip fracture (%)	37%	25%
Mortality at 2 year after hip fracture (%)	42%	33%

In order to evaluate muscle strength, coordination, agility, and balance, one of the most used assessment tools is the *five times sit to stand* (FTSTS) that investigates the ability of patients to stand up from a chair five times, without using arms. In particular, it was suggested that men unable to complete this exercise were about eight times more likely to experience hip fracture than those able to finish the test in less than 9 s, and approximately three times compared to men completing the test in more than 12.6 s [15, 16].

Unipedal stance time (UST) is a viable assessment tool for fall risk identification, consisting of standing on 1 foot up to 45 s. The test has to be performed for three times, and the best result is recorded and assessed according to the cutoffs proposed by Springer et al. [17]. Patients that fail to perform this test have an increased RR of 11.6 of falling compared to patients able to complete the test [18].

An objective way to assess the physical performance is the *short physical performance battery* (SPPB), a widespread used assessment tool with an excellent reliability [19], representing a predictor of the loss of mobility in elderly; in fact, subjects with low SPPB score have an increased risk of disability and hospitalization [20, 21]. SPPB has three subitems: standing balance, usual gait speed, and sit-to-stand test. The sum of the whole test ranges from 0 (worst score) to 12 (best score) [22]. Moreover, SPPB score allows to identify four categories, according to the risk of poor functional status: patients with SPPB score ranging from 0 to 3 are at very high risk of poor physical performance; those with 4 to 6 and from 7 to 9 are at high and intermediate risk, respectively, whereas those with a SPPB score from 10 to 12 are at low risk of poor functioning.

Moreover, bone-specific physical activity questionnaire (BPAQ) is a quick and simple self-administered tool that might be used to assess lifetime physical activity with age-specific effects of mechanical loading on the skeleton in male population. This questionnaire records the type, frequency, and years of physical activity involvement (see Table 19.2 for further details) [23].

Environmental risk factors for falls are often not well evaluated, but should be taken into account because more than 70% of falls occurred at home. It must be avoided the use of low or soft chairs, carpets, slippery surfaces, raised thresholds, inadequate lighting, and unsuitable shoes, and attention must be paid to wires and other obstacles as well as stair climbing (especially the first and last step) [11, 24].

Hip fracture could also be prevented wearing hip protectors, soft tissue pads able to reduce the energy resulting from the impact of a fall, even if its effectiveness seems to be limited to elderly institutionalized patients [25].

Several guidelines recommended physical activity for improving both physical performance and BMD. It is well known that bone mass is strictly related to skeletal muscle mass and strength. As a result, strengthening and balance exercises demonstrated to improve not only muscle performance and to reduce the rate of falls but to improve also bone strength [26]. Physical activity has presumably direct effects upon bone turnover increasing bone formation via mechanical stimuli, improving or maintaining hip and vertebral BMD. Increased mechanical loading results in a reduction of sclerostin secreted by the osteocytes. This glycoprotein through the canaliculi reaches the osteoblastic-lining cells, where it binds to specific

Table 19.2 Functional and fall screening assessment tools

Outcome measures	Equipment	Time to administer (min)	Outcomes	Cutoffs
HGS (Andrews et al. 1996) [13]	Handheld dynamometer	5	Muscle strength	According to age and gender
FTSTS (Bohannon et al. 2006) [15]	Standard chair (43–45 cm height) Stopwatch	<5	Lower limb muscle strength Lower limb muscle power Balance	60–69 years: 11.4 s 70–79 years: 12.6 s 80–89 years: 14.8 s
UST (Springer et al. 2007) [17]	Stopwatch	2	Balance	According to age and gender
SPPB (Guralnik et al. 1994) [22]	Standard chair (43–45 cm height) Stopwatchr	10	Lower limb functioning Balance Physical performance	Low performance: 0–3 Moderate performance: 4–6 High performance: 7–9 Very high performance: 10–12
BPAQ (Weeks et al. 2008) [23]	Questionnaire	10	Physical activity	According to age and gender

HGS hand grip strength test, *FTSTS* Five times sit to stand, *UST* unipedal stance test, *SPPB* short physical performance battery, *BPAQ* bone-specific physical activity questionnaire

co-receptors (LRP-5 and LRP-6), thus inhibiting the Wnt-β catenin signaling, with consequent reduction of osteoblasts commitment, differentiation and function, and therefore bone formation [27]. In men the correlation between hypersclerostinemia and loss of bone mass due to prolonged immobilization supports the hypothesis that sclerostin could be a link between the reduced mechanical load and disuse osteoporosis [28]. On the other side, even minimal increase in levels of physical activity reduces serum levels of sclerostin, confirming this glycoprotein effectively links mechanical loading and bone turnover [29].

Two types of physical exercise are generally recommended to improve or maintain hip and vertebral BMD: weight-bearing exercises and strength training. The first includes walking, stair climbing, playing sports such as tennis and volleyball, and brisk walking or jogging [30], whereas the second includes activities like lifting weights, push-ups, and squats [31].

Giangregorio et al. recommended a moderate intensity aerobic physical activity (≥30 min, ≥5 days per week) or at least 20–60 min of high-intensity aerobic physical activity ≥3 times per week in osteoporotic patients without vertebral fracture, pain, or hyperkyphosis. Moreover, authors also recommended balance exercises and resistance/strength training for preventing falls with a frequency ≥2 days per week [32].

Recently, tai chi was proposed as a viable and effective alternative approach in enhancing balance control in elderly people. This intervention originated in China

as a form of martial art and widely used also in Western countries to promote mental and physical health. This mind-body therapy can be practiced in different styles, particularly Yang and Wu styles for strengthening muscles and improving balance, respectively. Tai chi demonstrated to be an appropriate training for the prevention of falls among aged people, through low-impact weight-bearing exercises and controlled movements, such as semi-squat positions and controlled transfer of weight in coronal, sagittal, and transverse planes of movement [33, 34].

In terms of evidence-based medicine, a Cochrane review supported the beneficial role of group and home-based exercise programs, essentially based on balance and strength training exercises, as well as tai chi, in falls prevention (−29%), particularly in people who are not at high risk of falling [26].

Vertebral fragility fractures are generally spontaneous or result from low-impact daily life activities. However, also for patients at high risk, safe axial strength training (back extension resistive exercises from the prone position with reduction of kyphotic posturing) is strongly recommended for the prevention of compression fractures (see Table 19.3 for further details) [35].

Table 19.3 Primary prevention of osteoporotic fractures

Type of exercise	Objectives	Schedule	Setting
Aerobic exercises	– Endurance – Physical fitness – Muscle-tendon elasticity – Balance and gait control	30 min/die, 5 days per week with: – Brisk walking – Jogging	Outdoor
Upper and lower limb exercises	– Muscle strengthening – Recovery of range of motion – Recovery of independence	Three sets of ten repetitions, 3 days per week, with: – Biceps curl – Squat – Wall push-up – Chair squat	Indoor/ outdoor
Core stabilization	– Muscle strengthening – Back muscle elasticity – Spinal column stability – Balance control – Posture control	Three sets of five repetitions, holding the position for 3 s, 7 days per week, with: – Dorsal extension – Single-leg extensions, prone – Raised pelvis – Quadrupedal reach and roll	Indoor/ outdoor
Balance exercises	– Balance control – Posture control – Muscle strengthening – Muscle core stability	Three repetitions, 7 days per week, holding 10 s these positions: – Semi-tandem – Tandem – Single-leg stance Three sets of five repetitions of standing hip extension, holding the position for 3 s, 7 days per week Three sets of six repetitions (three for each side) of lateral walk, 7 days per week	Indoor/ outdoor

19.3 Physical Activity as Strategy of Secondary Prevention in Male Osteoporosis

Secondary prevention strategy includes all interventions aimed to reduce the risk of new fracture in patients who have already experienced a fragility fracture.

The reduction of this risk can be achieved increasing the bone strength with both pharmacological and non-pharmacological approaches. If drug therapy demonstrated to improve not only BMD but also bone quality, on the other hand, it was shown that bone strength can be significantly improved by physical activity. Indeed, regular physical exercise is recognized as a cornerstone of intervention programs also in the management of patients with fragility fractures, because its beneficial effects on several fracture risk factors, such as risk of falling. Moreover, physiatric approach to manage men with prevalent osteoporotic fractures should include a patient education and training with the purpose of improving balance, muscle strength, and mobility. This approach contrasts with the common belief that individuals with previous fracture must reduce their physical activity in order to decrease the risk of falls or new fracture. Although a restriction of heavy activities that result in high risk of fractures is advisable, it is widely known that a marked reduction of physical activity can accelerate bone loss. So, it should be paid the same attention to the prescription of adequate physical activity programs as it is done with drug therapy as preventive strategy of incident fractures.

Specifically, to prevent new vertebral fractures, osteoporotic men have to avoid to lift up heavy objects, twisting or flexing their spine, or to perform abrupt movements [32]. Physical exercise programs for patients with previous vertebral fracture should include strengthening training for trunk and lower extremity with the aim to improve spine stability and functioning [36]. Strengthening exercises for back extensor muscles associated with pelvic tilt exercises demonstrated to reduce the lumbar lordosis and thoracic hyperkyphosis [35] and to improve lower extremity physical function in osteoporotic older men [37]. However, this intervention is supported by inconclusive evidence, particularly in male population, about its efficacy on pain relief, physical function improvement, and better quality of life [38].

Taking into account that the improvement of gait and balance are the most important factors for reducing risk of falls in particular after hip fracture, specific physical exercise training for motor control, endurance, and balance should be prescribed to improve gait efficiency and activities of daily living (ADL) (see Table 19.4 for further details) [39].

19.4 Principles of Rehabilitation in Male Patients with Fragility Fractures

19.4.1 Rehabilitation in Male Patients with Hip Fractures

Hip fracture represents the most disabling fracture in men affected by osteoporosis. According to Magaziner et al. [3] after 1 year from hip fracture, 20% of men lose their ability to put on pants without assistance; the 50% needs assistance to walk

Table 19.4 Secondary prevention of osteoporotic fractures

Type of exercise	Objectives	Schedule	Setting
Aerobic exercises	– Endurance – Physical fitness – Muscle-tendon elasticity – Balance and gait control	30 min/die, 5 days per week with: – Brisk walking – Jogging	Outdoor
Upper and lower limb exercises	– Muscle strengthening – Recovery of range of motion – Recovery of independence	Three sets of eight repetitions, 3 days per week, with: – Biceps curl – Squat – Wall push-up – Chair squat	Indoor/ outdoor
Core stabilization	– Muscle strengthening – Back muscle elasticity – Spinal column stability – Balance control – Posture control	Three sets of three repetitions, holding the position for 3 s, 7 days per week, with: – Dorsal extension – Single-leg extensions, prone – Raised pelvis – Quadrupedal reach and roll	Indoor/ outdoor
Balance exercises	– Balance control – Posture control – Muscle strengthening – Muscle core stability	Three repetitions, 7 days per week, holding 3 s these positions: – Semi-tandem – Tandem – Single-leg stance	Indoor/ outdoor

around a room, 50% to rise from a chair, 55% to walk a block, 66% to use the toilet, and over 90% to climb stairs.

Rehabilitation after hip fracture must be intensive and multidisciplinary in order to regain as much as possible the pre-injury functional status. Commonly, hip fractures should be early surgically treated to avoid prolonged bed rest and immobilization, thus reducing clinical complications, disability, and death.

The choice of the rehabilitative approach might be influenced by several factors: patient's clinical condition (i.e., comorbidity, mental status), type of fracture (intracapsular or extra-capsular), and type of surgical approach (mini-invasive, lateral or medial, and use of total hip arthroplasty, hemiarthroplasty, or open reduction internal fixation).

Commonly, weight bearing is gradually allowed, ranging from a partial weight bearing to total weight bearing as tolerated, taking into account to avoid negative effects on the surgical fixation (both in cases of arthroplasty and osteosynthesis). If it is possible, partial weight bearing can be allowed immediately after the surgical intervention.

In hospital care settings, rehabilitation includes exercises designed to recover range of motion (ROM), muscle strength, and independence (i.e., walking, stairs climbing), usually with two sessions per day.

Subsequently, a home-based rehabilitation program should be performed five times per week for 3–6 months until the best functional recovery is obtained.

A systematic review and meta-analysis claimed that an extended (over 6 months) exercise program after hip fracture improves patients' physical function, as showed by significant effect sizes (ESs) in knee extension strength for the affected (ES: 0.47; $p < 0.001$) and non-affected side (ES: 0.45; $p = 0.002$), balance measurements (ES: 0.32; $p < 0.001$), physical performance-based tests (ES: 0.53; $p < 0.001$), Timed Up and Go Test (ES: 0.83; $p = 0.003$), and fast gait speed (ES: 0.42; $p = 0.008$) [40].

19.4.2 Rehabilitation in Male Patients with Vertebral Fractures

Vertebral fractures are a clinical and public burden associated with back pain, disability, and impairment in HRQoL. These fractures are often underdiagnosed: in particular, less than 15% of incident radiographic new vertebral fractures are clinically diagnosed in men [41], whereas this percentage reaches up 25% in women [42].

The age-standardized incidence of new morphometric fractures is 5.7/1000 per year in men and 10.7/1000 per year in women [43].

A clinical vertebral fracture is characterized by pain and functional limitation, commonly treated with immobilization in spinal bracing and analgesic therapy. Rehabilitation begins during spinal bracing and continues also after its removal, improving back extensor muscles strength and performing core stability exercises.

After vertebral fragility fracture, surgery, such as vertebroplasty, kyphoplasty, and rarely spinal stabilization with or without fusion, could be suggested according to age, general clinical condition, type of fracture and spinal stability, involvement of the spinal cord, bone quality, and time from the fracture [44].

A prompt rehabilitative approach should start after surgery with breathing exercises and back extensors strengthening exercises. This muscle strengthening is obtained by a progressive load with short lever arms [45].

A long-term goal in the rehabilitation plan is enhancing physical functioning by improving spine mobility, muscle strength, balance during postural changes, and gait pattern.

Moreover, rehabilitation must include a home-based program consisting in dedicated physical exercises, associated to educational interventions targeted to avoid twisting or flexion of the spine, quick and repetitive movements, and sitting or standing for a long-term period [32].

19.4.3 Rehabilitation in Male Patients with Other Fractures

Fragility fractures affecting other skeletal sites, such as the humerus, forearm, pelvis, rib, tibia, fibula, clavicle, scapula, and sternum, are common disabling issues in men, with a resulting increased healthcare cost [2, 46, 47].

There is a high incidence of non-hip and non-vertebral (NHNV) fragility fractures in older European men, representing over the 70% of incident osteoporotic fractures [2].

In Italian male population, after the hip and spine, the most common site of fragility fracture is the humerus, followed by the distal forearm and ankle [46].

Most *fractures of the proximal humerus* are minimally displaced or nondisplaced, preferentially managed by a conservative treatment with casts or upper extremity orthotics, allowing passive motion exercises for the fingers, hand, and wrist. ROM exercises have to be performed at 2 weeks after injury, and orthosis should be removed within 4 weeks. In the case of unstable and nondisplaced fractures, an immobilization period should last not less than 4 weeks, and ROM exercises should start only after clinical bone healing. The rehabilitative approach should follow general principles of shoulder rehabilitation, including exercises for mobility, muscle performance, and upper limb functioning, with the ultimate goal to regain independence for basic ADLs.

Unstable and displaced fractures require a surgical treatment, as closed reduction with or without percutaneous pinning or open reduction and internal fixation. In male osteoporotic patients, displaced proximal humeral fractures are commonly treated with arthroplasty.

After surgery, a rigorous rehabilitation program should be performed in order to reduce pain and recover the upper limb functioning [48]. In very old men or in patients with severe comorbidities, a conservative treatment is the most appropriate choice, despite fracture displacement.

Distal forearm fractures represent about 10% of fractures in men and are commonly due to low-energy trauma resulting from a simple fall from standing height or less [47]; these fractures range from stable and nondisplaced to comminuted injuries.

Considering the differences in terms of pathoanatomy, therapeutic approaches for these fractures range from splinting or casting, or percutaneous pinning, to open reduction and internal fixation, or external fixation.

After cast removal, or in the case of stable fractures surgically treated, a rehabilitation plan, consisting of flexibility exercises, muscle strengthening exercises, and occupational therapy, should be early performed [49].

Ankle fractures, rare in men, are probably the most challenging fractures to manage. In the case of stable fractures, cast immobilization for 4 weeks could be performed; on the other hand, in cases of dislocated fractures or joint instability, a surgical approach is necessary. Rehabilitation should start after cast removal or surgical treatment in order to reduce pain and improve ankle mobility. Passive motion exercises are suggested in the first stages for recovering the ROM, especially for the ankle dorsiflexion. Weight-bearing exercises and gait training have to be included, as soon as possible and tolerated, in the specific rehabilitative program. Finally, particular attention should be paid to exercises to regain balance and proprioceptive function.

19.5 Conclusions

Male osteoporosis is a major issue and a growing burden for public health system that should be adequately diagnosed and managed. Physical exercise is both feasible and effective preventive strategy to reduce the incidence of fractures and rehabilitation strategy is required to obtain a better functional outcome after conservative or surgical management of men with fragility fractures.

In both clinical scenarios, exercise type, frequency, and duration should be modulated taking into account general health conditions, age, cognitive and emotional issues, and motivation, in order to provide an adequate patient-oriented rehabilitation.

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Conclusive Remarks

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Osteoporosis is a chronic skeletal metabolic disorder that has reached epidemic numbers all over the industrialized countries. Epidemiological reports confirm the propensity to a significant increase of individuals affected by osteoporosis and fragility fractures in the future years, due to the increase of life expectancy, with important socioeconomic and health issue consequences. Age, both in male and female population, increases the risk of developing osteoporosis, which affect millions of women, but lately, also men. Interestingly, osteoporosis has always been considered a female disease, but it has become clear, during the last decades, that osteoporosis affects men as well. Unfortunately, osteoporosis is underestimated, underdiagnosed, and undertreated in men especially in later decades of life, with dramatic consequences including increased mortality after fragility femur fractures. Indeed, femur fractures in old men is often linked to a worst outcome as compared to women. Thus, since several factors, such as genetic, environmental, nutritional, hormonal, play an important role in determining this disorder, attention must be given to the fact that these factors might affect male skeleton differently from the female skeleton. Thus, this health issue must be approached by researchers, politicians, mass-media, and the public in order to approach in a correct manner this skeletal alteration in the male as well as in the female population. In fact, osteoporosis is the most common chronic disorder in the industrialized societies affecting elderly subjects, with important effects on individual quality of life as well as on health economics (medical expenses, lost income as a result of disability, and complications of fragility fractures). Therefore, this skeletal disorder must be considered in the male individuals as well in order to produce preventive appropriate strategies.

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Most reports agree that among other factors, lack of physical activity, as well as non-equilibrated nutrition and drugs play a role in the development of bone loss, altered skeletal homeostasis and, thus, skeletal fragility in male osteoporosis, thus an interdisciplinary approach must be recommended and planned.

In this book, the authors' contributions focus on the large spectrum of the multidisciplinary, and interdisciplinary, approach to male osteoporosis, ranging from physiological characteristics to epidemiology, to clinical characteristics and pharmacological approaches.

The experts of the different disciplines, who have been involved in this editorial project, have made a strong effort to produce manuscripts with robust evidence-based biological and medicine contents, stressing the importance of a translational approach with a viewpoint from multiple disciplines in order to properly approach men affected by osteoporosis.

The book will be useful to physicians, scientists, postgraduate students, and students of various disciplines dealing with male osteoporosis.