Male Osteoporosis

Gender Differences in Pathophysiology, Clinical Aspects, Diagnosis and Treatment
Trends in Andrology and Sexual Medicine

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Male Osteoporosis

Gender Differences in Pathophysiology, Clinical Aspects, Diagnosis and Treatment
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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

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
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

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>National Osteoporosis Foundation</td>
<td>All women &gt;65 years and postmenopausal women with risk factors</td>
</tr>
<tr>
<td>International Society for Clinical Densitometry</td>
<td>All men &gt;70 years or men aged 50–69 years with risk factors</td>
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<tr>
<td>Endocrine Society</td>
<td></td>
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<tr>
<td>World Health Organization</td>
<td>Women &gt;65 years old</td>
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<tr>
<td>American Association of Clinical Endocrinologist</td>
<td>No recommendation</td>
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<tr>
<td>American Academy of Family Physicians</td>
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<tr>
<td>Canadian Osteoporosis Society</td>
<td>Women &gt;65 years</td>
</tr>
<tr>
<td>American College of Physicians</td>
<td>Men &gt;65 years</td>
</tr>
<tr>
<td>UK National Osteoporosis Guideline Group</td>
<td>Assess the risk factors and consider DXA scan for those at risk for osteoporosis</td>
</tr>
</tbody>
</table>
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 Osteoporosis 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
osteooporosis [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.

References

Anatomy and Histology of Male Skeletal Tissue: Gender Differences

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
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].
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
different depending on the analyzed bone site. At the radius, men aged from 20 to 90 years show an 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
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...