Bone Health in Men

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Introduction

Osteoporosis is characterized by a reduction in bone density, associated with skeletal fragility and an increased risk of fracture after minimal trauma. Osteoporosis is often thought of as a women's disease, as it is particularly common after menopause. The reality is osteoporosis also affects men. Up to 20% of symptomatic vertebral fractures and 30% of hip fractures occur in men [1]. The number of men presenting with these fractures is rising, because of increasing life expectancy and a doubling of the age-specific incidence of fractures over the past three decades.

The key challenge facing healthcare professionals and policymakers is to ensure that men, who are clearly at high risk of suffering fragility fractures, get the care they need. A gender-specific approach to screening, diagnosis, and treatment should reduce the morbidity and mortality of the disease, particularly in men over 70. Therefore, screening for men who have already suffered a fragility fracture would be the first step. A broken bone is a very clear signal of elevated future fracture risk—nevertheless osteoporosis assessment and treatment rates among these men are very low—being mostly under 20%. A report from the "international osteoporosis foundations" [2], reported that there is a near universal absence of secondary fracture prevention systems for men who have already suffered fragility fractures. Similar poor attention to bone health is evident among men receiving androgen deprivation therapy for prostate cancer or glucocorticoid treatment for many other conditions, the most common causes of secondary osteoporosis in men.

To avert this calamity, a concerted international effort is required to improve the awareness of osteoporosis in men among both doctors and the community and to implement systems of care to prevent fragility fractures. In this regard, there is good news. There are a range of therapies now available that have proven effective in the treatment of osteoporosis in men. These treatments have been shown to work against the various types of osteoporosis which can affect men, including primary (or idiopathic) osteoporosis and when secondary causes are responsible for bone loss (e.g., glucocorticoids or low sex hormone levels).

After analyzing why bone health in men is important, this chapter will present the epidemiology of osteoporosis in men as well as bone development in different stages of the man's life from childhood through to older adult phase. The chapter will expand to discuss pathogenesis of osteoporosis in men and the role of hormones, causes of osteoporosis in men, as well as criteria for the diagnosis. The chapter will conclude with

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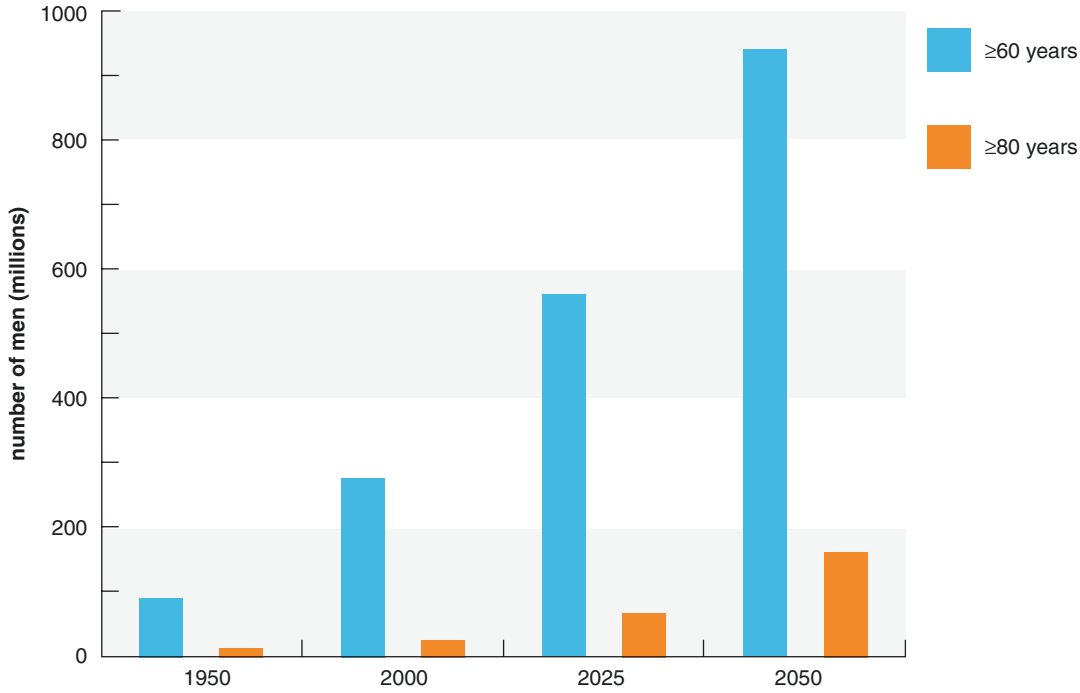

Fig. 5.1 the ageing of the world's male population 1950–2050 [3]

a clinical approach to assessment of men at risk of osteoporosis in the standard clinical practice.

Why Bone Health in Men Is Important?

The world's men are ageing fast; by 2050 the number of men aged 60 years or over will increase ten-fold (Fig. 5.1) [3]. Consequence of aging is the reduced functional capacity, due to malfunctions of the body systems, which reflects negatively on the individual autonomy and independence. The rate of decline of functional capacity depends on intrinsic factors such as the existence of diseases, as well as environmental factors including social and economic factors. Frailty and disability belong to geriatric syndromes and affect the quality of life and older people's functionality. Disability is defined as the inability of the older adult to perform everyday life activities, to self-handling and to be independent. Frailty is a common geriatric syndrome that affects nervous, musculoskeletal, endocrine, and immune system. These people have an increased risk of fall, fractures, hospitalization disability, and mortality [4, 5].

Osteoporotic fractures are associated with substantial morbidity in both men and women. There is considerable disability after hip fracture in men; only 21% are living independently in the community a year later, whereas 26% are receiving home care and 53% are living in an institution [2]. Men with symptomatic vertebral fractures commonly complain of back pain, loss of height, and kyphosis but also have significantly less energy, poorer sleep, more emotional problems, and impaired mobility compared with age-matched control subjects [6].

On another front, although the overall prevalence of fragility fractures is higher in women, men generally have higher rates of fracture related mortality [7, 8]. For example, while the mortality rate in men after hip fracture, as in women, increases with age and is highest in the year after a fracture, over the first 6 months, the mortality rate in men approximately doubled that in similarly aged

women [9]. Vertebral crush fractures are also associated with excess mortality of about 18% at 5 years, due mainly to coexisting conditions associated with osteoporosis rather than the fracture itself [10].

It is estimated that the residual lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is up to 27%, higher than the lifetime risk of developing prostate cancer of 11.3% [11, 12]. Furthermore, the combined lifetime risk for hip, forearm, and vertebral fractures coming to clinical attention is around 40%, equivalent to the risk for cardiovascular disease [13]. On another front, osteoporosis takes a huge personal and economic toll. In Europe, the disability due to osteoporosis is greater than that caused by cancers (with the exception of lung cancer) and is comparable or greater than that lost to a variety of chronic noncommunicable diseases, such as rheumatoid arthritis, asthma, and high blood pressure-related heart disease [14].

Epidemiology

Worldwide, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds [13]. By 2050, the worldwide incidence of hip fracture in men is projected to increase by 310% and 240% in women, compared to rates in 1990 [15]. The prevalence of fracture spine or hip in men is about one-third that in women [16]. In men, there seems to be a lag period, such that an exponential increase in fracture incidence begins 10-years later in men than in women [17], coinciding with the phase of accelerated bone loss after the age of 70 [18]. Although women have a higher overall prevalence of fracture, the increase in fracture risk for each standard deviation decrease in bone mineral density (BMD) seems to be higher in men. Moreover, mortality associated with hip fracture is two or three times higher in men that in women [19, 20].

It is estimated that the residual lifetime risk of experiencing an osteoporotic fracture in men over the age of 50 is up to 27% [11]. The following observations illustrate the magnitude of the problem in men:

- Worldwide, 39% of annual osteoporotic fractures occur in men [21, 22].
- A 60-year-old man has an approximately 25% chance of having an osteoporotic fracture during his lifetime [23].
- By the age of 90 years, one of every six men will have a hip fracture. The prevalence of vertebral or hip fracture in older men is approximately one-third that in women (5 to 6% versus 16 to 18%) and Colles' fracture one-sixth as common (2.5 versus 16%) [24].
- The mortality rate associated with hip fractures, as well as vertebral and other major fractures, 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) [25].

Although low BMD confers increased risk for fracture, most fractures occur in postmenopausal women [26–28] and elderly men [29] at moderate risk. This is of significant epidemiological impact as fragility fractures are more prevalent among older adults. Considering fragility fractures, men fare particularly badly and are the "weaker sex." A national registry study [30] from Denmark published in 2010 echoed the findings of previous studies [31–34]: Hip fractures in men are associated with greater mortality compared with women, with rates as high as 37% in the first year following fracture. In addition, mortality is increased after most fragility fractures in men, not only following hip fractures [35].

Bone Development and Loss in Men

Childhood through to Young Adulthood

While many factors influence the growth of the human skeleton and maintenance of its bone mass throughout life, changes in bone mass pass in different stages of development (this was

reviewed in an article published by the international osteoporosis foundation [2]). Up to the age of 10–12 years, there are no significant differences in bone mass between boys and girls. However, at the onset of puberty, the bone mass increases more in males, and both males and females attain peak bone mass between ages 20 and 30 years [36] (Fig. 5.2).

Why does this occur? Accrual of bone mass during childhood and adolescence is controlled by sex steroids and the growth hormone/insulin-like growth factor 1 (IGF-I) axis of the endocrine system [36]. A study of young men from Gothenburg sought to establish whether androgens increase the size of cortical bone and whether estrogens have the opposite effect [37]. Levels of free testosterone and estradiol were measured and correlated with the size of cortical bone. The results supported the notion that androgens increase, whereas estrogens reduce, cortical bone size. Consequently, during puberty, boys develop larger bones than girls and so accrue greater bone mass. The size of bones and the thickness of their cortex are major determinants of bone strength, and thus men generally have larger bone size and greater bone strength than women.

The importance of normal sex steroid production in the acquisition of peak bone mass is illustrated by the findings of low bone mass in young men with idiopathic hypogonadotropic hypogonadism (IHH) [38]. Because idiopathic hypogonadotropic hypogonadism is almost always a congenital abnormality due to gonadotropin-releasing hormone (GnRH) deficiency, this disorder provides a valuable model to assess the effects of hypogonadism on pubertal bone development (i.e., the attainment of peak bone mass). Both cortical and trabecular bone density (Fig. 5.3) are markedly decreased in these men [39]. Osteoporosis can be detected even before the attainment of skeletal maturity, suggesting that it is due to inadequate pubertal bone accretion rather than post-maturity bone loss.

Although the observation that peak BMD is reduced in men with congenital hypogonadism illustrates the importance of gonadal steroids in bone development, those findings do not indicate whether androgens, estrogens, or both are primarily responsible for the pubertal increase in

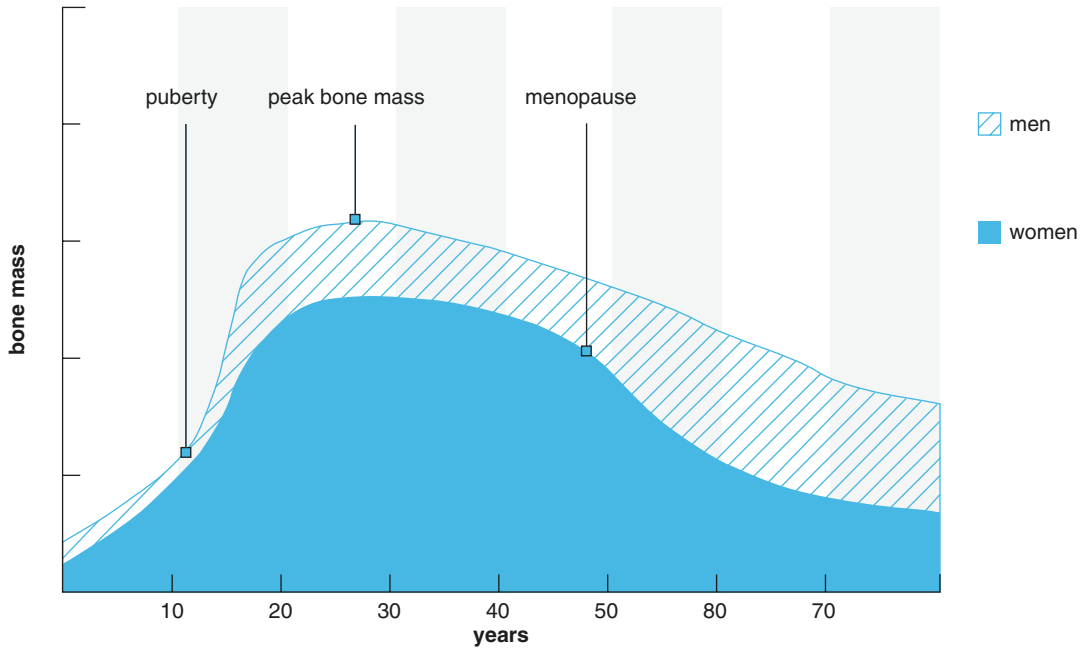

FIG. 5.2 Bone mass throughout the life cycle [61, Springer is the publisher; do we need permission or just put the reference?]

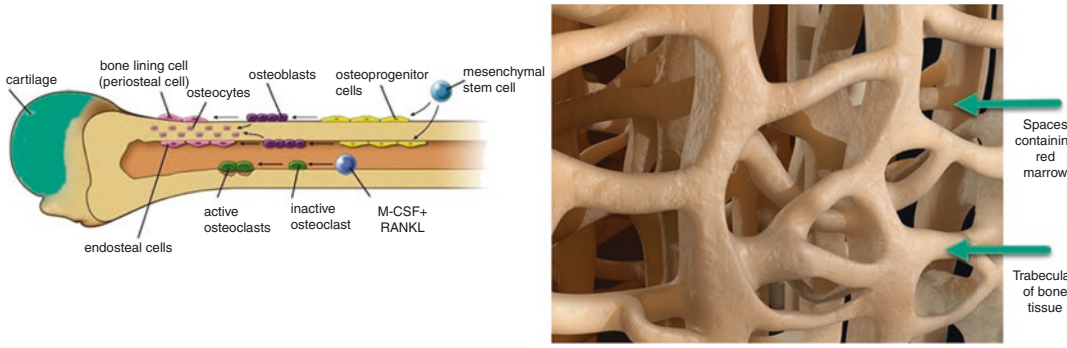

Fig. 5.3 Cortical and Trabecular bone. (M-CSF: Macrophage colony-stimulating factor, RANKL: receptor activator of nuclear factor κβ ligand)

BMD and the attainment of peak bone mass. Reports that BMD is markedly reduced in men with null mutations in the estrogen receptor-alpha, so that responsiveness to estrogen is essentially absent, or in men with null mutation in the aromatase gene, so that synthesis of estradiol is virtually absent, strongly suggest that estrogens provide the primary hormonal stimulus to the attainment of peak bone mass [40].

Another important determinant of peak bone density is the timing of puberty. In adult men with history of constitutionally delayed puberty, BMD of the radial shaft, lumbar spine, and proximal femur is significantly lower than in age-matched normal men, and it does not appear to improve with time [40, 41]. Similar findings have been reported in adolescent boys with delayed puberty [42]. These observations suggest that there is a critical time period during which the skeleton is responsive to sex steroids.

Achieving one's genetic potential for peak bone mass during childhood and adolescence is the primary objective during this first stage of the skeleton's life cycle. The consequence of not doing so has been illustrated by computer modelling developed to predict the relative influences of peak bone mineral density (BMD), menopause, and age-related bone loss on the development of osteoporosis in women [43]. A 10% increase in peak BMD was predicted to delay the development of osteoporosis by 13 years.

Important influences on peak bone mass for young males include as follows.

Exercise In a report published by Australia's "Building healthy bones throughout life strategy" [44], it was stated that "Childhood and adolescence may represent the optimal window of opportunity in which exercise can improve bone strength and protect against osteoporosis and associated fragility fractures in old age, assuming the gains achieved are maintained in later life." Systematic literature review has reported beneficial effects on BMD for children participating in moderate to high impact weight-bearing physical activities [45]. Long-term follow-up from the Australian Schools Health and Fitness Survey conducted in 1985 suggests that higher levels of fitness as a child are predictive of greater peak bone mass at age 30 years [46].

Calcium intake: approximately 40% of adult peak bone mass is acquired during the two years around puberty [47]. Accordingly, ensuring adequate dietary calcium intake during this period of growth is essential. In this regard, it is of great concern that a multinational study of calcium intakes in adolescent boys reported levels of only 60% of country-specific requirements [48].

Vitamin D Levels The association between vitamin D deficiency and rickets is well documented and understood. Consequently, it is expected that the impact that vitamin D deficiency in childhood has on bone health at the population level is also likely to be significant [49]. Reports from Europe [50–55], the Middle East [56], North America [57], and Oceania [58–

61] suggest that low levels of vitamin D in children are a cause for concern throughout the world. The Institutes of Medicine report on dietary intakes of vitamin D and calcium defined the adequate intake of vitamin D of infants (0–12 months old) to be 400 IU and the recommended dietary allowance of vitamin D for children aged 1–18 years to be 600 IU/day [62].

Protein Intake Proteins can be considered as building blocks and, subsequently, help to maintain strong bones. Conversely, low protein intake is associated with impaired skeletal growth thereby influencing peak bone mass [63]. Proteins positive effect on bone and muscle may be medicated through hepatic production of insulin-like growth factor I (IGF-I) [64]. Serum levels of IGF-I are closely related to growth, increasing from birth to puberty. Furthermore IGF-I is considered as a major factor for bone longitudinal growth, stimulating chondrocyte from the growth plate and stimulating the production of active form of vitamin D (1,25 dihydroxyvitamin D) in the kidney. Dairy products, fish, meat, nuts, and legumes are a good dietary source of proteins. Both animal and plant proteins sources appear to favor strong bones.

Other factors which can adversely affect peak bone mass and BMD in young males include delayed puberty [65], smoking [66–68], alcohol consumption [66], and certain childhood diseases such as acute lymphoblastic leukemia [69], and medications such as glucocorticoids [70] and anti-epileptic drugs [71].

Ages: 20–60 Years

During these decades of adulthood, the primary objective is to avoid premature bone loss and maintain a healthy skeleton. On account of the muscular system being the generator of the strongest mechanical forces applied to bones [72], avoiding loss of muscle mass (sarcopenia) is also of paramount importance in this stage of life. Accordingly, as for younger males, regular exercise has an important role to play. Recommendations for building healthy bones in healthy adults [43, 73, 74] provide an illustration of the type and frequency of activities that current knowledge suggests will be of benefit (Table 5.1).

Bone loss appears to start soon after young men reach peak bone mass. A study from Sweden investigated changes in BMD in men aged between 17 and 26 years [75]. A significant year-on-year loss of BMD at the hip was observed from age 19 years, when peak bone mass had occurred. Analysis of bone density data from these young men's fathers suggested that 25% of BMD at the hip may be lost by 50 years of age and that bone remodelling may be regulated differently at the hip than at other sites.

There are important differences between the ways in which bone loss occurs with aging in men as compared with women. To appreciate these differences, the basics of bone biology must be firstly considered.

Table 5.1 Recommendations for building healthy bones in healthy adults

Form of physical activity	
Weight bearing	Participating regularly in moderate impact weight-bearing physical activity is highly recommended. This can be in the form of high impact training (e.g. 50–100 jumps) or related impact loading sports for at least 30 minutes 3–5 days per week
Muscle-strengthening exercises	Muscle-strengthening exercises should be practiced regularly on at least 2 days per week. To achieve maximum benefits, the program should be high intensity (60–80% of peak capacity), become progressively more challenging over time, and, in particular, target the major muscles around the hip and spine
Multi-modal exercise regimen	Participation in a multi-modal exercise regimen, where possible, is recommended (inclusive of weight bearing/high impact/high intensity resistance exercise) at least three times per week
Calcium and vitamin D intake	Men should aim to comply with the relevant international/ national calcium and vitamin D intake recommendations

Bone is a living tissue able to impart tremendous strength to support the human bodies, yet simultaneously must also have the capacity to be flexible to absorb shock without breaking. As illustrated in Fig. 5.3, bone comes in two major forms, the cortical bone, which forms the casing or outer shell, and the trabecular bone—also known as spongy or cancellous bone—which forms a honeycomb-type mesh within the cortex. The trabecular bone provides structural support when loads are applied and enables the entire bone to be flexible.

Bone is in a perpetual state of remodelling throughout life, with the entire skeleton being replaced every 10 years [76]. One group of cells—osteoclasts—are drawn to sites of microdamage to remove old bone (bone resorption). Once the osteoclasts have completed their task, bone forming cells—osteoblasts—deposit new bone to fill the gap created. This process is known as the bone remodelling cycle and is represented in Fig. 5.4 for a healthy young adult. For bone mass to remain constant, the amount of bone being resorbed by the osteoclasts needs to be equivalent to the amount of bone being formed by the osteoblasts.

As men age, the rate of bone resorption by osteoclasts on the inside surface of cortical bone increases (known as endocortical resorption). At the same time, new bone is being deposited on the outer surface of the cortex (known as periosteal apposition). These concurrent processes lead to an increase in the circumference of bones, which serves to increase the bone size and moves the cortex further away from the center of the bone. From a biomechanical perspective, both of these changes result in greater bone strength. However, the cortex also becomes thinner which reduces bone strength. So, in men aged younger than 70 years, there is a degree of balance between these two competing processes.

In postmenopausal women, there is evidence to suggest that the rate of endocortical resorption is such that periosteal apposition cannot serve as a sufficient compensatory mechanism to prevent bone fragility [77–80]. The change in cross-sectional structure of bone for men and women with ageing is illustrated in Fig. 5.5. These seemingly subtle differences in the way that our bones change with aging contribute to our understanding of why fracture rates increase in women to a greater extent than in men.

Another aspect whereby men differ from women is in the mechanisms underlying age-related trabecular bone loss. In men trabecular, thinning occurs and may be associated with decreases in IGF-1, whereas in women, there is resorption and loss of trabeculae, particularly horizontal trabeculae, associated with estrogen deficiency at the time of menopause [81]. This is another reason why skeletal fragility is higher in women.

Bone wise, after attainment of peak bone mass, men lose approximately 30 percent of their trabecular bone and 20 percent of their cortical bone during their lifetimes. Trabecular bone loss appears

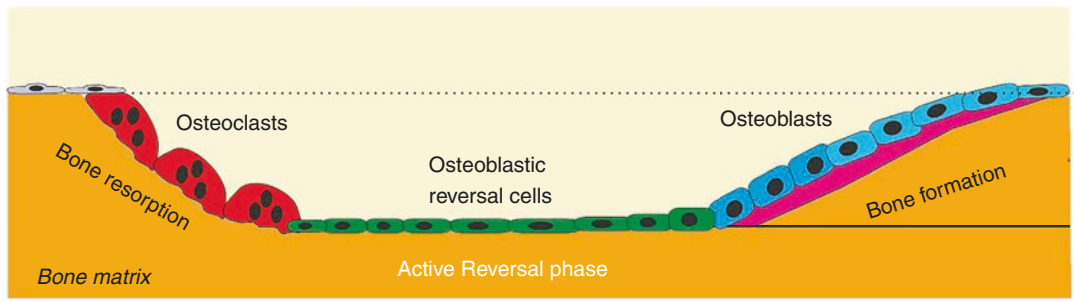

Fig. 5.4 Balanced and coupled bone remodelling. Bone resorption begins when osteoclasts remove a portion of the bone to be replaced later by the action of osteoblasts. This is a vital step for signaling bone formation. Osteoblasts lay down collagen and mineral deposits over the area previously remodelled by osteoclasts. Osteoblast activity is vital for maintaining bone mineral density and bone strength

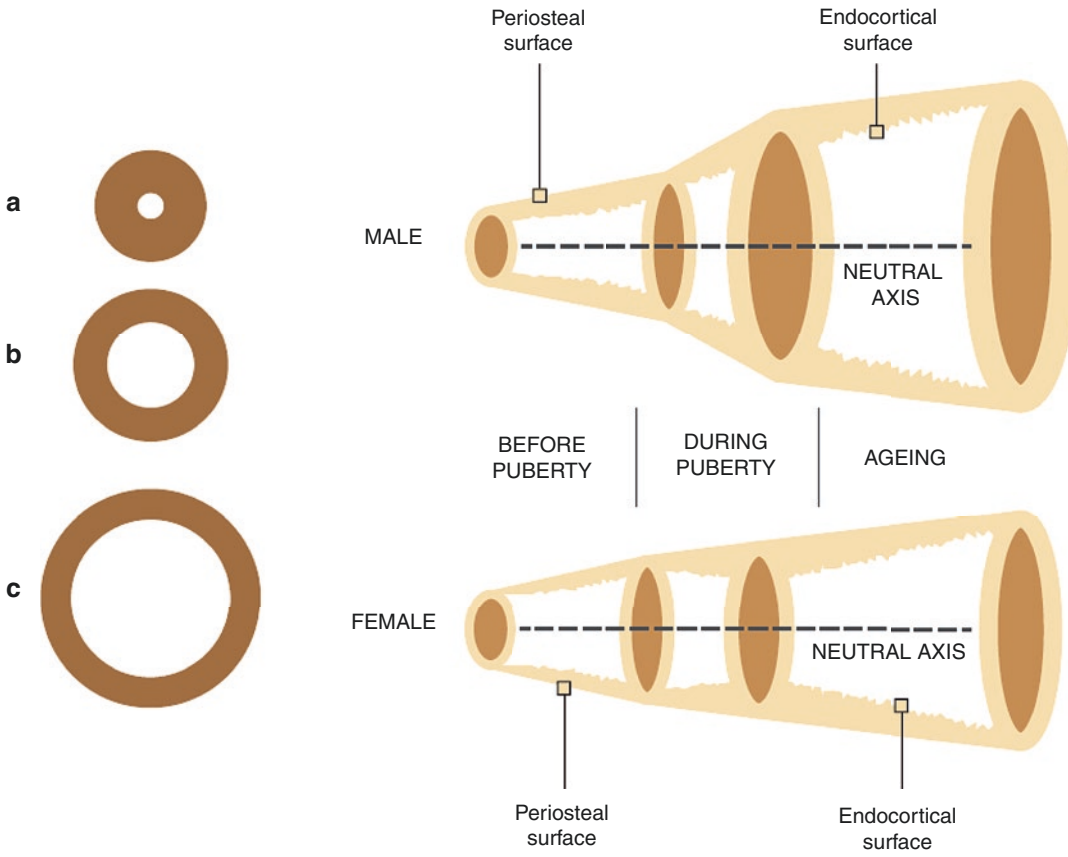

Fig. 5.5 The influence of bone geometry on bone strength105. (IOF: osteoporosis in men). LEFT: For the same areal BMD, bone C has progressively greater bending strength and axial strength than bone B and bone A because the mass of bone C is distributed further away from the center—adapted from Bouxsein [106]. RIGHT: Sex and aging differences in periosteal apposition and endocortical resorption in tubular bones. Adapted from Seeman [107]

to start in young adult life, whereas cortical bone loss is either less pronounced or begins later in life [81]. In some studies, the decline in femoral neck density began shortly after attainment of peak bone mass [82, 83], and the rate of femoral neck bone loss increased with aging [84]. One study reported that bone mineral content of the proximal and distal radius declined at a rate of approximately 1% per year after the age of 30 years, whereas another study found that cortical BMD remained stable until later in life [81, 85].

Patterns of change in spine BMD vary depending upon the measurement technique. When measured by quantitative computed tomography (QCT), which assesses only vertebral body trabecular BMD, spine BMD declines more rapidly than hip or radius BMD [86]. When spine BMD is measured by dual-energy X-ray absorptiometry (DXA) in the posterior-anterior projection, it often appears to increase in older men [87, 88], likely due to degenerative changes in the posterior spinous elements [87]. Thus, posterior-anterior DXA should be interpreted cautiously when assessing bone density of the spine in older men.

Age 70 Years and Onwards

Longitudinal studies suggest that in men bone loss accelerates after the age of 70 years [89]; rapid bone loss is more common with deficient

testosterone or estradiol levels [90]. In contrast to bone loss in women, who lose trabeculae with age due to increased bone resorption; in men bone loss due to trabecular thinning is secondary to reduced bone formation [91]. The preservation of trabecular numbers in men may help explain their lower lifetime risk of fractures. In long bones, bone loss in the marrow cavity is not compensated by bone deposition on the periosteum, which results in loss of cortical bone [92]. A systematic review established that men aged over 70 years were 50% more likely to suffer a fragility fracture than younger men [93].

Other than secondary causes, similar to women, aging is a primary cause of bone loss in men; it induces bone loss through hormonal changes and age-related osteoblast dysfunction.

1. *Hormonal Changes During Aging.*

Hormonal changes during aging are responsible for bone loss; in particular, decreased levels of sexual steroid and relative increase in cortisol negatively influence bone remodeling.

It is widely accepted that the decrease in sex steroid concentrations with age is associated with decreased bone density and increased fracture risk in men [94–96]; nevertheless, the decline of testosterone in men is gradual and not common to all the aged population. In fact, the decrease in bioavailable estradiol more than in testosterone appears to be the cause of bone loss in old men [97].

Excess of glucocorticoids both endogenous and exogenous is known to be detrimental for bone; glucocorticoids affect bone mainly by decreasing osteoblast function [98]. Glucocorticoid action is dependent upon the expression of 11 beta-hydroxysteroid dehydrogenase isozymes, which interconvert active cortisol and inactive cortisone. Bone tissue is able to convert cortisone into active cortisol thanks to this enzyme, whose expression increases with aging [99]. Thus, old persons are more sensible to endogenous and exogenous glucocorticoid; this results in a relative hypercortisolism and possibly in bone damage.

2. *Age-Related Osteoblast Dysfunction.*

In old persons, osteoblasts' dysfunction with a consequent decrease in bone formation has been proposed as one of the underlying mechanisms of osteoporosis in the elderly. Analysis of age-related changes in osteoblasts recruitment, differentiation, and function was carried out. It is known that osteoblasts are derived from the differentiation of skeletal mesenchymal stem cells. The ancestral mesenchymal stem cells are able to differentiate in vitro into osteoblasts, adipocytes, or chondrocytes [100] and to self-renew [101]. It has been suggested that a reduced ability of mesenchymal stem cells to differentiate into osteoblasts may play a role in aging-related bone loss [102–108]. The ability of mesenchymal stem cells to differentiate into osteoblasts has also been studied and a recent work done in mice suggests that age impairs this ability [109, 110]. Thus, this could be one of the mechanisms explaining reduction in bone formation with age.

Moreover, osteoblasts may modify their environment by acquiring a typical senescent secretory phenotype involving inflammatory cytokines, growth factors, and proteases [111, 112], thus contributing to increased osteoclasts activity and bone loss.

3. *Vitamin D Deficiency*.

It is well known that vitamin D plays an important role in regulating calcium metabolism and that its deficiency leads to bone demineralization and increased fracture risk [37]. More than 80% of vitamin D derives from cutaneous synthesis, whereas only 20% comes from diet; cholecalciferol is converted into its active form 1,25-dihydroxyvitamin D3 [1,25$(OH)_2$D3] by two hydroxylations in the liver and in the kidney. Kidney cells hydroxylate vitamin D thanks to the enzyme 1-alpha hydroxylase that is under parathyroid hormone control. 1,25$(OH)_2$D3 binds its nuclear receptor (VDR) and contributes to calcium and phosphorus homeostasis; in the small intestinal cells, the activation of vitamin D receptor (VDR) increases calcium absorption and maintains appropriate calcium levels thus

Table 5.2 Serum 25-Hydroxyvitamin D [25(OH)D], cutoff points for vitamin D serum levels (insufficiency/ deficiency / optimum) and health status (as reported by Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for Calcium and Vitamin D. Washington, DC: National Academy Press, 2010)

Serum vitamin D status	Nmol/L*	Ng/mL**	Health status
Deficiency	<30	<12	Associated with vitamin D deficiency, leading to rickets In infants and children and osteomalacia in adults
Insufficiency	30 to <50	12 to <20	Generally considered inadequate for bone and overall health In healthy individuals
Optimum	50–75	20 to 30	Generally considered adequate for bone and overall health In healthy individuals
Normal	75 to 125	30 to 50	Adequate for bone and overall health In healthy individuals
High	>125	>50	Emerging evidence links potential adverse effects to such High levels, particularly >150 nmol/L (>60 ng/mL)

(Serum concentrations of 25(OH)D are reported in both nanomoles per liter (nmol/L) and nanograms per milliliter (ng/mL). ** 1 nmol/L = 0.4 ng/mL)

improving bone mineralization [38]. If the calcium intake is reduced, parathyroid hormone rises and more vitamin D is converted into $1,25(OH)_2D3$; this active form of vitamin D increases calcium level by stimulating osteoclasts activity, thus increasing bone resorption with calcium and phosphorus release in the blood stream [38, 39].

Hypovitaminosis D (Table 5.2) was reported to be largely prevalent among adult population of both genders. The incidence of hypovitaminosis D in older adults has been attributed not only to changes in lifestyle but also to decreased cutaneous synthesis [45]. For the important role vitamin D plays in bones as well as calcium homeostatis, hypovitaminosis D has been considered in the diagnostic processes of male osteoporosis in the elderly, and a correct vitamin D supplementation has to be guaranteed in order to ensure maximum benefit of treatment. Table 5.3 shows the recommended calcium and vitamin D intakes as advised by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, 2010.

Pathogenesis: The Role of Hormones

Although gonadal steroids appear to play a crucial role in the attainment of peak bone mass, whether they play a significant role in age-related bone loss is less clear. Unlike women, the rate of age-related gonadal steroid decline is less abrupt in men, and thus, the skeletal impact of these more subtle declines are unclear. However, gonadal levels at the extremes of deficiency have been associated with low BMD and bone loss in older men. Numerous epidemiologic studies have reported associations between gonadal steroids and BMD or fractures [112–116]. These associations are weak, however, as might be expected when studying different populations and relating a single hormone measurement to complex endpoints like bone density and fracture.

Testosterone Some studies have reported significant associations between testosterone, free testosterone, and/or bioavailable testosterone and BMD, rates of bone loss, and prevalent fragility fractures [112–114]. As an example, in the Osteoporotic Fractures in Men Study (MrOS), a cross-sectional and longitudinal study of 2447 men over age 65 years, the prevalence of osteoporosis in the hip or rapid hip bone loss was threefold higher in men whose total testosterone levels were <200 ng/dL (6.9 nmol/L) compared with >200 ng/dL [112].

Estrogen In general, associations of bone density with estrogens have been slightly stronger than associations with androgens [115]. In the MrOS study, the prevalence of osteoporosis in the hip (T-score < −2.5) increased progressively as total or bioavailable estradiol levels fell [112].

Table 5.3 Recommended Calcium and Vitamin D Intakes (as reported by the Food and Nutrition Board, Institute of Medicine, National Academy of Sciences, 2010. [https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/])

Life stage	Calcium (mg/day)		Vitamin D IU (mcg)		Total upper intake level	Pregnancy	Lactation
	Men	Women	Men	Women			
0–12 months	200	200	400 (10mcg)	400 (10mcg)	0–6 months: 1000 IU 7–12 months: 1500 IU		
1–13 years old	1–3 years: 700 4–8 years: 1000 9–18 years: 1300	1–3 years: 700 4–8 years: 1000 9–18 years: 1300	600 (15mcg)	600 (15 mcg)	1–3 years: 2500 4–8 years: 3000 9–18 years: 4000		
14–18 years	1300	1300	600 (15mcg)	600 (15 mcg)	4000	Calcium:1300 Vitamin D: 600 IU	Calcium:1300 Vitamin D: 600 IU Tolerable upper intake: 4000 IU
19–50 years	1000	1000	600 (15mcg)	600 (15 mcg)	4000	Calcium: 1000 Vitamin D: 600 IU	Calcium: 1000 Vitamin D: 600 IU Tolerable upper intake: 4000 IU
51–70 years	1200	1200	600 (15mcg)	600 (15 mcg)	4000		
>70 years	1200	1200	800 IU (20mcg)	800 IU (20mcg)	4000		

In addition, low serum estradiol levels have been associated with an increased risk of future hip fracture in men [116]. Fracture risk appears to be even greater in men with low serum estradiol and testosterone concentrations [115, 116].

Estrogen Versus Testosterone Several studies have evaluated the relative contributions of sex steroids in the regulation of bone resorption and formation (as measured by urinary and serum markers as well as BMD) in adult men [117–119]. Estrogen appears to have the dominant effect on bone resorption and formation. In one physiologic study of induced hypogonadism, 198 healthy men (ages 20 to 50 years) were treated with a GnRH agonist (to temporarily suppress endogenous sex steroid production) and were then randomized to receive 0 (placebo), 1.25, 2.5, 5, or 10 grams of a testosterone gel daily for 16 weeks [119]. A second group of 202 healthy men received the same agents plus anastrozole (to suppress aromatization of testosterone to estradiol). By comparing changes in bone turnover markers, BMD by DXA, and BMD by QCT between men who did and did not receive anastrozole; the study demonstrated that increases in bone resorption and decreases in BMD in hypogonadal men were largely due to estrogen deficiency. The risk of developing hypogonadal bone loss appeared to be small until serum estradiol levels fell below 10 pg/mL and/or serum testosterone levels fell below 200 ng/dL.

Complete Androgen Insensitivity Subjects with complete androgen insensitivity provide a valuable model to assess whether the sexual dimorphism in peak bone density is genetically or hormonally determined. In these subjects, who are genetic males but phenotypic females, radial shaft density is lower than that of normal men but similar to that of normal women. In contrast, lumbar spine density is lower than expected for either men or women of the same age [120–122]. These findings suggest that androgen action con-

Table 5.4 Secondary causes of osteoporosis in men

Causes	Clinical/lab clues
Common causes	
Corticosteroids	At least 5 mg prednisone daily for >3 months
Family history	Family history of minimal-trauma fracture, genetics
Lifestyle	Smoking; high alcohol consumption (i.e., >2 drinks/units daily)
Primary or secondary hypogonadism	Primary or secondary hypogonadism (serum testosterone levels <300 ng/dL); medication use (e.g., corticosteroids, opioids, androgen deprivation therapy)
Vitamin D deficiency and low calcium intake	Serum 25-hydroxyvitamin D <30 ng per mL [74.88 nmol per L]; after correction for renal disease, urinary calcium <50 mg daily suggests inadequate calcium and/or vitamin D intake. Inadequate calcium intake (<600 mg per day)
Less common	
Antiepileptic drugs	Use of phenytoin, phenobarbital, primidone, or carbamazepine
Chronic liver or kidney disease	Elevated creatinine; elevated liver enzymes or other abnormalities of liver function tests
Cushing syndrome	24-hour urine for free cortisol; consider testing in men with clinical signs of Cushing syndrome and unexplained vertebral fractures
Eating disorders	Low body mass index (<20 per m^2); preoccupation with weight; hypotension; electrolyte abnormalities
Endocrine disease	Type I diabetes mellitus, thyrotoxicosis, primary hyperparathyroidism
Inflammatory	Rheumatoid arthritis, inflammatory bowel disease, ankylosing spondylitis
Immobilization	Prolonged bed rest/ chronic illness/neurological deficit
HIV infection	Positive HIV antibodies; treatment with protease inhibitors
Hypercalciuria	High urinary calcium (>250 mg daily) may suggest excessive intake of calcium or vitamin D or impaired renal retention of calcium
Malabsorption (e.g., celiac disease)	Low levels of serum 25-hydroxyvitamin D and/or urinary calcium; positive tissue transglutaminase antibodies
Multiple myeloma or other monoclonal gammopathies	Anemia; renal insufficiency; elevated calcium and erythrocyte sedimentation rate; abnormal immunoglobulin protein (M protein) on serum and urine protein electrophoresis
Organ transplantation	Use of immunosuppressive agents (e.g., cyclosporine, tacrolimus)
Osteomalacia	Serum 25-hydroxyvitamin D may be very low (<15 ng per mL [37.44 nmol per L]); high-normal or elevated alkaline phosphatase and low-normal or low serum calcium or phosphorous
Rare	
Mastocytosis	Fractures, unexplained osteoporosis, and bone pain; high serum tryptase levels (Tryptase levels of 11.5 ng/mL or greater are indicative of either mast cell activation (as in anaphylaxis) or increased total mast cell levels (as in mastocytosis)
Osteogenesis imperfecta	Fractures; hearing loss; positive collagen type I genetic test

tributes to the normal sexual dimorphism in cortical bone density and that the Y chromosome, per se, is not sufficient to guarantee the higher cortical density of normal men. Insufficient replacement of estradiol after gonadectomy, however, cannot be excluded as a reason for these results. As an example, in one study, noncompliance with estrogen replacement therapy after gonadectomy correlated with lower lumbar spine bone density [121].

Other Hormones Other hormonal changes that may be associated with age-related bone loss include higher serum parathyroid hormone (PTH) concentrations and lower serum 25-hydroxyvitamin D and insulin-like growth factor-1 (IGF-1) concentrations [123–125]. Suppression of gonadal steroids in older men with a GnRH agonist increases the skeletal responsiveness to pharmacologic doses of exogenous parathyroid hormone, an observation that might help to explain bone loss in men with hypogonadism [126].

Causes of Osteoporosis in Men

There are two main types of osteoporosis: primary and secondary. In cases of primary osteoporosis, either the condition is caused by age-related bone loss (sometimes called senile osteoporosis)

or the cause is unknown (idiopathic osteoporosis). The term idiopathic osteoporosis is typically used only for men younger than 70 years old; in older men, age-related bone loss is assumed to be the cause.

Male osteoporosis is often secondary and the majority of men with osteoporosis have at least one (sometimes more than one) secondary cause. Epidemiological surveys suggest that causes or contributing factors for osteoporosis can be identified in 40 to 60% of men who have osteoporotic fractures [127–129]. In cases of secondary osteoporosis, the loss of bone mass is caused by certain lifestyle behaviors, diseases, or medications. Some of the most common causes of secondary osteoporosis in men include exposure to glucocorticoid medications, hypogonadism (low levels of testosterone), alcohol abuse, smoking, gastrointestinal disease, hypercalciuria, and immobilization [130, 128–132]. Table 5.4 shows list of the disorders that have been linked to osteoporosis in men.

Additional testing for secondary causes is based on clinical or routine laboratory evaluation. Initial laboratory testing should include complete blood count; liver function test; and thyrotropin (TSH), serum testosterone, 25-hydroxyvitamin D, calcium, and creatinine levels (consider measuring 24-hour urine calcium and creatinine.

Some of the common causes for osteoporosis in men include as follows.

Hypogonadism

Hypogonadism refers to abnormally low levels of sex hormones. It is well known that loss of estrogen causes osteoporosis in women. In men, overt hypogonadism causing reduced levels of sex hormones have been recognized as a possible cause of osteopenia or osteoporosis [133, 134].

Although it is natural for testosterone levels to decrease with age, in contrast with women, there should not be a sudden drop in this hormone level that is comparable to the drop of estrogen levels experienced by women at menopause. However, medications such as glucocorticoids, cancer treatments (especially androgen depletion therapy used for prostate cancer), and many other factors can affect testosterone levels (Table 5.5). In addition to inducing bone loss directly, corsticosteroids may act indirectly by causing hypogonadism. A dose-dependent decrease in serum testosterone is thought to result from both suppression of hypothalamic gonadotropin-releasing hormone secretion and direct effects on testicular testosterone production [135].

Bone turnover increases and bone density decreases in men with serum testosterone levels that are below approximately 200 ng/dL, likely due to a concomitant decline in serum estradiol levels to below 10 to 15 pg/mL [43]. Research suggests that estrogen deficiency may also be a cause of osteoporosis in men. For example, estrogen levels are low in men with hypogonadism and may play a part in bone loss. Osteoporosis has been found in some men who have rare disorders involving estrogen. Therefore, the role of estrogen in men is under active investigation. Furthermore, the low bone density does not appear to be due to dihydrotestosterone deficiency, as men treated with finasteride, which inhibits conversion of testosterone to dihydrotestosterone, do not have accelerated bone loss [136].

Osteoporosis has also been reported in hypogonadal men with hemochromatosis [137, 138] and anorexia nervosa [139]. In these men, it is difficult to determine whether the osteopenia is due to concomitant liver disease and nutritional deficiencies or to hypogonadism. There have been few longitudinal studies of men at risk for osteoporosis as a result of hypogonadism. However, bone density decreases in young men who are castrated for sexual delinquency [140] and in older men with advanced prostate cancer who undergo androgen ablation therapy [141–144].

Testosterone replacement therapy may be helpful in preventing or slowing bone loss. Its success depends on factors such as age and how long testosterone levels have been reduced. Also, it is not yet clear how long any beneficial effect of testosterone replacement will last. Therefore, doctors usually treat the osteoporosis directly,

Table 5.5 Causes of hypogonadism

Primary hypogonadism (testicular pathology)	Secondary hypogonadism (hypothalamus or pituitary gland pathology)
Genetic/chromosomal disorders (Klinefelter's syndrome XXY)	*Idiopathic:*
Anorchia (congenital or post-orchidectomy)	Kallmann syndrome (anosmia and hypogonatrophic hypogonadism)
Cryptorchidism (a condition in which one or both of the testes fail to descend from the abdomen into the scrotum)	*Functional*
Chemotherapy (alkylating agents), radiotherapy	Excessive exercise, weight change
Orchitis (mumps, HIV, autoimmune)	Low BMI
Testicular trauma or torsion	Systemic or intercurrent illness
Medications (glucocorticoids, colchicine)	*Structural*
Alcohol	Pituitary or hypothalamic tumor, prolactinoma
Chronic liver or kidney disease	Infiltration (sarcoidosis, hemochromatosis, histiocytosis X, lymphoma)
Hemochromatosis	Cranial irradiation, surgery, head trauma
	Medications/iatrogenic
	Androgen deprivation therapy for treatment of prostate cancer
	Opioids, marijuana
	Exogenous administration of androgens

Table 5.6 Causes of osteoporosis in men

Endocrine diseases	*Connective tissue diseases*
Hypogonadism	Osteogenesis imperfecta
Primary	Ehlers-Danlos syndrome
Secondary	Marfan syndrome
Delayed puberty	Homocystinuria
Estrogen deficiency	*Drugs*
Hypercortisolism	Alcohol
Hyperthyroidism	Heparin
Hyperparathyroidism	Glucocorticoids
Vitamin D deficiency	Thyroxine-suppressive therapy
Growth hormone deficiency	Anticonvulsant drugs
Diabetes mellitus (type 1 and 2)	Gonadotropin-releasing hormone analogs
Gastrointestinal diseases	Cyclosporine
Malabsorption syndromes (e.g., celiac disease, postoperative states)	Chemotherapy
Inflammatory bowel disease	HIV medications (e.g., tenofovir)
Cirrhosis	*Miscellaneous causes*
Hematologic disorders	Eating disorders (e.g., anorexia nervosa)
Multiple myeloma	Hypercalciuria
Chronic hemolytic anemia	Immobilization
Systemic mastocytosis	Rheumatoid arthritis
	Renal disease
	Hepatic disease
	Tobacco

using medications approved for this purpose (Table 5.6).

Steroids

Glucocorticoids are steroid medications used to treat diseases such as asthma, inflammatory arthritic conditions, as well as autoimmune diseases. Bone loss is a very common side effect of these medications. The bone loss these medications cause may be due to their direct effect on bone, muscle weakness or immobility, reduced intestinal absorption of calcium, a decrease in testosterone levels, or, most likely, a combination of these factors.

Glucocorticoids induce the apoptosis of osteocytes. Osteocytes have a role in the repair of bone micro-damage. Loss of osteocytes by the apoptosis of bone cells interrupts osteocyte-canaliculi network used to obtain nutrients from the blood supply and communicate among themselves and other cells on bone surfaces. As a result, it causes failure to detect signals that normally occur in case of processes associated with the replacement of damaged bone. Disruption of this network system can interrupt fluid flow with the network affecting changes in bone remodeling. Glucocorticoids affect the function of osteocytes, by modifying the elastic part which surrounds osteocytic lacunae to cause osteoporosis in men [145].

Glucocorticoids also enhance the activation of osteoclasts. Glucocorticoids enhance the expression of Interleukin-6, an osteoclastogenic cyto-

kine, and suppress the expression of interferon-beta, an inhibitor of osteoclastogenesis. Those drugs decrease the apoptosis of osteoclasts. As a result, there is increased number of osteoclasts, and the enhanced and prolonged bone resorption is observed in glucocorticoid-induced osteoporosis in men.

When glucocorticoid medications are used on an ongoing basis, bone mass often decreases quickly and continuously, with most of the bone loss in the ribs and vertebrae. Therefore, people taking these medications should be considered for having a bone mineral density test. Men should also be tested to monitor testosterone levels, as glucocorticoids often reduce testosterone in the blood.

A treatment plan to minimize loss of bone during long-term glucocorticoid therapy may include 1. consider discontinuing the medication, 2. use the minimal effective, or 3. administer it through the skin or locally (e.g., intra-articular), if possible. Adequate calcium and vitamin D intake is important, as these nutrients help reduce the impact of glucocorticoids on the bones. Other possible treatments include testosterone replacement and/ or osteoporosis medication [130].

Alcohol Consumption

There is a wealth of evidence that alcohol abuse may decrease bone density and lead to an increase in fractures. Low bone mass is common in men who seek medical help for excessive alcohol consumption.

Alcohol consumption can disrupt the balance of calcium level through hormones, vitamins, and local growth factors which impacts negatively on the bone status. In their study, Laitinen and colleagues [146] reported that each person who receives approximately 5 to 11 standard drinks has increased parathyroid hormone (PTH) levels in their bloodstreams which results in loss of bone mass.

In cases where bone loss is linked to alcohol abuse, the first goal of treatment is to help the patient stop, or at least reduce, his consumption of alcohol. More research is needed to determine whether bone lost to alcohol abuse will rebuild once drinking stops, or even whether further damage will be prevented. It is clear, though, that alcohol abuse causes many other health and social problems, so quitting is ideal. A treatment plan may also include a balanced diet with lots of calcium- and vitamin D-rich foods, a program of physical exercise, and smoking cessation.

Smoking

Bone loss is more rapid, and rates of hip and vertebral fracture are higher, among men who smoke, although more research is needed to determine exactly how smoking damages bone. Tobacco, nicotine, and other chemicals found in cigarettes may be directly toxic to bone, or they may inhibit absorption of calcium and other nutrients needed for bone health.

Several theories have been suggested to explain the negative impact of smoking on human bones. One of the mechanisms is that smoking induces the production of nitric oxide (NO). Nitric oxide is a free radical involved in the regulation of many physiological processes, such as vascular relaxation, platelet aggregation, and immune regulation. During the last decade, it has become apparent that nitric oxide has also an influence on bone cell function [147]. Nitric oxide free radical causes oxidative stress, which presumably increases with age. Continuous oxidative stress in the body normally damage cells, organs, and hormones involved in keeping bones healthy or causes an imbalance between the production of free radicals and the ability of the body to eliminate their harmful effects through neutralization by antioxidants [148]. Oxidative stress caused by free radicals are involved in osteoblastogenesis, in apoptosis of osteocytes and osteoblasts and in osteoclastogenesis, which results in bone resorption as shown in animal and in vitro studies [149].

Another effect of smoking in the body is to increase serum cortisol level. Lewis [150] stated that called smoking, a “stressor,” and described

it as an unwelcomed guest in the body. Smoking has multiple impacts on hormone secretion including the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamic-pituitary-adrenal axis plays an important role in how the body responds to physical and mental stress. When the body is on stress such as smoking, the cerebral cortex recognizes physiologic stressor and activates limbic system to stimulate hypothalamus, which in turn stimulates the sympathetic nervous system leading to excess production of cortisol in the adrenal gland. Earlier research also reported that small, but persistent, increases in cortisol are associated with reduced bone mineral density.

Quitting is the ideal approach, as smoking is harmful in so many ways. However, as with alcohol, it is not known whether quitting smoking leads to reduced rates of bone loss or to a gain in bone mass [151].

Diabetes-Related Osteoporosis

The link between type 1 diabetes mellitus and osteoporosis has been recognized decades ago [152]. While a number of cellular mechanisms have been postulated to mediate this association, it is now established that defects in osteoblast differentiation and activity are the main culprits underlying bone fragility in type 1 diabetes mellitus. Other contributing factors include an accumulation of advanced glycation end products and the development of diabetes complications (such as neuropathy and hypoglycemia), which cause further decline in bone mineral density, worsening geometric properties within bone, and increased fall risk. As a result, patients with type 1 diabetes mellitus have a 6.9-fold increased incidence of hip fracture compared to controls. Despite this increased fracture risk, bone fragility remains an underappreciated complication of type 1 diabetes mellitus and is not addressed in most diabetes guidelines. There is also a lack of data regarding the efficacy of therapeutic strategies to treat osteoporosis in this patient population [153].

Hypercalciuria

Hypercalciuria is a disorder that causes too much calcium to be lost through the urine, which makes the calcium unavailable for building bone. Idiopathic hypercalciuria (IH) is defined as urinary excretion of calcium >4 mg/kg/day in women and >4.5 mg/kg/day in men without any underlying metabolic cause. There is an association between hypercalciuria and low BMD, and the prevalence is increased among Ca-containing stone formers [154]. This is consistent with studies that report a four-fold increased risk of vertebral fracture observed among urolithiasis patients compared with healthy controls [154]. The deleterious skeletal effects of hypercalciuria in the absence of stone formation is not as well established as in stone formers, and consideration should be given to a radiographic evaluation for asymptomatic stones in osteopenic patients, as this could alter management decisions [155]. Clearly bone loss needs to be aggressively addressed in stone-forming idiopathic hypercalciuria, and the significance of increased urinary Calcium in the absence of stone formation needs to be determined by the clinician on a case-by-case basis. Decreased BMD is even seen in children with idiopathic hypercalciuria and is associated with decreased 25-(OH)D3 levels [156].

The precise mechanism of bone loss in idiopathic hypercalciuria remains incompletely understood despite recent advances. Bone histomorphometry studies have consistently documented decreased osteoblastic activity, mineralization rates, and osteoid surfaces [154]. Idiopathic hypercalciuria is characterized by increased intestinal calcium absorption, increased bone resorption, and decreased renal tubular calcium reabsorption [157]. In 40%–60% of hypercalciuric stone formers, elevated circulating 1,25-dihydroxyvitamin D3 ($1,25(OH)_2D3$) levels are found, as well as increased monocyte expression of vitamin D receptor (VDR) [158, 159]. Animal studies have confirmed role of $1,25(OH)_2D3$ in urinary calcium concentration and decreased BMD [160,

161]. The significance of these findings needs to be determined in humans, but they begin to provide insights into potential pathogenic mechanisms of idiopathic hypercalciuria-related bone disease.

Immobilization

Weight-bearing activity is essential for maintaining healthy bones. Without it, bone density may decline rapidly. Prolonged bed rest (following fractures, surgery, spinal cord injuries, or illness) or immobilization of some part of the body often results in significant bone loss. It is crucial to resume weight-bearing activities (such as walking, jogging, and dancing) as soon as possible after a period of prolonged bed rest. If this is not possible, all efforts should be made to minimize other risk factors for osteoporosis.

Gastrointestinal Disorders

Several nutrients, including amino acids, calcium, magnesium, phosphorous, and vitamins D and K, are important for bone health. Induced by their impaired absorption of these nutrients, disorders of the stomach and intestines can lead to bone disease. In such cases, treatment for bone loss may include taking supplements to replenish these nutrients.

Calcium and vitamin D: In observational studies, vitamin D deficiency is associated with osteoporosis, poor physical performance, and an increased risk of fractures [162]. Evidence supporting the benefit of calcium and vitamin D supplementation in men with osteoporosis comes largely from prospective, randomized, placebo-controlled trials [163, 164]. Although a number of trials have reported a beneficial effect of calcium or calcium plus vitamin D on bone density in postmenopausal women and older men [163–167], the data on fracture rates are more variable [81]. This topic is reviewed in detail separately.

Idiopathic Osteoporosis

The 40 to 60% of men with osteoporosis in whom a cause cannot be identified are said to have idiopathic osteoporosis. Histomorphometric studies suggest that many have diminished bone formation [168–170], but some have increased bone resorption [171]. Many of these men probably have a genetic predisposition to osteoporosis [172].

Serum insulin-like growth factor-1 (IGF-1) concentrations are low in some men with idiopathic osteoporosis. Approximately 2 to 3% of men have a history of delayed puberty, which could be a precursor of idiopathic osteoporosis. Estrogen deficiency may also be responsible for otherwise unexplained osteoporosis in some men.

Diagnosis

Worldwide, a lack of awareness of the threat that osteoporosis poses to men, is evident among men themselves, healthcare professionals responsible for their care and the policymakers determining priorities within health systems. Until recently, the diagnosis of osteoporosis in men was based on the development of fractures after minimal trauma. Osteoporosis can be effectively treated if it is detected before significant bone loss has occurred. A medical workup to diagnose osteoporosis can include a complete medical history, X-rays, and urine and blood tests.

In contrast to fractures, which may be the initial presentation in most men with osteoporosis causing significant pain, disability, and functional impairment; men may present with asymptomatic loss of height (measurement of bone mineral density (BMD) should be considered in men who have lost more than 1.5 inches in height). The most common fracture sites in men are the hip, vertebrae, forearm, and humerus [173].

In the clinical setting, important information includes medications used, chronic diseases, alcohol or tobacco abuse, falls and/or fractures as an adult, as well as family history of osteoporo-

sis. Physical examination should assess patient height in comparison to maximum height, kyphosis, balance, mobility, overall frailty, as well as evidence of causes of secondary osteoporosis. These include testicular atrophy, signs of hyperthyroidism, and evidence of chronic obstructive pulmonary disease. Men for whom bisphosphonate therapy is considered should have an examination of the teeth.

The introduction of dual-energy X-ray absorptiometry for the measurement of bone density has stimulated interest in the diagnosis of osteoporosis before fractures occur. The World Health Organization (WHO) has defined osteoporosis as a BMD 2.5 standard deviations or more below the mean value for young adults (T score equal or less than −2.5), but this has been established only for women. Studies show a similar relationship between absolute bone density measurements and the risk of fracture in both sexes [174]. Furthermore, work from the USA demonstrated that the prevalence of a T-score less than −2.5 at the hip, spine, or forearm in men over the age of 50 year is broadly similar to the lifetime risk of fractures at these sites [175]. This suggests that the WHO criteria may be applicable to the diagnosis of osteoporosis in men and women.

Recent epidemiologic data suggest that for any given absolute bone mineral density value at the spine or hip, the risk of fracture is similar among men and women of the same age. Nevertheless, the average bone mineral density in men who fracture a hip is higher than in women, suggesting that other factors (bone microarchitecture or trauma) may contribute to the risk of fracture more in men than in women. For diagnostic purposes, this discrepancy is addressed by use of a sex-specific T-score, but this practice remains controversial [176].

Using male-specific cutoffs for hip bone mineral density, the National Health and Nutrition Examination Survey III study showed that 6% of US men who were 50 years of age or older had osteoporosis and 47% had osteopenia, as compared to corresponding prevalence in women of 18% and 50%, respectively. If female reference ranges were used in men, the prevalence of osteoporosis and osteopenia would be reduced by two thirds.

Bone densitometry is recommended in men 70 years of age or older—or earlier in men with major risk factors for osteoporosis. Measurements of bone mineral density at the femoral neck are preferable to spinal measurements. Patients should be assessed routinely for risk factors for osteoporosis and for clinical signs of secondary causes.

FRAX®, the WHO fracture risk assessment tool, is used to predict the absolute ten-year fracture risk with or without BMD [177]. It includes key risk factors for osteoporosis such as:

- A prior fragility fracture.
- Parental history of hip fracture.
- Current tobacco smoking.
- Long-term use of oral glucocorticoids.
- Rheumatoid arthritis.
- Other causes of secondary osteoporosis.
- Daily alcohol consumption of three or more units.

Secondary causes of osteoporosis should be sought in men presenting with fragility fractures and/or low BMD by careful history taking, physical examination, and appropriate investigation. Investigations should include full blood count, erythrocyte sedimentation rate, biochemical profile, thyroid function tests, serum testosterone, sex hormone-binding globulin, and gonadotrophins, together with serum and urine electrophoresis in men with vertebral fractures [7]. Prostate-specific antigen should also be measured in men with vertebral fractures and symptoms of prostatism or evidence of sclerosis on X-rays. In elderly men with osteoporosis, serum 25-hydroxyvitamin D, and intact parathyroid hormone measurements may exclude vitamin D insufficiency and secondary hyperparathyroidism, but these are probably unnecessary if calcium and vitamin D supplementation is planned.

Clinical Approach

Men with osteoporosis usually present with low-trauma fractures or radiographic osteopenia discovered incidentally during evaluation for

musculoskeletal pain (e.g., back pain). Osteoporosis should be suspected in men with diseases or treatments known to be associated with bone loss such as hypogonadism, inflammatory bowel disease, or glucocorticoid therapy. The same disorders that cause osteoporosis in women can cause osteoporosis in men, including endocrine diseases, gastrointestinal disorders, connective tissue diseases, drugs, and hematologic conditions. Most osteoporotic men have secondary causes of bone loss, especially alcohol abuse, excess glucocorticoid therapy and hypogonadism [178]. One of the most important causes of severe hypogonadism is androgen deprivation therapy for prostate cancer. Those with idiopathic disease can present at any age but are most dramatic in younger men.

Male patients should be screened for risk factors for osteoporosis. The clinical approach to the diagnosis of male osteoporosis is as follows [179]:

- Screen male patients routinely for risk factors.
- Look for clinical signs of secondary causes.
- Perform a FRAX® calculation.
- Perform a BMD test if the male patient is more than 70 years old, or younger with major risk factors.

Risk factor for osteoporosis in men:

- Past fracture at the of 50 years or older.
- Family history of minimal trauma fracture.
- Physical inactivity.
- High risk of falls, recurrent falls.
- Use of sedatives.
- Low body mass index.
- Smoking.
- Excessive alcohol consumption.
- Taking one of the osteoporosis induced medications.
- Has one of the secondary causes of osteoporosis in men.

Advised Lat Tests Baseline osteoporosis blood profile include measuring serum calcium, phosphate, creatinine (with estimated glomerular filtration rate), alkaline phosphatase, liver function, 25-hydroxyvitamin D [25(OH)D], total testosterone, complete blood count, and 24-h urinary calcium (creatinine and sodium) excretion, in men being evaluated for osteoporosis or considered for pharmacological treatment with bone-active agents.

If history or physical examination suggests a specific cause of osteoporosis, further testing should be done. Depending on the findings of the history and physical examination, such testing may include (but is not limited to) calculated free or bioavailable testosterone (using measurements of SHBG), serum protein electrophoresis with free κ and λ light chains and/or urine protein electrophoresis, tissue transglutaminase antibodies (for celiac disease), thyroid function tests, and parathyroid hormone levels.

In men with low bone mass (osteopenia) or osteoporosis who might have previously undiagnosed vertebral fractures, vertebral fracture assessment (VFA) is recommended, using DXA equipment. If vertebral fracture assessment (VFA) is not available or is technically limited, lateral spine radiographs should be considered.

DXA Scan Interpretation

Interpretation of BMD measures in men has been controversial. Data suggesting that the risk of fracture is similar in men and women at the same absolute level of BMD has led some to recommend that the definition of osteoporosis based on T-scores be the same for both sexes [180]. However, this approach results in fewer men over age 50 being identified as at risk. The ISCD Position Development Conference held in July 2003 reviewed this controversy and recommends using a combination of risk factors and T-scores [181]. However, the 2019 ISCD Official Positions on adult osteoporosis reported that in men age 50 and older, T-scores should be used and osteoporosis diagnosed if the T-score is −2.5 or below the young normal mean for men. Below age 50 years old, T-scores may be used and osteoporosis diagnosed if both the T-score is

equal to or less than −2.5 and other risk factors for fracture are identified. Men at any age with secondary causes of low BMD may be diagnosed clinically with osteoporosis supported by findings of low BMD. The diagnosis of osteoporosis in men under age 50 years should not be made on the basis of densitometric criteria alone. The diagnosis in men under age 50 must be made on clinical grounds. Longitudinal studies are needed to better define the BMD-fracture risk relationship in men [182].

When spine BMD is measured by dual-energy X-ray absorptiometry (DXA) in the posterior-anterior projection, it often appears to increase in older men [183–186] /31,34,35], likely due to degenerative changes in the posterior spinous elements (Fig. 5.4) [185] /34]. Thus, posterior-anterior DXA should be interpreted cautiously when assessing bone density of the spine in older men.

Laboratory Tests

Further testing is strongly indicated to rule out secondary causes in men whose z score is below −2.0 (2 SD below the age-specific mean) on bone densitometry. Routine tests include measurements of serum calcium and creatinine levels, liver function tests, measurement of the thyrotropin level, and a complete blood count. If clinically indicated, serum protein electrophoresis and tests for urinary Bence Jones protein (to check for monoclonal gammopathy), antitissue transglutaminase antibodies (to check for celiac disease), 24-hour urinary cortisol or calcium, and human immunodeficiency virus antibodies should be performed.

Since hypogonadism is often difficult to detect; on the basis of the patient's history and the physical examination alone, measurement of the total testosterone level is recommended in all men with osteoporosis. Sex hormone-binding globulin levels may provide additional information in some cases (e.g., in men with insulin resistance or obesity, in whom low levels of sex hormone-binding globulin may complicate interpretation of total testosterone levels).

Serum levels of 25-hydroxyvitamin D should also be measured. Levels below 30 ng per millilitre (75 nmol per liter) should be treated. There are limited data relating markers of bone turnover to the risk of fracture among men [187]. These markers show high biologic variability, and their measurement has not been shown to improve outcomes in men with osteoporosis, so their routine use in practice cannot currently be recommended. However, they may be useful for men in whom no apparent cause of osteoporosis can be detected on other tests and for men with very low bone mineral density to detect low levels of bone formation [188].

Vertebral Fracture Assessment

A history of a minimal trauma fracture after the age of 50 years is the strongest clinical risk factor for fracture [189]. Recognition of fractures is important for risk stratification, particularly in men with osteopenia. Among minimal trauma fractures, vertebral fractures are most common and are often clinically silent. Spinal radiography is useful for diagnosis, but it involves a relatively high dose of radiation [190]. Assessment of vertebral fracture is also possible with dual-energy X-ray absorptiometry [191], with high sensitivity and specificity for moderate fractures (height loss, 30 to 40%) and severe fractures (height loss, more than 40%), but spinal radiographs remain the gold standard [192].

The finding of mild vertebral deformities with the use of dual-energy X-ray absorptiometry is less specific and should be differentiated from non-osteoporotic short vertebral height (height loss, 15% or less, without central endplate compression), a common finding on spinal radiographs [193].

Figure 5.6 shows a clinical approach to men clinical approach to men at risk of having osteoporosis in standard clinical practice.

In conclusion, osteoporosis and consequent fracture(s) are not limited to postmenopausal women. There is increasing attention being paid to osteoporosis in men, particularly older adults. Men suffer osteoporotic fractures about 10 years

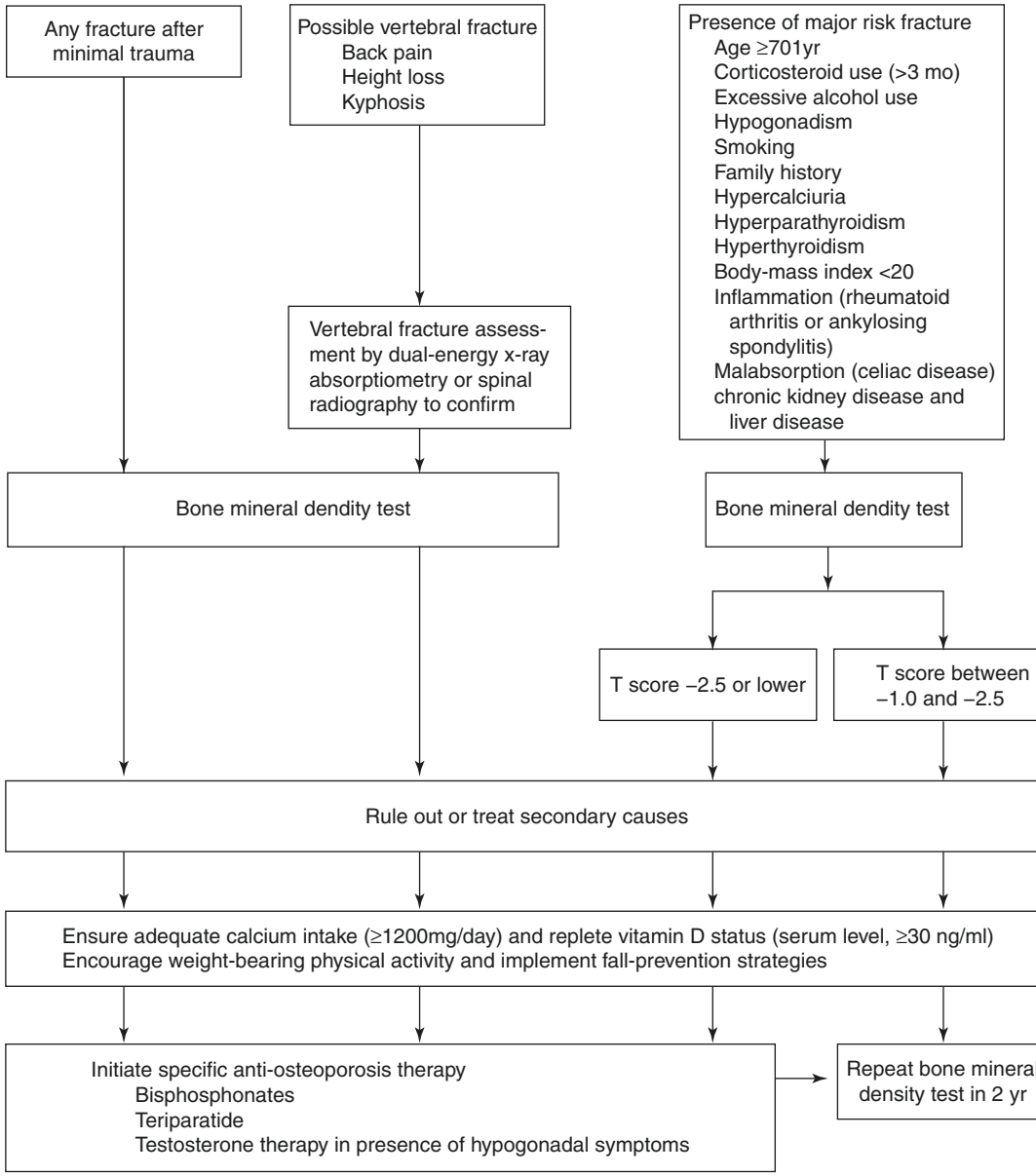

Fig. 5.6 Clinical approach to men at risk of having osteoporosis in standard clinical practice. Excessive alcohol use is defined as 18 oz. (533 ml) or more of full-strength beer, 7 oz. (207 ml) or more of wine, or 2 oz. (59 ml) or more of spirits per day

later in life than women. However, as life expectancy for men is getting longer, this makes men live long enough to fracture. This finding is of utmost importance, as the fracture consequences are greater in men than in women, with men having about twice the 1-year mortality rate after hip fracture, compared to women. Men at high risk for fracture include those men who have already had a fragility fracture, men on oral glucocorticoids, or those men being treated for prostate cancer with androgen depletion therapy. Beyond these high risk men, there are many other risk

factors and secondary causes of osteoporosis in men. Evaluation includes careful history and physical examination to reveal potential secondary causes, including many medications, a short list of laboratory tests and bone mineral density testing by dual energy X-ray absorptiometry (DXA) of spine and hip. International organizations have advocated a single normative database for interpreting DXA testing in men and women. There are several choices of therapy for osteoporosis in men, with most fracture reduction estimation based on studies in women.

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