Bone Health in Women

4

Yasser El Miedany

Introduction

Bone is a living, dynamic tissue that undergoes constant remodeling throughout life. This is necessary to allow the skeleton to increase in size during growth, respond to the physical stresses placed on it, and repair structural damage due to structural fatigue or fracture. This process requires a range of proteins and minerals, which are absorbed from the bloodstream [1]. In childhood, bones grow and repair very quickly, but this process slows down as you get older. Bones stop growing in length between the ages of 16 and 18 but continue to increase in density until late 20s. From about the age of 35, gradually lose bone density. This is a normal part of aging, but for some people it can lead to osteoporosis and osteoporosis is a condition that affects the bones, causing them to become weak and fragile and more likely to break [2]. Before a woman reaches 30 years of age her body gains more bone than it loses. Around age 30, this process balances out. However, for most women, bone mass remains stable until menopause, when the loss of estrogen in conjunction with aging is associated with a decline in bone mineral content. The onset of menopause around 50 years of age may speed up the rate of bone loss. If bone loss becomes severe, a woman may develop osteoporosis [3]. Family history, gender, and race are responsible for the majority of peak bone mass; however, diet and exercise behaviors are responsible for up to 25%.

Risk for osteoporosis is greater for women than men. Established risk factors for women include increased age, Caucasian or Asian ethnicity, postmenopausal status, late menarche or early menopause, low peak bone mass, family history of osteoporosis or fracture, low dietary intake of calcium and vitamin D, lack of physical activity, smoking, excess alcohol consumption, and long-term use of certain medications, such as steroids, anticonvulsants, immunosuppresants, and heparin [4, 5]. Female bone health can be stratified into phases outlined by the woman's age. In postmenopausal women, osteoporosis is usually the result of accelerated bone turnover due to estrogen deficiency, whereas in aging women and men, vitamin D insufficiency and secondary hyperparathyroidism may further contribute to bone loss. In these subjects, osteoporosis is diagnosed when their hip or spine bone mineral density (BMD) is two and a half standard deviations (SD) or more lower than the young adult mean (T-score ≤ -2.5) [6, 7]. Together with prevalent fragility fractures (typically spine or hip), T-scores equal to or below −2.5 are considered as clear indications for osteoporosis therapy, although age and clinical risk factors that modulate fracture probability may also have to be taken into account [9]. In contrast, low bone mass

Y. El Miedany (✉)
Canterbury Christ Church University,
Canterbury, Kent, UK

Y. El Miedany (ed.), *New Horizons in Osteoporosis Management*,
https://doi.org/10.1007/978-3-030-87950-1_4

in children and adolescents has been defined as an areal bone mineral density (aBMD) more than 2 SD below the age-adjusted mean value (Z-score <−2SD) [8], and it has been recommended that bone fragility should not be diagnosed on the basis of low bone mass alone but requires the presence of fractures due to low trauma [10]. On the other hand, in comparison to childhood and postmenopausal/ elderly subjects, diagnosis and treatment of osteoporosis in young adults, i.e., between 20 and 50 years of age, remain poorly defined. The true difficulty resides in differentiating between those young healthy individuals whose apparently low aBMD reflects low peak bone mass in relation to their body size, pubertal timing, genetic background, and environment during growth [11–13], which does not necessarily represent a pathological condition, and those who may truly have osteoporosis with bone fragility at a young age, resulting from altered bone modeling and/or remodeling during growth and/or thereafter. The latter situation is most commonly associated with a chronic disorder and may also occur as a genetic or idiopathic condition. Distinguishing between these two situations can be difficult base up to 30% of young women and 50% of young men have had fractures during childhood and adolescence, usually traumatic but not uncommonly multiple [14–17]. These fractures are associated with decreased bone mass acquisition and lower peak bone mass in otherwise healthy individuals [16], i.e., without an underlying pathophysiological mechanism. It would, therefore, be inappropriate to investigate for osteoporosis, e.g., perform a DXA examination, and to search for secondary causes of osteoporosis in most young people with prevalent fractures, unless the circumstances (low trauma), frequency (over two fractures), and/or site of fractures (e.g., vertebrae) appear unusual.

This chapter will discuss the physiological and pathological changes in young adult women, pregnancy and lactation, followed by changes in both the pre-menopausal and post-menopausal period and lastly elderly women. The chapter will then discuss the diagnostic criteria for osteoporosis in women. It will also propose a clinical approach to the patients' assessment in standard practice.

Young and Adulthood

Between 8 and 18 years of age, bone mineral content (BMC) more than doubles, whereas the true volumetric bone mineral density (vBMD) barely changes [18]. This bone mass accumulation pertains primarily to an increase in bone size (diameter) and cortical thickness by periosteal apposition (modeling) and, to a lesser extent, to trabecular bone formation and thickening [19]. Meanwhile, endosteal surfaces undergo both modeling and remodeling in order to achieve, approximately by the age of 20, bone mass, geometry, and microstructure of the adult skeleton [20]. In turn, peak bone mass is a major determinant of bone strength and fragility throughout life, hence, the increase in bone diameter and mass in growing females, which occurs at approximately the same rate as in males. However, this increase lasts longer in men leading to a 10–15% greater peak bone mass on average, consequently, it plays an important role in explaining the lesser and later propensity to fractures in aging men compared to women. Nevertheless, as a result of continuous bone remodeling, loss of cortical and trabecular bone starts soon after peak bone mass is achieved in both genders, albeit in variable proportions in weight-bearing and non-weight-bearing bones and accelerates in women after menopause and in aging men [21–24].

Heredity, that is, the additive effects of genes and their polymorphisms, accounts for 50 to 80% of the variation in bone mass and structure among individuals [25] and likely contributes to some of the phenotypic differences between the male and female skeleton [26]. Yet gene expression depends on both the internal and external milieu, i.e., on hormone levels, particularly gonadal steroids (puberty) and the growth hormone (GH)–IGF-1 axis; nutrition, such as calcium and protein intake; physical activity, particularly load-bearing exercise; lifestyle; etc. [19] (Fig. 4.1 shows developmental risk factors for osteoporosis). Therefore, any disorder that might occur during growth that alters one or more of these parameters will exert a negative influence on bone modelling and remodelling; consequently, will affect bone mass acquisition

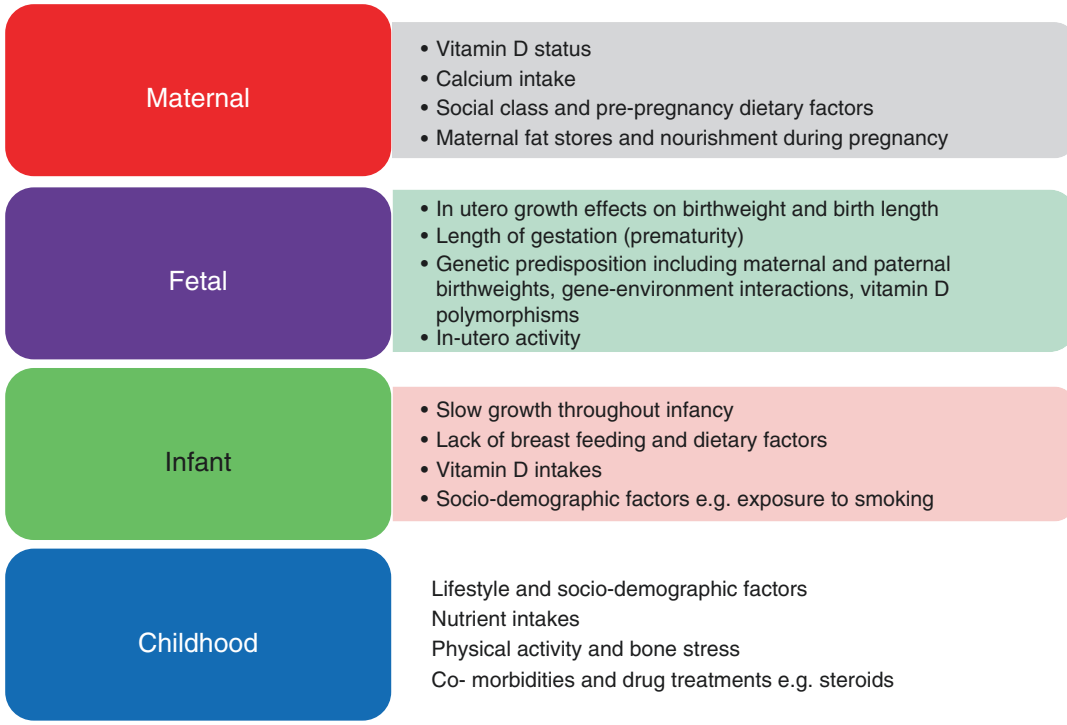

Fig. 4.1 Developmental risk factors for osteoporosis

and its distribution in the cortical and/or trabecular compartment; and could thereby cause bone fragility not only during growth but later on in young adults. Similarly, endocrine, nutritional, and other disturbances appearing during early adulthood will precipitate bone loss at a younger age. A good example would be inflammatory bowel diseases (IBD), particularly Crohn's disease, which impair bone mass accrual and/or accelerate bone loss because of malabsorption and poor nutrient intake; low levels of physical activity; delayed puberty or secondary amenorrhea, in addition to systemic inflammation, and, in many cases, effects of corticosteroid treatment [27]. Another example of the complex pathophysiology of osteoporosis in the young is illustrated by thalassemia major, which causes hormonal deficiencies (GH–IGF-1 and gonadal steroids), expands bone marrow at the expense of bone tissue, interferes with mineralization due to iron overload, and, additionally, defers oxamine treatment that inhibits osteoblastic function [28]. Among numerous pharmacological agents implicated in bone loss (Fig. 4.2), depot progesterone acetate (Depo-Provera), used as a contraceptive agent, has raised huge concerns [29, 30].

Pregnancy and Lactation

A moderate increase of bone turnover (Fig. 4.3) has been reported during pregnancy [31], although it is still uncertain whether significant changes of bone mass occur. A small decrease in aBMD has been observed at the lumbar spine, but in long bones, this might be compensated by endosteal and periosteal appositions [32]. While during pregnancy the mother's intestinal calcium absorption is increased; it returns to normal values during lactation [33], putting further pressure on the skeleton to compensate for the need of calcium associated with breastfeeding. The body adapts by increasing bone resorption and reducing renal calcium excretion, influenced by increase in parathyroid hormone production and hypo-estrogenic state secondary to high prolactin

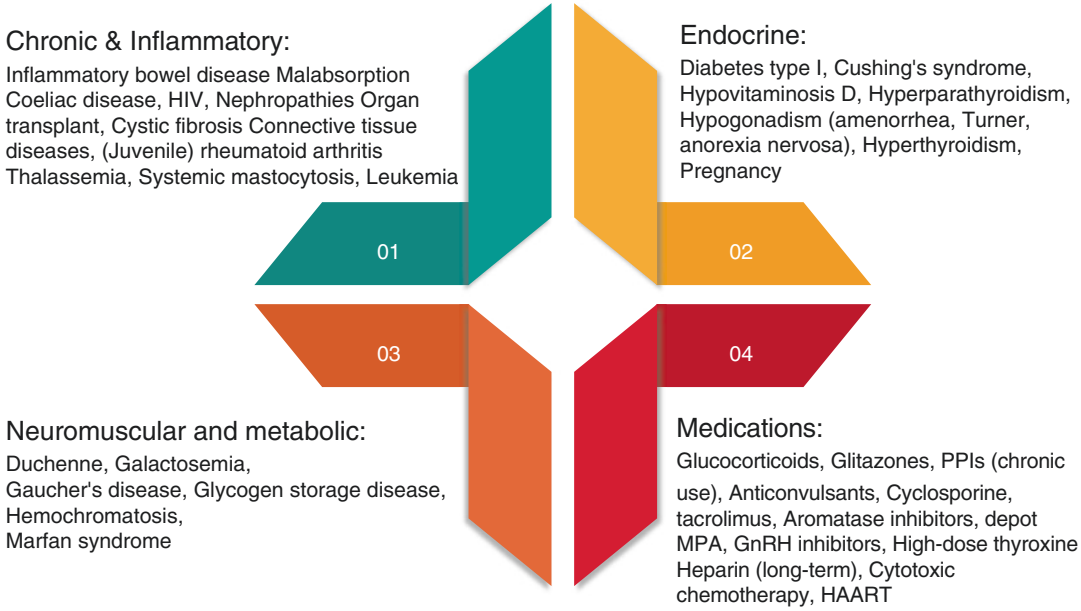

Fig. 4.2 Causes of secondary osteoporosis in the young. (*HIV* human immunodeficiency virus, *MPA* medroxyprogesterone acetate (used as contraceptive), *HAART* highly active antiretroviral therapy, *PPIs* proton pump inhibitors)

levels [32, 34, 35]. The decrease in bone mass, observed mainly in the trabecular compartments of bones, is generally restored 6 to 12 months after weaning [36].

Pregnancy-associated osteoporosis is a rare condition, which can present in the form of spinal osteoporosis or transient osteoporosis of the hip, as well as associated with prolonged heparin use [37]. Transient osteoporosis of the hip is associated with uni- or bilateral hip pain and may be complicated with a fracture, sometimes spontaneous [38]. Post-pregnancy osteoporosis can lead to vertebral fractures, height loss, and severe back pain [39], as well as clinical fractures at other sites. Pre-existing low BMD and high bone turnover during pregnancy and lactation may both play a role [34]. In women of reproductive age with established osteoporosis, it could, therefore, be recommended to avoid breastfeeding. Randomized doubleblind placebo-controlled study on postpartum healthy women revealed that calcium supplementation did not prevent bone loss during lactation and only slightly enhanced gain in bone density after weaning [40].

Premenopausal Women

Osteoporosis is less common in premenopausal women than in postmenopausal women. However, both fractures and low bone mineral density do occur in the premenopausal years, and young women with these conditions require specialized clinical considerations. Osteoporosis in premenopausal women results from either a low peak bone mass, increased bone loss prior to menopause, or both [41]. As noted earlier, peak bone mass is reached by 30 years of age with 90% of the development completed by 18 years of age. For most women, bone mass remains stable until menopause, when the loss of estrogen in conjunction with aging is associated with a decline in bone mineral density. Peak bone mass variations are genetic in 60–70% of cases [42]. The loss of bone results from an imbalance in bone formation by osteoblasts and bone resorption by osteoclasts. Most treatments for osteoporosis aim to adjust this imbalance [43]. In the case of premenopausal osteoporosis, secondary causes are responsible for at least half of cases [41]. Secondary causes are listed in Table 4.1.

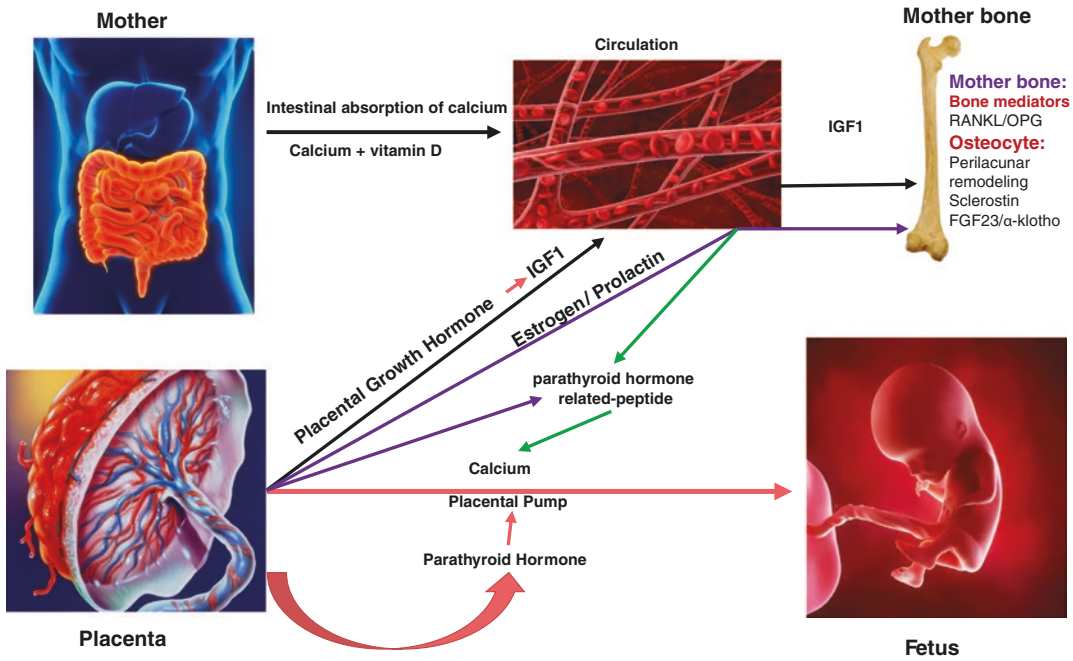

Fig. 4.3 Main changes in the mother and the feto-placental unit to facilitate adequate transfer of calcium to the fetal skeleton. The mother is the main source of calcium transferred to the fetus. Three main domains, mother/ mother bones, placenta, and fetus. The changes in the maternal domain include an increased intestinal absorption of calcium. Further calcium supply is provided via maternal parathyroid hormone related-peptide and by local changes within maternal bone, where receptor activator of nuclear factor kappa B ligand/osteoprotegerin (RANKL/OPG) and osteocytes may participate. The calcium drainage is partly counterbalanced by an increased anabolic process, where IGF1, stimulated by placental growth hormone may be involved. Other potential factors are prolactin and estrogens. Despite the reactive bone formation process, the bone balance seems negative for the mother. The placental calcium gradient is sustained by the placental pump, where fetal parathyroid hormone and parathyroid hormone related-peptide are determinant

Earlier study (the Michigan Bone Health Study), which included over 600 premenopausal women followed for 6 years, revealed varied changes in lumbar spine BMD but a 1.6% decrease in femoral neck BMD starting in a woman's mid 20s [44]. Risk factors for low BMD in premenopausal women include low body weight, amenorrhea, lack of physical activity, smoking, low dietary calcium or vitamin D, personal or family history of fracture, pregnancy, and Caucasian or Asian race [42]. Minimal bone loss is noted during pregnancy and breastfeeding; however, this loss is usually corrected shortly after pregnancy and breastfeeding are complete [45].

Healthy premenopausal women experience a 0.25–1% loss in BMD annually after reaching peak bone mass (commonly at the femoral neck); however, no link has been established between this gradual loss in BMD and fracture risk in healthy women. Low Z-scores (2.5 standard deviations below other age matched females) are seen in 0.5% of premenopausal women [42]. Another study [41] revealed that in Spanish women 20–44 years of age, 0.34% will have osteoporosis at the lumbar spine, and 0.17% will have osteoporosis at the femoral neck based on BMD alone. Overall, 50–90% of premenopausal women have a secondary cause for osteoporosis (e.g., eating disorders or glucocorticoid use, among others), whereas the remaining women were diagnosed with idiopathic osteoporosis [46]. Fracture risk in premenopausal women with osteoporosis remains low due to the small baseline fracture risk in younger women. The incidence of fractures in females under the age of 35 years is more difficult to detect due to the low

Table 4.1 Secondary causes of osteoporosis in premenopausal women

Hormonal
Any childhood disease that has affected puberty and/or skeletal development
Premenopausal amenorrhea (e.g., pituitary diseases, medications, athletic amenorrhea)
Premature menopause (<40 years)
Endocrine
Cushing syndrome
Hypogonadism
Hypopituitarism
Hyperthyroidism
Primary hyperparathyroidism
Diabetes (types 1)
Hyperprolactinemia
Chronic and inflammatory conditions
Vitamin D, calcium,
Inflammatory bowel disease
Cystic fibrosis
Rheumatoid arthritis, SLE, other inflammatory conditions
Malnutrition/malabsorption
Anorexia nervosa
Intestinal bypass/gastrointestinal surgery
Celiac disease
Malabsorption
Primary biliary cirrhosis
Connective tissue diseases
Osteogenesis imperfecta
Marfan syndrome
Ehlers Danlos syndrome
Turner's and Klinefelter's syndromes
Systemic and metabolic
Renal disease
Liver disease
Hypercalciuria
Other rare diseases, including mastocytosis, Gaucher disease, hemochromatosis, hypophosphatasia
Lifestyle changes
High salt intake
Smoking (active/passive)
Alcohol abuse
Immobilization
Low calcium intake
Excess vitamin A
Organ transplantation
Solid organ and bone marrow transplants
Medications (some have not been studied in premenopausal populations)
Glucocorticoids
Immunosuppressants (e.g., cyclosporine)
Antiepileptic drugs (particularly cytochrome P450 inducers such as phenytoin, carbamazepine)
Cancer chemotherapy/aromatase inhibitors
Gonadotropin-releasing hormone (GnRH) agonists (when used to suppress ovulation)
Depo medroxyprogesterone acetate (DepoProvera)
Heparin
Other medications with probable relationships to osteoporosis: Proton pump inhibitors, selective serotonin reuptake inhibitors, low molecular weight heparin

incidence of three fractures per 100,000 patient-years but is noted to increase to 21 per 100,000 patient-years in women aged 35–44 years [41]. Premenopausal fractures are associated with a 1.5- to three-fold increase in the risk of postmenopausal fractures [42]. Fracture risk is doubled or tripled once a loss of 10% in BMD has occurred; however, treatments resulting in a 5% increase in BMD may decrease fracture risk [47].

A third study [48] assessed premenopausal women referred for a bone disease at a tertiary medical center and looked for secondary versus idiopathic osteoporosis. A retrospective review of all premenopausal women referred for fracture or low bone mass over 1 year (n = 61) was conducted, and 39% of the total cohort of patients were found to have idiopathic osteoporosis, while 49% of the 29 women who had a history of low trauma fracture had idiopathic osteoporosis. This is consistent with other measures in premenopausal women. Low trauma fracture was defined as that occurring due to a fall from standing height or less, with the exception of digit or skull fracture. Over half of the women (57%) reported a family history of osteoporosis. Secondary osteoporosis was due to amenorrhea in 34%, anorexia nervosa in 16%, glucocorticoid use in 13%,and celiac disease in 10%. Premenopausal women with secondary osteoporosis had lower BMD at the spine (Z-score: −2.39 vs −1.58; p = 0.001) and hip than those with idiopathic osteoporosis, indicating a greater need for treatment in those women with secondary causes. Of the women referred due to a fracture, 28% did not have a low BMD. Bisphosphonates were used by 47% of women with low BMD, but no history of fracture and by 50% of women with idiopathic

osteoporosis, which may indicate overuse of osteoporosis treatments in this population. Therefore, further insight to clarify the role of osteoporosis treatments in younger, premenopausal women is needed [49].

Postmenopausal Osteoporosis (Type I Osteoporosis)

There is a direct relationship between the lack of estrogen during menopause and the development of osteoporosis. Initially, 2 basic types of osteoporosis have been identified. Type I osteoporosis uses the postmenopausal woman as the prototype (although men also rarely may suffer from the abrupt loss of sex steroids that impact greatly on the retention of bone tissue), and Type II osteoporosis, discussed in the next section, is age-related and typically occurs in both genders in the later decades of life (the causation of Type II is poorly understood, but it accelerates when the musculoskeletal system functions decline). At the bone level, type I and II osteoporosis can also be differentiated. Whereas the accelerated cancellous (trabecular) bone loss caused by estrogen deficiency at menopause (type I) results predominantly from trabecular perforation and loss of connectivity, the later phase of slower bone loss (type II) that occurs in both older women and men primarily affects cortical sites and is associated with a decrease in osteoblast number and bone formation rate (Fig. 4.4). Additionally, bone loss in older men is associated with trabecular thinning rather than perforation [50].

Estrogen deficiency causes loss of bone associated with an increase in the bone remodeling rate, increased osteoclast and osteoblast numbers, and increased resorption and formation, albeit unbalanced. Conversely, estrogens decrease bone resorption, restrain the rate of bone remodeling, and help to maintain a focal balance between bone formation and resorption. These effects are the result of hormonal influences on the birth rate of osteoclast and osteoblast progenitors in the bone marrow, as well as pro-apoptotic effects on osteoclasts and anti-apoptotic effects on mature osteoblasts and osteocytes [50–52]. However, estrogen deficiency can be also closely linked or intercorrelated to the aging process in postmenopausal women. While the onset of cortical bone loss in women is closely tied to estrogen deficiency, attesting to the adverse effect of estrogen deficiency on skeletal homeostasis and its contribution to the age-associated bone loss [53], a significant proportion of trabecular bone loss throughout life is age-related and estrogen-independent [52, 53]. The age-dependent loss of trabecular bone in the spine accelerates after the menopause, as does the rate of fractures at the wrist, spine, and hip. Between menopause and the age of 75 years, women lose approximately 22 percent of their total body bone mineral. It has been estimated that of this, 13.3 percent is due to aging and 7.75 percent is due to estrogen deprivation. In the femoral neck, 14 percent of the loss is "age related" and only 5.3 percent because of estrogen deprivation [54].

The accelerated phase of cancellous (trabecular) bone loss caused by menopause results predominantly from trabecular perforation and loss of connectivity. This phase is followed few years later by a phase of slower bone loss that primarily affects cortical sites. The slower phase occurs in both women and men and is associated with a decrease in osteoblast number and bone formation rate and reduced number of trabeculae. In line with this, decreased wall width, the hallmark of decreased osteoblast work output, is the most consistent histological finding in older women and men with osteoporosis [55–57].

Estrogen deficiency may also contribute to the development of osteoporosis in men [58, 59]. Estrogens derived from androgen aromatization and acting via the estrogen receptor are important for skeletal homeostasis in men, as evidenced by bone abnormalities in men with ER or aromatase mutations, as well as results of short-term clinical experimentation with administration of aromatase inhibitors [60]. In addition, several clinical studies show correlation between a decrease in bioavailable estradiol, but not testosterone, and bone mass in older men [51]. Studies of mouse models with targeted deletion of the ER and the androgen receptor in specific cell types have elucidated that the antiresorptive effects of estrogens

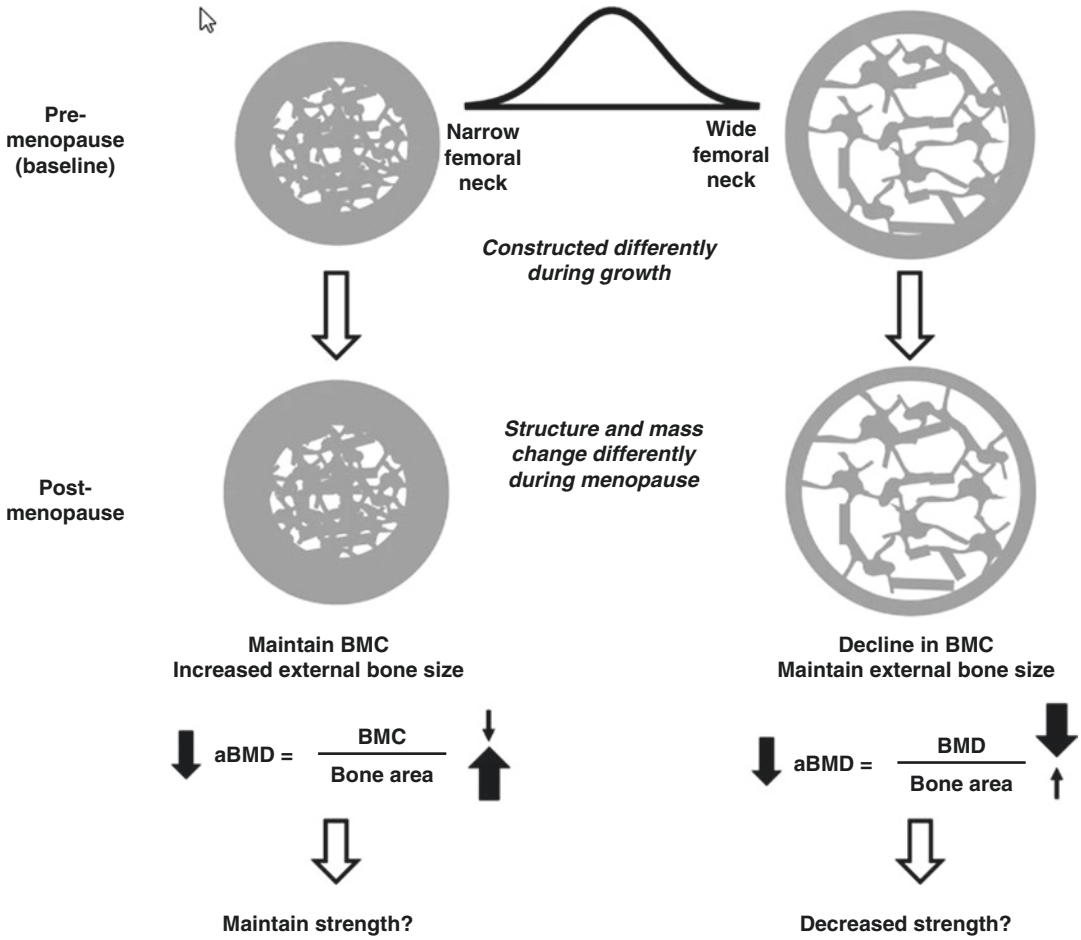

Fig. 4.4 Areal BMD as determined by DXA declines with aging for different reasons. With aging, women with smaller femoral necks tend to increase bone area through an increase in cortical thickness by an increase in periosteal and endosteal bone formation. Since BMD may only decrease slightly but bone area increases more, the result is lower areal BMD as measured by DXA despite likely having little change in bone strength. In the case of women with larger femoral necks, the endosteal cortex undergoes excessive resorption without periosteal expansion resulting in a thinner cortex. The result is a lower BMC without significant change in bone area. The DXA areal BMD decreases and may result in a bone with less strength. (Quoted under open access scheme from Choksi, P., Jepsen, K.J. & Clines, G.A. The challenges of diagnosing osteoporosis and the limitations of currently available tools. Clin Diabetes Endocrinol 2018; 4: 12)

or androgens in the cancellous versus the cortical bone compartment are mediated by different cell types [60–62]. The protective effects of estrogens on the cancellous bone compartment are mediated via signaling through the estrogen receptor-alpha expressed in cells of the osteoclast lineage [63, 64]. On the other hand, estrogen receptor-alpha signaling in cells of the osteoblast lineage is responsible for the protective effect of estrogens against endocortical resorption in females, but it plays no role in their effects on cancellous bone resorption. Whether estrogen receptor-alpha also plays a role on cancellous or cortical bone formation remains controversial [62, 65–68].

Osteoporosis is the most prevalent metabolic bone disease. Approximately 70% of people with osteoporosis are women, hence the importance of postmenopausal osteoporosis. Half of postmenopausal women over 50 will experience an

osteoporotic fracture at some point [45]. The most common fracture locations are the vertebrae (spine), proximal femur (hip), and distal radius (wrist). Most fractures cause pain, many produce lingering disability, and, in the case of hip fracture, it can result in death. Furthermore, osteoporosis exacts a psychological toll on individuals and their families, especially when the discomforts and limitations of fracture lead to depression and loss of independence. On another front, postmenopausal osteoporosis raises a major economic concern, bearing in mind osteoporosis-linked costs attained through acute care admissions, rehabilitation, long-term care, drug costs, and productivity losses, among others [69].

Osteoporosis in Elderly Females

In view of the progressive aging of most of the world's populations, it can be expected that the incidence of age-related conditions will grow and therefore the treatment and management of these individuals will gain increasing priority. Osteoporosis and frailty, which together greatly increase the risk of fracture, are of particular concern. Hip fractures are the most serious osteoporotic fractures, with high risk of mortality. A large proportion of patients (more than 50%) admitted to hospital with hip fracture are over 80 years old [70]. The survivors have a high risk of sustaining another major fracture and face deterioration in their quality of life and risk of dependency. Furthermore, Patients over the age of 80 years are often denied having bone mineral density assessment or osteoporotic treatments because it might be felt that the treatments do not work or they are "too late to treat" [71].

Old age and estrogen deficiency are the two most critical factors for the development of osteoporosis in both women and men. However, it is unknown whether the cellular and molecular events responsible for the imbalance between resorption and formation in old age versus sex steroid deficiency are similar or distinct or whether and how much sex steroid deficiency contributes to the age-dependent involution of the skeleton. Because of the abrupt decline of ovarian function at menopause in women and a slower decline of both androgen and estrogen levels in men with advancing age, the two conditions inevitably overlap, making it impossible to dissect their independent contribution to the cumulative anatomic deficit. However, findings from the mouse model suggest that the adverse effects of old age on the skeleton are independent of estrogens and are due to molecular mechanisms that are distinct from those responsible for the effects of sex steroid deficiency [72–74]. Such bone-intrinsic molecular mechanisms likely include mitochondria dysfunction, oxidative stress, declining autophagy, DNA damage, osteoprogenitor and osteocyte senescence, senescence-associated secretory phenotype (SASP), and lipid peroxidation [75].

In both women and men, the balance between bone formation and resorption becomes progressively negative with advancing age (Fig. 4.3). Age-related bone loss begins immediately after peak bone mass for either sex, but most bone loss occurs after age 65 years. Men, however, are less likely to develop osteoporosis than women for two reasons. First, they gain more bone during puberty, and second, they lose less bone during aging because, unlike women, men do not experience an abrupt loss of estrogens. Older residents in long-term care have the greatest risk. Eighty-five percent of nursing home women over age 80 years have osteoporosis. Hip and nonvertebral fractures in older residents of nursing homes are 2.5 to 3.5 times more common than in the community [76].

Most fractures after age 65 years occur at predominantly cortical sites. High-resolution peripheral quantitative computed tomography (HRpQCT) of the radius and post-mortem femurs of women between ages 50 and 80 years have revealed that most bone loss in old age is the result of increased intracortical porosity (Fig. 4.4) [77]. Importantly, the age-dependent increase in cortical porosity is not captured by dual-energy x-ray absorptiometry (DXA) bone mineral density (BMD) [78].

Besides its effects on bone mass, aging increases the risk of fractures, independently of bone mass, as highlighted by evidence that for the

same BMD, a 20-year increase in age is accompanied by a fourfold increase in fracture risk (Fig. 4.4) [79]. Consistent with this, human cadaveric specimens demonstrate significant declines in whole bone strength with age, with younger specimens being three- to tenfold stronger than older specimens. Furthermore, population-based studies with 3D-QCT imaging have demonstrated significantly greater declines in vertebral compressive strength over life in women than men (−43 versus −31 percent). Declines in femoral strength in a sideways fall configuration are also significantly greater in women than men (−55 versus −39 percent) and exceed the declines in femoral BMD (−26 and − 21 percent for women and men, respectively). In addition, cortical porosity increases by 176 percent and 259 percent from 20 to 90 years of age (Fig. 4.5).

Muscle strength and power decline 10 to 20 percent per decade after age 50 years. These declines obviously impact the risk of falls, and perhaps the severity of falls, but may also influence loads applied to vertebral bodies during daily activities. The influence of muscle strength on vertebral body compressive forces depends on the activity being performed. Vertebral compressive forces may remain unchanged, decrease, or greatly increase with reduced muscle strength.

The aging process is driven at the cellular level by random molecular damage that slowly accumulates with age. Although cells possess mechanisms to repair or remove damage, they are not 100% efficient and their efficiency declines with age. At the bone level, there are several bone-intrinsic molecular mechanisms which impact on bones in older adults. These include:

- *Oxidative stress* – Oxidative stress is a shared mechanism of the pathogenesis of several degenerative disorders associated with aging,

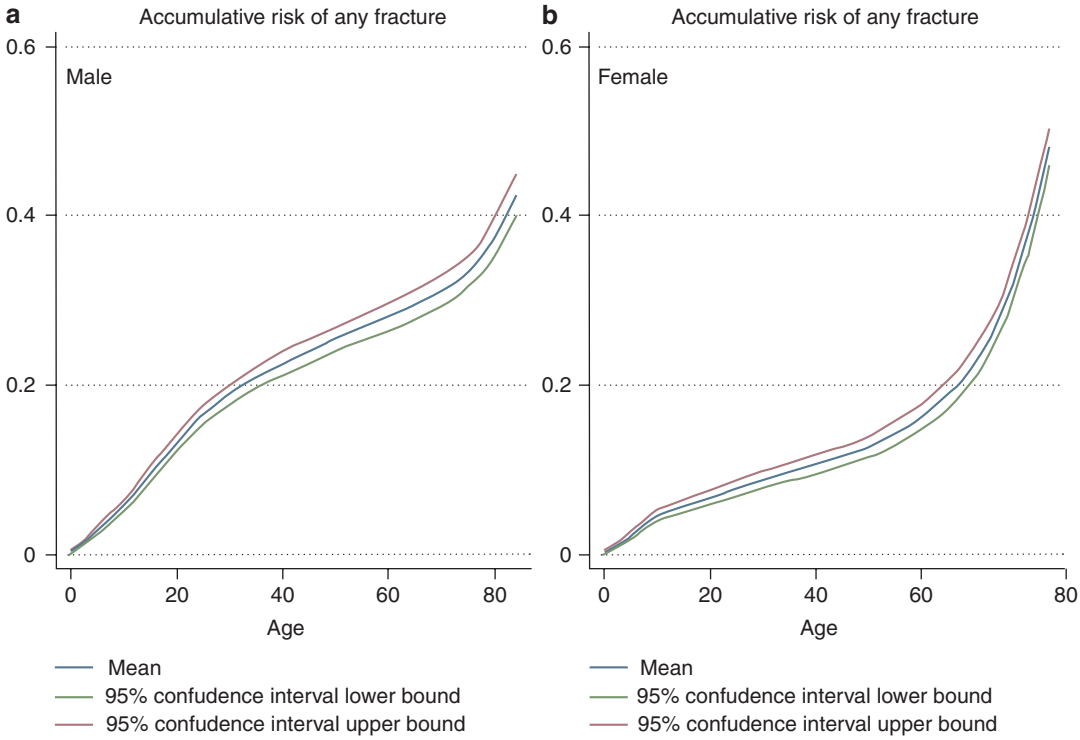

Fig. 4.5 Cumulative risk of having any fracture hospitalization since birth in both men and women. (Quoted under open access scheme under the Creative Commons Attribution License from Liang W and Chikritzhs T. The Effect of Age on Fracture Risk: A Population-Based Cohort Study. Journal of Aging Research. 2016, Article ID: 5071438 (https://doi.org/10.1155/2016/5071438))

including osteoporosis [80, 81]. An increase in reactive oxygen species (ROS) has been implicated in the decreased bone formation associated with advancing age, as well as the increased resorption associated with estrogen deficiency [81]. In line with this evidence, increased reactive oxygen species production in osteoblasts stimulates apoptosis and decreases bone formation. On the other hand, reactive oxygen species, and in particular, H_2O_2, is a critical requirement for receptor activator of nuclear factor kappa-B ligand (RANKL)-induced osteoclast generation, activation, and survival [82].

- *Osteoblast and osteocyte senescence* – Cellular senescence is a process in which cells stop dividing and undergo distinctive phenotypic alterations, including profound chromatin and secretome changes termed senescence-associated secretory phenotype (SASP) [83]. Nonproliferating, terminally differentiated cells also become senescent and exhibit the senescence-associated secretory phenotype (SASP). Cellular senescence is one of the hallmarks of aging in most, if not all, tissues [84]. Osteoblast progenitors as well as osteocytes from old mice exhibit typical features of cellular senescence [85–87]. Furthermore, cellular senescence of osteoprogenitors is associated with a decline in their number by more than 50 percent between 6 and 24 months of age in both female and male mice, as well as increased production of senescence-associated secretory phenotype (SASP)-associated pro-osteoclastogenic cytokines, such as tumor necrosis factor (TNF)-alpha, interleukin (IL)-1-alpha, matrix metalloproteinase 13 (MMP13), SDF1, and RANKL. Senescent osteocytes similarly exhibit senescence-associated secretory phenotype (SASP), including some of the same cytokines found in the osteoprogenitors. Prevention of apoptosis by deleting Bak and Bax, two genes essential for apoptosis, in osteoblasts and osteocytes greatly potentiates the effects of old age on cortical porosity [88]. Notably, attenuation of apoptosis stimulates cellular senescence [89, 90]. Increased production of senescence-associated secretory phenotype (SASP) cytokines by senescent, apoptotic, or dysfunctional osteocytes and probably their affected neighbors (paracrine senescence), stimulate osteoclastogenesis, matrix degradation, focal bone resorption, and cortical porosity.
- *Autophagy* – Autophagy is a major adaptive response to cellular starvation and an essential protein/organelle quality control. Declining autophagy with advancing age is a big component of the loss of proteostasis, another one of the hallmark mechanisms of aging. Attenuation of autophagy in osteocytes, by conditional deletion of the ATG7 gene, recapitulates most of the effects of old age in six-month-old mice, including cortical porosity. Along with several other lines of evidence [91–93], these findings support of the general idea that in line with the seminal role of osteocytes in the choreography of physiologic bone remodeling, in conditions of overwhelming stress, the physiological mechanisms of bone repair are exaggerated and become disease mechanisms [94].

Definition of Osteoporosis

In Young/Premenopausal Females In young age where the peak bone mass has not been achieved, the definition of osteoporosis based on T-score cannot be implemented. Hence, low bone mass in children and adolescents has been defined by a Z-score below −2. This definition could also be extended beyond 20 years of age in those with delayed puberty, as is often the case with chronic diseases from childhood [9, 10].

However, it has to be noted that by extension and considering that in young adults T- and Z-scores are virtually identical, the 2007 International Society for Clinical Densitometry Official Positions has suggested keeping the use of Z-scores to define “low bone mass” in young adult (premenopausal) women [95]. On the other hand, and for the sake of coherence with the WHO operational definition of osteoporosis, the

T-score-based definition of the disease for young adults is also kept, unless it appears that the young adult is still growing. Therefore, in young adults living with a chronic disorder known to affect the bone metabolism, a T-score below −2.5 at spine or hip should be considered as diagnostic of osteoporosis. On another front, it is important to note, that the relationship between aBMD and fracture risk is not well established among young adults and that fracture prediction tools, such as FRAX®, are not valid for the young population. In the absence of secondary causes, occurrence of fragility fractures, in addition to the low T-score, may indicate genetic or idiopathic osteoporosis. Hence, the detection of prevalent vertebral fractures, which in the absence of major back trauma most likely indicate bone fragility, plays an important role in the identification of young adults with osteoporosis. For this purpose, DXA-based vertebral fracture assessment (VFA) tools now appear as major add-ons to aBMD evaluation [96].

According to a T-score ≤−2.5, in theory, only 0.5% of young women aged 30–40 years would fulfill the criteria of osteoporosis and another 15% would be considered as osteopenic (T-score between −2.5 and − 1) in any population [97]. This is corroborated by several observations, including a study of 282 premenopausal healthy women (mean age 34.8 years) without family history or secondary causes of bone fragility, which reported osteopenia in 10.6% of cases [98]. Similar prevalence of low bone mass in 579 Spanish premenopausal women (aged 20–44 years) was observed, with lumbar spine BMD characterized as osteoporosis and osteopenia in 0.3% and 13.1% of the cases, respectively, and in 0.2% and 12.6%, respectively, using femoral neck BMD [99].

Against this background of low prevalence of osteoporosis in healthy young individuals, the prevalence of osteoporosis and/or fragility (vertebral) fractures can reach 15% to 50% in young subjects with inflammatory bowel disease [100–102], celiac disease [103–105], cystic fibrosis [106–108], type 1 diabetes [109–111], rheumatoid arthritis [112], and anorexia nervosa [113–115], among other causes of secondary osteoporosis.

Special considerations are required for interpretation of BMD results in premenopausal women. Dynamics of Peak BMD Accrual BMD in premenopausal women depends primarily upon achievement of peak bone mass. Attainment of peak bone mass varies according to gender [116, 117], ethnicity [118], body size, menarchal age [119, 120], and region of bone. In healthy girls, the peak period of bone mass accrual occurs between ages 11 and 14 [121], and the rate of bone mass accrual slows dramatically by approximately 2 years after menarche [116]. Although at least 90 percent of peak bone mass is acquired by the late teen years [122, 123], studies have documented small additional gains between the ages of 20 and 29 [124]. Moreover, population-based, cross-sectional studies suggest that the timing of peak bone mass accrual may be site-specific [116], with women reaching peak bone mass at the proximal femur in their 20s and at the spine and forearm around age 30 [125]. When interpreting BMD measurements in premenopausal women, the possibility that peak bone mass has not yet been achieved must always be considered.

Physiologic Changes in the Bone Mass in Association with Pregnancy and Lactation

The majority of epidemiological studies in humans suggest that the net effect of the loss and regain of bone mass during and after lactation does not affect postmenopausal bone mass or long-term fracture risk [126–128]. However, other studies show that multiparity and longer periods of lactation are associated with decreased bone mineralization [129–134]. Additionally, studies performed in Turkey, China, and Mexico suggest that there may be an impact of lactation history on postmenopausal BMD in some populations [130, 135, 136]. Differences in population age, stature, parity, socioeconomic conditions, study duration and design, analysis techniques, and covariates included must be taken into account when interpreting these differing results.

Because of these physiologic bone mass changes associated with reproduction, interpretation of BMD results in premenopausal women must take into account the timing of any recent pregnancy or lactation. Based on available data, BMD at the lumbar spine is likely to have returned to that individual's premenopausal baseline by 12 months post-weaning [137].

Pregnancy- and Lactation-Associated Osteoporosis In some women, premenopausal osteoporosis may first present with low trauma fracture(s), usually at trabecular sites such as the vertebrae, occurring in the last trimester of pregnancy or during lactation [136–139]. Given the physiologic bone mass changes described above, pregnancy and lactation may represent particularly vulnerable times for the premenopausal woman's skeleton, particularly if low bone mineral density is present before pregnancy.

However, premenopausal fractures, including those associated with pregnancy and lactation, remain quite rare, suggesting that additional factors contribute to bone fragility in women who present with fractures during this time. Women with low trauma fractures sustained during pregnancy and/or lactation require the same thorough evaluation for secondary causes as do young women with fractures that are not associated with reproductive events. We have included women with pregnancy- and lactation-associated osteoporosis, in whom no cause is found after extensive evaluation, in cohorts defined to have idiopathic osteoporosis [140, 141].

Post-Menopausal and Elderly Women Several clinical groups have been involved in the diagnosis and recommendations concerning the treatment of osteoporosis in postmenopausal women. Two of these, the National Osteoporosis Foundation (NOF) in the USA [148]and the National Osteoporosis Guideline Group (NOGG) in the UK [143], have provide an interesting contrast in views with respect to their use of FRAX as a tool for patient identification and decisions on intervention (Table 4.2). While NOF suggests that a FRAX calculation is warranted when the BMD indicates elevated fracture risk, the decision to treat rests mainly on BMD; NOGG suggests that FRAX should be used in a case-finding exercise and the BMD should be performed in cases where the risk estimate is in a borderline zone [144].

Table 4.2 Xomparison between NOF and NOGG regarding guidelines for intervention in osteoporosis, with a focus on older individuals

	NOF	NOGG
BMD testing	Women aged ≥65 years Men aged ≥70 years Initiate therapy in those with T-scores ≤2.5 (at femoral neck, total hip or lumbar spine)	If suggested by FRAX case-finding analysis
Vertebral Imaging	Women aged ≥70 years Men aged ≥80 years	Not mentioned
	Its use is warranted in patients with low femoral neck BMD. Noted that using FRAX in patients with low BMD at the lumbar spine with relatively normal levels at the femoral neck leads to an underestimation of fracture risk	Case finding using FRAX in all post-menopausal women and men aged ≥50 years Initiate therapy following discussion of risk with patient

NOF National Osteoporosis Foundation (USA) [142]
NOGG National Osteoporosis Guideline Group (UK) [143]

In cases where the diagnostic threshold is crossed (i.e., elevated risk), additional clinical data might be sought to determine whether treatment should be initiated. This could be BMD (as suggested by NOGG), if not already done. Biomarker analysis might also be of potential interest, since high levels of bone turnover markers are associated with increased fracture risk in post-menopausal women [145]. One of the goals of this risk analysis exercise is to improve the targeting of anti-osteoporosis medication to ensure that the individuals who need to be treated are identified and presented with their therapeutic options.

The guidance of NOF concerning the intervention thresholds for treatment (while focusing on men and women 50 years and older) is to treat

if T-score ≤ −2.5 at femoral neck or if the T-score is between −1.0 and − 2.5 and the 10-year probability of fracture (on FRAX) is ≥3% for hip or ≥ 20% for a major fragility fracture. The guidance of NOGG is to treat when the age-related fracture probability exceeds the intervention threshold given by FRAX (where the FRAX threshold is the risk equivalent to a woman with a prior fragility fracture). The age-dependent intervention threshold favored by NOGG is designed to avoid under-prescription of treatment in eligible younger patients as well as the over-prescription in older age groups that could arise from a fixed threshold.

The FRAX defined intervention threshold therefore corresponds to "severe osteoporosis," i.e., the presence of at least one fragility fracture [146]. Other definitions of severe osteoporosis or high-risk patients could include that used in the GLOW study (Global Longitudinal Study of Osteoporosis in Women) [147], of patients having an age ≥65 years and a prior fracture or at least 2 other FRAX risk factors (parental hip fracture, current smoker, less than or equal to three alcoholic drinks/day, rheumatoid arthritis, current corticosteroid use, body mass index (BMI) <20 kg/m^2, or secondary osteoporosis).

Clinical Approach to Patient Identification and Diagnosis

Young/Premenopausal Females

Identifying individuals prone to have osteoporosis in the standard clinical practice represents the cornerstone in their management process. Young individuals suffering from a chronic disease (Table 4.1) and/or presenting with a low trauma fracture, particularly in the vertebrae (>20% loss of the vertebral height), and/or multiple low force long bone fracture (more than two) should be targeted for the possibility of having osteoporosis. The evaluation process starts with thorough medical history and examination (Table 4.3). Medical history should include full personal as well as family history (bearing in mind the genetic causes for osteoporosis) of bone fragility and/or endocrine, metabolic, and inflammatory disorders. Also, it should include past and present medications, age of menarche and/or history of amenorrhea, food intolerance, abdominal pain and bowel movements, urticaria, timing of recent pregnancies and lactation, as well as dietary and exercise patterns. Physical examination should particularly seek signs of Physical examination should seek signs of: nutritional deficiency or eating disorder, Cushing syndrome, thyroid hormone excess, connective tissue disorders (e.g., osteogenesis imperfecta, Ehlers Danlos syndrome, Marfan syndrome), and inflammatory conditions (e.g., rheumatoid arthritis, SLE) [148].

Table 4.3 Clinical approach of osteoporosis in the young / premenopausal females rely mainly on the patient's history and clinical assessment. Many secondary causes can be identified by a detailed history and physical examination

Medical history should include information on
Adult and childhood fractures
Adult and childhood illnesses and medication exposures
Menstrual history
Timing of recent pregnancy or lactation
Dieting and exercise behavior
Gastrointestinal symptoms
Nephrolithiasis
Family history of osteoporosis and/or nephrolithiasis
Physical examination should pursue signs of
Low height and/or BMI
Abdominal tenderness
Cutaneous signs of allergy (urticaria)
Hyperpigmentation or decreased pilosity (hypogonadism)
The presence of kyphosis
Limb deformities
Joint inflammation
Hyperlaxity
Blue sclerae
Poor dentition

Laboratory assessment: In addition to clinical assessment, lab tests are carried out to screen for the most common bone and mineral disorders (Table 4.4). Basic osteoporosis blood profile should be carried out for all patients. This aims to identify the common causes of bone thinning, including vitamin D deficiency, primary hyperparathyroidism, thyroid dysfunction, diabetes, renal impairment and hepatic dysfunction, systemic inflammation, and in men, hypogonadism

Table 4.4 Laboratory evaluation of young patients prone to have osteoporosis. The laboratory evaluation should aim to identify conditions such as vitamin D and/or calcium deficiency (and laboratory evidence that may distinguish osteomalacia from osteoporosis), hyperthyroidism, hyperparathyroidism, Cushing syndrome, early menopause, renal or liver disease, celiac disease, as well as other forms of malabsorption and idiopathic hypercalciuria

Basic osteoporosis blood profile	Specific laboratory evaluation
Complete blood count Electrolytes, renal function Serum calcium, phosphate Serum albumin, transaminases, total alkaline phosphatase Serum TSH Serum 25-hydroxyvitamin D PTH 24-hour urine for calcium and creatinine	Estradiol, LH, FSH, prolactin Screening for Cushing syndrome: 24 hour urine for free cortisol (or dexamethasone suppression test) Celiac screen (serologies) Serum/urine protein electrophoresis ESR or CRP Vitamin A/retinol level Specific testing for other rare conditions (e.g., mastocytosis, Gaucher disease, hypophosphatasia, hemochromatosis) If genetic diseases such as Gaucher disease, hypophosphatasia, or osteogenesis imperfecta are considered, genetic testing may be pursued Bone turnover biomarkers Transiliac crest bone biopsy

(particularly in the presence of other clinical signs). It is particularly important to exclude the possibility of vitamin D deficiency ($25(OH)_2$ vitamin D <10 ng/ml or 25 nmol/L), as this may affect bone mineralization and be translated into low aBMD, without being osteoporosis (Osteomalacia). Bearing in mind the secondary causes of osteoporosis in this cohort of patients, some patients might require specific laboratory tests. It is worth noting that celiac disease (prevalence 1%) may present in occult form, particularly since most adults will change their diet to avoid food intolerance/bowel symptoms, and should be suspected especially in the presence of low 25-hydroxyvitamin D. An elevated titer of antiendomysial or antitissue transglutaminase antibodies has an excellent positive predictive value for this disease [149]. In patients suffering from inflammatory bowel disease (IBD), Crohn's disease and ulcerative colitis are commonly delayed up to 2 years after the appearance of the first digestive symptoms. Hence, patients with low bone mass/bone fragility and abdominal symptoms/signs who test negative for antitissue transglutaminase Ab (and who may have inflammatory markers) should be assessed for fecal calprotectin and referred to a specialist for further intestinal investigations.

An additional set of selected diagnostic tests can be applied particularly when the clinical and/or baseline laboratory results orient towards a specific condition. Although systemic mastocytosis (SM) is a rare (0.3/10,000) condition, it is diagnosed in 0.4 to 1% of bone biopsies referred for the investigation of osteoporosis [150]. It becomes clinically manifest as urticaria pigmentosa in 60% of the patients, gastrointestinal manifestations in 40%, and idiopathic anaphylactoid reactions in 20%. However, all of these symptoms can be absent and the skeletal manifestation can be the sole presentation, with osteoporosis reported in up to 30% of patients with systemic mastocytosis [58, 59]. An elevated serum tryptase (>20 ng/ml) has a positive predictive value of 98% for systemic mastocytosis [151].

Besides bone alkaline phosphatase isoenzyme (BALP), it can be assessed in patients presenting with persistently elevated alkaline phosphatase level. If elevated, after growth is completed, it can orient toward osteomalacia (together with low 25(OH) vitamin D levels), Paget's disease, or bone neoplasia; and if low, it raises the possibility of hypophosphatasia.

The utility of bone biomarkers—that is, procollagen peptides (N and C terminals, PINP, and PICP, respectively) for bone formation and telopeptide cross-links of collagen type I (N and C terminals, NTX, and CTX, respectively), deoxypyridinoline/pyridinoline, and tartrate-resistant acid phosphatase for bone resorption—in the investigation of osteoporosis in the young remains controversial [152–154]. So far, the predictive role of bone biomarkers for fracture risk in secondary osteoporosis has not been fully documented, although they have been correlated with BMD changes in some diseases

(inflammatory bowel disease) [155]. Several examples have been reported to show such poor association. Firstly, bone biomarkers are correlated to the level of 25(OH) vitamin D, IGF-1, physical activity, etc. [156–159]; and in the case of a chronic disorder, bone biomarkers can be elevated, normal, or low depending on the nature of the underlying disease, its severity and relapses, past and current therapy, as well as the subject's mobility and nutrition. Secondly, in premenopausal women with idiopathic osteoporosis, bone turnover may also be high, normal, or low [160]. Furthermore, bone biomarkers have been negatively correlated with HbA_1C in type 1 diabetes, i.e., were lower with poor glucose control [161]. In contrast, when the achievement of peak bone mass is delayed, as is often the case with chronic disorders starting during childhood or adolescence, bone biomarkers may remain elevated into young adulthood (between 20 and 25 years of age) as a reflection of the ongoing physiological bone modeling/remodeling state rather than a catabolic state. In addition, a recent fracture may also cause an elevation of biomarkers for several months. Furthermore, patients with osteogenesis imperfecta, levels of PINP, and ß-CTX are normal or low, whereas osteocalcin is normal or high, reflecting the alterations in collagen metabolism on one side and bone turnover on the other side [162].

Despite these difficulties in interpreting bone biomarkers, normal bone biomarkers in a young adult with low aBMD would argue for an acquired low peak bone mass, whereas high bone biomarkers would point toward an ongoing process of bone loss, as seen, for instance, in anorexia nervosa compared to constitutionally lean women. Taken together with a low T-score and some evidence of bone fragility, elevated bone biomarkers could, therefore, prompt further investigations for an underlying cause and could be useful for therapeutic guidance [163]. On the other hand, low bone turnover has been observed in a subset of young women with idiopathic osteoporosis in association with a more pronounced deficit in bone microarchitecture and stiffness [160].

All patients suspected to have osteoporosis should have a DXA (ideally combined with VFA) scan. For those individuals with a T-score < −2.5 and/or fragility fractures but no known secondary cause, a search for underlying disorders and/or medications potentially associated with osteoporosis should be initiated (Fig. 4.5). Low aBMD alone and/or together with bone and muscle pain (and weakness in the latter) can be due to vitamin D deficiency, eventually osteomalacia, i.e., not necessarily osteoporosis. Moreover, when vitamin D levels are adequate, low aBMD without fragility fractures, including the absence of vertebral crush fractures as evaluated by VFA and/or lateral X-rays, does not necessarily represent a pathological situation, particularly in subjects of small body size [24]. Investigations in this case should be limited in the absence of symptoms and/or signs of a chronic disorder.

Postmenopausal Females

Identifying postmenopausal women at risk of osteoporosis/ osteoporotic fracture relies primarily on population screening. At present, there is no universally accepted policy for pop-

Table 4.5 Clinical risk factors used for the assessment of fracture probability

Risk factors for osteoporosis/osteoporotic fracture
Age
Sex
Low body mass index
Previous fragility fracture, particularly of the hip, wrist, and spine including
Morphometric vertebral fracture
Parental history of hip fracture
Glucocorticoid treatment (by mouth for 3 months or more)
Current smoking
Alcohol intake of 3 or more units daily
Secondary causes of osteoporosis include
rheumatoid arthritis
untreated hypogonadism in men and women
inflammatory bowel disease
prolonged immobility
organ transplantation
type I diabetes
thyroid disorders
chronic obstructive pulmonary disease

ulation screening; however, in most cases, the patients are identified opportunistically using a case-finding strategy on the finding of a previous fragility fracture or the presence of significant risk factors. The risk factors that are used for clinical assessment are summarized in Table 4.5. Algorithms that integrate the weight of clinical risk factors for fracture risk with or without information on BMD have been developed—FRAX™. The FRAX™ tool (www.shef.ac.uk/FRAX) computes the 10-year probability of hip fracture or a major osteoporotic fracture (clinical spine, hip, forearm and humerus fracture) [164]. Probabilities can be computed for several countries, categorized for different levels of risk.

Similar to young females, the same approach should be undertaken in all patients with osteoporosis. However, the range of clinical and biological tests depend on the severity of the disease, age at presentation, and the presence or absence of vertebral fractures [165]. The aims of the clinical history, physical examination, and clinical tests (Table 4.6) are to:

- Exclude diseases that mimic osteoporosis (e.g., osteomalacia, myelomatosis).
- Identify the cause of osteoporosis and contributory factors.
- Assess the risk of subsequent fractures.
- Select the most appropriate form of treatment.
- Perform baseline measurements for subsequent monitoring of treatment.

Table 4.6 Routine procedures proposed in the investigation of postmenopausal osteoporosis

Basic osteoporosis profile
History and physical examination
Blood cell count, sedimentation rate, serum calcium, albumin, creatinine, phosphate, alkaline phosphatase, vitamin D, and liver transaminases
Lateral radiograph of lumbar and thoracic spine
Bone densitometry (dual energy X-ray absorptiometry)
Other tests
X-ray—Vertebral fracture assessment
Markers of bone turn over (when available/appropriate)

Approach 1: Quantitative Assessment

The diagnosis of osteoporosis relies on the quantitative assessment of bone mineral density (BMD), usually by central dual energy X-ray absorptiometry (DXA). Bone mineral density at the femoral neck provides the reference site. It is defined as a value for BMD 2.5 SD or more below the young female adult mean (T-score less than or equal to −2.5 SD). Severe osteoporosis (established osteoporosis) describes osteoporosis in the presence of 1 or more fragility fractures [164].

However, diagnostic thresholds differ from intervention thresholds for several reasons. Firstly, the fracture risk varies markedly in different countries and at different ages, even with the same T-score. Other factors that determine intervention thresholds include the presence of clinical risk factors, high indices of bone turnover, and the cost and benefits of treatment as well as presence of other comorbidities [166].

In addition to the bone mineral density assessment, assessment for falls should also be carried out particularly among elderly women. Several tools are available to assess for the falls risk in standard practice that vary between using for research or standard clinical practice [167].

Approach 2: Probability-Based Assessment

Women with a prior fragility fracture should be considered for treatment. In the presence of other clinical risk factors, the 10-year probability of a major osteoporotic fracture (clinical spine, hip, forearm, or humerus) should be determined using FRAX™ (www.shef.ac.uk/FRAX). Women with probabilities below the lower assessment threshold can be reassured (Fig. 4.6). Women with probabilities above the upper assessment threshold can be considered for testing with BMD and their fracture probability reassessed. Women with probabilities above the intervention threshold should be considered for treatment. The intervention threshold at each age is set at a risk equivalent to that associated with a prior fracture

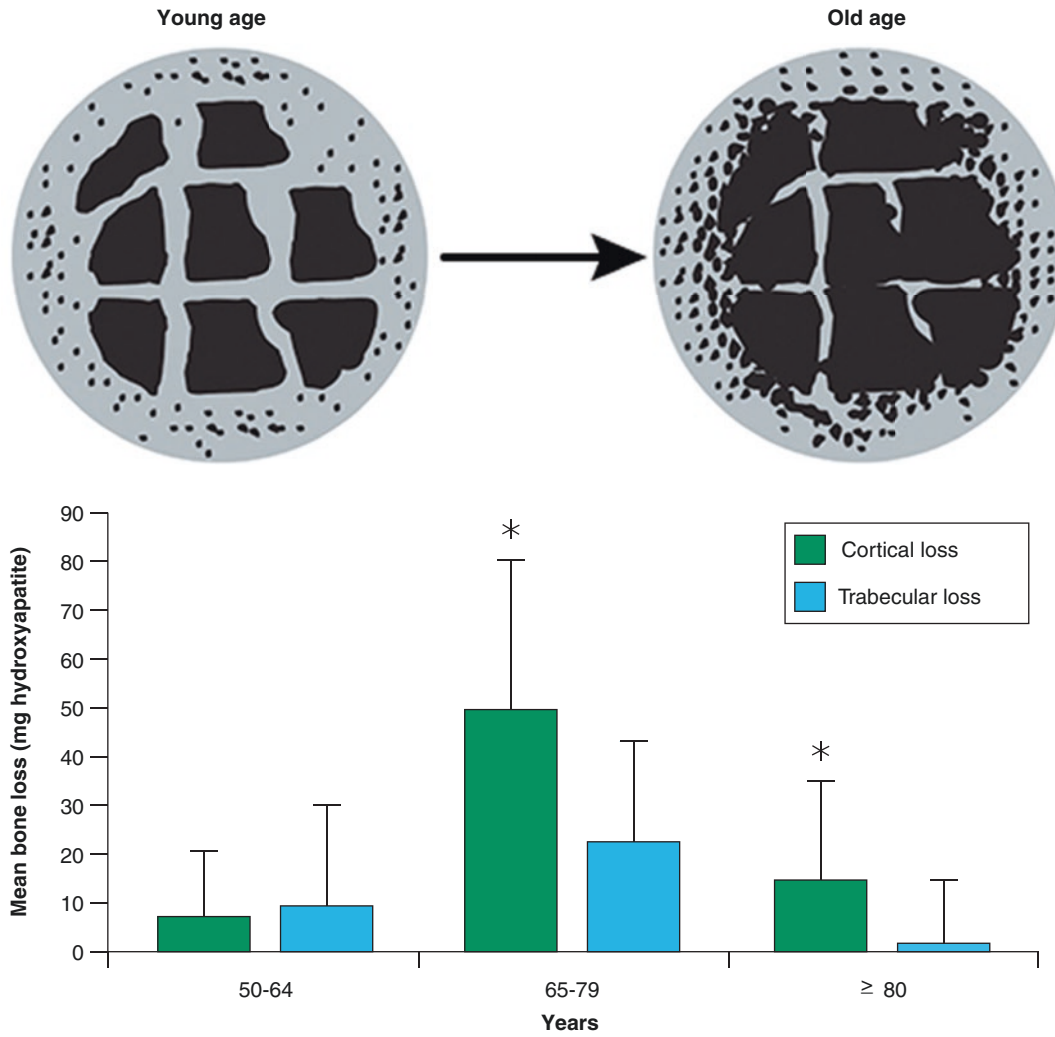

Fig. 4.6 The mg of hydroxyapatite lost with age was measured using high-resolution peripheral CT of the distal radius in a cross-sectional study of 122 white women with a mean age of 62.8 (range 27 to 98) years. Please note that most bone lost after the age of 65 was cortical. Cortical porosity was measured using scanning electron microscopy of postmortem specimens of femora from 24 women with a mean age of 69 (range 29 to 99) years and is depicted in a schematic fashion. (*CT* Computed tomography. *$p < 0.0001$. Reproduced from: Zebaze et al. [83]. Illustration used with the permission of Elsevier Inc. within the STM permissions guidelines. Figure 4.5: Assessment threshold for BMD testing (left) and treatment threshold (right))

and therefore rises with age. But the proportion of women in the UK potentially eligible for treatment rises from 20 to 40% with age.

Without computer access, the following management algorithm can be used. Women with a prior fragility fracture should be considered for treatment. In the presence of other clinical risk factors, BMD should be measured at the femoral neck. The chart (Fig. 4.7) gives average fracture probabilities according to BMD T-score and the number of clinical risk factors. The chart is color coded. Green denotes that an individual's risk lies below the intervention threshold, i.e., treatment is not indicated. Red denotes that the fracture probability is consistently above the upper assessment threshold, irrespective of the mix of clinical risk factors, so that treatment can ordinarily be strongly recommended. The intermedi-

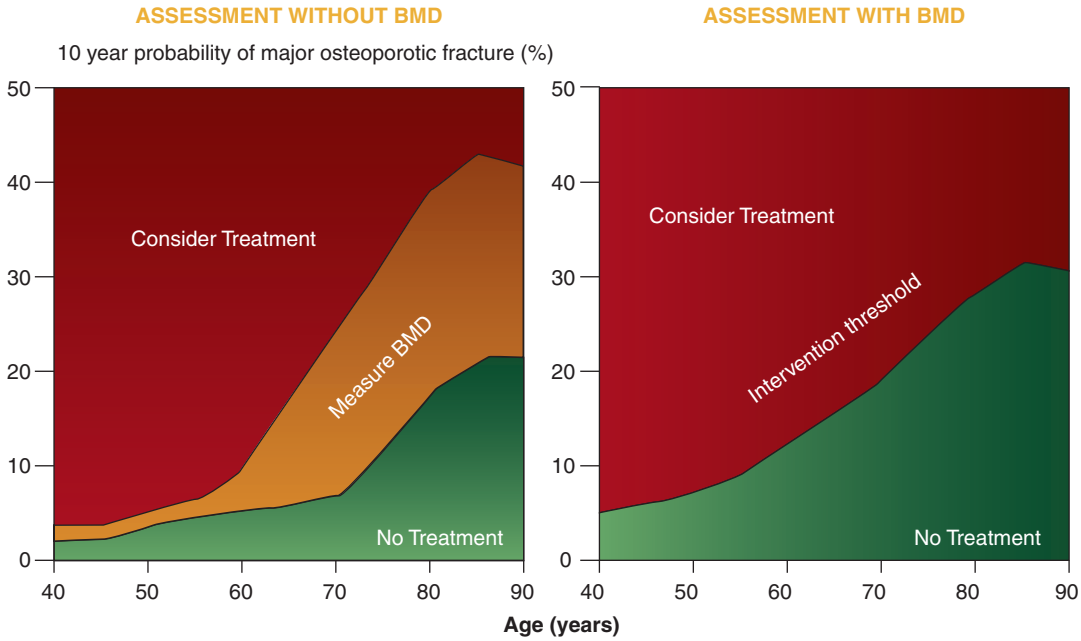

Fig. 4.7 Assessment and treatment thresholds in the absence of a BMD test (left) and with a BMD test to compute fracture probability (right) for men and women. (Quoted from nogg National Osteoporosis guideline Group. JA Kanis, J Compston, A Cooper, C Cooper, R Francis, D Marsh, EV McCloskey, D Reid, P Selby and M Wilkins, on behalf of the National Osteoporosis Guideline Group (NOGG). Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. https://iofbonehealth.org/sites/default/files/PDFs/National%20Guidelines/nogg_pocket_guide-healthcare_professionals.pdf (Accessed on 18th October 2020))

ate category (orange) denotes that probabilities lie between these limits and that treatment can be recommended in those with the stronger risk factors. Smoking and alcohol are weak risk factors, glucocorticoids and secondary causes of osteoporosis are moderate risk factors, and a parental history of hip fracture is a strong risk factor. However, it has to be noted that the only secondary cause of osteoporosis that should be used with BMD is rheumatoid arthritis [166] (Fig. 4.8).

Specific Clinical Situations

Idiopathic Osteoporosis in the Young

In some cases of low trauma fracture in premenopausal women, no known secondary cause can be found after extensive evaluation. These women are said to have idiopathic osteoporosis (IOP). Based on current guidelines, the term IOP applies only to those with a history of low trauma fractures, and not to those with low BMD and no history of fractures [148].

Idiopathic osteoporosis has been reported in premenopausal women, but its pathophysiology is less well understood. A recent bone biopsy study in 45 premenopausal women with fragility fractures, 19 with low aBMD and 40 controls, indicated that the group with idiopathic osteoporosis has significantly thinner cortices and trabeculae, and a lower mean wall thickness, i.e., a bone formation deficit [168]. Other studies, utilizing central quantitative CT, peripheral high-resolution CT, and microCT of transiliac bone biopsy samples, demonstrated similar findings with markedly thinner cortices, fewer, thinner, widely separated, and heterogeneously distributed trabeculae and lower estimated stiffness in IOP women compared to normal controls. Studies

Fig. 4.8 Assessment of men and assessment of women with no previous fracture according to body mass index (BMI) and the number of clinical risk factors (CRFs). (Quoted from nogg National Osteoporosis guideline Group. JA Kanis, J Compston, A Cooper, C Cooper, R Francis, D Marsh, EV McCloskey, D Reid, P Selby and M Wilkins, on behalf of the National Osteoporosis Guideline Group (NOGG). Guideline for the diagnosis and management of osteoporosis in postmenopausal women and men from the age of 50 years in the UK. https://iofbonehealth.org/sites/default/files/PDFs/National%20Guidelines/nogg_pocket_guide-healthcare_professionals.pdf (Accessed on 18th October 2020))

of biochemical and bone remodeling characteristics suggest that the pathogenesis of IOP is heterogeneous, with some women exhibiting evidence of low bone turnover while others have evidence of high bone turnover [168, 169].

Therefore, pathogenesis is likely to be diverse; etiologies including excess urinary calcium excretion and IGF-1 axis abnormalities have been implicated [137]. However, bone turnover and indices of bone remodelling are extremely heterogenous in these women. Only in a subgroup with low bone formation rate and more severely disrupted microarchitecture were serum IGF-1 levels elevated, suggesting a resistance against this growth factor. In another study, young women with idiopathic osteoporosis were reported to have lower free estradiol levels and higher bone turnover than normal [170]. It should be noted that hypercalciuria may be present in premenopausal women with idiopathic osteoporosis [171].

Premenopausal Women with Fractures or Low BMD Related to Known Secondary Causes.

In premenopausal women with low BMD or low trauma fractures and a known secondary cause of osteoporosis, the first goal of management should be to address the underlying cause. Bone density benefits have been shown in the context of intervention for several such secondary causes in premenopausal women:

- Estrogen replacement for those with estrogen deficiency [172–174].
- Discontinuation of medications, for example, depot medroxyprogesterone acetate (Depo Provera) [175, 176].
- Gluten-free diet for celiac disease [177–179].
- Nutritional rehabilitation and weight gain for anorexia nervosa [180].
- Parathyroidectomy for primary hyperparathyroidism [181].

Although thiazides are used for idiopathic hypercalciuria, and appear to have beneficial effects on BMD in men64, few data are available in young women. Continuing or severe effects of the secondary cause may lead to a necessity for pharmacological therapy.

In conclusion, bone health in females is an important topic that requires careful consideration. Most premenopausal women, with low trauma fracture(s) or low BMD have a secondary cause of osteoporosis or bone loss. Women who present with unexplained fractures or low BMD should have a thorough clinical and laboratory evaluation to search for known causes of fractures and/or bone loss. Post-menopausal and elderly women are highly prone to develop fractures. Where possible, treatment of the underlying cause should be the focus of management. Women with an ongoing cause of bone loss and those who have had, or continue to have, low trauma fractures may require pharmacological intervention.

An example is given in Fig. 4.7 for a woman with rheumatoid arthritis aged 60 years on oral glucocorticoids with a BMD T-score of −1 SD (i.e., two clinical risk factors). The chart gives an average10-year fracture probability of 12% for any combination of 2 CRFs and is coded orange. With the 2 moderate risk factors in this woman, the probability is close to the average (11%) and exceeds the treatment threshold. With weak risk factors (e.g., smoking and alcohol), the probability would be lower (6.8%) and fall below the treatment threshold. The range (6.7–12%) is not a confidence interval but, because the weight of different risk factors varies, is a true range.

References

1. Johnell O, Kanis JA. An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporosis Int. 2004;15:897–902.
2. Kanis JA. WHO technical report. UK: University of Sheffield; 2007. p. 66.
3. Abirami P, Nithya M, Priyanka K, Hemalatha G. Assess the prevalence of osteoporosis among middle aged women in Mamandur. Int J Pharmaceutical and Clin Research. 2017;9(11):690–5.
4. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization task force for osteoporosis. Osteoporos Int. 1999;10:259–64.
5. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. N Engl J Med. 1995;332:767–73.
6. World Health Organization. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Technical report series. In. Geneva; 1994.
7. Seeman E, Bianchi G, Khosla S, Kanis JA, Orwoll E. Bone fragility in men—where are we? Osteoporos Int. 2006;17:1577–83.
8. Kanis JA, Oden A, Johnell O, et al. The use of clinical risk factors enhances the performance of BMD in the prediction of hip and osteoporotic fractures in men and women. Osteoporos Int. 2007;18:1033–46.
9. Bianchi ML. Osteoporosis in children and adolescents. Bone. 2007;41:486–95.
10. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S. Official positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD position development conference. J Clin Densitom. 2008;11:75–91.
11. Bonjour JP, Chevalley T, Rizzoli R, Ferrari S. Gene–environment interactions in the skeletal response to nutrition and exercise during growth. Med Sport Sci. 2007;51:64–80.
12. Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. J Clin Endocrinol Metab. 2005;90:44–51.
13. Ferrari S, Rizzoli R, Slosman D, Bonjour JP. Familial resemblance for bone mineral mass is expressed before puberty. J Clin Endocrinol Metab. 1998;83:358–61.
14. Bailey DA, Wedge JH, McCulloch RG, Martin AD, Bernhardson SC. Epidemiology of fractures of the distal end of the radius in children as associated with growth. J Bone Joint Surg Am. 1989;71:1225–31.
15. Clark EM, Ness AR, Bishop NJ, Tobias JH. Association between bone mass and fractures in children: a prospective cohort study. J Bone Miner Res. 2006;21:1489–95.

16. Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R. Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility? J Bone Miner Res. 2006;21:501–7.
17. Khosla S, Melton LJ 3rd, Dekutoski MB, Achenbach SJ, Oberg AL, Riggs BL. Incidence of childhood distal forearm fractures over 30 years: a population-based study. JAMA. 2003;290:1479–85.
18. Rizzoli R, Bianchi ML, Garabedian M, McKay HA, Moreno LA. Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly. Bone. 2010;46:294–305.
19. Rauch F, Travers R, Glorieux FH. Cellular activity on the seven surfaces of iliac bone: a histomorphometric study in children and adolescents. J Bone Miner Res. 2006;21:513–9.
20. Seeman E. Pathogenesis of bone fragility in women and men. Lancet. 2002;359:1841–50.
21. Nordstrom P, Neovius M, Nordstrom A. Early and rapid bone mineral density loss of the proximal femur in men. J Clin Endocrinol Metab. 2007;92:1902–8.
22. Riggs BL, Melton LJ, Robb RA, Camp JJ, Atkinson EJ, McDaniel L, Amin S, Rouleau PA, Khosla S. A population-based assessment of rates of bone loss at multiple skeletal sites: evidence for substantial trabecular bone loss in young adult women and men. J Bone Miner Res. 2008;23:205–14.
23. Riggs BL, Wahner HW, Melton LJ 3rd, Richelson LS, Judd HL, Offord KP. Rates of bone loss in the appendicular and axial skeletons of women. Evidence of substantial vertebral bone loss before menopause. J Clin Invest. 1986;77:1487–91.
24. Ferrari S, Bianchi ML, Eisman JA, Foldes AJ, Adami S, Wahl DA, Stepan JJ, de Vernejoul M-C, Kaufman J-M. For the IOF Committee of Scientific Advisors Working Group on osteoporosis pathophysiology osteoporosis in young adults: pathophysiology, diagnosis, and management. Osteoporos Int. 2012;23:2735–48.
25. Ferrari S. Human genetics of osteoporosis. Best Pract Res Clin Endocrinol Metab. 2008;22:723–35.
26. Karasik D, Ferrari SL. Contribution of gender-specific genetic factors to osteoporosis risk. Ann Hum Genet. 2008;72:696–714.
27. Sylvester FA. IBD and skeletal health: children are not small adults! Inflamm Bowel Dis. 2005;11:1020–3.
28. Haidar R, Musallam KM, Taher AT. Bone disease and skeletal complications in patients with beta thalassemia major. Bone. 2011;48:425–32.
29. Kaunitz AM, Shields WC. Contraceptive equity and access in the United States: a 2005 update. Contraception. 2005;71:317–8.
30. Lopez LM, Grimes DA, Schulz KF, Curtis KM. Steroidal contraceptives: effect on bone fractures in women. Cochrane Database Syst Rev. 2011:CD006033.
31. Kovacs CS. Calcium and bone metabolism during pregnancy and lactation. J Mammary Gland Biol Neoplasia. 2005;10:105–18.
32. Oliveri B, Parisi MS, Zeni S, Mautalen C. Mineral and bone mass changes during pregnancy and lactation. Nutrition. 2004;20:235–40.
33. Kent GN, Price RI, Gutteridge DH, Rosman KJ, Smith M, Allen JR, Hickling CJ, Blakeman SL. The efficiency of intestinal calcium absorption is increased in late pregnancy but not in established lactation. Calcif Tissue Int. 1991;48:293–5.
34. Kovacs CS. Calcium and bone metabolism in pregnancy and lactation. J Clin Endocrinol Metab. 2001;86:2344–8.
35. Kovacs CS, Fuleihan Gel H. Calcium and bone disorders during pregnancy and lactation. Endocrinol Metab Clin N Am. 2006;35:21–51.
36. Sowers M, Corton G, Shapiro B, Jannausch ML, Crutchfield M, Smith ML, Randolph JF, Hollis B. Changes in bone density with lactation. JAMA. 1993;269:3130–5.
37. Bianchi ML. Osteoporosis during pregnancy. Eur Musculoskel Rev. 2009;4:30–4.
38. Csotye J, Sisak K, Bardocz L, Toth K. Bilateral spontaneous displaced femoral neck fractures during pregnancy. J Trauma. 2010;68:E115–6.
39. Khovidhunkit W, Epstein S. Osteoporosis in pregnancy. Osteoporos Int. 1996;6:345–54.
40. Kalkwarf HJ, Specker BL, Bianchi DC, Ranz J, Ho M. The effect of calcium supplementation on bone density during lactation and after weaning. N Engl J Med. 1997;337:523–8.
41. Martinez-Morillo M, Grados D, Holgado S. Premenopausal osteoporosis: how to treat? Rheumatol Clin. 2012;8(2):93–7.
42. Vondracek SF, Hansen LB, McDermott MT. Osteoporosis risk in premenopausal women. Pharmacotherapy. 2009;29(3):305–17.
43. Langdahl BL, Martin F, Shane E, et al. Teriparatide versus alendronate for treating glucocorticoid-induced osteoporosis: an analysis by gender and menopausal status. Osteoporos Int. 2009;20(12):2095–104.
44. Bainbridge KE, Sowers MF, Crutchfield M, Lin X, Jannausch M, Harlow SD. Natural history of bone loss over 6 years among premenopausal and early postmenopausal women. Am J Epidemiol. 2002;156(5):410–7.
45. National Osteoporosis Foundation. What Women Need to Know. National Osteoporosis Foundation, Washington, DC, USA; 2013.
46. Bhalla AK. Management of osteoporosis in premenopausal women. Best Pract Res Clin Rheumatol. 2010;24(3):313–27.
47. Teng K. Premenopausal osteoporosis, an overlooked consequence of anorexia nervosa. Cleve Clin J Med. 2011;78(1):50–8.
48. Cohen A, Fleischer J, Freeby M, McMahon D, Irani D, Shane E. Clinical characteristics and medication use among premenopausal women with osteoporosis and low BMD: the experience of an osteoporosis referral center. J Women's Health. 2009;18(1):79–84.

49. McLendon A, Woodis C. A review of osteoporosis management in younger premenopausal women. Womens Health. 2014;13(73):59–77.
50. Manolagas SC. Birth and death of bone cells: basic regulatory mechanisms and implications for the pathogenesis and treatment of osteoporosis. Endocr Rev. 2000;21:115.
51. Manolagas SC, Kousteni S, Jilka RL. Sex steroids and bone. Recent Prog Horm Res. 2002;57:385.
52. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev. 2010;31:266.
53. Khosla S, Melton LJ 3rd, Riggs BL. The unitary model for estrogen deficiency and the pathogenesis of osteoporosis: is a revision needed? J Bone Miner Res. 2011;26:441.
54. Recker R, Lappe J, Davies K, Heaney R. Characterization of perimenopausal bone loss: a prospective study. J Bone Miner Res. 2000;15:1965.
55. Parfitt AM, Villanueva AR, Foldes J, Rao DS. Relations between histologic indices of bone formation: implications for the pathogenesis of spinal osteoporosis. J Bone Miner Res. 1995;10:466.
56. Han ZH, Palnitkar S, Rao DS, et al. Effects of ethnicity and age or menopause on the remodeling and turnover of iliac bone: implications for mechanisms of bone loss. J Bone Miner Res. 1997;12:498.
57. Parfitt AM. Skeletal heterogeneity and the purposes of bone remodeling: implications for the understanding of osteoporosis. In: Marcus R, Feldman D, Nelson D, Rosen C, Eds. Osteoporosis, 3rd ed., Elsevier, San Diego; 2007. p.71.
58. Smith EP, Boyd J, Frank GR, et al. Estrogen resistance caused by a mutation in the estrogen-receptor gene in a man. N Engl J Med. 1994;331:1056.
59. Jones ME, Boon WC, McInnes K, et al. Recognizing rare disorders: aromatase deficiency. Nat Clin Pract Endocrinol Metab. 2007;3:414.
60. Santen RJ, Brodie H, Simpson ER, et al. History of aromatase: saga of an important biological mediator and therapeutic target. Endocr Rev. 2009;30:343.
61. Manolagas SC, O'Brien CA, Almeida M. The role of estrogen and androgen receptors in bone health and disease. Nat Rev Endocrinol. 2013;9:699.
62. Almeida M, Iyer S, Martin-Millan M, et al. Estrogen receptor-α signaling in osteoblast progenitors stimulates cortical bone accrual. J Clin Invest. 2013;123:394.
63. Ucer S, Iyer S, Bartell SM, et al. The effects of androgens on murine cortical bone do not require AR or ERα Signaling in osteoblasts and osteoclasts. J Bone Miner Res. 2015;30:1138.
64. Nakamura T, Imai Y, Matsumoto T, et al. Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts. Cell. 2007;130:811.
65. Windahl SH, Börjesson AE, Farman HH, et al. Estrogen receptor-α in osteocytes is important for trabecular bone formation in male mice. Proc Natl Acad Sci U S A. 2013;110:2294.
66. Määttä JA, Büki KG, Gu G, et al. Inactivation of estrogen receptor α in bone-forming cells induces bone loss in female mice. FASEB J. 2013;27:478.
67. Melville KM, Kelly NH, Khan SA, et al. Female mice lacking estrogen receptor-alpha in osteoblasts have compromised bone mass and strength. J Bone Miner Res. 2014;29:370.
68. Kondoh S, Inoue K, Igarashi K, et al. Estrogen receptor α in osteocytes regulates trabecular bone formation in female mice. Bone. 2014;60:68.
69. Tarride JE, Hopkins RB, Leslie WD, et al. The burden of illness of osteoporosis in Canada. Osteoporos Int. 2012;23(11):2591–600.
70. Chevalley T, Guilley E, Herrmann FR, Hoffmeyer P, Rapin CH, Rizzoli R. Incidence of hip fracture over a 10-year period (1991–2000): reversal of a secular trend. Bone. 2007;40:1284–9.
71. Aw D, Masud T. Osteoporosis in the very elderly. GM2 Midlife and Beyond; 2009. p. 25. https://www.gmjournal.co.uk/media/21565/gm2june2009p25.pdf.
72. Liu W, Qi M, Konermann A, et al. The p53/miR-17/Smurf1 pathway mediates skeletal deformities in an age-related model via inhibiting the function of mesenchymal stem cells. Aging (Albany NY). 2015;7:205.
73. Almeida M, Laurent MR, Dubois V, et al. Estrogens and androgens in skeletal physiology and pathophysiology. Physiol Rev. 2017;97:135.
74. Ucer S, Iyer S, Kim HN, et al. The effects of aging and sex steroid deficiency on the murine skeleton are independent and mechanistically distinct. J Bone Miner Res. 2017;32:560.
75. Manolagas SC. The quest for osteoporosis mechanisms and rational therapies: how far We've come, how much further we need to go. J Bone Miner Res. 2018;33:371.
76. Vu MQ, Weintraub N, Rubenstein LZ. Falls in the nursing home: are they preventable? J Am Med Dir Assoc. 2006;7:S53.
77. Zebaze RM, Ghasem-Zadeh A, Bohte A, et al. Intracortical remodelling and porosity in the distal radius and post-mortem femurs of women: a cross-sectional study. Lancet. 2010;375:1729.
78. Nicks KM, Amin S, Atkinson EJ, et al. Relationship of age to bone microstructure independent of areal bone mineral density. J Bone Miner Res. 2012;27:637.
79. Hui SL, Slemenda CW, Johnston CC Jr. Age and bone mass as predictors of fracture in a prospective study. J Clin Invest. 1988;81:1804.
80. Balaban RS, Nemoto S, Finkel T. Mitochondria, oxidants, and aging. Cell. 2005;120:483.
81. Manolagas SC. From estrogen-centric to aging and oxidative stress: a revised perspective of the pathogenesis of osteoporosis. Endocr Rev. 2010;31:266.
82. Bartell SM, Kim HN, Ambrogini E, et al. FoxO proteins restrain osteoclastogenesis and bone resorption by attenuating H2O2 accumulation. Nat Commun. 2014;5:3773.

83. Kang C, Xu Q, Martin TD, et al. The DNA damage response induces inflammation and senescence by inhibiting autophagy of GATA4. Science. 2015;349:aaa5612.
84. López-Otín C, Blasco MA, Partridge L, et al. The hallmarks of aging. Cell. 2013;153:1194.
85. Kim HN, Chang J, Shao L, et al. DNA damage and senescence in osteoprogenitors expressing Osx1 may cause their decrease with age. Aging Cell. 2017;16:693.
86. Piemontese M, Almeida M, Robling AG, et al. Old age causes de novo intracortical bone remodeling and porosity in mice. JCI Insight. 2017;2
87. Farr JN, Fraser DG, Wang H, et al. Identification of senescent cells in the bone microenvironment. J Bone Miner Res. 2016;31:1920.
88. Jilka RL, O'Brien CA, Roberson PK, et al. Dysapoptosis of osteoblasts and osteocytes increases cancellous bone formation but exaggerates cortical porosity with age. J Bone Miner Res. 2014;29:103.
89. Schmitt CA, Fridman JS, Yang M, et al. A senescence program controlled by p53 and p16INK4a contributes to the outcome of cancer therapy. Cell. 2002;109:335.
90. Crescenzi E, Palumbo G, Brady HJ. Bcl-2 activates a programme of premature senescence in human carcinoma cells. Biochem J. 2003;375:263.
91. Emerton KB, Hu B, Woo AA, et al. Osteocyte apoptosis and control of bone resorption following ovariectomy in mice. Bone. 2010;46:577.
92. Kennedy OD, Herman BC, Laudier DM, et al. Activation of resorption in fatigue-loaded bone involves both apoptosis and active pro-osteoclastogenic signaling by distinct osteocyte populations. Bone. 2012;50:1115.
93. Tomkinson A, Reeve J, Shaw RW, Noble BS. The death of osteocytes via apoptosis accompanies estrogen withdrawal in human bone. J Clin Endocrinol Metab. 1997;82:3128.
94. Manolagas SC. Pathogenesis of osteoporosis. https://www.uptodate.com/contents/pathogenesis-of-osteoporosis.
95. Lewiecki EM, Gordon CM, Baim S, et al. Special report on the 2007 adult and pediatric position development conferences of the International Society for Clinical Densitometry. Osteoporos Int. 2008;19:1369–78.
96. Jager PL, Jonkman S, Koolhaas W, Stiekema A, Wolffenbuttel BH, Slart RH. Combined vertebral fracture assessment and bone mineral density measurement: a new standard in the diagnosis of osteoporosis in academic populations. Osteoporos Int. 2011;22:1059–68.
97. Kanis JA, Delmas P, Burckhardt P, Cooper C, Torgerson D. Guidelines for diagnosis and management of osteoporosis. The European Foundation for Osteoporosis and Bone Disease. Osteoporos Int. 1997;7:390–406.
98. Liu JM, Zhao HY, Ning G, Chen Y, Zhang LZ, Sun LH, Zhao YJ, Xu MY, Chen JL. IGF-1 as an early marker for low bone mass or osteoporosis in premenopausal and postmenopausal women. J Bone Miner Metab. 2008;26:159–64.
99. Diaz Curiel M, Garcia JJ, Carrasco JL, Honorato J, Perez Cano R, Rapado A, Alvarez Sanz C. Prevalence of osteoporosis assessed by densitometry in the Spanish female population. Med Clin (Barc). 2001;116:86–8.
100. Bernstein CN, Blanchard JF, Leslie W, Wajda A, Yu BN. The incidence of fracture among patients with inflammatory bowel disease. A population-based cohort study. Ann Intern Med. 2000;133:795–9.
101. Heijckmann AC, Huijberts MS, Schoon EJ, et al. High prevalence of morphometric vertebral deformities in patients with inflammatory bowel disease. Eur J Gastroenterol Hepatol. 2008;20:740–7.
102. Schulte CM. Review article: bone disease in inflammatory bowel disease. Aliment Pharmacol Ther. 2004;20(Suppl 4):43–9.
103. Thomason K, West J, Logan RF, Coupland C, Holmes GK. Fracture experience of patients with coeliac disease: a population based survey. Gut. 2003;52:518–22.
104. Ali T, Lam D, Bronze MS, Humphrey MB. Osteoporosis in inflammatory bowel disease. Am J Med. 2009;122:599–604.
105. Vestergaard P, Emborg C, Stoving RK, Hagen C, Mosekilde L, Brixen K. Fractures in patients with anorexia nervosa, bulimia nervosa, and other eating disorders—a nationwide register study. Int J Eat Disord. 2002;32:301–8.
106. Elkin SL, Fairney A, Burnett S, Kemp M, Kyd P, Burgess J, Compston JE, Hodson ME. Vertebral deformities and low bone mineral density in adults with cystic fibrosis: a cross-sectional study. Osteoporos Int. 2001;12:366–72.
107. Rossini M, Viapiana O, Del Marco A, de Terlizzi F, Gatti D, Adami S. Quantitative ultrasound in adults with cystic fibrosis: correlation with bone mineral density and risk of vertebral fractures. Calcif Tissue Int. 2007;80:44–9.
108. Sermet-Gaudelus I, Castanet M, Retsch-Bogart G, Aris RM. Update on cystic fibrosis-related bone disease: a special focus on children. Paediatr Respir Rev. 2009;10:134–42.
109. Ahmed LA, Joakimsen RM, Berntsen GK, Fonnebo V, Schirmer H. Diabetes mellitus and the risk of non-vertebral fractures: the Tromso study. Osteoporos Int. 2006;17:495–500.
110. Miao J, Brismar K, Nyren O, Ugarph-Morawski A, Ye W. Elevated hip fracture risk in type 1 diabetic patients: a populationbased cohort study in Sweden. Diabetes Care. 2005;28:2850–5.
111. Vestergaard P, Rejnmark L, Mosekilde L. Relative fracture risk in patients with diabetes mellitus, and the impact of insulin and oral antidiabetic medication on relative fracture risk. Diabetologia. 2005;48:1292–9.

112. Burnham JM, Shults J, Weinstein R, Lewis JD, Leonard MB. Childhood onset arthritis is associated with an increased risk of fracture: a population based study using the general practice research database. Ann Rheum Dis. 2006;65:1074–9.
113. Legroux-Gerot I, Vignau J, Collier F, Cortet B. Bone loss associated with anorexia nervosa. Joint Bone Spine. 2005;72:489–95.
114. Lucas AR, Melton LJ 3rd, Crowson CS, O'Fallon WM. Long-term fracture risk among women with anorexia nervosa: a population-based cohort study. Mayo Clin Proc. 1999;74:972–7.
115. Zipfel S, Herzog W, Beumont PJ, Russell J. Osteoporosis. Eur Eat Disord Rev. 2000;8:108–16.
116. Bonjour JP, Theintz G, Buchs B, Slosman D, Rizzoli R. Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence. J Clin Endocrinol Metab. 1991;73:555–63.
117. Nguyen TV, Maynard LM, Towne B, et al. Sex differences in bone mass acquisition during growth: the fels longitudinal study. J Clin Densitom. 2001;4:147–57.
118. Walker MD, Babbar R, Opotowsky AR, et al. A referent bone mineral density database for Chinese American women. Osteoporos Int. 2006;17:878–87.
119. Chevalley T, Rizzoli R, Hans D, Ferrari S, Bonjour JP. Interaction between calcium intake and menarcheal age on bone mass gain: an eight-year follow-up study from prepuberty to postmenarche. J Clin Endocrinol Metab. 2005;90:44–51.
120. Rosenthal DI, Mayo-Smith W, Hayes CW, et al. Age and bone mass in premenopausal women. J Bone Miner Res. 1989;4:533–8.
121. Theintz G, Buchs B, Rizzoli R, et al. Longitudinal monitoring of bone mass accumulation in healthy adolescents: evidence for a marked reduction after 16 years of age at the levels of lumbar spine and femoral neck in female subjects. J Clin Endocrinol Metab. 1992;75:1060–5.
122. Bachrach LK, Hastie T, Wang MC, Narasimhan B, Marcus R. Bone mineral acquisition in healthy Asian, Hispanic, black, and Caucasian youth: a longitudinal study. J Clin Endocrinol Metab. 1999;84:4702–12.
123. Bailey DA, McKay HA, Mirwald RL, Crocker PR, Faulkner RA. A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study. J Bone Miner Res. 1999;14:1672–9.
124. Recker RR, Davies KM, Hinders SM, Heaney RP, Stegman MR, Kimmel DB. Bone gain in young adult women. JAMA. 1992;268:2403–8.
125. Lofman O, Larsson L, Toss G. Bone mineral density in diagnosis of osteoporosis: reference population, definition of peak bone mass, and measured site determine prevalence. J Clin Densitom. 2000;3:177–86.
126. Alderman BW, Weiss NS, Daling JR, Ure CL, Ballard JH. Reproductive history and postmenopausal risk of hip and forearm fracture. Am J Epidemiol. 1986;124:262–7.
127. Cummings SR, Nevitt MC, Browner WS, et al. Risk factors for hip fracture in white women. Study of osteoporotic fractures research group. N Engl J Med. 1995;332:767–73.
128. Michaelsson K, Baron JA, Farahmand BY, Ljunghall S. Influence of parity and lactation on hip fracture risk. Am J Epidemiol. 2001;153:1166–72.
129. Chowdhury S, Sarkar NR, Roy SK. Impact of lactational performance on bone mineral density in marginally-nourished Bangladeshi women. J Health Popul Nutr. 2002;20:26–30.
130. Dursun N, Akin S, Dursun E, Sade I, Korkusuz F. Influence of duration of total breast-feeding on bone mineral density in a Turkish population: does the priority of risk factors differ from society to society? Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2006;17:651–5.
131. Hopkinson JM, Butte NF, Ellis K, Smith EO. Lactation delays postpartum bone mineral accretion and temporarily alters its regional distribution in women. J Nutr. 2000;130:777–83.
132. Laskey MA, Prentice A. Bone mineral changes during and after lactation. Obstet Gynecol. 1999;94:608–15.
133. Lissner L, Bengtsson C, Hansson T. Bone mineral content in relation to lactation history in pre- and postmenopausal women. Calcif Tissue Int. 1991;48:319–25.
134. More C, Bettembuk P, Bhattoa HP, Balogh A. The effects of pregnancy and lactation on bone mineral density. Osteoporosis international: a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA. 2001;12:732–7.
135. Khoo CC, Woo J, Leung PC, Kwok A, Kwok T. Determinants of bone mineral density in older postmenopausal Chinese women. Climacteric. 2011;14:378–83.
136. Rojano-Mejia D, Aguilar-Madrid G, Lopez-Medina G, et al. Risk factors and impact on bone mineral density in postmenopausal Mexican mestizo women. Menopause. 2011;18:302–6.
137. Cohen A. Premenopausal Osteoporosis. Endocrinol Metab Clin N Am. 2017;46(1):117–33. https://doi.org/10.1016/j.ecl.2016.09.007.
138. O'Sullivan SM, Grey AB, Singh R, Reid IR. Bisphosphonates in pregnancy and lactation-associated osteoporosis. Osteoporos Int. 2006;17:1008–12.
139. Blanch J, Pacifici R, Chines A. Pregnancy-associated osteoporosis: report of two cases with long-term bone density follow-up. Br J Rheumatol. 1994;33:269–72.

140. Kovacs CS, Ralston SH. Presentation and management of osteoporosis presenting in association with pregnancy or lactation. Osteoporos Int. 2015;26:2223–41.
141. Cohen A, Recker RR, Lappe J, et al. Premenopausal women with idiopathic low-trauma fractures and/or low bone mineral density. Osteoporos Int. 2011 Mar 2; Epub ahead of print.
142. National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. National Osteoporosis Foundation, Washington DC; 2013. http://www.nof.org/files/nof/public/content/resource/913/files/580.pdf. Accessed 2 July 2013.
143. Compston J, Bowring C, Cooper A, Cooper C, Davies C, Francis R, Kanis JA, Marsh D, McCloskey EV, Reid DM, Selby P. Diagnosis and management of osteoporosis in postmenopausal women and older men in the UK: National Osteoporosis Guideline Group (NOGG) update 2013. Maturitas. 2013;75:392–6.
144. Rizzoli R, Branco J, Brandi M-L, Boonen S, Bruyère O, Cacoub P, Cooper C, Diez-Perez A, Duder J, Fielding RA, Harvey NC, Hiligsmann M, Kanis JA, Petermans J, Ringe JD, Tsouderos Y, Weinman J, Reginster J-Y. Management of osteoporosis of the oldest old. Osteoporos Int. 2014; https://doi.org/10.1007/s00198-014-2755-9.
145. Chopin F, Biver E, Funck-Brentano T, Bouvard B, Coiffier G, Garnero P, Thomas T. Prognostic interest of bone turnover markers in the management of postmenopausal osteoporosis. Joint Bone Spine. 2012;79:26–31.
146. Kanis JA, Burlet N, Cooper C, Delmas PD, Reginster JY, Borgstrom F, Rizzoli R. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. Osteoporos Int. 2008;19:399–428.
147. Guggina P, Flahive J, Hooven FH, Watts NB, Siris ES, Silverman S, Roux C, Pfeilschifter J, Greenspan SL, Diez-Perez A, Cooper C, Compston JE, Chapurlat R, Boonen S, Adachi JD, Anderson FA Jr, Gehlbach S. Characteristics associated with anti-osteoporosis medication use: data from the global longitudinal study of osteoporosis in women (GLOW) USA cohort. Bone. 2012;51:975–80.
148. Cohen A. Premenopausal Osteoporosis. Endocrinol Metab Clin N Am. 2017;46(1):117–33. https://doi.org/10.1016/j.ecl.2016.09.007.
149. Leffler DA, Schuppan D. Update on serologic testing in celiac disease. Am J Gastroenterol. 2010;105:2520–4.
150. Kann PH, Pfutzner A, Delling G, Schulz G, Meyer S. Transiliac bone biopsy in osteoporosis: frequency, indications, consequences and complications. An evaluation of 99 consecutive cases over a period of 14 years. Clin Rheumatol. 2006;25:30–4.
151. Bains SN, Hsieh FH. Current approaches to the diagnosis and treatment of systemic mastocytosis. Ann Allergy Asthma Immunol. 2010;104:1–10, quiz 10–12, 41.
152. Barete S, Assous N, de Gennes C, et al. Systemic mastocytosis and bone involvement in a cohort of 75 patients. Ann Rheum Dis. 2010;69:1838–41.
153. Vasikaran S, Eastell R, Bruyere O, et al. Markers of bone turnover for the prediction of fracture risk and monitoring of osteoporosis treatment: a need for international reference standards. Osteoporos Int. 2011;22:391–420.
154. Glover SJ, Gall M, Schoenborn-Kellenberger O, Wagener M, Garnero P, Boonen S, Cauley JA, Black DM, Delmas PD, Eastell R. Establishing a reference interval for bone turnover markers in 637 healthy, young, premenopausal women from the United Kingdom, France, Belgium, and the United States. J Bone Miner Res. 2009;24:389–97.
155. Dresner-Pollak R, Karmeli F, Eliakim R, Ackerman Z, Rachmilewitz D. Increased urinary N-telopeptide cross-linked type 1 collagen predicts bone loss in patients with inflammatory bowel disease. Am J Gastroenterol. 2000;95:699–704.
156. Adami S, Bertoldo F, Braga V, Fracassi E, Gatti D, Gandolini G, Minisola S, Battista Rini G. 25-Hydroxy vitamin D levels in healthy premenopausal women: association with bone turnover markers and bone mineral density. Bone. 2009;45:423–6.
157. Adami S, Bianchi G, Brandi ML, Giannini S, Ortolani S, DiMunno O, Frediani B, Rossini M. Determinants of bone turnover markers in healthy premenopausal women. Calcif Tissue Int. 2008;82:341–7.
158. Adami S, Gatti D, Viapiana O, Fiore CE, Nuti R, Luisetto G, Ponte M, Rossini M. Physical activity and bone turnover markers: a cross-sectional and a longitudinal study. Calcif Tissue Int. 2008;83:388–92.
159. Adami S, Zivelonghi A, Braga V, Fracassi E, Gatti D, Rossini M, Ulivieri FM, Viapiana O. Insulin-like growth factor-1 is associated with bone formation markers, PTH and bone mineral density in healthy premenopausal women. Bone. 2010;46:244–7.
160. Cohen A, Dempster DW, Recker RR, et al. Abnormal bone microarchitecture and evidence of osteoblast dysfunction in premenopausal women with idiopathic osteoporosis. J Clin Endocrinol Metab. 2011;96:3095–105.
161. Maggio AB, Ferrari S, Kraenzlin M, Marchand LM, Schwitzgebel V, Beghetti M, Rizzoli R, Farpour-Lambert NJ. Decreased bone turnover in children and adolescents with well controlled type 1 diabetes. J Pediatr Endocrinol Metab. 2010;23:697–707.
162. Garnero P, Schott AM, Prockop D, Chevrel G. Bone turnover and type I collagen C-telopeptide isomerization in adult osteogenesis imperfecta: associations with collagen gene mutations. Bone. 2009;44:461–6.
163. Cohen A, Shane E. Treatment of premenopausal women with low bone mineral density. Curr Osteoporos Rep. 2008;6:39–46.
164. Kanis JA on behalf of the World Health Organization Scientific Group. Assessment of osteoporosis at the primary health-care level. Technical Report. WHO Collaborating Centre, University of Sheffield, UK; 2008.

165. Kanis JA, Johnell O, Oden A, Johansson H, McCloskey E. FRAX™ and the assessment of fracture probability in men and women from the UK. Osteoporos Int. 2008;19:385–97.
166. Kanis J, Cooper C, Burlet N, Delmas P, Reginster Y, Borgstromand F, Rizzoli R. European guidance for the diagnosis and management of osteoporosis in postmenopausal women. On behalf of the European society for clinical and economical aspects of osteoporosis and osteoarthritis (ESCEO). (file:///C:/Users/Yasser/Documents/Books%20Medicine%20El%20Miedany/Osteoporosis%20New%20Horizons/Section%20I/Female%20bone%20health/pocket-guidelines-esceo-english.pdf) Accessed on 30th June 2019.
167. El Miedany Y, ….. FRAS.
168. Cohen A, Dempster D, Recker R, et al. Abnormal bone microarchitecture and evidence of osteoblast dysfunction in premenopausal women with idiopathic osteoporosis. J Clin Endocrinol Metab. 2011;96:3095.
169. Peris P, Ruiz-Esquide V, Monegal A, et al. Idiopathic osteoporosis in premenopausal women. Clinical characteristics and bone remodelling abnormalities. Clin Exp Rheumatol. 2008;26:986–91.
170. Rubin MR, Schussheim DH, Kulak CA, Kurland ES, Rosen CJ, Bilezikian JP, Shane E. Idiopathic osteoporosis in premenopausal women. Osteoporos Int. 2005;16:526–33.
171. Peris P, Martinez-Ferrer A, Monegal A, Martinez de Osaba MJ, Alvarez L, Ros I, Muxi A, Reyes R, Guanabens N. Aetiology and clinical characteristics of male osteoporosis. Have they changed in the last few years? Clin Exp Rheumatol. 2008;26:582–8.
172. Cundy T, Ames R, Horne A, et al. A randomized controlled trial of estrogen replacement therapy in long-term users of depot medroxyprogesterone acetate. J Clin Endocrinol Metab. 2003;88:78–81. [PubMed] [Google Scholar].
173. Liu SL, Lebrun CM. Effect of oral contraceptives and hormone replacement therapy on bone mineral density in premenopausal and perimenopausal women: a systematic review. Br J Sports Med. 2006;40:11–24. [PMC free article] [PubMed] [Google Scholar].
174. Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Cochrane Database Syst Rev. 2003:CD001297.
175. Kaunitz AM, Miller PD, Rice VM, Ross D, McClung MR. Bone mineral density in women aged 25–35 years receiving depot medroxyprogesterone acetate: recovery following discontinuation. Contraception. 2006;74:90–9. [PubMed] [Google Scholar].
176. Scholes D, LaCroix AZ, Ichikawa LE, Barlow WE, Ott SM. Change in bone mineral density among adolescent women using and discontinuing depot medroxyprogesterone acetate contraception. Arch Pediatr Adolesc Med. 2005;159:139–44.
177. Ciacci C, Maurelli L, Klain M, et al. Effects of dietary treatment on bone mineral density in adults with celiac disease: factors predicting response. Am J Gastroenterol. 1997;92:992–6. [PubMed] [Google Scholar].
178. Mautalen C, Gonzalez D, Mazure R, et al. Effect of treatment on bone mass, mineral metabolism, and body composition in untreated celiac disease patients. Am J Gastroenterol. 1997;92:313–8. [PubMed] [Google Scholar].
179. McFarlane XA, Bhalla AK, Robertson DA. Effect of a gluten free diet on osteopenia in adults with newly diagnosed coeliac disease. Gut. 1996;39:180–4.
180. Miller KK, Lee EE, Lawson EA, et al. Determinants of skeletal loss and recovery in anorexia nervosa. J Clin Endocrinol Metab. 2006;91:2931–7.
181. Lumachi F, Camozzi V, Ermani M. FDEL, Luisetto G. bone mineral density improvement after successful parathyroidectomy in pre- and postmenopausal women with primary hyperparathyroidism: a prospective study. Ann N Y Acad Sci. 2007;1117:357–61.