



How to manage osteoporosis before the age of 50

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ABSTRACT

This narrative review discusses several aspects of the management of osteoporosis in patients under 50 years of age. Peak bone mass is genetically determined but can also be affected by lifestyle factors. Puberty constitutes a vulnerable period. Idiopathic osteoporosis is a rare, heterogeneous condition in young adults due in part to decreased osteoblast function and deficient bone acquisition. There are no evidence-based treatment recommendations. Drugs use can be proposed to elderly patients at very high risk. Diagnosis and management of osteoporosis in the young can be challenging, in particular in the absence of a manifest secondary cause. Young adults with low bone mineral density (BMD) do not necessarily have osteoporosis and it is important to avoid unnecessary treatment. A determination of BMD is recommended for premenopausal women who have had a fragility fracture or who have secondary causes of osteoporosis: secondary causes of excessive bone loss need to be excluded and treatment should be targeted. Adequate calcium, vitamin D, and a healthy lifestyle should be recommended. In the absence of fractures, conservative management is generally sufficient, but in rare cases, such as chemotherapy-induced osteoporosis, antiresorptive medication can be used. Osteoporosis in young men is most often of secondary origin and hypogonadism is a major cause; testosterone replacement therapy will improve BMD in these patients. Diabetes is characterized by major alterations in bone quality, implying that medical therapy should be started sooner than for other causes of osteoporosis. Primary hyperparathyroidism, hyperthyroidism, Cushing's syndrome and growth hormone deficiency or excess affect cortical bone more often than trabecular bone.

1. Introduction

Osteoporosis is defined by the World Health Organization (WHO) as a 'progressive systemic skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue, with a consequent

increase in bone fragility and susceptibility to fracture' [1]. Fractures in premenopausal women are less frequent than in postmenopausal women, but they may be an important indicator of underlying poor bone quality and future fracture risk [2]. According to the WHO, in postmenopausal women, osteoporosis is diagnosed when hip or spine

Abbreviations: AN, Anorexia nervosa; BMC, Bone mineral content; BMD, Bone mineral density; aBMD, areal Bone mineral density; vBMD, volumetric bone mineral density; DMPA, Depot medroxyprogesterone acetate; GnRHa or LHRHa, Gonadotropin-Releasing Hormone Agonist; GH, Growth Hormone; HA, Hypothalamic Amenorrhoea; HRpQCT, High Resolution Peripheral Quantitative Computed Tomography; IGF1-1, Insulin Growth Factor 1-1; IOF, International Osteoporosis Foundation; OC, Oral contraceptives; PTH, Parathyroid hormone; PHPT, Primary hyperparathyroidism; PBM, Peak bone mass; SERMs, Selective estrogen receptor modulators; TGF-beta, Transforming Growth factor- beta; TBS, Trabecular bone score; T1DM, Type 1 Diabetes Mellitus; T2DM, Type 2 diabetes mellitus; VFA, Vertebral fracture assessment; WHO, World Health Organization

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bone mineral density (BMD) is two and a half standard deviations or more below that of the young adult mean (T-score ≤ -2.5). There is no consensus, however, on the diagnostic criteria for osteoporosis in premenopausal women [2]. As a matter of fact, the relationship between BMD and fracture risk is not so well established in premenopausal women [2]. Consequently, the diagnosis can only be considered in premenopausal women with clinically relevant fragility fractures or in case of other fragility fractures in combination with low bone mass [2]. During life, diseases or treatments known to affect peak bone mass (PBM) or cause bone loss and fractures could also be major drivers of premenopausal osteoporosis and deserve full characterization. Compared to postmenopausal osteoporosis, treatment of premenopausal osteoporosis has less often been studied because fractures are substantially less common in premenopausal women than in postmenopausal women. The management of osteoporosis in the young is challenging, because after treatment of the underlying condition, few bone-specific treatments have shown evidence of a true benefit on fracture risk.

2. Methods

The Belgian Bone Club (BBC) consists of a multidisciplinary group of specialists in clinical chemistry, endocrinology, epidemiology, gerontology and geriatrics, gynecology, internal medicine, nephrology, radiology, rheumatology, physiotherapy, primary care, and public health focused on updating the current existing guidelines for the management of osteoporosis. The target end-users are primary care physicians as well as specialists involved in osteoporosis care in Belgium.

In 2018, the Belgian Bone Club board invited a panel of experts in musculoskeletal diseases (endocrinologists, rheumatologists, paediatricians, clinical epidemiologists and scientists) to be part of a working group, discussing the management of osteoporosis before 50 with a special focus on various issues of potential relevance to the clinician: the achievement of PBM, low bone mass in children, the diagnosis and risk assessment in young individuals, the treatment of osteoporosis related to endocrine conditions, and the treatment of premenopausal osteoporosis. A narrative review of each topic was presented by the different reviewers for each section during a national meeting, during which comments were brought by the audience. Following this meeting a manuscript was prepared and further amended by the various board members of the BBC who are listed as authors. The outcomes of this working group are discussed in this narrative review.

3. Achievement of peak bone mass

An individual's fracture risk at any given age is largely determined by one's actual bone mass, which is the result from bone acquired during growth and young adulthood and the subsequent ageing-related loss of bone. PBM, which is a framework concept rather than a true biologic event, is defined as the maximum amount of bone that is accrued during skeletal maturation and the subsequent consolidation in early adulthood [3]. It is supposed to coincide with or represent peak bone strength, and as it is a major determinant of bone mass, osteoporosis and fracture risk in later life, optimal acquisition of PBM during the first decades of life is of importance (Fig. 1).

During childhood, bone mass accrual is mainly driven by increasing bone size. Bones grow in length and width due to chondrocyte proliferation, differentiation, and subsequent enchondral ossification at the growth plate, modeling by periosteal resorption more distant to the growth plate, and periosteal apposition as well as endosteal resorption at the diaphysis. Until puberty, bone mass accrual is rather slow and stable, without important differences between boys and girls, and no apparent changes in trabecular or cortical volumetric BMD occur during this period [3–7]. In contrast, notable gender differences in bone development arise at the onset of puberty, a period characterized by

accelerated longitudinal and radial bone growth resulting in peak height gain and peak bone mineral accretion. During male puberty, accelerated periosteal apposition and continued endosteal expansion result in a marked increase in bone diameter and an increase in cortical thickness. In turn, bone development during female puberty is characterized by a smaller increase in periosteal apposition, but also with less endosteal expansion or even endosteal bone formation, leading to a similar increase in cortical thickness but a smaller increase in bone diameter [5–8]. From late puberty onwards, gender differences are also observed in trabecular structure, with greater increases in trabecular thickness and bone volume over tissue volume in boys as compared to girls [9,10]. Further, whereas cortical BMD increases more in girls, an increase in trabecular BMD is only observed in boys [6,9,11,12]. As a result of these differential changes, by the end of puberty, bone strength in men is approximately 30–50 % higher than in women, despite a similar or even lower cortical BMD, and more cortical porosity [6,9–15]. Timing of peak bone mineral accretion during puberty also differs between boys and girls (Fig. 2). For instance, a study in children of European ancestry found that for total body bone mineral content (BMC), peak bone mineral accretion rate occurs at 12.5 ± 0.9 years in girls and 14.1 ± 0.9 years in boys. [16] As there is a lag time between peak height gain (thus bone growth) and PBM accretion, children probably experience a period of relatively impaired bone strength during the growth spurt which could explain the higher fracture rate in both boys and girls around this age [9,11]. Importantly, 39 % of total body BMC is acquired during the 4 years surrounding peak bone mineral accretion and by 4 years following the peak, 95 % of adult bone mass has been achieved. [16] It is thus not to be emphasized that this pubertal period of rapid bone mass accrual is a crucial but vulnerable period for the achievement of PBM and that illnesses or treatments during puberty might impact future bone strength.

PBM is generally considered to be achieved during the second or third decade of life, but the exact timing is site- and gender-dependent. Some longitudinal studies have suggested that PBM at the lumbar spine is achieved by the end of sexual maturation in both men and women, [17,18] whereas others showed that bone mineral accrual at this site continues into the third decade or even later [19–21]. Likewise, achievement of PBM at the hip has been suggested to occur between age 16 and 19 years in women [20], whereas studies in men have shown either decreases [20–22] or increases [17] in hip areal BMD during the third decade of life. Ultimately, estimates of PBM age will vary depending on the bone characteristic, population, gender and skeletal site investigated and methodology applied. For instance, findings from the GOOD study in young adult men suggested a plateau or decreases in aBMD at the hip shortly after the age of 20 whereas cortical thickness at the radius continued to increase thereafter [21,23].

The process of bone mass accrual is largely determined by genetic factors, explaining 60–80 % of the variability in bone mass. [14,24] Part of this is reflected in associations between bone mass indices, pregnancy duration, birth weight, pubertal timing, height and lean mass [25–27], and it has been demonstrated that idiopathic osteoporosis in men partly results from a heritable deficit in bone mass acquisition [28,30]. In addition, successful achievement of PBM depends on general health status, illnesses and treatments, and certain lifestyle factors during childhood and young adulthood. Again reflecting the importance of the pubertal growth spurt, constitutional delay of puberty is an established risk factor for low BMC at adulthood and even in the general population pubertal timing is associated with bone mass indices at later age. [25,31] In this regard, it should be noted that depot medroxyprogesterone acetate (DMPA) injections should be avoided as the resulting hypo-estrogenic state is associated with only partially reversible deficits in bone mass accrual [3]. (This subject is discussed further, in the section about osteoporosis in premenopausal women). Data on effects of oral contraceptive (OC) use in young adolescent girls are conflicting. Although OC use in adult women has no or only minimal effects on bone metabolism and is considered beneficial in

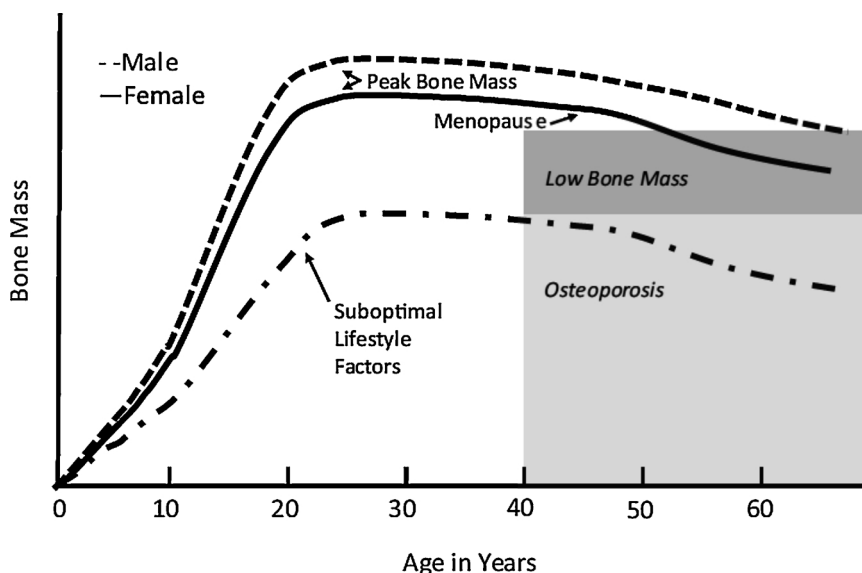


Fig. 1. Schematic illustration of bone mass acquisition to reach peak bone mass (PBM) in men and women. The impact of suboptimal lifestyle factors on PBM is shown (adapted from reference [3]).

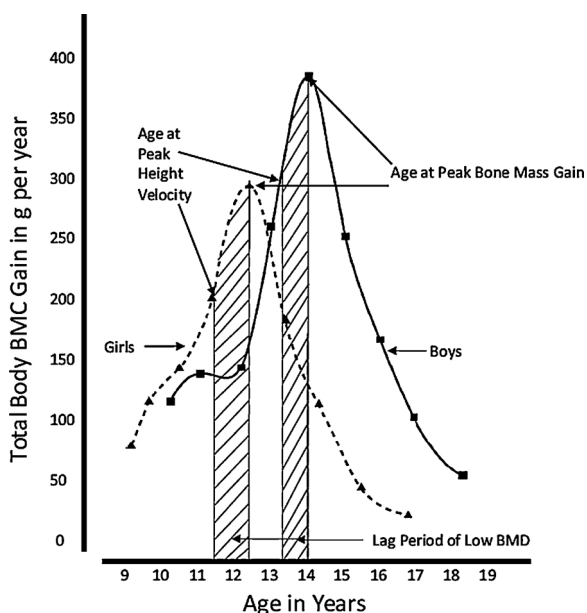


Fig. 2. Timing of peak bone mineral accretion during puberty also differs between boys and girls. Peak bone mineral accretion rate occurs at 12.5 ± 0.9 years in girls and 14.1 ± 0.9 years in boys [16]. As there is a lag time between peak height gain (thus bone growth) and peak bone mass accretion, children probably experience a period of relatively impaired bone strength during the growth spurt which could explain the higher fracture rate in both boys and girls around this age [9,11]. Importantly, 39 % of total body BMC is acquired during the 4 years surrounding peak bone mineral accretion and by 4 years following the peak, 95 % of adult bone mass has been achieved. Figure adapted from [16].

peri- and postmenopausal women, there is growing concern on a possible negative impact of low-dose combined OC use on bone health in adolescent girls, especially when treatment is started during early puberty. It is hypothesized that the estrogenic exposure resulting from low-dose OC use corresponds to that of the early follicular phase, which would mean that these girls are for the remainder of their pill cycle relatively hypoestrogenic. However, several studies addressing this issue have failed to observe that bone indices vary according to OC estrogen dose. In addition, other studies suggested a possible mediating effect of the progestogenic components of combined OC, which would

depend on their anti- or pro-androgenic activity [32]. Except for the before mentioned adverse effects of DMPA administration, bone effects other progesterone-only OC methods (e.g. implants or pills) are considered neutral in adult women but have not been thoroughly addressed in adolescent girls [33,34].

Further, confirming mechanical loading as one of the most important determinants of bone metabolism, several studies have found a positive effect of physical activity on bone size and accrual. [14,35–39] Effects were greatest if activities were dynamic, moderate to high in load magnitude, short in load duration, odd or non-repetitive in load direction, and applied quickly. These responses, however, vary by sex, maturational and nutritional status, and are site-specific. Reflecting both physical activity and shared heritability, bone mass indices are associated with lean mass in both men and women [36,40,41], and lean mass accrual seems to precede bone mass accrual. [42,43] Obviously, adequate nutritional intake is a prerequisite for optimal bone mass accrual and bone mass deficits are found in children with malnutrition, malabsorption, or eating disorders [25]. With respect to specific nutrients and dietary patterns, there is evidence for positive effects of a dairy-rich food pattern and randomized clinical trials reported benefits of supplemental calcium and vitamin D intake on bone mass accrual, although this is probably only relevant in children with low baseline intake [3,42]. Finally, harmful behavior such as smoking or excessive consumption of alcohol and illicit drugs, especially during early puberty, is associated with less favorable bone mass indices at adulthood [3,44–48].

In summary: Taken together, optimal achievement of PBM is important for one’s future bone strength. As for other aspects of physical development and growth, this process is largely genetically determined but can be heavily affected by general health status and lifestyle factors. Especially during puberty, the crucial but vulnerable period of life when the majority of total bone mass is acquired, factors influencing bone health should receive appropriate attention.

4. Assessment and treatment of low bone mass in children and adolescents with chronic diseases

Low bone mass in children is defined by a decreased bone mineral content (BMC) or density (BMD) z-score (of the whole skeleton or at a specific skeletal site) below - 2 SD for chronological age, height or stage of pubertal development [49]. Low bone mass, when adjusted for age, gender, height and weight, results in decreased bone skeletal strength

and increased fracture risk [50]. Osteoporosis in children has been defined by additional clinical criteria, such as the presence of one or more vertebral compression fracture(s) in the absence of local disease or high energy trauma, or both a BMD z-score below the $-2SDs$ with 2 or more long bone fractures by age 10, or 3 or more long bone fractures by age 19 years of age [51].

4.1. Clinical presentation

Low bone mass or osteoporosis must be suspected in children in the presence of fracture for minimal trauma, chronic bone (back) pain, or radiological evidence of rarefied bone or vertebral compression [52]. Osteoporosis can be primary, related to an intrinsic (and mostly genetic) skeletal problem, or secondary, related to chronic diseases or their treatments. In contrast to healthy children and adolescents, presenting mainly with forearm fractures after trauma, children with osteoporosis may sustain fractures at the distal femur during turning in bed, at the distal thoracic vertebra during convulsions, at the fingers or upper arm during dressing, at the distal tibia when stepping down from stairs or at the ribs during physical therapy, or spontaneously, especially at the vertebrae [52]. Vertebral compression fractures are frequently under-diagnosed as most children with secondary osteoporosis have no symptoms.

4.2. Bone densitometry

Despite its limitations (providing areal BMD rather than volumetric BMD, no differentiation between trabecular and cortical bone), DXA is the most widely available and used technique for the evaluation of BMD in children and adolescents [53]. Whole body BMD and lumbar spine BMD corrected for height are considered as valuable parameters for respectively cortical and trabecular bone strength in children at risk for osteoporosis. Measurements at the distal femur can provide a useful alternative, when measurements at whole body or lumbar spine are not possible (due to severe scoliosis, metal implants [54]). The vertebral fracture assessment (VFA) seems of little utility in pediatric patients, because of poor visibility, especially at thoracic level [55]. Up to now, no reference data for trabecular bone score (TBS) have been developed, although the lumbar spine TBS was found to correlate with the stress-strain index in adolescents suffering from anorexia nervosa (AN) [56].

4.3. Bone mass in children with chronic diseases

Several chronic medical conditions may result in a deficient bone mass and/or increased fracture risk during childhood, including endocrine diseases (Cushing syndrome, primary ovarian insufficiency, type 1 diabetes mellitus), neuro-muscular diseases (cerebral palsy, Duchenne muscular dystrophy), rheumatic diseases (juvenile idiopathic arthritis) and other chronic inflammatory diseases (inflammatory bowel disease, cystic fibrosis), nutritional and intestinal disorders (AN, cystic fibrosis, celiac disease), haematological and oncological diseases (thalassemia major, acute lymphoblastic leukemia, bone marrow transplantation) [57].

Fracture risk in adolescents with AN is nearly 60 % higher than healthy weight controls [58]. The decrease in bone mineral content in adolescents with AN might be attributed to nutritional deprivation, chronic acidemia, and several associated functional hormonal disturbances (secondary hypogonadism and hypothyroxinemia, hypercorticism, low IGF1 – 1 production and hypoleptinemia). The bone deficit in girls with AN is not responding to estrogen/progestin treatment and is not always recovered after weight gain. The topic of AN and osteoporosis is also discussed further in the section about osteoporosis in premenopausal women).

Non-traumatic fractures, especially of the distal femur and vertebra, increase with advancing age and degree of lumbar spine or distal femoral BMD deficit in children with cerebral palsy. Beside the chronic

immobilization, nutritional deprivation (feeding problems), associated growth hormone deficiency and chronic use of anticonvulsants impact negatively on bone mineral accrual [59]. Assisted standing alone (total time between 180–675 min/week), standing on vibrating platforms, GH treatment and nutritional interventions can increase BMD in these patients, but the greatest increase in BMD occurs with intravenous administration of pamidronate [60]. It is also well established that Duchenne muscular dystrophy is associated with an increased fracture risk, especially in case of glucocorticoid treatment [61]. More than one third of Duchenne muscular dystrophy patients on glucocorticoids have a history of femoral or humeral fractures.

Bone mass can be severely reduced in children with chronic rheumatic disorders, such as juvenile idiopathic arthritis, systemic lupus erythematosus, juvenile dermatomyositis. The chronic inflammation, the production of pro-osteoclastic cytokines, and glucocorticoid treatment are responsible for a decreased bone mass [62]. Vertebral fracture risk in these diseases is associated with a decrease in lumbar spine BMD following the first 6 months of glucocorticoid treatment. Also, children with inflammatory bowel disease show a low BMD, especially when receiving high prednisolone doses for several years. Beside the chronic inflammation, poor nutrition, delayed puberty and low muscle mass also impact bone mineral accrual in pediatric patients with Crohn's disease, whereas anti-TNF- α therapy is associated with improvements in trabecular BMD as well as cortical structure [63].

Children with acute lymphoblastic leukemia may present with incident vertebral fractures in the first year of chemotherapy. Low spinal BMD at diagnosis and low back pain are important risk factors for fractures in these children [64].

In children with cystic fibrosis, no increased risk for fractures has been found, despite the frequent finding of low BMD values. On the other hand, poor nutritional status, frequent lung exacerbations, hyperglycemia, and low vitamin D status in addition to glucocorticoid therapy are risk factors for osteopenia [65].

4.4. Screening and monitoring

Evaluation of bone mass should be focused on those chronically diseased children, who may benefit from interventions to decrease their risk of clinically significant fractures. Despite low BMD, no consistent increased fracture rate has been described in children with Turner syndrome, celiac disease and type 1 diabetes mellitus. Routine DXA screening has been advocated for children with Duchenne muscular dystrophy (annual), cystic fibrosis (starting at ages 8–12 years and repeated after 1–5 year, depending on the severity of the bone deficit), inflammatory bowel disease (at diagnosis with additional risk factors or history of clinically significant fractures) [66]. The recommended time interval for follow up measurement during treatment or disease progress is between six and twelve months [67].

4.5. Treatment

Effective control of the underlying disease should remain the best first line approach [68]. Adherence to a gluten free diet is associated with a complete recovery of the bone mineral deficit in celiac disease. Lowering of the glucocorticoids to greatest extent possible, use of alternate day administration of glucocorticoids if possible, and stimulating regular physical activity and providing optimal vitamin D and calcium supplementation are to be advised, from the early months of glucocorticoid therapy in all steroid responsive chronic diseases. Addressing vitamin D deficiency, encouraging regular physical activity and ensuring normal growth (by increasing caloric and protein intake) and pubertal progression (by estrogen or testosterone supplementation), stopping smoking, limiting the intake of carbonated drinks and avoiding the use of intramuscularly contraceptive DMPA are additional measures favouring bone mineral accrual or preventing further bone mineral loss during childhood and adolescence. In addition, avoidance

of jarring activities (e.g. horseback riding, roller coasters), contact sports, forward flexion exercises, and heavy backpacks might be advised in children with fragility fractures.

Bisphosphonates, especially when given intravenously, have proven their efficacy in stimulating bone mineralization and decreasing the fracture incidence, in severe primary osteoporosis, such as osteogenesis imperfecta and osteoporosis-pseudoglioma syndrome, as well as in severe secondary osteoporosis, such as glucocorticoid induced osteoporosis and cerebral palsy [69]. The finding of a low bone mass on itself is however not sufficient to install a bisphosphonate therapy, which in general is given for 2–4 years. In osteogenesis imperfecta (with exception of the type 2 form), at least more than 2 fractures a year and/or deformities of the long bones and vertebrae are required. In chronic diseases, the fracture history and additional risk factors (glucocorticoid therapy, immobilization, familial history of osteoporosis should guide the decision for bisphosphonate treatment. Children with a low lean body mass may not have an increased risk of fragility fractures despite a low BMD. Practitioners have been inclined to treat all causes osteoporosis with the OI pamidronate protocols of 0.5–1 mg/kg dose on 3 consecutive days every 2–4 months, although significant improvements in BMD can be achieved with a single pamidronate infusion every 3–6 months. Single day infusions of zoledronate in a dose of 0.025–0.05 mg /kg every 6 months are replacing the pamidronate treatments in children, without the risk of more side-effects and at a lower price [70].

5. Idiopathic osteoporosis of young adults (IO)

Four cases of idiopathic osteoporosis in young adults were described by Albright in the 1940s as “clinical manifestations similar to those in post-menopausal or senile osteoporosis but where the individual is not post-menopausal nor senile” [71]. In a study of the Mayo Clinic screening individuals aged 20–44, the incidence of fragility fractures and low bone mass was estimated at 4.1 cases per 100.000 person years, but only 9% did not have secondary osteoporosis; thus, the incidence of idiopathic osteoporosis in this age group was only 0.4 cases per 100.000 person years, with an equal distribution of cases between genders [72]. It is a diagnosis of exclusion: all secondary cause of osteopenia and monogenic osteoporosis must be excluded before it is established. A low PBM, largely genetically determined [29,73], seems to be implicated, and could be the major culprit at least in males. Bone histology is characterized by a low trabecular volume, cortical thickness and low trabecular wall thickness, suggesting a deficient osteoblastic function [72,74,75]. Several studies have confirmed that formation was low, at least in some patients [76,77], and in vitro studies showed that osteoblast proliferation [78] and/or function were altered [79,80]. Also, the expression of genes linked to osteoblast proliferation and function has been found decreased in males with idiopathic osteoporosis [81]. Alterations of the matrix mineralization and constitution were also detected and could contribute to bone fragility [82,83]. Low formation could result from a low free-IGF1, found to be associated to osteoblastic surface [84], particularly in men [85,86], a relative IGF1 insensitivity in women [77] or modified sensitivity to mechanical strain [87]. A low free serum estradiol was also found associated with wall thickness in males [86]. Lapauw et al. [30] also observed a low estradiol in young male patients and their offspring, which could explain in part low PBM acquisition. Most histomorphometric studies did not show increased activation frequency; some indicated that the eroded surface tended to be higher than in controls, which would indicate an increased delay between resorption and formation. Serum resorption markers were found to be increased in some study [88,89], but bone turnover markers did not differ in patients with IO from the reference range of pre-menopausal control subjects in most [29,87,90]. Some patients have hypercalciuria, but for most there is no alteration of calcium metabolism. When analyzed by High Resolution Peripheral Quantitative Computed Tomography (HRpQCT) in women with IO,

bone architecture is severely altered, at the trabecular and cortical level in weight bearing tibia, at the trabecular level alone in the non-weight bearing radius [87], with a decreased estimated bone strength by finite element analysis. The structural alteration was not significantly different between a group of young women recruited on the basis of fragility fracture and one recruited on the basis of a low bone mass, suggesting that it is essential when taking care of these young people with low bone mass to assess bone architecture by histomorphometry or HRpQCT [87,91,92]. Patients should be given directives for a general healthy way of life: sufficient calcium and protein in the diet, vitamin D repletion, soft but regular physical activity, refrain from smoking and limit alcohol consumption. There are no data from controlled, randomized, trials to establish validated guidelines for pharmacological treatment, and pilot studies were not powered for fracture. Pharmacological treatment should be proposed only in those with a history of fracture or with a high absolute risk of fracture, or severe structural alterations at bone biopsy or HRpQCT. It should be avoided whenever possible in pre-menopausal women, because of the possible adverse effect on fetal development in case of pregnancy. Bisphosphonates may increase BMD and bone strength in men with idiopathic osteoporosis [93]. In a pilot study including 21 pre-menopausal women with IO, teriparatide 20 µg/d for 18–24 months increased spine and hip BMD and improved trabecular architecture and strength estimated by finite element analysis [94,95], particularly at the tibia which is a weight bearing site. However, a significant amount of the gain in BMD at the spine was lost during the 2 years following the treatment discontinuation [96], suggesting that an antiresorptive treatment might be required after PTH.

In summary, idiopathic osteoporosis is a rare, heterogeneous condition in young adults of both genders, with altered bone structure and strength due at least in part to decreased osteoblast function and deficient bone acquisition during growth. There are no recommendations for treatment based on evidence; drugs which decrease fracture risk in senile and post-menopausal osteoporosis can be proposed to patients having a very high fracture risk or profound alteration of bone structure.

6. Osteoporosis in premenopausal women

Osteoporosis affects particularly older women after menopause, but occasionally premenopausal women are also affected [97]. When premenopausal osteoporosis is suspected, it is important to identify whether it is due to failure to attain a sufficient PBM or from exaggerated bone loss, as the therapeutic strategy will differ. As in postmenopausal osteoporosis, one should strive to correct risk factors that induce bone loss.

6.1. Assessment of premenopausal osteoporosis

In this population particular attention should be given to reproductive dysfunction (often amenorrhea). In case of amenorrhea, after having ruled out pregnancy, Follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol, prolactin, thyroid-stimulating hormone (TSH) need to be assessed, in order to establish the cause of the amenorrhea (Table 1).

6.2. Etiologies

6.2.1. Hypothalamic amenorrhea

(HA) is the most common cause of amenorrhea, with the exception of pregnancy, in young women. It can result from AN, or excessive exercise. Amenorrhea may also be due to iatrogenic causes such as the use of DMPA, or gonadotropin-releasing hormone (GnRH) agonist. Amenorrhea may also result from hyperprolactinemia. AN is the major concern for osteoporosis.

Table 1

Major causes of amenorrhea due to abnormalities in the hypothalamic-pituitary-ovarian axis Adapted from Corrine K Welt, Robert L Barbieri, William F Crowley, Jr, Mitchell E Geffner, Kathryn A Martin, Uptodate 2019.

Abnormality	Causes
Hypothalamic dysfunction	Isolated GnRH deficiency Functional hypothalamic amenorrhea - Weight loss, eating disorders - Excessive exercise (including but not exclusively: running, ballet dancing, figure skating, gymnastics) - Stress - Severe or prolonged illness Inflammatory or infiltrative diseases Brain tumors – e.g., craniopharyngioma Cranial irradiation Traumatic brain injury Other syndromes - Prader-Willi, Laurence-Moon-Biedl, leptin mutations
Pituitary dysfunction	Hyperprolactinemia, including lactotroph adenomas Other pituitary tumors - acromegaly, corticotroph adenomas (Cushing's disease) Other tumors - meningioma, germinoma, glioma Genetic causes of hypopituitarism Empty sella syndrome Pituitary infarct or apoplexy
Ovarian dysfunction	Primary ovarian insufficiency (premature ovarian failure) - Turner syndrome, fragile X permutation, chemotherapy and radiotherapy, somatic chromosomal defects, autoimmune, idiopathic
Other	Polycystic ovary syndrome Hyperthyroidism Hypothyroidism Uncontrolled diabetes mellitus types 1 and 2 Exogenous androgen use

HPO: hypothalamic-pituitary-ovarian; GnRH: gonadotropin-releasing hormone.

6.2.2. Osteoporosis in patients with anorexia nervosa (AN)

AN affects most commonly women with a median age of 18 years [98,99]. The lifetime prevalence of AN ranges from 0.6 % to 4.2 % [98]. Almost all AN patients suffer from osteopenia and one in two from osteoporosis [98,99]. The typical triad consists of low energy intake, amenorrhea and osteoporosis. AN is associated with marked endocrine changes: in addition to low estradiol, there are abnormalities in thyroid hormones, in hormones regulating appetite (oxytocin, leptin and peptide tyrosine tyrosine (PYY)), low levels of IGF-1, GH resistance, hypercortisolemia and low levels of testosterone also contribute to the clinical complications of these patients [98,99]. Biological markers of bone turnover, may be increased in adults with AN while they may be low in adolescents with AN [100,101]. AN patients have also lower levels of 25OHD and 1,25(OH)2D [102]. Trabecular bone loss at the lumbar spine is more marked and common in these patients [103]. They also often have a reduced PBM [104]. It is not surprising therefore, that their fracture risk is much increased (2- to 7-fold) [105–107]. This increased fracture risk seems to persist more than 10 years after the diagnosis [106].

The ultimate treatment consists in restoring weight gain, which will often initiate a normal menstrual cycle and improve bone mass. Nevertheless, a complete catch-up does not always occur [101]. AN patients should be supplemented with calcium and vitamin D to attain daily ingestions of about 1200 mg calcium and 800 IU vitamin D. Several studies reported that estrogen-progestin oral contraceptives, and even those containing high-dose estrogen, do not provide an efficient treatment for the AN associated bone loss [107], while menopausal hormone therapy (MHT), such as 100 µg transdermal 17-beta-estradiol with cyclic micronized progesterone, resulted in BMD gains. Androgen replacement is not recommended in AN patients. There are no large studies about bisphosphonates in these patients [108,109]. While, it is acceptable to prescribe them to older AN patients, they

should not be prescribed to younger AN and certainly not to those who may become pregnant. Similarly, Denosumab and Teriparatide should also not be prescribed for AN associated osteoporosis in young patients.

To summarize, AN predominantly affects young women. Most will suffer from osteoporosis as a consequence of major endocrine changes, for which a multidisciplinary approach is needed. The goal is to restore a normal body weight and the recover a normal cycle. Besides promoting a healthy lifestyle, one should supplement these patients with calcium and vitamin D. MHT is indicated in adolescent girls with sustained low body weight, low BMD and amenorrhea when other causes of amenorrhea have been excluded. Other anti-osteoporosis drugs may be prescribed in older women with severe bone loss.

6.2.3. Hyperprolactinemia

Hyperprolactinemia is a common clinical problem, with a prevalence of 0.4 % in unselected adults and of 9–17 % in women with reproductive diseases. It may be drug-induced or result from a micro (or less often macro) prolactinoma. Hyperprolactinemia may lead to anovulation and infertility, (oligo-) amenorrhea and galactorrhea. Hyperprolactinemic women have reduced bone densities compared to controls [110,111]. It is likely that only women with increased prolactin and amenorrhea and a hypoestrogenic state are at risk for osteoporosis. Nevertheless, there is no correlation between prolactin levels and bone density [112].

Treatment: One need to rule out iatrogenic induced hyperprolactinemia. Imaging of the pituitary gland using computed tomography or magnetic resonance imaging is indicated to rule out a pituitary adenoma. Hyperprolactinemic women, who do not have pituitary tumors, menstruate regularly and do not desire to become pregnant, may not require therapy. Similarly, women with so-called macroprolactinemia do not need to be treated. [113]. Cabergoline and Bromocriptine are effective in normalizing serum prolactin, restoring menstrual cycle and reducing bone loss and fracture risk in symptomatic hyperprolactinemic women. Surgery or radiological treatment is seldom indicated for the treatment of pituitary macroadenoma [113].

6.2.4. Drug induced

Depot medroxyprogesterone acetate (DMPA) is a safe injectable contraceptive but it may not be indicated in women with suspected osteoporosis or at risk of osteoporosis. Similarly, DMPA may not be the first-choice contraception before achieving PBM, because the circulating estrogen concentrations are rather low (similar to those found in the early follicular phase) and DMPA may be associated with a slight (reversible) decrease in BMD [114].

Gonadotropin-Releasing Hormone Agonist (GnRHa or LHRHa) suppress ovarian function through the inhibition of the hypothalamic-pituitary axis. Less than 6 month GnRHa is associated with limited and reversible bone loss, while GnRHa therapy for more than 6 months induces important bone loss. The current indication is severe endometriosis, before surgery or before IVF, since patients with uterine fibroids, are nowadays treated with Ulipristal acetate instead of GnRHa [115].

6.2.5. Premature ovarian insufficiency (POI)

Premature ovarian insufficiency is defined as menopause before the age of 40. It can occur after a bilateral salpingo-oophorectomy, chemotherapy or radiotherapy, or be associated with chromosome abnormalities (especially X chromosome), FSH receptor gene polymorphisms, inhibin B mutations, enzyme deficiencies and autoimmune diseases, but in the majority of cases, the cause remains unknown. Diagnosis should be confirmed by repeated elevated FSH level, over 40 IU/L and an estradiol level lower than 50 pmol/L, in the absence of bilateral oophorectomy. Untreated POI increases not only the osteoporosis risk but also the cardiovascular one. MHT is indicated in these patients till the age 50 years. Spontaneous ovulations occur occasionally, but these patients need often to be helped with donor- oocytes- in

vitro fertilization. POF patients should be treated in specialized units capable of dealing with their multiple needs [116].

To summarize: BMD measurement is recommended for premenopausal women with known secondary causes of osteoporosis or history of a fragility fracture. On the other hand, excessive bone loss needs to be excluded. An etiological treatment needs to be initiated in women with a secondary cause of osteoporosis. All patients should be supplemented with calcium and vitamin D. In all cases, risk factors should be corrected when possible. When no accelerated bone loss or fractures are documented, conservative management is sufficient. In rare cases of premenopausal osteoporosis, other medication such as bisphosphonates or denosumab will be used.

6.2.6. Down syndrome

Adults with Down Syndrome have lower bone mineral density compared to the general population. Their BMD declines more rapidly with age. As a consequence, they have a higher risk of osteoporosis, which requests early screening and treatment when needed [117].

7. Diagnosis of osteoporosis and fracture risk assessment in young adults

The general definition of osteoporosis as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with consequently enhanced bone fragility and increased fracture risk, is applicable to all age groups from children to seniors both female and male. Things are different as to an operational definition of osteoporosis and indications for osteoporosis therapy, which have primarily been developed and validated for postmenopausal women and later for older subjects of both sexes. In these subjects, an aBMD at the lumbar spine or the hip ≥ 2.5 SD below the young adult mean, i.e. an aBMD T-Score ≤ -2.5 or lower, is considered as osteoporosis and if there is also a typical fragility fracture prevalent, this is usually considered an indication for treatment. According to a more recently introduced alternative approach, indication for treatment is based on an ‘unacceptably high’ (10 year) probability of fracture as estimated on the basis of clinical risk factors with or without aBMD (FRAX®). In children, the diagnosis of osteoporosis is based on a combination of low aBMD and prevalent fragility fractures. Osteoporosis in young adults between 20 and 50 years of age, in turn, did not receive much attention with diagnosis and indications for treatment in this age group remaining rather poorly defined [118].

A difficulty in the approach to osteoporosis in young adults is to differentiate between two distinct situations. On the one hand, healthy young individuals may have a low aBMD indicating a low PBM and have less favorable bone geometry and microarchitecture, without specific underlying pathophysiologic mechanisms or manifest ongoing deterioration. In these individuals low aBMD results from genetic and environmental influences during growth, including age at puberty [29,118–121]. The low aBMD is often congruent with body size and does not necessarily represent a pathologic situation even if the low PBM is associated with a somewhat higher fracture risk [122–124]. On the other hand, young adults may have osteoporosis with bone fragility resulting from pathologically altered bone modeling and/or remodeling during growth and/or thereafter. In most of the latter patients a secondary cause of osteoporosis is involved, the remaining may have a genetic cause or idiopathic disease [118]. The distinction between ‘healthy individuals with low PBM’ and young ‘individuals with true osteoporosis’ may not be easy on the background of a anyhow high incidence of usually traumatic but not infrequently multiple bone fractures in young individuals, with up to 30 % of young women and 50 % of young men having a history of fracture as child or adolescent [118].

In subjects over age 20 who do not have a fully mature skeleton and have not yet reached PBM because of delayed puberty, which is not uncommon in chronic disease, low bone mass is logically defined

Table 2

Some possible secondary causes of osteoporosis and bone fragility in young adults.

Gastrointestinal-related
- Inflammatory bowel disease (in particular Chron’s disease)
- Malabsorption
- Coeliac disease
- Cystic fibrosis
Endocrine-related
- Hyperparathyroidism
- Hypovitaminosis D
- Turner syndrome
- Klinefelter’s syndrome
- Anorexia nervosa
- Other hypogonadisms
- Cushing’s syndrome
- Type 1 diabetes
- Pregnancy
Systemic-, hematologic- and inflammatory diseases
- Juvenile/rheumatoid arthritis
- Connective tissue diseases
- Leukemia
- Organ transplant
- Systemic mastocytosis
- Nephropathies
- Human immunodeficiency virus disease
Various genetic diseases
- Hemochromatosis
- Osteoporosis imperfecta
- Marfan syndrome
- Gaucher’s disease
- Galactosemia
- Duchenne
- Thalassemia
Medications
- Glucocorticoids
- Anticonvulsants
- GnRH agonists/antagonists
- Aromatase inhibitors
- Cytotoxic chemotherapy
- Long-term Heparin
- Long-term Proton Pump Inhibitors

similarly as in children as an aBMD 2 SD or more below the age-specific population mean, i.e. a Z-score of ≤ -2 or lower. Considering that in young adults there is little difference between T- and Z-score, it is proposed by the International Society for Clinical Densitometry to report aBMD in premenopausal women and men younger than 50 years also as Z-Score with low aBMD defined as Z-Score ≤ -2 [121]. On the other hand, a working group of the IOF has proposed, for the sake of coherence with the WHO operational definition of osteoporosis, to stick with a T-score-based definition of the disease for young adults. According to this approach, in a young individual who suffers from a chronic disorder known to adversely affect bone metabolism and has a fully mature skeleton, an aBMD T-Score < -2.5 at the lumbar spine or the hip is considered diagnostic for osteoporosis [118]. A non-exhaustive list of chronic disorders involved as secondary causes of osteoporosis in young adults is shown in Table 2. Clinical series generally report high (40 %) up to very high (90 %) prevalence of secondary causes in young adults with osteoporosis or fragility fractures [124–126]. Still according to this approach, in absence of a secondary cause of osteoporosis, occurrence of a fragility fracture, i.e. often a vertebral fracture, in a subject with an aBMD T-Score < -2.5 may indicate a genetic cause of osteoporosis or idiopathic osteoporosis [118]. There are important caveats to any approach to operational definition of osteoporosis in young adults. First, although in young as in older subjects lower aBMD is associated with higher fracture risk, a more precise quantitative relationship between aBMD and fracture risk has not been well established for younger individuals. Moreover, this relationship may differ according to the underlying secondary cause of osteoporosis. It should also be reminded that low aBMD does not allow for differentiation between osteoporosis

and osteomalacia. Further, algorithms to estimate fracture risk on the basis of clinical risk factors (with or without aBMD) such as FRAX® are not valid for young subjects and should not be used.

For young adults with suspected osteoporosis, the following general clinical approach can be proposed (see 118 for comprehensive overview). Considering that fractures in childhood and adolescence are common and usually traumatic, history of such a fracture does not constitute an indication for osteoporosis-related investigations, including DXA. On the other hand, young adults who suffer from a chronic disease known to be potentially deleterious to the skeleton (Table 2), or who suffered a fragility fracture, in particular a vertebral crush fracture, or who have a history of multiple (i.e. > 2) fractures, should have an evaluation of BMD by DXA. Ideally this should be complemented with a screening for silent vertebral fractures, which can be done by DXA Vertebral Fracture Assessment (VFA). Young adults with aBMD < -2.5 and/or a (vertebral) fragility fracture, without known secondary cause, should be the subject of a thorough and systematic investigation to uncover a possible responsible disease, medication or extreme lifestyle habit. This should consist minimally of an extensive medical history, which includes present symptoms and medications as well as personal- and familial medical history, a thorough physical examination and a stepwise clinical biology testing. The latter should start with the routine parameters of bone and calcium-phosphate homeostasis and screening for the more common diseases before moving to testing for less common causes. Low aBMD with low vitamin D status, in particular if accompanied by bone and muscle pains is suspicious of osteomalacia. If vitamin D status is normal and no secondary cause of osteoporosis can be found, a T-score < -2.5 may not represent a pathological situation, in particular in persons with small body size. However, if there are fragility fractures, there may be a genetic cause or one may have to conclude to idiopathic osteoporosis.

Studies on treatment of osteoporosis in young adults are scarce and generally small scaled, often poorly controlled and of short duration, and without data on treatment effect on fracture risk. The focus should be on ruling out or correcting vitamin D deficiency, optimal treatment of the underlying secondary cause and limiting of its adverse bone effects. The latter often requires multifactorial interventions, e.g. nutritional interventions to prevent or correct vitamin D-, calcium-, protein- or other deficiencies, correction of sex steroid deficiencies, physical activity, and anti-inflammatory treatment. In general, there is limited evidence to support the use of specific osteoporosis medication in young subjects with osteoporosis. There is limited evidence for beneficial effects of bisphosphonates on BMD for particular secondary causes of osteoporosis (e.g. anorexia nervosa, estrogen deprivation in breast cancer) [118]. But in any case, the approach to use of bisphosphonates or other osteoporosis medication in young adults should be highly restrictive, in particular in idiopathic osteoporosis, which often result from deficient acquisition of PBM rather than from accelerated bone loss [126].

In conclusion, diagnosis and management of osteoporosis in the young can be challenging, in particular in the absence of a manifest secondary cause. Young adults with low aBMD do not necessarily have osteoporosis and it is important to avoid to inappropriately label individuals as having osteoporosis as this may result in unnecessary worries, stress and inappropriate treatments.

8. Treatment of osteoporosis in patients with endocrine conditions before 50

About two-thirds of men and even more in young men with osteoporosis can a secondary cause be identified [127]. Besides specific treatment of the causal condition, elimination of contributory risk factors of osteoporotic fractures, such as alcoholism, tobacco abuse and reduced physical activity should be part of the global therapeutic approach. It is mandatory to provide adequate calcium and vitamin D intake for preserving and enhancing bone mass in osteoporotic men.

While there are less data in men than in women, pharmacological therapies, essentially inhibitors of bone resorption, seem to be as effective in increasing BMD and probably in reducing fracture risk, but priority should be given to the control of the underlying condition.

8.1. Male hypogonadism

Hypogonadism induces increased bone remodeling bone loss and is a major cause of osteoporosis in men. Androgens play a determinant role for maintaining skeletal health in men [128]. In vitro, androgens stimulate osteoblastic cell proliferation, up-regulate TGF-beta and IGF-1, and down-regulate IL-6 [129]. Testosterone is also aromatized in estrogen in peripheral tissues (including osteoblasts and osteocytes). Estrogen plays a key role in bone resorption and formation and men with low estrogen or decreased aromatase activity, suffer from osteoporosis. [130,131]. While low testosterone levels are associated with decreased bone mass and muscle strength, a much stronger correlation with fracture risk is seen with low bioavailable estradiol levels or high sex hormone binding globulin levels [132,133]. Testosterone replacement therapy results in increases in serum levels of both estradiol and testosterone, and improves BMD in men with established hypogonadism, but antifracture efficacy data are lacking [134]. Bisphosphonates and denosumab are effective in increasing BMD in hypogonadal men but are more often used in elderly men, notably to counteract the effects of androgen deprivation therapy in prostate cancer and denosumab has been shown to decrease vertebral fracture rate in that particular setting [135,136].

8.2. Diabetes mellitus

Type 1 (T1DM) and 2 diabetes mellitus (T2DM) are increasingly associated with deleterious effects on the skeleton. A 12-fold increased risk of hip fracture has been described in women with T1DM and a 1.7-fold increase in women with T2DM [137]. Young individuals with T1DM have decreased BMD and fail to achieve PBM. DM is associated with low bone turnover osteoporosis and decreased markers of osteoblastic activity [138]. Insulin and amylin have anabolic effects on bone and are decreased in T1DM patients. This induces a decrease in IGF-1 concentrations and a reduced bone formation. Sustained exposure to high glucose concentrations can result in osteoblast dysfunction. Moreover, there is increased expression of Dkk1 and SOST, both antagonists of Wnt signaling and osteoblastogenesis [139]. The accumulation of advanced glycation end products and lower enzymatic collagen crosslinks contribute to altered biomechanical features of diabetic bone suggesting the importance of glycemic control over time. The increased bone marrow adiposity typical of diabetes probably plays a larger role in the bone disease associated with T2DM than in T1DM [140].

Current evidence is not based on RCT evaluating anti-fracture efficacy in diabetic patients, but on BMD responses in subgroups of patients with osteoporosis and diabetes mellitus. These data support the use of both anti-resorptive and anabolic agents in diabetic patients. A recent IOF Consensus paper concludes that BMD and FRAX may underestimate the risk of fracture in this population and suggest therefore a lower BMD threshold (T-score – 2 at spine or hip) for starting therapy [141].

8.3. Primary hyperparathyroidism (PTH)

Elevated PTH levels are known to be catabolic to the skeleton. Most patients with primary hyperparathyroidism (PHPT) are postmenopausal women. The contribution to osteoporosis is so well established that in patients with PHPT the presence of osteoporosis is considered an indication for parathyroidectomy. Being less than 50 years old is also an indication for parathyroidectomy [142]. PHPT preferentially affects cortical bone. It is therefore recommended to measure the BMD at the distal forearm and the femoral neck. Nevertheless,

these patients have also vertebral fractures. Increased bone turnover, low BMD and reduced bone quality appear to confer an increased risk of fracture in PHPT, highlighting the need for proactive screening of bone disease. In experienced hands, surgery is successful in more than 95 % of the cases. Osteopenia is only partially reversible, even in the long term, after successful surgery [143].

8.4. Hyperthyroidism

Thyrotoxicosis is an established cause of high-turnover osteoporosis, and untreated hyperthyroidism results in decreased BMD and increased fracture risk. Bone loss has been reported at all skeletal sites, but is affected preferentially at cortical sites, suggesting the use to screen distal forearm BMD [144].

8.5. Cushing's syndrome

Exogenous hypercortisolism is a major cause of secondary osteoporosis in young individuals. Endogenous causes, essentially including Cushing's disease due to a pituitary adenoma and cortisol-producing adrenal adenomas are rare causes of secondary osteoporosis. Most forms of endogenous Cushing's syndrome are potentially curable and, theoretically at least, cure could lead to the reversibility of glucocorticoid-induced skeletal changes. The treatment of skeletal fragility with specific anti-osteoporotic drugs in patients with endogenous Cushing's syndrome is challenging because there are no specific guidelines and available data not allow an evidence-based approach. A few case reports suggest that specific therapy for osteoporosis might not be necessary in severe osteoporosis due to Cushing's disease or cortisol-secreting adrenal adenoma after successful surgery [145].

8.6. Growth hormone deficiency or excess

Children with GH deficiency reach a short stature and have a reduced PBM. A marked reduction in bone turnover, particularly at cortical sites is observed by histomorphometry in adult-onset GH deficiency. This is associated with a lower BMD, and a 2–3-fold fracture risk compared to that of non-GH deficient osteoporotic patients. GH replacement therapy has been associated with a decrease fracture risk [146]. Acromegaly has been associated with an excess of GH and IGF-1 and a significant increase in bone turnover and an increased vertebral fractures incidence, although BMD can also be preserved [147].

In summary, osteoporosis in young men is often of secondary origin and hypogonadism is a major cause; testosterone therapy improves BMD in these patients but antifracture efficacy has not been demonstrated. The pathogenesis of diabetes bone disease is complex and alterations in bone quality play a major role in the increased fracture risk that is characteristic of diabetes, explaining why intervention threshold for starting medical therapy should be lower than for other causes of osteoporosis. Other endocrine causes include primary hyperparathyroidism, which affects cortical bone more often than trabecular bone, hyperthyroidism, Cushing's syndrome and GH deficiency or excess.

Contributors

S Rozenberg drafted the Introduction and the section 'Osteoporosis in Premenopausal women', and discussed the manuscript.

O Bruyère discussed the manuscript.

P Bergmann drafted the section 'Idiopathic osteoporosis of young adults' and discussed the manuscript.

E Cavalier discussed the manuscript.

E Gielen discussed the manuscript.

S Goemaere discussed the manuscript.

JM Kaufman drafted the section 'Diagnosis of osteoporosis and fracture risk assessment in young adults' and discussed the manuscript.

B Lapauw drafted the section 'Achievement of peak bone mass' and discussed the manuscript.

MR Laurent discussed the manuscript.

J De Schepper drafted the section 'Assessment and treatment of low bone mass in children and adolescents with chronic diseases' and discussed the manuscript.

JJ Body drafted the section 'Treatment of osteoporosis in patients with endocrine conditions before 50' and discussed the manuscript.

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