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REVIEW

Osteoporosis in young adults: pathophysiology, diagnosis, and management

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Abstract Postmenopausal osteoporosis is mainly caused by increased bone remodeling resulting from estrogen deficiency. Indications for treatment are based on low areal bone mineral density (aBMD, T-score≤−2.5), typical fragility fractures (spine or hip), and more recently, an elevated 10-year fracture probability (by FRAX®). In contrast, there is no clear definition of osteoporosis nor intervention thresholds in younger individuals. Low aBMD in a young adult may reflect a physiologically low peak bone mass, such as in lean but otherwise healthy persons, whereas fractures commonly occur with high-impact trauma, i.e., without bone fragility. Furthermore, low aBMD associated with vitamin D deficiency may be highly prevalent in some regions of the world. Nevertheless, true osteoporosis in the young can occur, which we define as a T-score below −2.5 at spine or hip in association with a chronic disease known to affect bone metabolism. In the absence of secondary causes, the presence of fragility fractures, such as in vertebrae, may point towards genetic or idiopathic osteoporosis. In turn, treatment of the underlying condition may improve bone mass as well. In rare cases, a bone-specific treatment may be indicated, although evidence is scarce for a true benefit on fracture risk. The International Osteoporosis Foundation (IOF) convened a working group to review pathophysiology, diagnosis, and management of osteoporosis in the young, excluding children and adolescents, and

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provide a screening strategy including laboratory exams for a systematic approach of this condition.

Keywords Diagnosis · IOF · Low bone mass · Osteoporosis · Secondary osteoporosis · Young adults

Introduction

Osteoporosis is a systemic skeletal disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk [1]. 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) [2, 3]. 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 [4]. Several national guidelines now recommend using FRAX® thresholds (10-year fracture probabilities) as indications for treatment decisions in women and men aged 50 and above [5–7]. On the other hand, low bone mass 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<−2 SD) [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 [9].

In contrast 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 [10–12], 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 all the more difficult because up to 30 % of young women and 50 % of young men have had fractures during childhood and adolescence, usually traumatic but not uncommonly multiple [13–16]. These fractures are associated with decreased bone mass acquisition and lower peak bone mass in otherwise healthy individuals [15], i.e., without an underlying pathophysiological mechanism. It would, therefore, be inappropriate to 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.

To help clinicians address this conundrum, the International Osteoporosis Foundation (IOF) convened a working group to review pathophysiology, diagnosis, and treatment of osteoporosis in the young and to outline a screening strategy including laboratory exams for a systematic approach to this condition. This approach requires, first, the exclusion of secondary causes [17] and, eventually, the assessment of whether any possible genetic disorders of bone fragility are involved [18].

Peak bone mass and pathophysiology of osteoporosis in the young

Between 8 and 18 years of age, bone mineral content (BMC) more than doubles, whereas the true volumetric bone mineral density (vBMD) barely changes [19]. 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 [20]. 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 [21]. 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 males, which occurs at approximately the same rate as in females but lasts longer, leading to a 10–15 % greater peak bone mass on average, 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 nonweight-bearing bones [22–24], and accelerates in women after menopause and in aging men.

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]. So any disorder appearing during growth that alters one or more of these

parameters will exert a negative influence on bone modeling and remodeling, affecting bone mass acquisition 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 typical 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 [8, 27]. Another good 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 (Table 1), depot progesterone acetate (Depo-Provera), used as a contraceptive agent, has recently raised huge concerns [29, 30].

Definition and prevalence of osteoporosis in the young

As long as peak bone mass has not been achieved, the T-score definition of osteoporosis cannot be used. Hence, low bone mass in children and adolescents has been defined by a Z-score below −2, and this definition could be extended beyond 20 years of age in those with delayed puberty, as is often the case with chronic diseases from childhood [8, 9]. 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 [31]. For the sake of coherence with the WHO operational definition of osteoporosis, however, we propose to keep the T-score-based definition of the disease for young adults, unless it appears that he/she is still growing. Hence, in young adults suffering from a chronic disorder known to affect bone metabolism (Table 1), a T-score below −2.5 at spine or hip should be considered as diagnostic of osteoporosis. It is important to note, however, 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 (see below). 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 [32].

According to a T-score≤−2.5, in theory, only 0.5 % of young women aged 30–40 years would fulfil the criteria of osteoporosis and another 15 % would be considered as

Table 1 Major causes of secondary osteoporosis in the young

Chronic and inflammatory	Inflammatory bowel disease	Malabsorption
	Coeliac disease	HIV
	Nephropathies	Organ transplant
	Cystic fibrosis	Connective tissue diseases
	(Juvenile) rheumatoid arthritis	Thalassemia
	Systemic mastocytosis	Leukemia
Endocrine	Diabetes type I	Cushing's syndrome
	Hypovitaminosis D	Hyperparathyroidism
	Hypogonadism (amenorrhea, Turner, anorexia nervosa)	
	Hyperthyroidism	Pregnancy
Neuromuscular and metabolic	Duchenne	Galactosemia
	Gaucher's disease	Glycogen storage disease
	Hemochromatosis	Marfan syndrome
Medications	Glucocorticoids	Glitazones
	PPIs (chronic use)	
	Anticonvulsants	Cyclosporine (tacrolimus)
	Aromatase inhibitors, depot MPA	GnRH inhibitors
	High-dose thyroxine	Heparin (long-term)
	Cytotoxic chemotherapy	HAART

HIV human immunodeficiency virus, *MPA* medroxyprogesterone acetate (used as contraceptive), *HAART* highly active antiretroviral therapy, *PPIs* proton pump inhibitors

osteopenic (T-score between −2.5 and −1) in any population [33]. 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 [34]. Similar prevalence of low bone mass in 579 Spanish premenopausal women (aged 20–44 years) was observed, with lumbar spine (LS) 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 (FN) BMD [35].

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 IBD [36–38], coeliac disease [39–41], cystic fibrosis [42–44], type 1 diabetes [45–47], rheumatoid arthritis [48], and anorexia nervosa [49–51], among other causes of secondary osteoporosis (Table 1).

Clinical approach of osteoporosis in the young

As mentioned above, young individuals suffering from a chronic disease (Table 1) and/or presenting with a low trauma fracture, particularly in vertebrae, and/or multiple fractures (more than two) should have a DXA (ideally combined with VFA) evaluation. 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. 1). 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 (see above) and/or lateral X-rays, does not necessarily represent a pathological situation, particularly in subjects of small body size [8]. Investigations in this case should be limited in the absence of symptoms and/or signs of a chronic disorder. Interestingly, in one study of constitutionally lean[1] young women without menstrual alterations, aBMD as well as trabecular and cortical microstructure at distal radius was found to be as low as in women with anorexia nervosa, and the calculated bone breaking strength of the constitutionally lean was lower than normal [54]. Although low aBMD in a particularly lean (BMI<18.5 kg/cm^2) but healthy individual could, therefore, represent an increased risk of fractures, there is no evidence, so far, for any therapeutic intervention in these cases. Similarly, late puberty has been associated with decreased peak bone mass, radius cortical vBMD, and thickness [55], but again, there is no evidence that this situation should prompt further investigations nor a therapeutic intervention in the absence of symptoms and/or signs for an underlying chronic disorder. In contrast, osteoporotic patients with low body mass index (<18.5 kg/cm^2 as underweight defined by WHO) and menstrual (for women), eating, and/or behavioral disorders must be investigated for the possibility of secondary osteoporosis (more specifically anorexia nervosa).

Some series indicate that in 44–90 % of young men and women with osteoporosis or clinical fractures, an underlying secondary cause can be determined (see Table 1) [56–58], and the large percentage gap between studies probably reflects more or less intensive searches to determine the cause of osteoporosis and/or different referral patterns. In practice, this search should include a complete medical history, including personal and a thorough family history (see genetic causes below) of bone fragility and/or endocrine, metabolic and inflammatory disorders, 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, and dietary and exercise patterns. Physical examination should particularly consider low height and/or BMI (see reasons above), abdominal tenderness, cutaneous signs of allergy (urticaria), hyperpigmentation or decreased pilosity (hypogonadism), as well as the presence of kyphosis, limb deformities, joint inflammation, hyperlaxity, blue sclerae, and/or poor dentition.

Laboratory tests

A set of laboratory tests to screen for the most common bone and mineral disorders (including vitamin D deficiency and primary hyperparathyroidism), thyroid dysfunction, diabetes, renal failure and hepatic dysfunction, systemic inflammation, and in men, hypogonadism (particularly in the presence of other clinical signs) is presented in Table 2. It is particularly important to discard the possibility of vitamin D deficiency (25OHD<10 ng/ml or 25 nmol/L), as this may affect bone mineralization and be translated into low aBMD, without being osteoporosis.

It is worth noting that coeliac 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 Ab has an excellent

[1] Constitutional thinness (CT), or Leanness, was identified over the last decades as a nonpathological state of underweight that does not meet the Diagnostic and Statistical Manual of Mental Disorders (DSM) IV criteria of anorexia nervosa. Contrary to the later pathology, the nonpathological state of CT in adult women is supported by the presence of menstruations, normal thyroid and cardiac functions, and normal insulin sensitivity. Moreover, CT individuals are characterized by a body weight that has always been in the lower percentiles for age, gender, and ethnicity. Familiality and heritability of thinness were also described or demonstrated. For further reading, see [52–54].

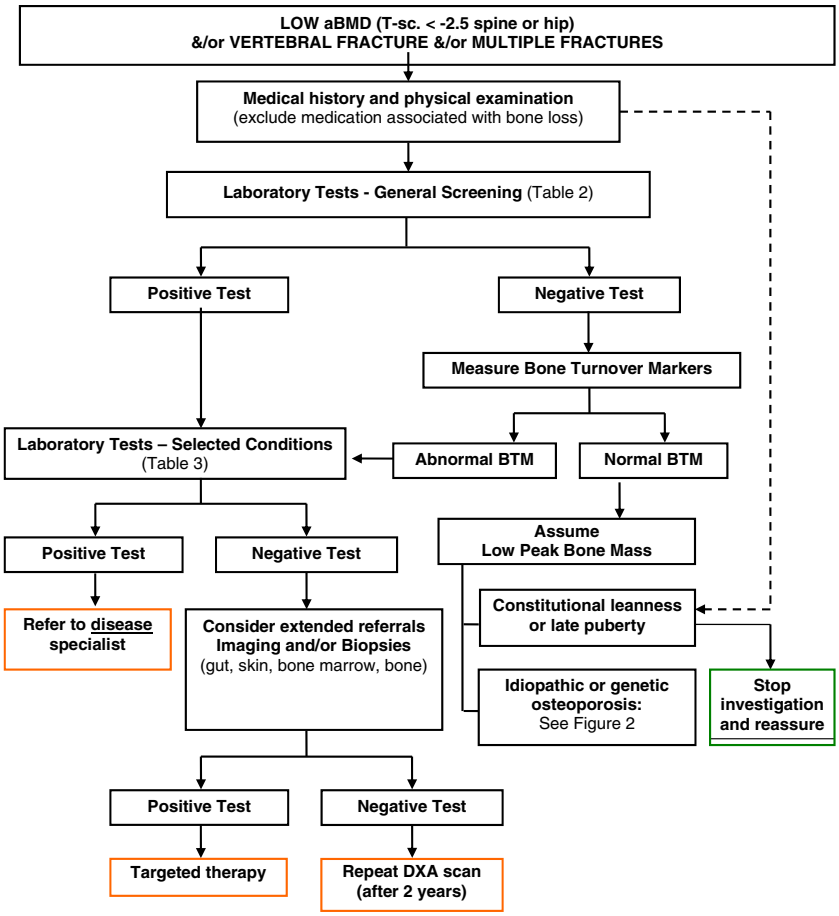

Fig. 1 Clinical pathway for determining the cause of bone fragility in young adults with low BMD, vertebral fracture, and/or multiple fractures

positive predictive value for this disease [59]. Note that diagnosis of IBD (Crohn's disease and ulcerative colitis) is 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 referred to a specialist for further intestinal investigations.

An additional set of selected diagnostic tests to be applied when the clinical and/or first laboratory results orient towards a specific condition is shown in Table 3. 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 [60], and an even higher prevalence has sometimes been reported. 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 isolated, with osteoporosis in up to 30 % of patients with SM [61, 62]. An elevated serum tryptase (>20 ng/ml) has a positive predictive value of 98 % for SM [61].

Besides bone alkaline phosphatase (BALP) which levels, if high after growth is completed, can orient towards osteomalacia (together with low 25OHD levels), Paget's disease, or bone neoplasia, and if low, towards hypophosphatasia (see below), the utility of bone turnover markers (BTMs)—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 [63] (for reference range in young women, see [64]). First, data demonstrating a predictive role of BTMs for fracture risk in secondary osteoporosis are lacking, although they have been correlated with BMD changes in some diseases (i.e., IBD) [65]. Second, BTMs are correlated with the level of 25OHD, IGF-1, physical activity, etc. [66–69], and in the case of a chronic disorder, BTMs 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. In premenopausal women with idiopathic osteoporosis, bone turnover may also be high, normal, or low [70]. BTMs have been negatively correlated with HbA1C in type 1 diabetes, i.e., were lower with poor glucose control [71]. In contrast, when the achievement of peak bone mass is delayed, as is

Table 2 Laboratory tests—general screening

Mineral metabolism	Serum calcium (corrected for albumin)
	Serum phosphate
	Creatinine
	25(OH)D
	iPTH
	ALP (bone specific)
	BTMs (for instance, s-CTX and s-PINP)[a]
Inflammation, hematopoietic disorder	Blood cell count
	ESR or CRP
Hepatic disease	GOT, GPT, γ-GT
Diabetes (primary or secondary)	Fasting glucose, Hba1C
Thyroid dysfunction	TSH
Hypogonadism (men)	Total testosterone
Malabsorption, Coeliac disease	24-h urinary calcium
	Anti-endomysial, anti-transglutaminase

25OHD 25-hydroxyvitamin D, *iPTH* intact parathyroid hormone, *ALP* alkaline phosphatase, *BTM* bone turnover markers, *s-CTX* serum carboxy-terminal cross-linking telopeptide of type I collagen, *s-PINP* serum procollagen type I N propeptide, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *GOT* glutamic oxalacetic transaminase, *GPT* glutamic pyruvic transaminase, *γ-GT* γ-glutamyltransferase, *TSH* thyroid-stimulating hormone

[a] See text for details

often the case with chronic disorders starting during childhood or adolescence, BTMs 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. A recent fracture may also cause an elevation of BTMs for several months. Note that in patients with osteogenesis imperfecta (OI), 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 [72].

Despite these difficulties in interpreting BTMs, normal BTMs in a young adult with low aBMD would argue for an acquired low peak bone mass, whereas high BTMs would point towards an ongoing process of bone loss, as seen, for instance, in anorexia nervosa compared to constitutionally lean women [54]. Taken together with a low T-score and some evidence of bone fragility (see above), elevated BTMs could, therefore, prompt further investigations for an underlying cause (Fig. 1) and could be useful for therapeutic guidance [73]. 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 [70].

Table 3 Laboratory tests—selected conditions

Background	Test
TSH alterations	Free T4
Altered glucose, Cushing's syndrome	24-h free urinary cortisol
Altered testosterone (men)	LH/SHBG (free testosterone)
Amenorrhea, hypogonadism (women)	FSH/estradiol
Altered renal function (CRF)	$1,25(OH)_2D_3$
Hemochromatosis	Ferritin
Hypophosphatasia	ALP, BALP, urinary phosphoethanolamine
Mastocytosis	Tryptase, IgE
Gaucher's disease	Glucocerebrosidase

TSH thyroid-stimulating hormone, *LH*/*SHBG* luteinizing hormone/sex hormone-binding globulin, *FSH* follicle-stimulating hormone, *CRF* chronic renal failure, *BALP* bone-specific alkaline phosphatase, *IgE* immunoglobulin E

Genetic osteoporosis

A thorough family history of bone fragility should always be considered when investigating osteoporosis in the young, in particular for those individuals with extremely low bone mass and/or multiple fractures. In the absence of secondary causes, an autosomal-dominant or autosomal-recessive mutation could indeed be responsible for bone fragility (Fig. 2). To date, there are more than 300 monogenic disorders with

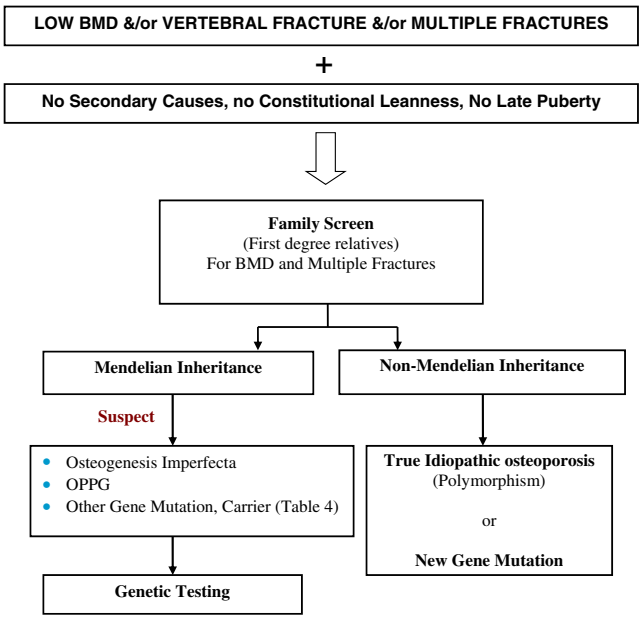

Fig. 2 Clinical pathway for young adults, with either low BMD and/or vertebral fracture, and/or multiple fractures, where no secondary causes of osteoporosis (including constitutional leanness and delayed puberty) were found

skeletal manifestations [74], including a number associated with bone fragility, such as connective tissue (OI and Marfan), lysosomal storage (Gaucher's and Pompe disease), and endocrine syndromes (including hypogonadotrophic hypogonadism, estrogen receptor, and aromatase mutations in men) [75–77]. However, skeletal complications are usually neither the first nor the predominant manifestations in most of these diseases, with the exception of OI, hypophosphatasia [78], and osteoporosis-pseudoglioma (OPPG) (Table 4), the latter also characterized by presence of congenital or infancy-onset blindness [79]. In nonosteoporotic young adults with repeated low-trauma fractures (including vertebral fractures) and no secondary causes, mild forms of OI should be excluded (genetic screening of Col1A1 and Col1A2 mutations) [80].

Idiopathic osteoporosis in the young

A particular situation occurs in young men with idiopathic osteoporosis, i.e., after secondary causes including hypogonadism, alcoholism, and medications have been excluded. These men are characterized by lower body weight and lower aBMD most prominent at the LS, reflecting low (trabecular and cortical) vBMD and smaller bone size. Long bone cortices are thinner due to larger endosteal cavities. Vertebral fractures, which are common in idiopathic male osteoporosis (IMO), have been associated with increased cortical porosity on iliac crest bone biopsies [81]. In these men, there is usually no evidence of either accelerated bone loss or increased bone turnover. Overall, the data points toward a defect in bone formation leading to decreased bone mass acquisition [82]. Lower circulating levels of IGF-1 and (free or bioavailable) estradiol, and higher SHBG could play a role in IMO. Moreover, there is a strong familial and genetic component involved, with a substantial proportion of sons being affected. Functional gene polymorphisms in the LDL-receptor-related protein 5 gene (*LRP5*) have been associated with this condition [83].

Idiopathic osteoporosis also exists 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, indicates that the group with idiopathic osteoporosis has significantly thinner cortices and trabeculae, and a lower mean wall thickness, i.e., a bone formation deficit [70]. However, bone turnover and indices of bone remodeling 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 [84]. It should be noted that hypercalciuria may be present not just in a subset of men, but also in premenopausal women with idiopathic osteoporosis [85].

Osteoporosis in pregnancy and lactation

A moderate increase of bone turnover has been observed during pregnancy [86], although it is still uncertain whether significant changes of bone mass occur. A small decrease in aBMD has been observed at the LS, but in long bones, this might be compensated by endosteal and periosteal appositions [87]. While during pregnancy the mother's intestinal calcium absorption is increased, during lactation, it returns to normal values [88], 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 PTHrP production and hypoestrogenic state secondary to high prolactin levels [87, 89, 90]. The decrease in bone mass, observed mainly in the trabecular compartments of bones, is generally restored 6 to 12 months after weaning [91].

Pregnancy-associated osteoporosis is a rare condition, which can present in the form of spinal osteoporosis or transient osteoporosis of the hip (TOH), as well as associated with prolonged heparin use [92]. TOH is associated with uni- or bilateral hip pain and may be complicated with a fracture, sometimes spontaneous [93]. Postpregnancy osteoporosis can lead to vertebral fractures, height loss, and severe back pain [94], as well as clinical fractures at other sites. Preexisting low BMD and high bone turnover during pregnancy and lactation may both play a role [89]. In women of reproductive age with established osteoporosis, it could, therefore, be recommended to avoid breastfeeding. Note that in a randomized double-blind placebo-controlled study on postpartum healthy women, calcium supplementation did not prevent bone loss during lactation and only slightly enhanced gain in bone density after weaning [95].

Treatment of osteoporosis in the young

Once vitamin D deficiency has been ruled out and/or corrected (i.e., 25OHD levels≥20 ng/ml or 50 nmol/L), the approach to osteoporosis in the young should primarily target the underlying disorder. Since the mechanisms leading to secondary osteoporosis in the young are rarely unique (see IBD, for instance [27]), interventions should be multifactorial, i.e., target vitamin and nutritional deficiencies, particularly vitamin D, calcium and protein intake, physical activity, inflammation, corticosteroid treatment, and/or gonadal steroids. With vitamin D insufficiency being such a common finding in most subjects with secondary osteoporosis,

Table 4 Main monogenic disorders primarily manifest as bone fragility

Monogenic disorders	Gene mutations	Familial pattern of inheritance	Description and main clinical outcome	Incidence
Osteogenesis imperfecta	Col I α1 and Col I α2	Autosomal dominant (types I–V)	Fragility fractures, bone deformity, and low BMD	Estimated at 6 to 7 per 100,000 people worldwide
	LEPRE1 and CRTAP (some OI types II, III, and VII)	Autosomal recessive (some types II, III, VII, and IX)	Dentinogenesis imperfecta	Types I and IV are the most common forms, affecting 4 to 5 per 100,000 people
	PPIB in type IX		Mild forms may be manifest as low aBMD only	
Hypophosphatasia	ALPL	Autosomal dominant (adult form)	Defective mineralization, leading to softening of the bones (osteomalacia)	Severe forms affect an estimated 1 in 100,000 newborns. Milder cases, such as those that appear in adulthood, probably occur more frequently
		Autosomal recessive (perinatal)	Recurrent fractures in the foot and thigh bones inducing chronic pain	
			Loss of adult teeth prematurely	
			Joint pain and inflammation	
Osteoporosis-pseudoglioma syndrome (OPPG)	LRP5 (11q13.4)	Recessive	Fragility fractures, bone deformity, low BMD and partial blindness	Unknown
			Carrier state may be manifest as bone fragility only	

vitamin D supplementation (1,000–2,000 IU) should be given first, prior to eventually considering any bone-specific drug (see below), since it has the potential to improve aBMD by restoring proper bone matrix mineralization, preventing secondary hyperparathyroidism and moderate bone turnover. In contrast with their beneficial effects in secondary osteoporosis, there is little evidence that general measures such as physical exercise, calcium and vitamin D supplementation improve bone mass in young adults with idiopathic osteoporosis. Furthermore, there is no evidence for the use of bone-specific drugs in this context.

Small and often poorly controlled studies have shown that specific interventions to target the primary disease in turn have beneficial effects on aBMD, although data on fracture prevention are virtually nonexisting (Appendix). Among those targeted interventions are TNF inhibitors, such as infliximab in IBD [96, 97] and rheumatoid arthritis [98], and gluten-free diet in coeliac disease [99]. Adequate iron chelation with more recent iron chelator, i.e., not deferoxamine, and hormonal substitution of hypogonadism may have beneficial effects in thalassemia major [28]. Besides the favorable effects of weight recovery in anorexia nervosa, the role of hormone therapy (HT)±IGF-1 remains controversial [100]. In a meta-analysis of prospective cohort studies and randomized clinical trials, HT in young women with anorexia nervosa significantly improved LS BMD, but to a lesser extent, FN BMD [101]. Contrasting with the improvement of bone mass associated with the treatment of most secondary causes of osteoporosis, administration of antiretroviral therapy (ART) for HIV, particularly tenofovir, can further aggravate bone loss and fracture risk in these patients [102].

Evidence is limited to recommend bone-specific drugs, such as bisphosphonates (BPs) in young adults with secondary osteoporosis. Young women with anorexia nervosa and treated with daily risedronate had significant improvements of LS BMD after 6 and 9 months compared to a control group, although no changes occurred for total body and hip BMD [103]. Bone loss can also be reduced in premenopausal women who develop chemotherapy-induced amenorrhea using selective estrogen receptor modulators (SERMs) or BPs [104–107]. LS BMD was improved with risedronate and zoledronic acid in young women with ovarian failure after allogeneic stem cell transplant, which was not observed with HT alone [108]. Young endometriotic women treated with gonadotropin-releasing hormone (GnRH) agonists are also prone to bone loss due to severe estrogen deprivation. In these subjects, BMD levels can be stabilized and even increased at some skeletal sites by combining GnRH treatment with 'add-backs' such as human parathyroid hormone (hPTH-1-34), HT, or danazol [75, 109]. BPs given with infliximab have been shown to improve BMD in patients with Crohn's disease [97], and alendronate and zoledronate to increase aBMD in cystic fibrosis [110–112]. Calcitonin and most

BPs can decrease bone turnover and bone pain and improve aBMD in thalassemia major [28]. Two small randomized clinical trials of zoledronic acid (4 mg i.v. every 3 months) have shown increases of aBMD in this disease [113, 114], and a meta-analysis including five studies but only 100 patients also indicates beneficial effects of zoledronic acid on aBMD (LS > FN) in thalassemia major [115]. In ten patients with SM and osteoporotic fractures, the combined effects of interferon alpha and monthly pamidronate (1 mg/kg) increased LS BMD by 12.6 % and hip BMD by 1.9 % per year and no fractures developed under treatment [116]. Whether BPs dosing higher than usually prescribed in osteoporosis is actually required for patients with thalassemia major or SM, however, remains poorly substantiated, as the long-term effects of BP therapy in these young individuals have not been evaluated. In HIV-associated osteopenia and osteoporosis (mostly men), two small RCTs of, respectively, zoledronate once yearly and alendronate once weekly have shown significant improvements of aBMD [117–119]. It is, however, questionable if HIV-infected patients with osteopenia and without evidence of fragility fractures should receive an antiresorptive therapy. A discussion about the utility of BPs in OI is beyond the scope of this review (see reviews [120, 121]).

Certain BPs, as well as teriparatide, have been shown to reduce bone loss in glucocorticoid-induced osteoporosis, and several guidelines have been recently developed to address this topic [122–124]. The evidence of their effect on fracture risk reduction in premenopausal women and men is scarce. However, as reported by the IOF-ECTS recommendations, bone protective therapy may be appropriate in some premenopausal women and younger men, particularly in individuals with a previous history of fracture or those receiving high doses of glucocorticoids [124].

There is an important concern about the risk of congenital malformations with the administration of BPs in women of childbearing age [125] and teriparatide is contraindicated in pregnancy. On the other side, several case reports in mothers and their infants have demonstrated the safety of BPs during pregnancy and lactation [126–130]. Contrasting results exist on the improvement of LS BMD and reduction of future fracture risk in pregnancy-associated osteoporotic women [131]. This small retrospective study on pregnant and lactating women, where BMD levels at baseline were low (FN −2 SD and LS −2.8 SD on average), attempted to look at the effects of certain BPs on fracture rate and BMD, but the study was largely underpowered [131]. Generally, caution must be taken in prescribing BPs to reproductive women, since BPs are known to be stored and released from bones for long periods of time and have shown to affect fetal skeletal ossification in rat models [132, 133]. Their effect on bone growth in infants in the long-term is still unknown.

Conclusions and perspectives

The diagnosis of osteoporosis in the young presents several challenges, since low bone mass and/or peripheral fractures with high-trauma are not necessarily associated with skeletal fragility. An apparently low aBMD (T-score<−2.5 at spine or hip by DXA) must be interpreted with caution in young individuals of small body size (constitutionally lean) and/or stunted growth. It should be emphasized that an inaccurate ‘diagnosis’ of osteoporosis in young subjects can lead to anxiety, unnecessary drug prescriptions, and in some countries, potential restrictions of insurance coverage. Thus, subjects with isolated low bone mass, although possibly deserving investigation depending on the context, for instance, to rule out vitamin D deficiency in regions of the world where this condition may be endemic, should not be classified as osteoporotic, and this diagnosis should be reserved for those subjects with evidence of skeletal fragility. Nevertheless, a truly low BMD and/or unusual fractures (such as low-trauma, multiple and vertebral) should prompt investigation for secondary causes of osteoporosis. Careful medical history, clinical, and laboratory investigations can reveal an underlying disease (mostly inflammatory, metabolic, and/or associated with gonadal insufficiency) that is amenable to specific medical interventions, which, in turn, will improve bone mass. BPs may improve BMD in young subjects with osteoporosis due to various disorders; however, the evidence is scarce so far, since the available studies were small, of limited duration, and there are no data on their antifracture efficacy. In any case, the indications and duration of antiresorptive treatment in the young should be as restrictive as possible, particularly in the absence of secondary causes (such as idiopathic osteoporosis, which may result from low peak bone mass rather than accelerated bone loss), multiple and/or fragility (vertebral) fractures, and high bone turnover accompanied by documented bone loss.

Ongoing developments of noninvasive technologies that can measure vBMD and bone microstructure in the cancellous and cortical bone compartments, such as high-resolution pQCT and derived estimates of bone strength (by finite element analysis), in the future could help the clinician to better evaluate the structural bases of bone fragility in the young [55, 134].

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Conflicts of interest None.

Appendix A. Effects of treatments (specific and bone drugs) on the various diseases

Secondary disease	Treatment	Benefits on bone	Reference
Inflammatory bowel disease: Crohn's disease	Infliximab	Tibia trabecular BMD and endosteal circumference Z-scores improved significantly over 12 months in children with Crohn's disease	[135]
	Infliximab	LS BMD: +8.13 % after 1 year follow up compared to baseline, vs. only +1.55 % in the control group ($p<0.01$)	[96]
	Infliximab + bisphosphonates	LS BMD: +6.7 %/year in patients on concurrent treatment vs. +4.46 %/year in those on oral bisphosphonates alone ($p=0.045$) over 2.2+0.99 years	[97]
Celiac disease	Gluten-free diet	4 % increase in LS and FN BMD after 1 year compared to baseline and up to 8 % for trochanter BMD. Lower values after 5-year follow-up	[99]
Cystic fibrosis	Alendronate	After 1 year of alendronate (70 mg once weekly for 1 year), BMD increased at the lumbar spine (5.2 % vs. −0.1 %) and at the hip (2.1 % vs. −1.3 %) compared with controls	[111, 112]
	Zoledronic acid	Compared with controls, LS BMD in zoledronic-treated group (2 mg i.v. every 3 months for 2 years) increased from baseline at 1 year (6.6 % vs. 0.35 %) and 2 years (6.14 % vs. 0.44 %), and femoral neck BMD increased at 1 year (4.12 % vs. −1.59 %) and 2 years (4.23 % vs. −2.5 %)	[110]
Adjuvant endocrine therapy for hormone-responsive breast cancer	Zoledronic acid	Zoledronic acid (4 mg intravenously every 6 months for 3 years) prevented bone loss at the spine and hip	[104, 136]
	Risedronate	In contrast to a significant decrease of BMD at the lumbar spine and hip in the placebo group, there was an increase in BMD in the risedronate group (30 mg/d, oral for 2 weeks, followed by 10 weeks without drug, repeated 8 times over 2 years). At 2 years, the mean difference (±SEM) between groups was 2.5 %±1.2 % at the lumbar spine ($p=.041$) and 2.6 %± 1.1 %, (95 % CI, 0.3 to 4.8) at the femoral neck ($p=.029$)	
Ovarian failure after allogeneic stem cell transplantation	Various (Ca + Vit. D; HRT, risedronate, zoledronic acid)	At 1 year, a significant decrease in LS and FN BMD was observed for the Ca + Vit. D group and a milder decrease in the HRT group. Risedronate treatment increased significantly LS BMD and prevented FN BMD loss. Zoledronic acid increased significantly both LS and FN BMD	[108]
Anorexia nervosa	Menstrual recovery	Stabilization of BMD with menstrual recovery	[137]
	Recombinant human IGF-I and HRT	BMD increased in women treated with rhIGF-I and HRT (1.8 %) vs. rhIGF-I alone (0.3 %)	[100]
	Risedronate	Increase of spine BMD of 4.9±1.0 % at 9 months (5 mg daily), even without significant weight gain	[103]
	Alendronate	Body weight was the most important determinant of BMD after 1 year of alendronate (10 mg/d oral)	[138]
Chemo-induced amenorrhea	Tamoxifen	At 3 years of follow-up, in amenorrheic patients who developed chemotherapy-induced early menopause, the LS BMD decreased −6.8 % in tamoxifen users and −9.5 % in the controls	[107]
	Pamidronate	At 1 year of follow-up of pamidronate (60 mg i.v. every 3 months), in amenorrheic patients who developed chemotherapy-induced early menopause, the LS BMD increased 1 % in tamoxifen users and decreased −4 % in the controls	[105]
Rheumatoid arthritis	Infliximab	At 1 year of follow-up, BMD loss was significantly reduced in the infliximab group compared with the placebo group at the femoral neck (−0.35 % vs. −3.43 %) and total hip (−0.23 % vs. −2.62 %) but not at the hand and spine	[98]
HIV	Alendronate	Alendronate (70 mg weekly for 96 weeks) increased BMD at sites with a T-score<−2.5 by 7.1 % vs. 1.0 % in the placebo ($p=0.0003$)	[119]
	Zoledronic acid	Bone density improved in a 12-month trial of 5 mg intravenous zoledronate compared to placebo	[118]

	Zoledronic acid	Between 2 and 6 years, after the second dose of zoledronic acid (4 mg intravenously yearly), LS BMD was greater by 3.7 % compared to placebo (p=0.03), as well as FN BMD and total body BMD	[117]
Thalassemia	Zoledronic acid	LS BMD was 8.9 % greater in patients treated for 2 years with 4 mg i.v. zoledronic acid every 3 months compared to placebo	[113]
	Zoledronic acid	At 2 years of follow-up, after 4 mg i.v. zoledronic acid every 3or 6 months for a year, BMD was significantly increased at all sites compared to baseline (p<0.01)	[114]
	Zoledronic acid	Zoledronic acid improved BMD by 0.69 SD (95 % confidence interval 0.47–0.90)	[115]

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