Metabolic Bone Disease and Osteoporosis in Children

Introduction

Pediatric osteoporosis (PO) is an important disorder that involves children and adolescents. It is characterized by low bone density for their age, gender, race, and body size, coupled with a history of clinically significant fragility fractures. While osteoporosis in children is not linked to increased mortality as in adults, it may have unpleasant effects on a child’s quality of life, resulting in pain, loss of function, and other severe, long-term effects.

The issue of low bone density in children and adolescents has attracted much attention in the last few years, and some groups of children may be at risk for osteoporosis. This condition is seen in children of both sexes at every age; however, it is more frequently described in adolescents with chronic diseases primarily affecting bone status and/or having drug-related osteoporosis. Furthermore a higher peak bone mass (PBM) may be one of the most important factors affecting the age of onset of osteoporosis in adulthood.

Bone mineral density (BMD) is regulated by many genes implied in bone metabolism regulation and in bone growth. However at the present time, the physio-pathogenetic role of these genes is not fully clear [1, 2]. PBM depends on sex and age and is for the large part genetically determined. PBM is naturally attained by 30 years of age; however 90% of PBM is reached by the age of 18 years in females and 20 years in males.

Learning Objectives

1. To understand the basics of pediatric bone metabolism and mechanisms underlying osteoporosis
2. To pay particular attention to specific diseases, such as Cushing syndrome, iatrogenic hypercorticism, rickets, and genetic and rheumatic diseases
3. To understand the approach to the diagnosis and follow-up of bone diseases
4. To study the treatment of pediatric osteoporosis

Case 1

An 8-year-old girl presented with fever, exudative pericarditis, arthralgia, myalgia, and hepatosplenomegaly. She also had anemia and neutrophilic leukocytosis.
Inflammatory diseases are associated with high levels of interleukin (IL)-1β and IL-6 that stimulate osteoblasts to produce RANKL, stimulate bone marrow stem cells to differentiate into osteoclasts, and hence increase bone resorption. However, severe osteoporosis can occur due to other factors as well, which play a crucial role in bone homeostasis, e.g., corticosteroid treatment, endogenous hypercorticism, reduction of muscular strength and fitness, low vitamin D levels, and acquired hypogonadism.

Bone, Growth Plates, and Remodeling Bone

The skeletal system has many functions: it supports the whole body and the muscles and tendons, it helps in locomotion, and it stores calcium and phosphorus needed for the metabolism of the muscles, heart, and other tissues. Its composition is divided into minerals (70%) and organic constituents (30%). The former is mainly constituted (95%) of hydroxyapatite, consisting of calcium and phosphorus. Magnesium, though present in low amounts, plays a key role in bone homeostasis. Most of the organic component (98%) consists of matrix, predominantly represented by type I collagen. Non-collagenous proteins, such as fibronectin, thrombospondin, osteocalcin, osteopontin, and osteonectin, represent about 5% of matrix.

Cells are the remaining 2% of the organic component and are responsible for formation, resorption, and maintenance of the remodeling cycle. Osteoblasts and osteoclasts are included in the extracellular matrix, and the matrix is rich in fibers, glycoproteins, and minerals. Osteoclasts are derived from mononuclear cells and resorb bone. Osteoblasts form osteoid and osteoid matrix. Osteocytes differentiate from osteoblasts and guarantee the integrity of the bone through a network of canaliculi. Osteoblasts help in the deposition of minerals in bones; in contrast osteoclasts induce continuous calcium resorption [3, 4].

Bone modeling begins during fetal life and continues till adolescence. Growing years are characterized by bimodal bone growth and modeling. The latter can be realized inside the bones at cortical, trabecular levels and on intracortical plane: this remodeling makes bone structure denser. Furthermore the modeling outside the bones, at the growth plates, permits an increase in the bone length, and the modeling at the periosteum makes it wider.

In addition, bone remodeling takes place on the trabecular surface and provides an adequate bone density increase in physiological condition, where bone formation is more important than bone resorption. Thus, bone modeling is the most important factor for bone strength in childhood,
while remodeling is the primary mechanism in adulthood. Furthermore a normal PBM in healthy individuals is genetically determined with an influence up to 80% [5].

Pubertal gain of PBM is crucial to have a good BMD and is influenced by prenatal and genetic factors as well. However calcium and vitamin D dietary intake [6], lifestyle, sport, sex hormones, and drugs contribute approximately 20% of the variance in PBM.

### Bone and Pediatric Diseases

Secondary PO is more frequent than expected and can be secondary to many causes such as chronic inflammation, eating disorders, chronic malnutrition and/or malabsorption, liver diseases, nephropathies, endocrine diseases, neuromuscular disabilities, and glucocorticoid (GC) use (Table 44.1).

**Table 44.1** Pediatric disorders linked to osteoporosis

| Disorder                                      |
|----------------------------------------------|
| Anorexia nervosa/female athlete triad         |
| Asthma                                       |
| Chondrodysplasias                            |
| Chronic liver and kidney disease             |
| Cushing syndrome                             |
| Cystic fibrosis                              |
| Diabetes                                     |
| Ehlers-Danlos syndrome                       |
| Endocrine disorders                          |
| Extensive burns                              |
| Gastrointestinal disorders                   |
| Gaucher disease                              |
| Hypophosphatasia                            |
| Idiopathic juvenile osteoporosis             |
| Klinefelter syndrome                         |
| Muscular dystrophies                         |
| Neoplastic diseases                          |
| Neuromuscular diseases                       |
| Nutritional rickets                          |
| Organ transplantation                        |
| Osteogenesis imperfecta                      |
| Osteoporosis-pseudoglioma syndrome           |
| Rheumatic diseases                           |
| Seizures and neurological diseases           |
| Sickle cell disease                          |
| Turner syndrome                              |

Children with chronic cholestatic disease show a reduced bone mass gain. Reduced hepatic IGF-1 synthesis might be responsible, at least in part, for the low bone mass of these patients [7].

Any cause of prolonged immobilization, such as cerebral palsy, reduces mechanical stress on the bone, inhibits osteoblast-mediated bone formation, and accelerates osteoclast-mediated bone resorption, resulting in a decreased BMD [8]. Neoplastic diseases (leukemia, lymphoma, solid tumors) and drugs (GC, anticonvulsants, aromatase inhibitors, lithium, heparin, LHRH analogs) are also involved in bone loss. Finally, a low dietary intake of calcium and vitamin D deficiency are additional risk factors for PO [9].

### Chronic Liver and Chronic Kidney Diseases

Chronic liver disease can be cholestatic or non-cholestatic, and both conditions can lead to osteopenia and osteoporosis through malabsorption of vitamin D and calcium or through an impaired vitamin D 25-hydroxylation. Progressive chronic kidney disease leads to “chronic kidney disease-mineral bone disorder” (CKD-MBD) [10]. Children with CKD-MBD have reduced bone density, slowed bone growth, and bone deformity. A short stature associated with bowed legs is characteristic (renal rickets). CKD-MBD is seen in every patient on dialysis, and it has also been detected in children with kidney disease even before they start dialysis. Transplantation of either the liver or kidney however is not followed by a sufficient gain in BMD, because the use of GC and immunosuppressants does not favor a complete recovery. In addition, residual disease and limb deformities from past dialysis therapy in patients with CKD may persist.

### Nutritional Rickets

Nutritional deficiency due to malabsorption of calcium, phosphate, or vitamin D can lead to softening and weakening of bones, typical features of nutritional rickets. Hereditary forms of
rickets, like chronic liver or kidney diseases, impair synthesis of vitamin D. The main source of 25-(OH)D₃ is dietary vitamin D₂. Ultraviolet light stimulates the production of vitamin D₃ from 7-dehydrocholesterol in the skin. However 25-(OH)D₃ is biologically inactive and is hydroxylated in the kidneys to the 1,25-(OH)₂D₃ hormone. The 1,25-(OH)₂D₃ hormone, calcitriol, stimulates intestinal absorption of calcium and increases serum calcium levels. Receptors for 1,25-(OH)₂D₃ are present on intestinal cells and modulate its action (Fig. 44.1).

These patients show low levels of vitamin D (below 10–15 ng/ml) and an increase in PTH. The main function of PTH is to maintain ionized calcium in the physiological range in the blood. Hypocalcemia stimulates PTH secretion, whereas hypercalcemia suppresses its secretion. PTH regulates calcium homeostasis by acting on the major calcium reservoir of the body, the skeleton. It stimulates osteoclastic activity and thereby bone resorption. It also stimulates the conversion of 25-(OH)D₃ to 1,25-(OH)₂D₃. Vitamin D deficiency is more frequent than expected even in industrialized countries, caused by insufficient sunlight exposure and/or inadequate diets [11].

The treatment of vitamin D deficiency is supplementation with calcium and vitamin D. However rickets need correction while a child is still growing; otherwise short stature and skeletal deformities may be permanent. The correction during the years of bone growth allows the resolution of the clinical features, and skeletal deformities diminish or disappear over the course of time.

**Cushing Syndrome and Bone**

A specific endocrine disease, Cushing syndrome (CS), is an important cause of structural and functional derangement of bone metabolism. The incidence of fractures in these patients is high (30–50%) and they frequently involve the spine. Furthermore osteoporosis is present in about half of these patients. When the diagnosis is delayed, long exposure to high steroid levels causes reduced growth velocity and bone age and also causes pubertal delay in the child. PBM is also
significantly compromised, in part secondary to a reduction in number and function of osteoblasts, as documented by the reduced levels of alkaline phosphatase and osteocalcin. As CS is typically associated with bone loss particularly in cancellous bones, it is useful to evaluate BMD at the lumbar spine by DXA.

Glucocorticoid-induced osteoporosis is reversible but the recovery is slow and may take 10 years to be complete, thus exposing these children to a high risk of fractures. For this reason some authors propose the use of alendronate especially in children with a persistent high level of cortisol, only in part controlled by surgical treatment. The results of cortisol level normalization are in fact less effective than alendronate, and the decision to discontinue the treatment should be based on clinical monitoring and DXA measurements [12].

**Bone and Glucocorticoids**

Glucocorticoids are frequently prescribed drugs for patients with pediatric rheumatic diseases, nephrotic syndrome, and hematological diseases. These patients are at risk of vertebral and peripheral fractures and reductions in bone mineral density on follow-up. Annual vertebral fracture incidence is 4–6% in patients with a recent diagnosis, and the prevalence in patients several years post-diagnosis is 7–28%. The fractures are often asymptomatic and thoracic in location and usually have mild, anterior wedge morphology. Patients affected by systemic diseases associated with a severe inflammation such as SoJIA, SLE, and JDM have a higher fracture risk. Neither glucocorticoid dose nor BMD are ideal predictors for risk of fractures. The muscle involvement and/or associated disease can contribute to the negative effect on bone strength.

Children and adolescents with these conditions seem to have an increased risk of long-bone fractures, especially in the forearm and wrist. However long-bone fractures are not predictive of vertebral fractures. Bone mass increase is typically suboptimal across the years, although the use of potent steroid-sparing anti-inflammatory agents may reverse the trend induced by GC and disease activity. Vitamin D insufficiency may contribute to the disease and warrants ongoing monitoring. Additional studies are useful to understand bone health risks in these children [13].

A systematic review and meta-analysis of existing literature to identify studies of BMD or fractures in children ≤18 years taking systemic GC therapy was performed. Sixteen studies met eligibility criteria, including ten on BMD (287 children) and six on fracture incidence (37.819 children). Spine BMD was significantly lower in children taking GC therapy, compared to age- and gender-matched healthy subjects. Incident clinical fracture rates were variable from 2 to 33%. However it is not clear if children receiving GC therapy have lower spine BMD compared to children with milder disease not requiring these drugs. Clinical and morphometric vertebral fractures are common in children, although only one study assessed fracture rates in healthy controls [14]. However vertebral fractures are an under-documented complication of childhood GC-treated diseases. Of note, normal variants mimicking fractures exist in all regions of the spine and can be distinguished in two groups:

1. The first group comprises variants mimicking pathological vertebral height loss, including not-yet-ossified superior and inferior vertebral apophyses, which can lead to a vertebral silhouette easily mistaken for an anterior wedge fracture, physiological beaking, or spondylolisthesis associated with reduced posterior vertebral height.

2. The second group includes variants mimicking other radiologic signs of fractures: anterior vertebral artery groove resembling an anterior buckle fracture, Cupid’s bow balloon disk morphology, Schmorl nodes mimicking concave endplate fractures, and parallax artifact similar to endplate interruption or biconcavity. If an unpredicted vertebral body shape is detected, attention to its site, detailed morphology, and serial transformations over time may clarify whether it is a fracture requiring change in management or just a normal variant [15].
Lateral thoracolumbar spine radiography and LS BMD were performed in 80 children with nephrotic syndrome after 37 days of GC therapy. Genant semiquantitative grading was used as the primary method for vertebral morphometry, and the algorithm-based qualitative (ABQ) method was used for secondary vertebral deformity analysis. Eight percent of these children manifested a single Genant grade 1 deformity. All deformities were mild anterior wedging. 5% showed one ABQ sign of fracture (loss of endplate parallelism). Two of the children with ABQ signs also had a Genant grade 1 deformity in the same vertebral body. None of the children with a Genant or ABQ deformity reported back pain. There was inverse correlation between LS BMD Z-score and glucocorticoid exposure for nephrotic syndrome [16].

GCs interfere with trabecular bone architecture. The primary effects are on osteoblasts and osteocytes. Glucocorticoids impair the replication, differentiation, and function of osteoblasts and induce the apoptosis of mature osteoblasts and osteocytes [17]. Although an inverse relationship exists between steroid exposure and LS BMD soon after glucocorticoid initiation in childhood nephrotic syndrome, there was a low rate of vertebral deformities [16].

Glucocorticoids also favor osteoclastogenesis and, as a consequence, increase bone resorption. The end point of these alterations is a net decrease in BMD and alterations in bone quality [18].

**Asthma**

GCs are used for control of inflammation associated with asthma in children. The oral use for longer than 3 months is associated with lower BMD; hence, short-term oral GC schedules and/or inhaled GCs are usually chosen. A dose-dependent decline in bone mineral acquisition and increased risk of osteopenia in boys, but not in girls, were seen when administered a short burst of oral GC treatment. Furthermore inhaled GC treatment was associated with a mild decrease in bone mineral acquisition in boys, but not in girls [19]. However inhaled GC treatment is not associated with an increased risk of fractures in children and adolescents [20]. In view of the fact that many patients on inhaled GCs may receive a supplement of oral GC, BMD may be measured in this population during childhood and adolescence.

**Bone and Rheumatologic Diseases**

Rheumatic diseases in childhood and adolescence can lead to secondary osteoporosis. The primary disease, drugs, especially glucocorticoids, and immobility contribute to the development of a reduced BMD.

Pro-inflammatory cytokines, such as tumor necrosis factor alpha (TNF-α), interleukin-1-β (IL-1-β), and IL-6, cause inflammation-associated osteoporosis by influencing the differentiation and function of osteoblasts and osteoclasts and uncoupling the bone remodeling cycle, with a consequent negative bone balance [21, 22]. Furthermore cytokines directly stimulate osteoclastogenesis, by acting on cells of the osteoclast lineage, and indirectly, by modulating synthesis in target cells of key molecules such as RANKL. Cytokines, especially IL-1-β and IL-6, can upregulate RANKL on osteoclast precursors and increase their sensitivity to RANKL concentrations [23–25]. However, T and B lymphocytes have a central role in the regulation of bone status, especially Th17 (Th17) [26]. IL-17 secreted by Th17 cells is a strong osteoclast activator [26].

Many studies showed that SLE patients have a higher incidence of decreased BMD [9, 24], with a prevalence of osteopenia and PO of 37.5% and 20.3%, respectively [9]. In dermatomyositis, along with other factors, the reduced mobilization also plays a major role [24]. A recent study on children with GC-treated rheumatic disorders reported that 6% of these children had vertebral fracture in the first 12 months of treatment [27]; however a significant bone loss occurs soon after the initial exposure to GC, especially in children with severe inflammation and systemic involvement such as those with SoJIA or connective tissue diseases. However, the effects of inflammation and GC treatment are tightly linked so that it is difficult to extrapolate their relative roles in
inducing bone demineralization. A study reported low bone mass (vertebral fractures) in children diagnosed with rheumatic disease even before they began GC therapy [28].

Decreased BMD is present [24, 29] in particular in polyarticular JIA and SoJIA. These patients show a reduced PBM and an increased risk to develop osteoporosis in adult age. Disease severity, inflammatory mediators, and GC have a definitive pathogenetic role for low BMD and reduced PBM [24, 29].

A recent study shows that JSLE has a higher cortical BMD than healthy subjects and JIA patients have a lower cortical BMD than controls. Both JSLE and JIA have a reduced trabecular BMD. Furthermore, JIA patients show a reduction in muscle area compared to JSLE [30].

An abnormal body composition with reduced muscle mass and increased fat is a pathological feature of children with rheumatic diseases and contributes to abnormal bone metabolism [31].

**Drugs for Rheumatic Diseases and Bone**

Methotrexate (MTX) has been found to reduce BMD in children with malignancies treated with high-dose protocols [32]. On the contrary, low-dose MTX use in JIA is not associated with a loss in BMD. In fact, the therapeutic effects on arthritis compensate in vivo the inhibitory effects produced in vitro on osteoblasts [33]. Treatment with growth hormone (GH) has been used in children with JIA with a positive effect on growth and BMD, bone geometry, and body composition [34–37]. GH treatment significantly increases total bone and muscle cross-sectional area (CSA) at final height. In accordance with an anabolic effect of GH, fat mass reached the lower limit of healthy children. At final height, cortical and marrow CSA, relative to total bone CSA, had normalized [38].

The selective and effective anti-inflammatory action of biological drugs is helpful in many areas: systemic and articular clinical outcome and bone health. The positive effects on bone metabolism are secondary to the reduction in inflammation, via the blockade of cytokines (TNF-α, IL-1, IL-6) and T-cell or B-cell function. Anakinra, canakinumab, tocilizumab, infliximab, etanercept, and adalimumab are the most used biologics in pediatric rheumatology. However studies on JIA are few [39].

Two studies on children with JIA treated with anti-TNF-α evaluated bone metabolism and documented a reduction in bone loss. Etanercept contributed to reduce bone demineralization after 1 year of treatment [40]. The second study on 16 patients with polyarticular JIA nonresponders to methotrexate documented a reduction in disease activity, an increase in growth velocity, and an improvement of BMD when etanercept was added to methotrexate [41].

**Genetic Causes of Bone Loss**

Many genes play an essential role in the pathogenesis of PO and may regulate 75–85% of the bone mass [8, 24, 42]. The PBM reached in healthy individuals is dependent on genetic determinants [43]. Environmental factors (endocrine, mechanical and nutritional influences, lifestyle, calcium and vitamin D dietary intake, drugs) account for 25% of variability in PBM, which is physiologically attained by 30 years of age [44].

The greatest loss of the bone and mineral occurs in genetic defects, such as osteogenesis imperfecta (OI) and X-linked hypophosphatemic (XLH) rickets, but enzymatic defects such as hypophosphatasia and homocystinuria, Wilson’s disease, and Menkes’ kinky hair syndrome (disorders of copper transport) can lead to severe bone demineralization as well. Rare causes of PO are idiopathic juvenile osteoporosis (IJO) [24], osteoporosis-pseudoglioma syndrome, and juvenile and early-onset Paget’s disease (Table 44.2) [45].

**Klinefelter and Turner Syndromes**

Klinefelter and Turner syndromes are classically associated with hypogonadism or delayed puberty. Low BMD is common and is particularly severe in patients who are not treated promptly with ade-
quate doses of sex hormones. The genetic defects in both syndromes may also contribute to variable degrees of low bone density, unrelated to low circulating levels of sex hormones and only partially secondary to GH resistance in Turner syndrome [46]. Genetic determinants influencing bone dysplasia also significantly contribute to a low BMD, and a high incidence of fractures has been documented in Turner syndrome [47, 48]. Increased fracture rates in untreated patients have been documented in Klinefelter syndrome as well [49]. Bisphosphonates have been shown to increase bone density in adult Klinefelter patients [49]. In patients with Turner syndrome, a combination of growth hormone and estrogen replacement therapy is effective in improving height and bone mass in adolescent patients [50].

### Idiopathic Juvenile Osteoporosis

Dent and Friedman defined idiopathic juvenile osteoporosis (IJO) in 1965 as a rare disease characterized by an insidious onset with back and bone pain, vertebral compression, and frequent long-bone fractures for several years, till puberty is completed. In fact the average age of onset is 7 years, and by puberty spontaneous resolution occurs. However many patients develop bone deformities (as spinal scoliosis or kyphosis) and have functional limitations. Growth can be sometimes impaired during the acute phase period; however, final height and puberty are not compromised. These patients can show knee, ankle, or lower back pain, kyphosis, loss of height, and a sunken chest. In rare cases severe disabilities are described.

The etiology is unclear. A reduced bone formation with a decrease in volume, thickness, and number of trabecular bone, without changes in cortical bone, is seen. Biopsy confirms that the trabecular compartment is more severely involved with reduction in bone formation and increase in bone resorption [51]. The presence of a normal number of osteoblasts is documented; however, their function is altered, leading to a decreased rate of matrix deposition. DXA confirms that BMD and bone quality parameters are impaired.

#### Table 44.2 Genetic causes of primary osteoporosis in children and adolescents

| Disease                                      | Genes                                      |
|----------------------------------------------|--------------------------------------------|
| Osteogenesis imperfecta                      | COL1A1, COL1A2, IFITM5, SERPINF1, CRTAP, LEPR1, PPBP, FKBPI0, BMP1, SP7, SERPINH1, WNT1, TMEM38B |
| X-linked hypophosphatemic rickets             | PHEX                                       |
| Homocystinuria                                | CBS                                                   |
| Hypophosphataemia                             | ALPL                                       |
| Wilson’s disease                              | ATP7B                                      |
| Menkes’ kinky hair syndrome                   | ATP7A                                      |
| Osteoporosis-pseudoglioma syndrome            | LRP5                                       |
| Idiopathic juvenile osteoporosis             | –                                          |
| Juvenile Paget’s disease                      | OPG                                        |
| Early-onset Paget’s disease                   | RANK                                       |
| Ehlers-Danlos syndrome                        | COL5A2, COL5A1, COL1A1, COL3A1, PLOD1, COL1A2, ADAMTS2, COL3A1, TNXB |
| Bruck syndrome                               | FKBPI0, PLOD2                              |
| Marfan syndrome                              | FBN1                                       |
| Hypophosphatemic nephrolithiasis/osteoporosis| SLC34A1, NPHLOP2                             |
| Hajdu-Cheney syndrome                         | NOTCH2                                     |
| Torg-Winchester syndrome                      | MMP2                                       |
| Shwachman-Diamond syndrome                    | SBDS                                       |
| Singleton-Merten syndrome                     | –                                          |
| Cleidocranial dysostosis                      | RUNX2                                      |
| Stuve-Wiedemann syndrome                      | LIFR                                       |
| Cole-Carpenter syndrome                       | –                                          |
| Geroderma osteodysplasticum                   | GORAB                                      |
| Noonan syndrome                              | PTPN11, SHOC2, KRASSOS1, RAF1, NRAS, BRAF, RIT1 |
| Neonatal hyperparathyroidism                  | CASR                                       |
| Other forms of hypophosphatemic rickets       | SLC34A3, FGF23, DMP1, ENPP1, CLCN5          |
| Hypocalcemic rickets                          | VDR, CYP2R1, CYP27B1                       |

M.C. Maggio and R. Cimaz
These children show reduced bone density, and the risk of fractures of the weight-bearing bones (especially in the metaphyses) and spine is increased, with collapsed or misshapen vertebrae.

The clinician must reach an early diagnosis of IJO to protect the child’s spine and other bones from fracture until postpubertal remission occurs. Long-term consequences for bone health are not yet clear [52]. Physical therapy and exercise (avoiding weight-bearing activities) and other supportive measures are the first choice. Vitamin D therapy along with calcium, as well as calcitonin, fluoride, and anabolic steroids, does not show efficacy. Treatment with bisphosphonates is reserved for severe cases and in some patients results in the complete recovery of painful symptoms, normalization of bone mineral status, and a reduction in fracture rate without changes in linear growth [53].

### Osteogenesis Imperfecta

Osteogenesis imperfecta (OI) includes a group of genetic disorders characterized by defective collagen that causes qualitatively abnormal, less dense, and easily broken bones. Many types of OI based on the genes affected have been identified (COL1A1, COL1A2, IFITM5, SERPINF1, CRTAP, LEPRE1, PPIB, FKBP10, BMP1, SP7, SERPINH1, WNT1, and TMEM38B) [54]. The clinical course of each type of OI can vary greatly from patient to patient; however, all types of OI have the tendency to develop low bone density and fractures, and osteoporosis is an almost universal consequence. Many studies have demonstrated that oral or intravenous bisphosphonates reduce fractures and pain and improve growth. These benefits appear in the first 2–4 years of treatment, and long-term effects are not yet fully characterized [55, 56]. The majority of studies with intravenous treatment showed a significant increase in lumbar projection area [57].

### Gaucher Disease

Gaucher disease is an inherited lysosomal storage disorder, caused by β-glucocerebrosidase deficiency. It is characterized by the accumulation of glucocerebroside in the spleen, liver, lungs, bone marrow, and brain. Patients with type 1 Gaucher disease (GD1) have significant bone complications resulting in morbidity. The progressive storage of glucocerebroside in the bone marrow is associated with osteopenia and osteoporosis, cortical thinning, osteolytic lesions, fractures, avascular bone necrosis, and osteosclerosis [58]. Chronic inflammation by Gaucher cells also induces the production of several cytokines. The treatment is enzyme replacement therapy, and this leads to reduction in fractures [59]. Early treatment prevents disruption of the immune system and reduces chronic inflammation by Gaucher cells in the bone marrow. There are a few reports of the successful use of bisphosphonates for this condition.

### Diagnosis of Low Bone Mass

Conventional X-ray study of the bone is insensitive in the estimation of BMD, and noninvasive methods for measuring bone mass and mineral content have been developed.

The most suitable technique for children because of low radiation (=3 mrem), speed, and accuracy is dual X-ray absorptiometry (DXA). DXA measures a composite of trabecular and cortical bone, considering that the ratio of cortical to trabecular bone differs in various parts of the skeleton. The choice of sites measured by DXA includes the one-third distal radius (95% cortical and 5% trabecular), the one-tenth distal radius (25% cortical and 75% trabecular), the lumbar vertebral bodies (5% cortical and 95% trabecular), the femoral neck (75% cortical and 25% trabecular), and the greater trochanteric area of the femur (50% cortical and 50% trabecular).

Another method is quantitative computerized tomography (QCT), applicable for measurements on the axial skeleton with a radiation exposure comparable to that of plain radiography. Peripheral QCT (pQCT) has lower radiation exposure, less than 0.03 mrem, and allows analysis of volumetric bone density of appendicular cortical and trabecular sites, as the radius or the tibia.
Peripheral QCT (pQCT) is currently the only technique in clinical use that differentiates between trabecular and cortical bone and determines bone density, bone geometry, and muscle cross-sectional area, all indicators of bone strength.

In younger children, the precision of pQCT measurements might be compromised by the partial volume effect; furthermore, an open question is if the pQCT measurements at the appendicular skeleton adequately reflect the situation of the whole skeleton, including axial bones. However pQCT maintains a good precision in the diagnosis of osteopenia and osteoporosis [60].

A new method is quantitative high-frequency sonography, a noninvasive, radiation-free, low-cost method evaluating the ultrasound wave transmission through bones. The speed of sound and broadband ultrasound attenuation (BUA) are the parameters measured, and normal values for healthy children have been established [61, 62]. BUA has the best correlation with BMD measured by DXA both in adults and in children and provides information about bone stiffness and elasticity [63].

Magnetic resonance imaging (MRI) is a good tool in the study of spine abnormalities of children treated with GC. MRI is more sensitive than traditional spinal radiographs for the diagnosis of vertebral fractures and shape deformities [64]. However the high cost does not allow the routine use of this diagnostic method in the study of BMD.

Treatment

In children and adolescents, effective and safe doses have not been defined for the many drugs used to prevent and treat osteoporosis in adults. These agents include bisphosphonates, teriparatide, calcitonin, denosumab, and activated forms of vitamin D. Potential toxicities are still unknown, due to differences between children and adults in bone modeling/remodeling, pharmacokinetics, and/or pharmacodynamics [65].

Treatment for genetic diseases has a few specific measures, such as gene therapy or stem cell transplantation, reserved for selected diseases. However the use of intravenous bisphosphonates in OI [8] and the use of phosphate and 1,25-dihydroxyvitamin D in XLH [8] are the accepted therapies.

Treatment with antiresorptive agents would be the most appropriate option for conditions in which bone resorption is the primary defect, while anabolic agents should be considered in association with appropriate management of the underlying condition for diseases in which lack of new bone formation is the predominant finding.

Vitamin D and calcium are keys for an adequate bone metabolism and help bone remodeling and growth. In a meta-analysis, there was no significant change in BMD after calcium supplementation in healthy children [66]. There is no good evidence in pediatric practice to support the routine use of calcium and vitamin D supplementation for a child with low BMD. This is useful only for children and adolescents with a documented vitamin D deficiency or a poor dietary calcium intake. Additionally, causes of the decreased vitamin D in the general population are reduced sun exposure, limited time spent in outdoor activities, an increased use of sunscreen, and finally an inadequate time devoted to physical activity.

A study on pediatric patients with osteoporosis or osteopenia documented decreased levels of 25-hydroxyvitamin D [67]. No direct connection with fracture risk was demonstrated; however, vitamin D supplementation in children with osteopenia and PO may reduce morbidity. Low vitamin D levels, decreased BMD levels, and high PTH levels were found in JIA patients treated with GC [8, 24]. The recommended daily dose of vitamin D may not be sufficient for patients undergoing bone-affecting treatments and for those suffering from primary bone disorders.

BMD is decreased in children on treatment with GC, but not in those patients receiving alendronate [8, 24]. Children with connective tissue disease [8, 24] were treated with alendronate safely and showed increased Z-scores. However, for primary prevention, the use of bisphospho-
nates in children receiving corticosteroids for chronic disease is not yet recommended [8].

Treatment with recombinant human parathyroid hormone (rhPTH) is approved in adults and is the most effective anabolic drug. However it is not safe in children, where there is a documented risk of developing bone sarcomas [8, 24]. rhPTH is administered only to pediatric patients affected by hypoparathyroidism; here long-term follow-up has not excluded the risk of osteosarcoma [68].

Conclusion

In conclusion, osteoporosis has become a pediatric disease as well. Advances in diagnosis and treatment have greatly improved the prognosis of these patients. Improving bone health during childhood and adolescence can have a major impact on subsequent life, and pediatricians should be aware of risk factors and possible treatments for low bone mass in the developing skeleton.

Take-Home Messages

1. PO is a rare but serious condition seen in children suffering from specific chronic illness and/or treated for a long period with steroids, antiepileptic drugs, etc.
2. Children and adolescents with connective tissue disease have a high risk of PO. An abnormal body composition with reduced muscle mass and increased fat is a feature of children with rheumatic diseases and might contribute to abnormal bone metabolism.
3. The most suitable technique for the evaluation of PO for children because of low radiation, speed, and accuracy is DXA.
4. Vitamin D and calcium are keys for an adequate bone metabolism and help bone remodeling and growth. Vitamin D supplementation in children with osteopenia and PO may reduce morbidity.
5. In children with connective tissue disease, the treatment with alendronate is safe; however, primary prevention is not recommended.
6. Physical activity has an important role in prevention and treatment of PO, especially in children with rheumatic diseases.

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