



Metabolic Bone Diseases in the Pediatric Population

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Bone plays an important role in regulating mineral balance in response to physiologic needs. In addition, bone is subject to a continuous remodeling process to maintain healthy bone mass and growth. Metabolic bone diseases are a heterogeneous group of diseases caused by abnormalities of bone mass, mineral structure homeostasis, bone turnover, or bone growth. In pediatrics, several significant advances have been made in recent years in the diagnosis of metabolic bone diseases (e.g., osteogenesis imperfecta, hyperparathyroidism, rickets, renal osteodystrophy, pediatric osteoporosis, and osteopetrosis). Imaging is fundamental in the diagnosis of these pathologies.

Bone is composed of proteins and minerals. Among proteins, the main component is type I collagen, and the most frequently encountered minerals are calcium and pyrophosphate (~85% of the body's phosphate and 99% of its calcium are contained in the skeleton as hydroxyapatite).¹

Bone is a dynamic structure that performs important functions in the body, such as locomotion, support, and protection of vital organs and reception of the bone marrow. Bone undergoes a continuous remodeling process divided into three phases, of variable duration, in which the bone tissue is renewed: resorption, inversion, and rest. In the resorption phase, the protagonist cells are the osteoclasts²; in the bone formation (inversion phase), the protagonist cells are the osteoblasts.³ The third type of cells involved in remodeling are osteocytes subject to endocrine signals, paracrine, and biomechanical complexes.⁴

Structural remodeling repairs damaged tissues, and homeostatic remodeling seems to respond to metabolic needs or hormonal changes, or it is due to pathologic processes. Furthermore, bone is involved in the homeostasis of calcium and phosphorus.

Calcitropic hormones such as vitamin D and parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23)/Klotho axis are critical for controlling calcium and phosphorus homeostasis.⁴ Any imbalance in the process can cause bone

disorders with clinical consequences. The decrease in serum calcium stimulates the secretion of PTH by the parathyroid gland that acts on the kidney to increase tubular calcium resorption and stimulate the production of 1,25 dihydroxycholecalciferol (1,25DHCC).⁵ In turn, 1,25DHCC targets the gastrointestinal tract to increase dietary absorption of calcium that closes the cycle by suppressing PTH.⁵ PTH also has direct effects on bone via PTH receptors in osteoblasts, resulting in increased calcium and phosphate flux via the receptor activator of nuclear factor-κB ligand (RANKL; tumor necrosis factor 11 ligand) superfamily dependent member, osteoclast-mediated bone resorption of mineralized bone.⁵

The role of bone has long been limited to serving as a mere reservoir of minerals. But the discovery of factor FGF23, synthesized by bone, that regulates serum phosphorus levels, both directly in the renal tubule (promotes the elimination of phosphorus) that through the regulation of the metabolism of vitamin D (blocks the synthesis of calcitriol and activates its catabolism) and of PTH itself (inhibits its production with Klotho), gives it a much more active role.⁴

Metabolic bone disease (MBD) refers to a broad spectrum of clinically diverse diseases that have in common an aberrant bone chemical environment, with alterations in the remodeling process or in calcium and phosphorus homeostasis, resulting in a defective skeleton and bone abnormalities.

Osteogenesis Imperfecta

Osteogenesis imperfecta (OI), also known as brittle bone disease, is a genetically heterogeneous skeletal dysplasia with an incidence of ~ 1 in 10,000 to 20,000 births.⁶

Most cases are associated with mutations in one of the two genes encoding type I collagen α chains (*COL1A1* and *COL1A2*), responsible for >90% of cases.⁷ Over the past 10 years, more additional genes have been identified involved in autosomal recessive and X-linked forms and posttranslational modification of type I collagen, signaling of bone cells, or regulation of bone matrix homeostasis, expanding the genetic spectrum of OI.⁸ Other forms of OI in which there is no mutation in the *COL1A1* or *COL1A2* genes have also been described.⁹ Mutations can also arise de novo.¹⁰

Although there is no direct genotype-phenotype correspondence, the type and location of mutations influence the phenotype, ranging in severity from mild clinical forms with a slight increase in fracture frequency to death in the perinatal period.⁶ These mutations can be divided into two categories: quantitative defects and mutations that affect the structure of type I collagen.

The 1979 Sillence classification divided OI into four types, based on severity, phenotype, and radiologic findings.¹¹ Patients were classified as having mild non-deformation (type I), moderate (type IV), severe with progressive deformation (type III), or perinatal fatal OI (type II).

Autosomal dominant mutations in *COL1A1* or *COL1A2* account for ~ 90% of OI cases.⁹ Type I OI results from a quantitative defect in collagen production due to a silenced allele of the *COL1A1* gene.¹² Usually due to a premature stop codon within the gene, these mutations lead to half of normal protein production. The structure of type I collagen protein produced is normal. Type I OI presents with fractures, typically before puberty. Long bone or spine deformities and dentinogenesis imperfecta are rare. With completion of growth, the incidence of fractures decreases. Blue or gray sclera and the risk of early hearing loss are common features.¹³

In comparison, OI types II, III, and IV are the result of structural defects in type I collagen due to missense mutations in the *COL1A1* or *COL1A2* gene. The most common mutations disrupt the assembly of the collagen triple helix, compromising its function and interactions with the extracellular matrix. Depending on the helical position of mutation and the resulting instability of the protein, the clinical phenotype can range from lethal to mildly deforming.¹³

Type II OI is the most severe form of OI, and infants generally do not survive beyond the perinatal period with 90% of affected infants dying by 4 weeks of age. Newborns have multiple intrauterine fractures, and severe long bone deformities and poor ossification of the facial bones and skull are detected on 18- to 20-week fetal ultrasound (US) scans. Pulmonary hypoplasia with multiple rib fractures or central nerve malformations usually results in death.⁹

Type III OI is the most severe nonlethal form, characterized by a history of multiple fractures from childhood, severe long bone deformities, and significant short stature. Infants have the typical triangular facies of a relatively large skull with

underdeveloped facial bones. Multiple vertebral compression fractures cause severe scoliosis, kyphosis, and rib cage deformity. Distortion of growth plates with partial calcification of the cartilage can lead to popcorn epiphysis. Walking is often limited to a wheelchair or with aids. Blue sclera and dentinogenesis imperfecta may be present, but sclera tends to turn less blue as it ages. Hearing may develop in adulthood.¹⁴

Type IV OI can present with long limb arches, vertebral fractures, and relative short stature. Most children are outpatients, although they may need walking aids.⁹

Additional types of OI (\geq V) have been described based on specific phenotypic characteristics and genetic findings. Type V OI is characterized by moderate to severe bone fragility and a calcified interosseous membrane on the forearm that can lead to secondary dislocation of the radial head, radiodense metaphyseal bands on long bone growth plates, and development of a hyperplastic callus after a trauma.¹⁵ Type V OI has an autosomal dominant pattern, and a hyperplastic callus can develop after fractures or surgery.¹⁵

Autosomal recessive forms of OI are rare conditions and account for ~ 2 to 5% of cases. Mutations in critical elements involved in type I collagen secretion and posttranslational modification (collagen 3 hydroxylation and chaperone defects) have been discovered as well as transcription and signaling factors involved in osteoblast function.^{9,16} Although autosomal recessive forms are rare, the discovery of more new genes responsible for OI has shed light on new mechanistic pathways and possible therapeutic approaches.⁹

The genetic heterogeneity of OI is further complicated by the wide phenotypic variability of each genetic locus and by the different modes of inheritance. There is no genotype-phenotype correlation accurate enough to predict mortality in a single case.¹⁷

To incorporate the new discovery of mutations that cause OI, genetic classification has expanded from the original Sillence classification. Functional classifications have been proposed to classify the OI subtype according to the underlying pathologic mechanism and not according to the mutation.⁶

Diagnosis of OI is based on history, clinical examination, evaluation of bone mineral density (BMD) of the lumbar spine using dual-energy X-ray absorptiometry (DXA), bone biochemistry, and radiographic findings.¹⁸ Genetic tests can help confirm the diagnosis; however, because > 1,500 dominant mutations in *COL1A1* or *COL1A2* have been identified so far, genetic sequencing of peripheral blood or cultured fibroblasts is required. Whenever possible, bone biopsy with histomorphometric analysis can provide additional diagnostic information.⁹

The radiographic examination consists of a selective skeletal investigation. Anteroposterior and lateral views of the long bones and spine and a lateral view of the skull are obtained.

The examination evaluates osteopenia and fractures, deformity of the long bones and the skull, and the presence of dense metaphyseal bands.¹⁹ In OI, radiographs reveal osteopenia as thinning of the cortical bone and excessive transparency of the trabecular bone. For it to be detectable, however, the reduction in calcined bone mass must be significant (30–50%) and is not specific for OI.¹⁹

Radiographs in OI document the presence of fractures, both at the axial and appendicular skeletal level, similar to those seen in normal children who have experienced trauma. Fractures most commonly occur in the shaft of long bones (most often in the lower, spiral, and transverse limbs), in the spine, and in the apophyses (avulsion fractures typically involving the olecranon or tibial tubercle).²⁰ They usually consolidate within the normal amount of time. Multiple thoracolumbar compression fractures and L5 spondylolysis may be observed in the spine, with or without associated spondylolisthesis. L5 spondylolysis is thought to be due to a fracture or lengthening of the pars interarticularis.^{19,21}

Another feature of OI is bone deformities, especially affecting the appendicular skeleton, that occur due to excessive bone malleability and plasticity.¹⁹ In severe forms of OI (mainly type III), long bones may appear thick and wide with a “bamboo cane appearance” or with characteristic deformities, such as a “shepherd’s crook” of the femur (anterolateral arch) and a “saber shin” of the tibia (anterior arch).¹⁹

In the skull, in contrast, there is a “mosaic” or “paved” appearance at the cranial vault due to the presence of multiple wormian bones (defined as having at least 10 wormian bones).¹⁹

On radiographs, ossification of the interosseous membrane in the forearm or leg (type V OI) and popcorn calcifications in the metaphyseal and epiphyseal regions of the knee (type III OI) may also be found.

Finally, dense metaphyseal bands may be observed in radiographs of children with OI treated with bisphosphonates and in type V OI regardless of any treatment¹⁹ (→ Fig. 1).

The use of DXA of the lumbar vertebral bodies is useful for a quantitative assessment of the individual’s BMD and for monitoring the effects of bisphosphonate treatment. Bone fragility in OI is due to reduced bone strength that reflects abnormalities both in BMD, which is low in these patients, and in bone quality.²²

Hyperparathyroidism

PTH is the major calcium hormone, and its secretion from the parathyroid glands is tightly controlled by ambient concentrations of extracellular ionized calcium. Under conditions of high concentrations of PTH, primary or secondary hyperparathyroidism occurs, resulting in increased bone resorption.²³

Primary hyperparathyroidism (PHPT) is a state of autonomous secretion of parathyroid hormone by the parathyroid glands and the lack of feedback inhibition by serum calcium. Primary hyperparathyroidism is usually caused by a parathyroid adenoma (90%), but in ~10% of cases it is the result of hyperplasia of the four glands, and, in extremely rare cases, of parathyroid carcinoma (<1%).²⁴ The hallmark of PHPT is hypercalcemia.

Secondary hyperparathyroidism, in contrast, is an adaptive response to low serum calcium levels. The most common cause is chronic renal failure, in which chronically elevated serum phosphate levels depress the serum calcium level, leading to compensatory hyperplasia of major parathyroid



Fig. 1 Plain radiograph of osteogenesis imperfecta patient that shows proximal metaphysis of tibia and femur with horizontal sclerotic lines after therapy with bisphosphonates.

gland cells. It can also be observed in vitamin D deficiency and dietary calcium deficiency.²³

PHPT is rare in infants and children, with an estimated incidence of only 2 to 5 in 100,000 and no apparent sexual predilection.²⁵ Approximately 5 to 15% of all PHPT cases are represented by genetic syndromes.²⁶ Furthermore, radiation exposure in childhood and the development of PHPT in subsequent years has been well established.²⁷ It is clinically symptomatic in most young patients and typically presents with signs or symptoms of hypercalcemia, skeletal complications, and/or nephrolithiasis.²⁷

PHPT can present within the first few days of life as neonatal severe hyperparathyroidism (NSHPT), a rare disease associated with inactivating mutations in the *CASR* gene whose primary function appears linked to the regulation of calcium homeostasis. It manifests itself as severe hypercalcemia and MBD. Diagnosis of NSHPT is based on the presence of elevated PTH levels along with relative hypocalciuria.²⁷

Clinical features of NSHPT include growth retardation, hypotonia, respiratory distress, and prominent skeletal involvement with skeletal abnormalities, marked bone demineralization, and fractures.

Infantile/adolescent PHPT, in contrast, is associated with single parathyroid adenomas or multiple adenomas (so-called parathyroid hyperplasia). Most patients have no symptoms attributable to hypercalcemia because values are (Normal serum calcium level: 8,5–10,5 mg/dl) slightly above normal.²⁷ In addition to the acquired form are also genetic forms. Among them, the most common is multiple endocrine neoplasia type 1, or MEN1. PHPT is present in > 90% of these patients, caused by diffuse hyperplasia or multiple adenomas. PHPT is relatively rare in MEN2a (in only 20–30% of patients) and almost never occurs in MEN2b, involving all four parathyroid glands, but often meta-synchronously or asynchronously.²⁶

In the genetic form, classical symptoms are kidney stones, MBD (reduced bone density, fractures, or rarely cystic fibrous osteitis), abdominal pain (due to gastric hyperacidity, pancreatitis, or constipation), polyuria, and cognitive or psychiatric dysfunction.^{26,27}

In 95% of patients with hyperparathyroidism, skeletal findings are more easily recognizable in the hand, with subperiosteal bone resorption beginning at the radial faces of the middle and index finger phalanges as lacelike irregularities and at distal phalangeal tufts as acro-osteolysis.²³ In the later stages, resorption is subperiosteal, appearing similar to scalloping, also affecting ribs, lamina dura (bone that surrounds the cavities of the teeth), humerus, and femur.²⁸ In the skull, bone resorption is described as a salt and pepper appearance and can lead to less differentiation between the inner and outer plates of the skull.

Trabecular, intracortical, endosteal, subchondral, and subligamentous or subtendinous bone resorption may also occur.²³ Trabecular resorption within the medullary bone is typical of the advanced stages of the disease, with loss of definition and disappearance of the trabeculae and granular structure of the cancellous bone. Intracortical resorption is also described as cortical tunneling. Endosteal resorption can lead to cortical thinning and can obscure the corticomedullary junction. Subchondral resorption can affect any joint, leading to an enlarged and uneven appearance. In the hands, subchondral resorption most often begins along the distal interphalangeal joints and progresses to the proximal metacarpophalangeal and interphalangeal joints. Subchondral resorption can also occur along the acromioclavicular, sternoclavicular, and sacroiliac joint (most pronounced on the iliac side, simulating inflammatory or infectious arthritis).^{23,28}

Even subligamentous or subtendineal resorption, although it can occur in any area, favors the calcaneus, clavicle, the major and minor tuberosities of the humerus, the major and minor trochanters of the femur, the anterior inferior iliac spine, and the ischial tuberosity.²⁴

Parathyroid imaging, through US of the neck and scintigraphy with sestamibi (99m technetium [Tc]-sestamibi) labeled with Tc 99, allows localization and characterization of parathyroid anomalies.^{29,30}

In addition to specific imaging for abnormal parathyroid tissue, extra-parathyroid imaging tests are required to assess PTH-related complications adequately at the skeletal and renal levels.^{29,31} In particular, US of the urinary tract may be

useful in excluding clinically silent nephrocalcinosis and nephrolithiasis, particularly in MEN1.^{29,31}

Measurement of bone mass by a DXA scan at the lumbar spine, hip, and distal third of the forearm can reveal reduced BMD that predisposes to an increased risk of fragility fractures.^{31,32} PHPT represents a specific condition in which the distal third DXA of the forearm is suggested electively. In fact, this skeletal segment is enriched in cortical bone, generally the first site that suffers from a decrease in BMD because PTH acts and preferentially affects cortical bone. In contrast, a DXA assessment of the lumbar spine, a skeletal site richer in trabecular bone, usually reveals a more conserved BMD, and a DXA assessment of the hip, where a mixture of cortical and trabecular bone is present, tends to show intermediate findings.^{31,32}

Rickets

Rickets is the result of a disturbance in the ossification of endochondral bone that occurs at the level of the epiphyseal growth plate due to a defect in the development and mineralization of osteoid tissue, which in turn leads to deformity and reduced growth of the whole immature skeleton.^{14,33}

The most common causes of rickets are hypovitaminosis D due to lack of sun exposure, dietary deficiency, and intestinal malabsorption.³³ Another cause of rickets is the reduced renal synthesis of 1,25D as a consequence of the deterioration of renal function.³⁴

Rickets also has genetic causes, particularly pseudo-vitamin D rickets (PDDR; also called vitamin D-dependent rickets type 1 [VDDR, type 1]), hereditary vitamin D-resistant rickets (HVDRR; also known as VDDR type 2), and X-linked hypophosphatemic rickets (XLH).³⁴

Rickets is divided into two main subtypes: calciopenic and phosphopenic. Both forms show failure of mineralization, but in the calciopenic form, hypocalcemia is characteristic and causes secondary hyperparathyroidism leading to increased bone resorption and osteopenia. In the phosphopenic, hereditary, or acquired forms, in contrast, osteopenia does not manifest because they are characterized by normocalcemia.¹⁴

Both groups of rickets are characterized by hypophosphatemia.³⁵ In calciopenic rickets, phosphaturia leading to hypophosphatemia occurs due to secondary hyperparathyroidism. In phosphopenic rickets, phosphate deficiency is the main defect that most commonly results from increased renal excretion of phosphate, and serum PTH values are normal or slightly elevated.³⁵

Radiologically, rickets presents with osteopenia, flexion of the bones, and enlargement of the growth plate, where the normal (slightly convex and clearly defined metaphysis) appearance is replaced by a concave moth-eaten appearance; furthermore there is cupping, expansion, demineralization, and disorganization of the metaphyses (– Fig. 2a, b). In fact, at the metaphyseal level, following the lack of mineralization, nonmineralized osteoid is concentrated with disorganized growth of the chondrocytes.²³ These anomalies are most evident in skeletal growth sites, such as the wrist, knee, proximal femur, distal tibia, proximal humerus, distal radius,

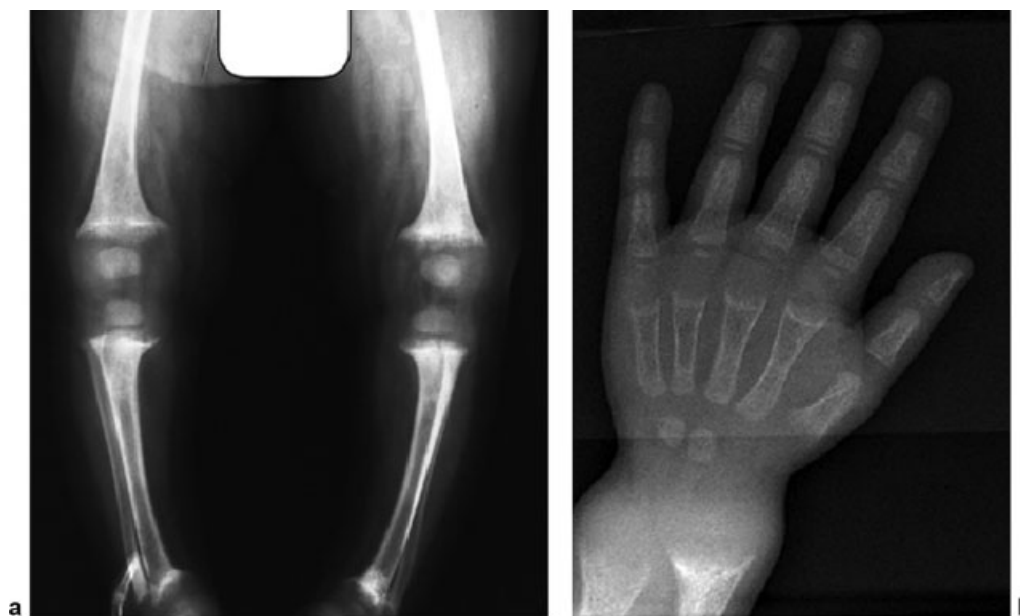


Fig. 2 A case of rickets. (a) Plain radiograph of the lower legs showing bowing bones, with widened physes and cupping and splaying of the metaphyseal tibia and femur. (b) Wrist and hand radiographs demonstrating widened physes, with metaphyseal flaring and coarse bones.



Fig. 3 Knee radiograph of a patient with vitamin D deficiency rickets: It is very evident in the enlargement of the growth plate, where the normal clearly defined convex appearance is replaced by a concave moth-eaten aspect.

and ulna²³ (→**Fig. 3**). On the thoracic level, costochondral swelling appears, the so-called rachitic rosary.

If patients undergo therapy, the classic appearance is replaced by a dense line of calcification at the metaphysis indicating healing.³⁶ In children with rickets, tooth eruption may be delayed, and if tooth enamel develops at a time of moderate hypocalcemia, it is hypoplastic.³⁴

Vitamin D deficiency rickets (also known as classical rickets) usually occurs in young children. The most common observation is the bowing of the legs that becomes evident when the child starts walking.³⁶ Additionally, motor development is often delayed due to a combination of muscle weakness, bone pain, and leg flexion. In young children, bowing typically occurs at the lower end of the shins, but older children may show genu valgum, genu varum, or a combination of the two, giving the legs a “windswept” appearance.³⁶ Other clinical manifestations include swelling of the wrists, poor growth, aches and pains, Harrison’s sulci (the drawing in of the lower ribs by the diaphragm due to bone weakness), and the rachitic rosary, which comes from the bulging of the costochondral junctions and seen as an inverted “V” parallel and lateral to the costal margins. Very young children may have craniotabes (a “ping-pong” ball skull).³⁶

Hypophosphatemic rickets is characterized by low tubular resorption of phosphate (from genetic or acquired causes) in the absence of secondary hyperparathyroidism, resulting in chronic hypophosphatemia. The main genetic disorder in this group is familial XLH, which is usually inherited in a dominant mode.³⁴ Another cause is Fanconi’s syndrome, a group of diseases (genetic or acquired) characterized by dysfunction of the proximal renal tubular, leading to loss

of renal phosphate, renal tubular acidosis, hypokalemia, glycosuria, and aminoaciduria.³⁴

Hypophosphatemic rickets typically becomes evident around 12 to 18 months of age. Affected patients develop coxa vara when they start walking, leading to a swaying or “intoxicating” gait resulting from medial tibial torsion. If left untreated, this can lead to shortened stature with disproportionate shortening of the lower limbs.³⁴

These children often have dental abscesses, due to the abnormal production of dentin resulting from chronic hypophosphatemia. They may also have craniosynostosis and skull distortion due to premature closure of the sutures.³⁷

Unlike vitamin D deficiency rickets, familial hypophosphatemic rickets does not cause hypotonia, myopathy, or tetany. Familial hypophosphatemic rickets has worse features in the lower limbs on radiographs, showing a thick cortex and coarse, prominent trabeculae.³⁴ Furthermore, this form can present severe calcification and occasionally ossification around the insertions of tendons and ligaments in the periosteum (enthesopathy) with a debilitating effect, limiting the movement of the spine, shoulder girdle, and pelvic girdle.³⁴

A disease associated with rickets is hypophosphatasia.³⁸ It is a hereditary disease characterized by a deficiency in bone and tooth mineralization and low levels of alkaline phosphatase (ALP) activity. A variety of mutations in the nonspecific tissue ALP gene have been described.³⁸

The severity of the disease usually depends on the age of presentation, with the earlier presentation the most severe. The clinical spectrum of the disease varies widely and can be classified into these four clinical phenotypes of decreasing severity: perinatal, infantile, childhood, and adult.^{23,38}

In the perinatal form, the disease is usually fatal. Mineralization is remarkably poor, with entire segments of the spine not represented (absent) on radiographs. Infants have skin-covered osteochondral spurs that protrude from the forearms or legs.³⁹

In infantile forms, patients may appear normal at birth; however, clinical signs of hypophosphatasia appear during the first 6 months. There may be craniosynostosis, which can cause an increase in intracranial pressure. Radiographs show diffuse demineralization, and characteristic “tongues” of radiolucency are present extending from the growth plate to the metaphysis. This form also has respiratory complications due to rachitic chest deformities. Hypercalcemia is also present, partly explaining irritability, poor diet, anorexia, vomiting, hypotonia, polydipsia, polyuria, dehydration, constipation, and hypercalciuria, often leading to renal failure, nephrocalcinosis, and recurrent vomiting.^{39,40}

The childhood form is characterized by skeletal deformities, such as dolichocephalic head, enlarged joints, delayed walking, short stature, and swaying gait. Signs of intracranial hypertension or growth retardation are typical.³⁹

Also the severity of radiographic changes decreases with increasing age at presentation. Premature loss of dentition is a common feature of the various forms, with deciduous incisors often the first to be affected. Odontohypophosphatasia is characterized by premature exfoliation of fully rooted primary teeth and/or severe dental caries.³⁹ Dental radio-

graphs show reduced alveolar bone, enlarged pulp chambers, and root canals.

The clinical features, radiologic findings, and/or biomarker levels of the disorder should raise suspicion and encourage inclusion of hypophosphatasia as a differential diagnosis. Biomarkers are an important contribution to the diagnosis.⁴⁰

Renal Osteodystrophy

Renal osteodystrophy refers to the complex of findings observed in the context of chronic renal failure. These include the results of rickets (and osteomalacia in adults) and secondary hyperparathyroidism.²³

In patients with chronic renal failure, radiographs may show a diffuse increase in bone radiodensity, a finding seen more often in the axial skeleton (that has more trabecular bone than cortical bone).²³ The etiology of this diffuse osteosclerosis is not well understood, although it probably reflects the anabolic effect of PTH. Despite the increase in radiodensity, bone is structurally weak and prone to stress fractures.²⁸ The vertebral column often exhibits a characteristic striped appearance (alternating bands of higher density along the end plates and decreasing density in the central portion of the vertebral body), also known as a rugger jersey spine.⁴¹

Clinically, renal osteodystrophy expresses itself with diffuse and nonspecific bone pain and may be associated with weightbearing. It has not been confirmed whether this pain is a consequence of the microfractures within the structurally weaker bone. The initial manifestation of pain occasionally is periarticular, similar to an exacerbation of an arthritic condition.⁴² Muscle weakness is commonly associated with renal disease, usually with a proximal myopathic distribution.⁴³ Stunted growth in children is the result of renal bone disease, malnutrition and chronic acidosis. Growth retardation is accompanied by progressive skeletal deformity that can affect both the appendicular and axial skeletons. Radiographically, the deformity resembles that seen in vitamin D-deficient rickets, with rachitic rosary, enlarged metaphyses (e.g., thickened wrists and ankles), long bone bowing (more classically, genu varum), frontal bossing, and ulnar deviation at the wrists.⁴² Slipped capital femoral epiphysis is observed in adolescents with renal disease. Although the physis was shown to be more vertically oriented in these children, it was not shown to be weaker.⁴²

Radiologically, renal osteodystrophy can present as osteomalacia, osteosclerosis, fracture, amyloid deposition, soft tissue calcification, and bone resorption.⁴²

Chondrocalcinosis can be observed in hyaline or fibrocartilage cartilage around the knee, in the pubic symphysis, or in the triangular fibrocartilage complex on the wrist.²⁸ Looser zones may be noted (microfracture lines or complete fractures following a pattern of osteoporotic insufficiency). Bone resorption can be subchondral, endosseous, subperiosteal, or subligamentous. The classic sites of subchondral resorption are the distal clavicle, the sacroiliac joints, and the pubic symphysis.²⁸ Endosteal resorption is evident in the shaft of the long bones. Subperiosteal resorption occurs at the joint margins, with the appearance of rheumatoid marginal

erosions; hands and feet show subperiosteal erosion along the radial edge of the middle phalanges and in correspondence with the tufts of the distal phalanges. Subligamentous or subtendinous erosions may be seen at the calcaneal insertion of the plantar fascia, the insertion of the triceps on the olecranon, and the attachment of the hamstring to the ischial tuberosities.⁴²

The gold standard for bone quality assessment is still bone biopsy and histomorphometry, but it is limited by invasiveness, especially in children, and also dynamic changes cannot be assessed. Noninvasive techniques evaluate the amount of bone primarily using DXA or technologies based on computed tomography (CT), such as quantitative peripheral CT (pQCT).⁴⁴

BMD measurement is used to assess fracture risk. DXA is the primary technique for this assessment, but it is neither related to bone histomorphometry nor provides information on bone microarchitecture. It also does not supply a compartmental assessment (cortical bone versus trabecular bone).^{45,46} QCT enables three-dimensional (3D) imaging of central and axial skeletal cross sections to provide spatial or volumetric bone mineral density (vBMD). It also allows the distinction between cortical and trabecular compartments. In chronic kidney disease (CKD), QCT measurements of trabecular bone density at the spine were correlated with histomorphometry of trabecular bone volume.⁴³

A pQCT avoids a large dose of ionizing radiation exposure for patients by focusing on the tibia and distal radius.⁴⁵ Fracture risk in patients with renal osteodystrophy was evaluated in a study that used DXA and pQCT to differentiate between cortical bone density (CBD) and trabecular bone density (TBD). Results showed higher TBD values than control subjects but lower CBD values (in stages 4–5 CKD).⁴⁷

A longitudinal study in stages 2 to 5 CKD revealed lower cortical BMD z scores and, more importantly, the deficits correlated with other biomarkers, particularly hyperparathyroidism and higher levels of calcitriol and hypocalcemia. This study also found an increased risk of fractures even in children who have a lower tibial pQCT.⁴⁸

The resolution of a QCT (0.5 mm) is not sufficient to detect the disruption of the trabecular architecture. However, the resolution of HR-pQCT is 100 μ m that also allows the evaluation of the trabecular microarchitecture (bone volume fraction, trabecular thickness, separation, and number).⁴⁵ The HR-pQCT of the radius and tibia was used to discriminate those with and without fractures in a cross-sectional study of 74 patients with stage 5D CKD (with 30 prevalent fractures) and 40 controls without kidney disease or fractures.⁴⁹ All HR-pQCT parameters differed significantly between patients with and without a history of tibial fracture, except for trabecular thickness.

Finite element analysis is used to reconstruct HR-pQCT images to study large regions of trabecular bone. This method tests the local stress and strain distributions in the trabeculae, as well as calculating the percentage of the total load borne by trabecular bone.⁴⁵

The use of high-resolution magnetic resonance imaging (HR-MRI) allows 3D imaging of bone geometry and trabecular microarchitecture in peripheral sites, without the use of

ionizing radiation. HR-MRI imaging is used to analyze the trabecular bone structure of the calcaneus to compare this technique with BMD from DXA in predicting therapy-induced bone loss and prevalent fractures. The strongest discriminators between patients with and without fractures were trabecular parameters, even after adjustment for age and BMD.⁴⁵

Pediatric Osteoporosis

Osteoporosis is a disease characterized by reduced bone mass and deterioration of the bone microarchitecture, resulting in an increased risk of fragility fractures. Although up to 80% of bone mass acquisition depends on genetic factors, environmental factors such as calcium intake, vitamin D status, and physical activity play a key role.⁵⁰

Pediatric bone status is a strong predictor of bone status in young adulthood, so it is important to assess whether there is reduced bone mass acquisition early on because it can cause osteoporosis in adults.⁵¹ Indeed, childhood and adolescence have been identified as “the most critical periods of skeletal mineralization,” and up to 95% of total bone mass is achieved by the end of adolescence.⁵¹

In children, osteoporosis manifests as vertebral or non-vertebral fragility fractures (or low-trauma fractures) (most commonly seen in the femur, tibia, forearm, humerus, feet, and ankles).⁵¹ In children with recurrent fractures, all secondary causes must be ruled out before primary osteoporosis is suspected.⁵¹

These individuals should undergo DXA scans only in the event of a fracture following a low-force impact, when vertebral bodies are involved, or when a child has two or more bone fractures up to 10 years of age or three or more long bone fractures at any age up to 19 years.⁵¹

Pediatric osteoporosis has primary and secondary forms.⁵² Primary forms are caused by genetic disorders such as OI, XLH, enzyme defects (such as hypophosphatasia and homocystinuria), copper transport disorders (such as Wilson’s disease), or accumulation of glucocerebrosides (such as Gaucher’s disease). A specific form of primary pediatric osteoporosis is represented by idiopathic juvenile osteoporosis.⁵⁰

Secondary forms of pediatric osteoporosis are caused by the harmful effects on bone mass of chronic systemic diseases and/or by their treatment.⁵³ Chronic inflammatory diseases (such as Crohn’s disease), eating disorders, malnutrition and/or malabsorption resulting in vitamin D deficiency, diseases affecting kidney, lung, or liver function, endocrine diseases, and neuromuscular disorders are associated with reduced BMD and pathologic fractures. In many diseases, bone involvement is progressive over the natural history of the disease.⁵⁰

Systemic inflammatory diseases are characterized by increased levels of proinflammatory cytokines (such as tumor necrosis factor α , interleukin [IL]-1 and IL-6) that impair osteoblast function and promote osteoclastogenesis by acting directly on cells or by increasing the expression of key molecules such as RANKL.⁵¹ In addition, prolonged high-dose treatment with glucocorticoids, typical of these diseases, also causes osteoporosis.

Glucocorticoids alter bone turnover, increasing its resorption and decreasing its formation.⁵⁴ High levels of glucocorticoids were also shown to impair bone growth due to an antiproliferative effect on chondrocytes in growth plates and a reduction in growth hormone levels.⁵⁴ High-dose glucocorticoid therapy also results in severe changes in bone microarchitecture resulting in reduced bone quality. Glucocorticoids act mainly on the trabecular bone, present in high percentages in the spine of children, increasing the risk of vertebral fractures.^{51,54} Finally, glucocorticoids influence calcium homeostasis by increasing its urinary excretion and reducing gastrointestinal absorption.⁵⁰

Glucocorticoids also act on muscles, causing muscle atrophy and replacement of fat tissue.⁵¹ This contributes to abnormal bone metabolism as a result of an alteration in the so-called muscle-bone functional unit, whereby muscles drive bone growth by uninterrupted dynamic stimulation through tendons to cortical bone. Therefore, reduced mechanical stimulation on the bones (such as in the case of muscle atrophy) could contribute to increased bone fragility and risk of fractures.⁵¹

The diagnosis of osteoporosis in childhood is strictly based on the clinical manifestations of bone fragility. Current recommendations emphasize that a definition of osteoporosis in children cannot be established basing on densitometric criteria alone.⁵⁵

DXA is the standard method for assessing pediatric bone mass because it is widely available and reproducible, low cost, and has reduced exposure to ionizing radiation⁵⁶ (►Fig. 4a–c). In children, DXA measurements are usually taken at the lumbar spine (L1–L4).⁵⁶ BMD measurements in children should be converted to age- and sex-specific standard deviation (SD) scores (z scores); however, BMD results are also affected by body size, ethnicity, bone age, and pubertal development.

The terms *osteoporosis* and *osteopenia* should not appear in pediatric DXA reports. Pediatric patients with BMD values ≤ 2 SDs should be described as having low bone mass for age. The reason is that other factors, such as retarded growth and/or pubertal development, can lead to a reduction in bone size.^{51,56}

To overcome this problem, BMD values representing an areal bone mineral density, vBMD (g/cm^3), or height z score-corrected BMD z scores can be extrapolated, and these values can be compared with the pediatric reference data.^{51,56}

However, DXA has limitations because it does not reliably differentiate between trabecular and cortical bone, which respond differently to stimuli such as pubertal changes, mechanical forces, and disease-related stress, and it is unable to assess bone geometry or mechanical properties.⁵¹

In 2013, the International Society for Clinical Densitometry (ISCD) recommended that pediatric osteoporosis be diagnosed in the presence of at least one vertebral compression fracture not related to local disease or high-energy trauma (regardless of densitometry measurements) or in the presence of both reduced bone mass (bone mineral content [BMC] or BMD z score, taking into account bone dimensions) and a clinically significant fracture history.^{50,55} In 2016, the American Academy of Pediatrics updated the ISCD 2013 report on the role of bone densitometry in children, recommending DXA assessment in children with lumbar spine fragility (L1–L4).⁵⁰

In children, a low BMD or BMC z score ≤ -2.0 or lower is a mandatory criterion for making a diagnosis of osteoporosis, due to the high frequency of long bone fractures in healthy children. However, children at high risk of fractures can sustain long bone fractures even with a BMD z score > -2.0 ; these children should be considered as having osteoporosis regardless of DXA values and should be treated as such.⁵¹ Finding one or more vertebral fractures, in the absence of local disease or high-energy trauma, should be considered indicative of osteoporosis regardless of densitometry z scores.⁵¹

Lateral thoracolumbar spine radiography with vertebral evaluation using Genant's semiquantitative method⁵³ is the most common imaging modality for evaluating spinal health. It is the gold standard for the identification of pediatric vertebral fractures⁵⁷ (►Fig. 5). However, this modality is associated with a high dose of ionizing radiation.

Spinal fractures can also be evaluated using DXA images through a technique called vertebral fracture evaluation (VFA) that has been confirmed as a practical screening tool for identifying vertebral fractures in children at risk for fragility fractures.⁵⁰ Despite the advantage that VFA exposes the patient to low radiation and can be performed during routine DXA evaluation, the evaluation of vertebral body VFA in the midthoracic region is still suboptimal, particularly in younger children.⁵⁰



Fig. 4 Dual-energy X-ray absorptiometry of a child with osteoporosis at different ages showing the remodeling of the proximal femur with aging. (a) Five years old. (b) Seven years old. (c) Ten years old.



Fig. 5 Lateral dorsolumbar spinal radiograph of a child with osteopetrosis. Clear evidence of bone rarefaction, thinning, reduction of trabeculae, and multiple vertebral fractures.

A pQCT of the radius and tibia can be used to study bone geometry and microarchitecture, quantifying the distribution of fat and muscles.⁵¹ Despite some promising studies in children, further studies are needed to clarify whether pQCT measurements at the level of the appendicular skeleton adequately reflect the situation of the entire skeleton including axial bones. Today, limited reference data are available, hindering direct comparisons between observed values and literature data. Furthermore, there is little evidence on the intra- and interobserver reproducibility of pQCT values and the possible risk of artifacts.⁵¹

Osteopetrosis

Osteopetrosis is a disease caused by impaired differentiation or function of the osteoclasts. This compromise causes excessive bone density and at the same time a deterioration in bone quality that predisposes to atraumatic fracture.⁵⁸

Several types of the disease have been described. Traditionally, the disorder was divided into two forms: the early malignant (congenital) form with autosomal recessive inheritance (AR) and severe symptoms, and the benign variety with autosomal dominant inheritance and relatively mild symptoms that occur in adults.^{59,60}

The AR form is pediatric and has a low incidence of 1 in 250,000 births.⁶⁰ It can be caused by six genetic mutations, two of which code for RANKL or its receptor (involved in the formation of osteoclasts).

The recessive form is usually lethal in infancy or childhood. It occurs classically in the first months of life and is characterized by brittle bones, radiologically long with funnel-like extremities, and narrowed medullary cavities.⁵⁸ The disruption of normal bone modeling and remodeling can give rise to skeletal deformity, resulting in short stature of varying degrees.

Macrocephaly and frontal prominence develop within the first year, resulting in a typical facial appearance. Changes in the skull can cause stenosis of the oral canal and hydrocephalus. Tooth eruption defects and severe dental caries are also common.⁶⁰

The reduced medullary cavity results in hematologic failure with anemia, leukopenia, and susceptibility to infection and extramedullary hematopoiesis. The bony overgrowth may cause neural complications, especially cranial nerve palsy, if the osseous foramina are severely narrowed. This can lead to blindness, deafness, and nerve palsies.^{59,60}

Biochemical analysis typically shows hypocalcemia (with risk of developing tetanic seizures and secondary hyperparathyroidism), elevated ALP, and reduced bone resorption markers.⁵⁸

Radiographs remain as the principal imaging method that demonstrate the extent and degree of formation of sclerotic bone and its effect on skeletal modeling. Although sclerosis of bones is widespread, in the skull it affects the base more than the calvaria, whereas in the tubular bones, the ends of the bones are the most affected. However, MRI shows that, despite sclerosis, the skull base exhibits substantial marrow activity.⁵⁹ Suppression of development of the paranasal sinuses is common. The frontal radiograph shows an appearance that has been likened to a “harlequin mask” or a “space alien.” The mandible is hypoplastic and often shows a characteristic triangular endobone extending from the condyle to the ramus and corresponding to the condylar cartilage center.⁵⁹ The formation of dental enamel is defective and caries supervene. In the thorax, ribs are usually uniformly sclerotic. Both the vertebral bodies and the appendages are sclerotic, exaggerating the normal anterior vascular notches.⁵⁹

The distribution of body bone marrow stores can be shown by Tc 99m sulfur colloid scintigraphy.⁵⁹ In the appendicular skeleton, the greatest amount of residual marrow

tends to lie in the less opaque regions of the bones shown on radiography and regions of intermediate or high signal intensity on T2-weighted MR sequences.

In the skull, where bone is sclerotic, that is, at the level of the skull base, T1- and T2-weighted sequences both show low signal intensity. Where marrow is present, the signal is intermediate in intensity.⁵⁹

Conclusion

Pediatric MBDs are a heterogeneous group of disorders with high mortality that affect the bones widely. They are heterogeneous in etiology, onset, severity, and clinical manifestations, but it is often difficult to diagnose them.

Understanding the underlying mechanism of these diseases, with the help of laboratory tests and imaging, helps the physician make a differential diagnosis. An early diagnosis is fundamental because the clinical consequences of these diseases in the pediatric population are highly disabling, such as reduced linear bone growth, bone deformities, and nontraumatic fractures that lead to bone pain and motor deficits.

Conflict of Interest
None declared.

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