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MINISYMPOSIUM

Rickets: Part II

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Abstract This is the continuation of a two-part review of rickets. This part emphasizes the specific pathophysiology, clinical features, pathoanatomy and radiographic findings of vitamin D deficiency rickets. Other forms of rickets, differential diagnostic considerations and the potential relationship between low levels of vitamin D metabolites and unexplained fractures in infants are also discussed.

Keywords Rickets · Vitamin D · Children · Bone · Radiographic findings · Nonaccidental trauma

Vitamin D deficiency rickets

Pathophysiology

Knowledge of the three classic stages of rickets, initially described by Fraser et al. [1] in 1967, is helpful in understanding the pathophysiolgy of rickets. In stage I, with developing vitamin D deficiency, intestinal absorption of calcium declines causing hypocalcemia, which can be clinically silent or lead to seizures or other manifestations. In response, 2° hyperparathyroidism (HPTH) develops, mobilizing calcium and phosphate from bone, increasing renal calcium reabsorption and phosphate excretion, and upregulating renal 25-hydroxy-vitamin D-1α-hydroxylase (1-OHase) to increase calcitriol and hence intestinal calcium absorption. These adaptations lead to stage II, defined by normalization of circulating calcium. Parathyroid hormone (PTH) and alkaline phosphatase are elevated and there is hypophosphatemia. Calcitriol levels can be elevated at this time, hence their measurement is generally not useful in the diagnosis of vitamin D deficiency. At this stage, physeal manifestations of rickets become apparent clinically and radiographically, consistent with the concept that hypophosphatemia, as the cause of failed chondrocyte apoptosis, is the common pathway for all rickets [2, 3]. With worsening vitamin D deficiency, substrate 25-hydroxy-vitamin D (25D) levels fall low enough that calcitriol can no longer be maintained despite PTH stimulation of 1-OHase. This leads to stage III, with decreased intestinal calcium absorption, return of hypocalcemia, worsening of 2° HPTH, and florid clinical and radiographic features. The ability to increase 1-OHase activity provides partial compensation for insufficient 25D, but this is not free. Rather, it comes at the expense of 2° HPTH and hence is part of the very pathophysiology of rickets. Bone disease usually begins during stage I with 2° HPTH, which causes bone resorption. Attention to this aspect of vitamin D deficiency is reflected by the use of the term "hypovitaminosis D osteopathy" by Parfitt [4] not only to include both rickets and osteomalacia, but also to include "the totality of osseous complications" of vitamin D deficiency, specifically referring to the clinically silent 2° HPTH that often precedes identifiable osteomalacia by years and results in significant bone loss.

Clinical presentation

The clinical features of vitamin D deficiency rickets are well-described [5–8]. It is most prevalent between 3 months

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and 18 months of age. Placental transfer of 25D affords protection during the first 3 months of age, although rickets can be seen earlier with severe maternal vitamin D deficiency. True congenital rickets is quite rare [9]. In cases of congenital (or early-onset) rickets presenting with hypocalcemic seizures, Orbak et al. [10] showed very low 25D levels and significantly elevated PTH in both the mothers and infants, suggesting maternal calcium depletion and hypocalcemia leading to insufficient calcium transfer to the fetus with associated fetal/neonatal HPTH. Kovacs [11] also suggests that congenital rickets likely requires maternal malnutrition, hypophosphatemia or calcium deficiency in addition to vitamin D deficiency. Although the three stages of rickets defined by Fraser et al. [1] are useful for understanding pathophysiological progression, they are not seen in all patients. Stage I is characterized by hypocalcemia that can cause seizures, laryngospasm or tetany, although most patients pass through this stage with no clinical manifestations. Symptomatic hypocalcemia might be precipitated by intercurrent illness and is age-related, seen in children younger than 3 years and in adolescents, suggesting that it reflects the increased demand for calcium during periods of rapid growth [5]. Craniotabes has been associated with vitamin D deficiency, although this finding is quite nonspecific as it has also been seen in other conditions including osteogenesis imperfecta, congenital syphilis and hydrocephalus and in some normal infants [12]. Other nonspecific findings in rickets include diminished longitudinal growth, hypotonia and muscle weakness, believed to be caused by deficient vitamin D signaling in skeletal muscle. In stage II, defined by the return of normocalcemia from 2° HPTH, the specific manifestations of disrupted endochondral ossification and mineralization at the physes become apparent. With accumulation of excessive disorganized hypertrophic (referring to zone of hypertrophy) cartilage, the metaphyses widen and appear clinically as swollen joints or, more accurately, "knobby knees." Similar expansion of the metaphyseal-equivalent regions at the costochondral junctions produces the rachitic rosary. Bowing of long bones, particularly anterior and lateral bowing of the femurs and tibias, might arise from bending of the excessive cartilage in the metaphyses or from bending of the shafts secondary to osteomalacia. Osteomalacia might be responsible for bone pain as well as other deformities of rickets such as Harrison grooves with depression of the chest wall at diaphragmatic insertions from rib softening [13]. Other clinical manifestations include delayed closure of fontanelles, frontal and parietal bossing, delayed tooth eruption and predisposition to craniosynostosis.

Pathoanatomy and radiographic features

Many excellent reviews cover the radiographic features of rickets [4, 7, 14–18]. Most important are those that reflect the disordered mineralization and ossification of the physes. Other findings include those of osteomalacia and HPTH, as well as deformities, largely caused by osteomalacia.

Early in the course of severe vitamin D deficiency in infancy, diffuse demineralization might precede the typical rachitic findings in the physes. Initially, demineralization is caused by 2° HPTH with subsequent contribution from osteomalacia. Whether demineralization at this time is considered to be a manifestation of rickets or of "hypovitaminosis D osteopathy" is less important than the practical considerations of whether it can be reliably interpreted radiographically, as radiographic evaluation of bone mineralization is highly dependent on technical factors and overall fraught with difficulty. Recognizing these limitations, evaluation of the skull has been described as useful for identifying infants with early rickets. Best known in the radiologic literature is the 1977 study by Swischuk and Hayden [19] that evaluated skull radiographs in infants with rickets. They considered loss of distinctness of the cortical margins of the facial bones, including the lamina dura surrounding teeth, and anterior cranial fossa to be the most useful signs for evaluation of demineralization. They found such demineralization in vitamin D deficiency rickets and other forms of rickets currently classified as calcipenic but not in those forms classified as phosphopenic. This is compatible with the concept that such initial demineralization is a manifestation of 2° HPTH. Absent from their study was a control group, and hence the ability to use these findings to distinguish rickets from normal was undetermined [20]. Similar skull findings were considered to be the earliest radiographic findings of rickets in the study by Fraser et al. [1] from 1967 that defined its pathophysiological stages and correlated them with radiographic findings, interpreted by J. S. Dunbar, Jr. Of nine patients with stage I rickets, six had only skull demineralization and three also had mild rachitic findings in the long bones. With progression to stage II and then stage III, there was progression of radiographic findings in the physes. All of the patients were known to have rickets and no control group was examined. Hence, while the correlation of radiographic and biochemical findings supports their concept of progressive stages of rickets (the purpose of the study), the indication that skull demineralization was present in all stage I infants is testimonial but provides no data concerning whether this finding can be used prospectively to distinguish infants with early rickets from normal.

The most diagnostic radiographic features of rickets are those that reflect the disorder of mineralization and ossification affecting the growth plate. These findings are best seen in the metaphyses of the fastest growing bones including the distal radius and ulna, distal femur, proximal and distal tibia, proximal humerus and the anterior ends of the middle ribs. Although involvement of the distal ulna but not radius might reflect its faster growth with no significant

proximal component, this should be interpreted cautiously since isolated ulnar cupping could be a normal finding [21]. Similarly, the findings of rickets are most prominent during times of most rapid bone growth and could be masked by growth failure (Fig. 1).

Histopathologically the resting and proliferative zones are normal. However, failure of apoptosis of hypertrophic chondrocytes leads to marked accumulation of hypertrophic cartilage, with much of the excessive cartilage having a disorganized appearance with loss of the normal columnar pattern. This buildup of cartilage leads to widening of the physis in the axial dimension (the dimension of longitudinal bone growth). The other pathological process involving the hypertrophic zone is failure of terminally differentiated chondrocytes to mineralize the cartilage matrix, which should form the zone of provisional calcification. The radiographic appearance can be quite variable and depends on the amount of hypertrophic cartilage that has accumulated and to what extent it is partially mineralized, as the mineralization defect might not match the arrest of endochondral ossification.

Although axial widening of the growth plate has been considered to be the first sign, this can be very difficult to recognize, particularly in infants, as the true width of physeal cartilage cannot be determined until there are well-developed ossification centers on both its metaphyseal and epiphyseal sides. More useful early findings reflect the decreased mineralization of terminally differentiated cartilage at the zone of provisional calcification (ZPC). With decreasing mineralization of the ZPC, this normally opaque line becomes progressively less distinct; eventually it is no longer visualized and metaphyseal trabecular bone fades into the lucent cartilage of the physis with no distinct margin. In other cases, the mass of hypertrophic cartilage is partly mineralized. As the ZPC represents calcified hypertrophic cartilage, this variably calcified or noncalcified mass can be thought of as a widened ZPC, although the pattern of mineralization is patchy and not as uniform as the normal ZPC. This region has also been referred to as the "pseudophysis" [22] and the "zone of preparatory calcification" [23]. As rickets becomes more severe, the enlarging mass of disorganized cartilage expands in multiple directions. In addition to widening the axial width of the physis, it expands the metaphyses transversely, producing the clinically apparent enlargement of bone ends. It might also expand into the metaphyseal region, causing collapse of the poorly mineralized trabecular bone, one of the mechanisms proposed for the development of metaphyseal cupping [16]. The margin between this cartilage mass and metaphyseal bone might be irregular, with tongues of cartilage projecting into the metaphysis, yielding a frayed appearance radiographically. Mineralization of the peripheral rim of bone formed by membranous ossification of the perichondrium is often less affected than the endochondral process, leading to a rim of bone surrounding the enlarged lucent physis, contributing to the appearance of metaphyseal cupping. The physeal findings of rickets are illustrated (Figs. 2, 3, 4, 5, 6, 7, 8, 9, 10 and 11). Although MR imaging is not needed for the diagnosis or management of rickets, it is important to recognize rickets as a cause of widened zones of cartilage at the physes to avoid misinterpretation [23]. An example using MR imaging is included in the section on X-linked hypophosphatemia.

The metaphyseal (Laval-Jeantet) collar is a short cylindrical segment of the metaphysis adjacent to the physis with parallel rather than flared margins, most often seen between 1 month and 2 years [24], although it might be seen up to 7 years of age [25]. Because it serves as a marker for the part

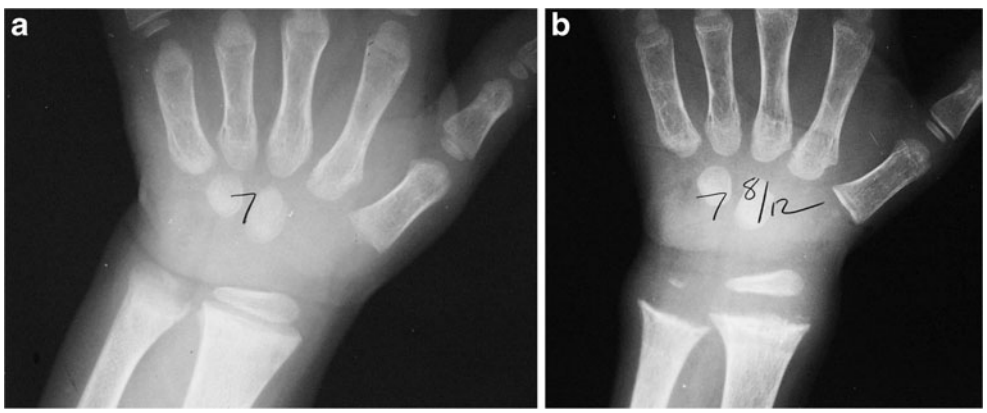

Fig. 1 Effect of growth. Images in a 7-year-old with chronic renal failure. **a** Hand radiograph shows mild rickets in the distal ulna and a relatively normal appearance of the distal radius. Because of growth failure associated with renal insufficiency, growth hormone therapy was begun. **b** A subsequent radiograph at 7 years 8 months taken while the child was on growth hormone shows marked widening of the distal radial and ulnar physes and interval loss of definition of the distal radial ZPC. The child's biochemical status had not deteriorated, but the radiographic findings had been masked by lack of growth

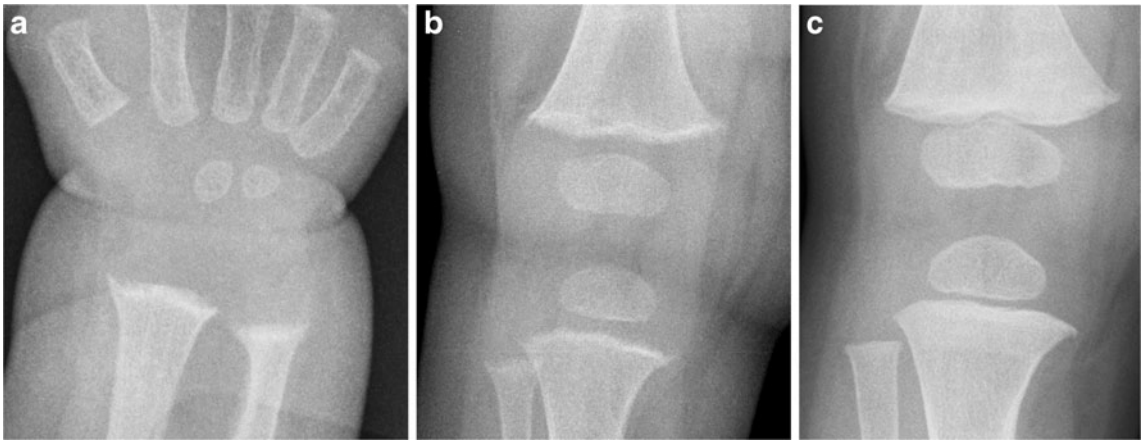

Fig. 2 Vitamin D deficiency rickets in a child age 8 months. Initial radiographs (**a**, **b**) show loss of distinctness but not absence of distal radial ZPC. The distal ulnar ZPC is nearly absent and there is mild cupping of the distal radius and ulna. The physeal widths cannot be assessed. The right knee also shows lack of distinctness of the distal femoral and proximal tibial ZPCs and absence of the proximal fibular ZPC. Widening of the distal femoral and proximal tibial physes is most convincingly shown by comparison with the subsequent radiograph (**c**) obtained 10 months after treatment began. This radiograph shows healing with improved definition of the ZPCs and normal physeal widths

of the metaphysis adjacent to the physis, it is the region that is replaced by nonmineralized cartilage and osteoid in rickets [22, 24]. Oestreich and Ahmad [22] have reported loss of visualization of the metaphyseal collar in nearly all cases of rickets, whereas it is maintained in several metaphyseal chondrodysplasias.

The physeal and metaphyseal findings can be quantified by the Thacher scale (Table 1) [26]. Evaluation of osteopenia was considered but rejected as too dependent upon radiographic technique.

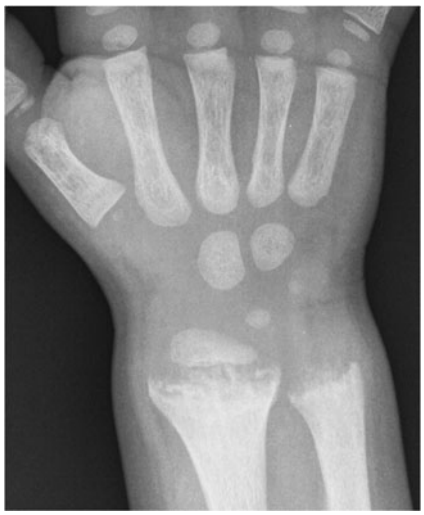

Fig. 3 Vitamin D deficiency rickets in a child age 3 years 2 months with 25D 5.6 ng/mL. PTH 944 pg/mL and alkaline phosphatase 1,263 IU/L were both elevated. There was poor definition of ZPCs. The physeal width cannot be clearly delineated. Trabecular bone of the metaphyses fades into the physes with no distinct border. For the distal radius, there is partial mineralization of the rachitic hypertrophic cartilage between the metaphysis and epiphysis. Cupping of the distal radial metaphysis is largely caused by mineralization of membranous bone formed by the osteoblastic transformation of perichondrial cells surrounding the rachitic hypertrophic cartilage

Involvement across the physis is usually uniform but might be limited to the medial aspects of the distal femoral and proximal tibial physes with genu varum, and hence is a frequent finding with X-linked hypophosphatemia (XLH) [27]. Less often, genu valgum might be associated with disproportionate involvement of the lateral aspects of these physes. These findings suggest that compressive stress exacerbates the already impaired bone growth and mineralization of the physes [27].

In adolescents, recognition of rickets at the wrists and knees becomes increasingly difficult as these physes narrow and begin to close. At this age, evaluation of the physes for the secondary ossification centers of the iliac crests and ischial tuberosities becomes more helpful [28].

In the growing skeleton, the margins of the ossification centers for the epiphyses and the small (non-tubular) bones of the hands and feet have the same histology as the metaphyseal growth plates [29]. Rachitic changes might also be seen in these regions, although their appearance is less pronounced because their growth is substantially slower than that of the metaphyses. Poor mineralization of the ZPC surrounding these ossification centers causes loss of definition of the thin opaque surrounding line. Initially internal trabecular bone is maintained but it fades away into lucent cartilage (Figs. 7 and 9), an appearance opposite that of scurvy where there is preservation or accentuation of the ZPC and internal trabecular rarefaction resulting in the Wimberger ring. With severe rickets and associated osteomalacia, the internal trabecular bone becomes progressively osteopenic to the point that the epiphyses may become unapparent. Overall, the epiphyseal ossification centers

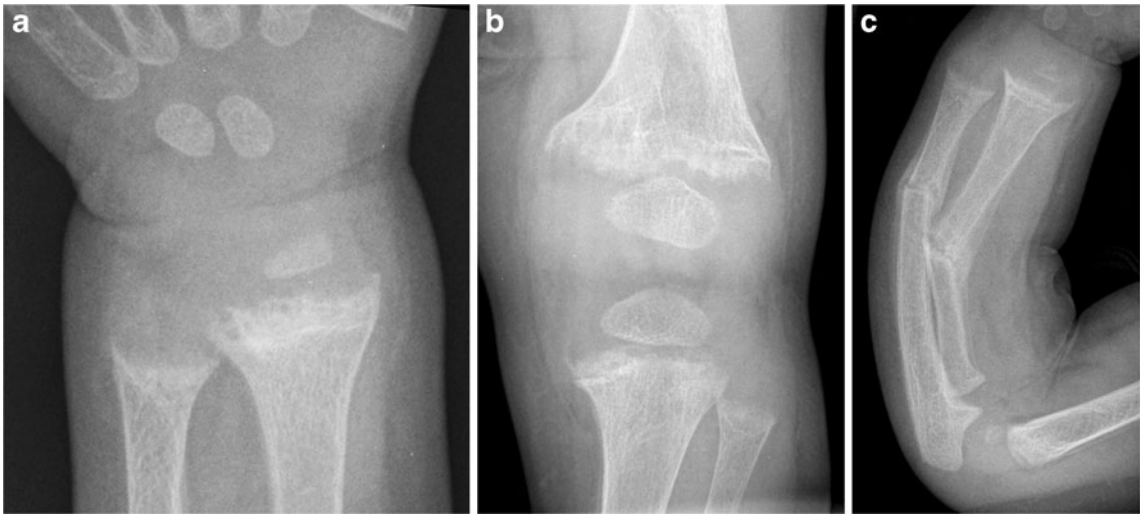

Fig. 4 Vitamin D deficiency rickets in a child age 1 year 9 months with 25D 4.9 ng/mL and PTH 287 pg/mL and alkaline phosphatase 1958 IU/L, both elevated. Radiographs of the wrist (**a**) and knee (**b**) show partial visualization of an opaque line in the distal radius, representing the ZPC at the time that rickets became active. Distal to this line, there is partial mineralization of the rachitic hypertrophic cartilage; note that this does not have the appearance of trabecular bone. Similar findings are seen in the distal femur and proximal tibia. The distal ulna and proximal fibula show cupping and loss of definition of the ZPC, but no mineralization of hypertrophic cartilage. Subtle subperiostal resorption along the radial aspect of the distal ulna is compatible with HPTH. Lateral views of both forearms (only left shown, **c**) demonstrate marked generalized demineralization, subperiosteal resorption and symmetrical healing bilateral radial and ulnar diaphyseal fractures

might be delayed in development, small, and poorly delineated, giving a false impression of delayed maturation. Although rickets does involve delayed endochondral ossification, the ossification defect involves failed apoptosis of hypertrophic chondrocytes, which is not an indicator of skeletal maturation, and this process is rapidly reversed with treatment. For comparison, true disorders of skeletal maturation, such as hypothyroidism, involve abnormal transition from proliferating to hypertrophic chondrocytes, a process controlled by parathyroid hormone related peptide (PTHrP) and influenced by multiple endocrine factors [30, 31].

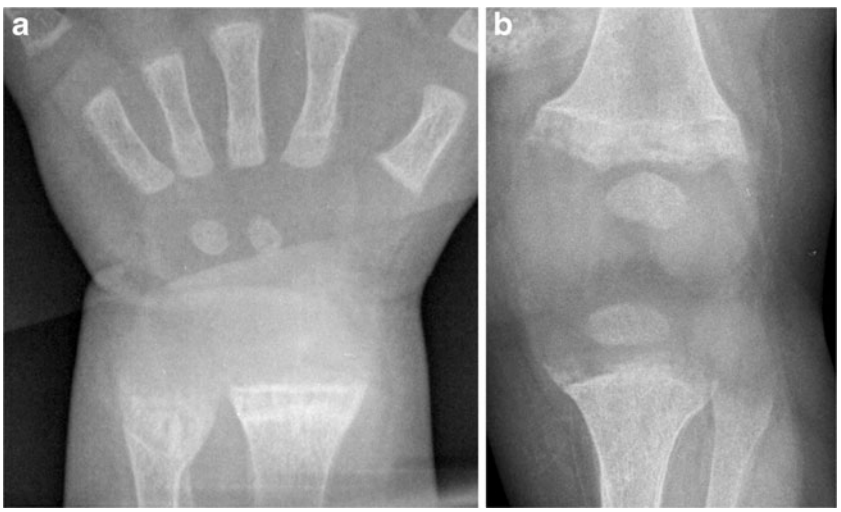

Fig. 5 Rickets with severe liver disease in a child age 6 months with 25D 9.8 ng/mL. Radiographs of the wrist (**a**) and knee (**b**) show marked variation in mineralization of rachitic hypertrophic cartilage. For the distal femur, the partly visualized opaque line at the margin of the metaphyseal trabecular bone is a remnant of a prior ZPC. Peripheral to this is a fairly well mineralized zone that appears to be mineralized hypertrophic cartilage rather than trabecular bone. The current ZPC, which should be at its leading edge, is not mineralized. For the proximal tibia, the old ZPC is also visualized, but there is only whispy mineralization of the more recent adjacent hypertrophic cartilage and no mineralization of the current ZPC. The distal radius has two parallel opaque lines. It is suggested that the more proximal of these is a remnant of an old ZPC with the more distal being the current ZPC, significantly better mineralized for the distal radius than the other bones. The distal ulna and proximal fibula are severely affected, with no mineralization of the ZPC and only minimal mineralization of hypertrophic cartilage for the ulna. Subperiosteal bone resorption for many metacarpals is indicative of HPTH

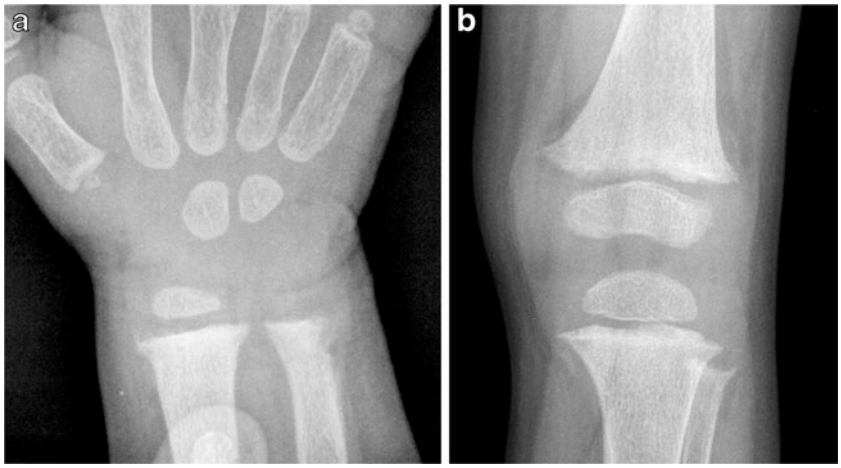

Fig. 6 Vitamin D deficiency rickets in a child age 1 year 10 months with 25D below a detectable level and elevated PTH of 1,239 pg/mL. Rachitic findings at the wrists (**a**) and knees (**b**) are relatively mild. Loss of definition of the ZPC is more prominent for the femur, fibula and ulna than the tibia and radius, and there is physeal widening. However, findings of HPTH are quite prominent, with extensive subperiosteal bone resorption along the medial aspect of the distal ulna

The radiographic findings of rickets in the shafts are considerably less specific than those at the physes and largely reflect the effects of 2° HPTH and osteomalacia. With vitamin D deficiency, and other forms of calcipenic rickets, 2° HPTH develops to maintain a normal circulating level of ionized calcium, in part by osteoclastic bone resorption. Subperiosteal resorption is the most specific radiographic sign of HPTH; other findings in the shafts include cortical thinning, intracortical tunneling and endosteal resorption. Osteomalacia can produce similar findings, although the pathophysiology is quite different. For example, excessive intracortical tunneling can be seen in both conditions. In HPTH this reflects increased bone turnover and excessive bone resorption whereas in osteomalacia turnover and intracortical resorption are normal, but the newly formed replacement bone is poorly mineralized, creating intracortical lucency. Osteomalacia also affects the trabeculae, which become lined with poorly mineralized osteoid, leading to overall demineralization, loss of visualization of small trabeculae and coarsening of the trabecular pattern (Fig. 4). The time course of diaphyseal findings is not clear. Although they are usually considered to lag behind those of the metaphyses, in early stages of vitamin D deficiency the only radiographic manifestations might be those of diffuse demineralization.

Other diaphyseal findings include insufficiency fractures, periosteal new bone and bowing. Although periosteal new bone is frequently a finding seen during healing, it might also be present with active rickets as a seemingly paradoxical osteoblastic effect of PTH. The location and degree of bowing are age-dependent. With weight-bearing, bowing is most pronounced in the lower extremities and most frequently produces genu varum from lateral bowing, although valgus might also be seen. Prior to weight-bearing, tibial bowing is often anterior from musculotendinous forces transmitted through the calcaneal tendon, and prominent forearm bowing might be seen from using the upper extremities for support while sitting or creeping. Other deformities

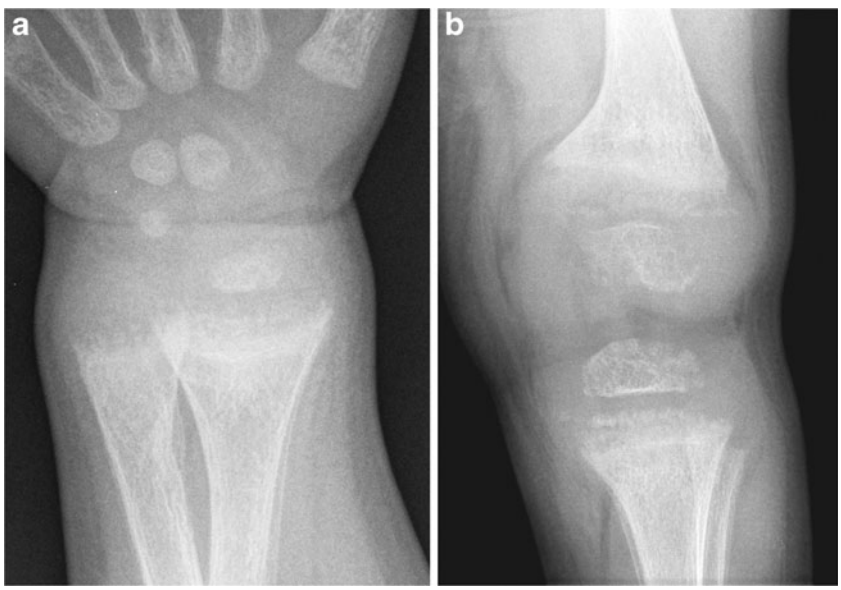

Fig. 7 Vitamin D deficiency rickets in a child age 1 year 9 months with 25D 17.9 ng/mL and elevated PTH of 510 pg/mL. There is severe rickets in all metaphyses with near-complete loss of definition of ZPCs in the wrists (**a**) and knees (**b**). Faint opacities are indicative of partial mineralization of rachitic hypertrophic cartilage. Epiphyses are involved, with loss of definition of ZPC surrounding them. There is varus bowing of the distal femur. Subperiosteal bone resorption involves the radial aspect of the distal ulna and there is also periosteal new bone, likely an osteoblastic effect of PTH

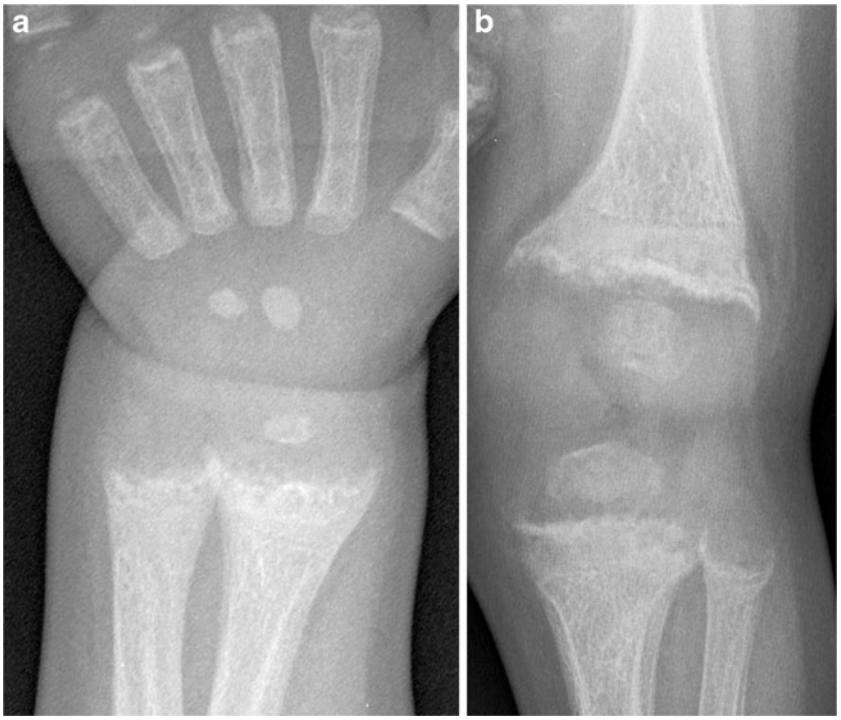

Fig. 8 Vitamin D deficiency rickets in a child age 1 year 2 months with varying mineralization of hypertrophic cartilage and 25D 17.3 ng/mL, as well as elevated PTH of 604 pg/mL. Radiographs of the wrist (**a**) and knee (**b**). In the distal femur and proximal tibia, there is hazy mineralization of rachitic hypertrophic cartilage between metaphyseal trabecular bone and the more recent ZPC. The more recent ZPC has irregular mineralization, which is more opaque than the partly mineralized cartilage between it and metaphyseal bone. There is also faint mineralization of the ZPC for the proximal tibial and (to a lesser extent) distal femoral epiphyses with residual lucency in the rachitic hypertrophic cartilage between those regions and internal trabecular bone of the epiphyses. The distal radius has only minimal mineralization of the hypertrophic cartilage and no mineralization of the ZPC. The distal ulna and proximal fibula have no mineralization of hypertrophic cartilage or ZPC. Cupping is most prominent in the distal radius and proximal fibula from membranous bone surrounding rachitic cartilage

in rickets are largely the result of associated osteomalacia and include biconcave vertebral deformity, abnormal kyphosis, scoliosis, platybasia, Harrison grooves and a triradiate appearance of the pelvis.

With treatment of vitamin D deficiency rickets, healing is usually seen radiographically within 2–3 months, with radiographic findings usually lagging behind clinical and biochemical improvement by a few weeks. With normalization of mineral ion concentrations, there is mineralization of the ZPC and restoration of normal endochondral ossification including terminal differentiation and apoptosis of chondrocytes, and ingrowth of vessels. The earliest radiographic finding of healing is visualization of the ZPC. In cases where the hypertrophic cartilage that built up during active rickets is entirely nonmineralized, the new ZPC can be seen as an opaque line that is separated from the rest of the shaft. The intervening space subsequently undergoes further ossification and mineralization, which might give a false impression of rapid growth, particularly if the epiphysis is not yet ossified to serve as a marker for the overall length of the bone. Equivalent findings of healing can be seen in the epiphysis, with remineralization of the ZPC surrounding the central epiphyseal trabecular bone (Fig. 12). Healing of the shafts is a slower process. Periosteal new bone, which is poorly mineralized during active rickets, becomes more apparent with treatment. Findings of osteomalacia and 2° HTPH also respond more slowly. Bowing of long bones and other deformities of rickets can persist for relatively long times.

Other forms of rickets

Following the discovery and production of vitamin D, the large epidemic of rickets of the late 19th and early 20th centuries was eliminated and individual patients were easily treated. However, a few patients did not respond to standard treatment, indicating that not all rickets is caused by vitamin D deficiency. The early use of the term “familial vitamin D resistant rickets” was applied to a condition that failed to respond to all forms of vitamin D therapy, now recognized as X-linked hypophosphatemia (XLH). Other clinically distinct groups were also recognized, now known to be caused by abnormalities of calcitriol synthesis or responsiveness. Also considered in this section to be “nutritional rickets variants” are vitamin D deficiency associated with malabsorption,

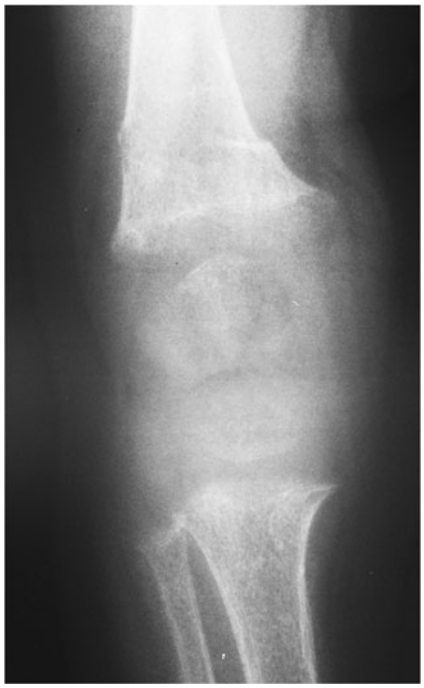

Fig. 9 Vitamin D deficiency rickets in a child age 1 year 5 months. The bones are quite demineralized and there is an impacted insufficiency fracture of the right distal femoral metaphysis. The knee epiphyses have not only lost definition of the ZPC but also show severe trabecular demineralization and are only faintly visualized (Reprinted from Caffey's Pediatric Diagnostic Imaging, 11th edn with permission from Elsevier)

hepatobiliary disease or other gastrointestinal disorders, and dietary calcium deficiency.

Nutritional rickets variants

Several conditions cause rickets with low 25D levels; these conditions have been considered to be distinct from nutritional vitamin D deficiency but are not clearly separated from it. These include intestinal malabsorption and hepatobiliary disease. While adequate intestinal absorption of dietary vitamin D is clearly needed, there is disagreement as to how important a factor this is in causing rickets. Some sources suggest that malabsorption from gastrointestinal, hepatobiliary or pancreatic disease is the most common cause of vitamin D deficiency in the United States [32], whereas others indicate that malabsorption alone seldom is sufficient to cause vitamin D deficiency [4]. Because 25-hydroxylation of vitamin D can be performed by multiple hepatic enzymes, insufficient hepatic production of 25D is seldom a problem, even with diffuse liver disease. Rather rickets or osteomalacia in patients with hepatic disease is more often caused by vitamin D deficiency or hepatic catabolism of vitamin D to inactive forms, stimulated either by drugs, PTH, or calcitriol [4]. Bile salts are needed for vitamin D absorption and hence vitamin D malabsorption can result from cholestyramine used for intestinal binding of bile salts or from biliary obstruction, accounting for rickets in biliary atresia [7].

An additional consideration for nutritional rickets is dietary calcium deficiency that could be the major cause of rickets or could interact with and exacerbate vitamin D deficiency. Calcium deficiency has been recognized as a cause of rickets in some regions with high sun exposure and diets containing cereals with calcium binding phytates and little if any dairy products, particularly in Nigeria, South Africa and Bangladesh [17, 33]. Like vitamin D deficiency, rickets results from insufficient intestinal absorption of calcium. This causes 2° HPTH, which increases synthesis of calcitriol. Calcitriol in turn promotes catabolism of 25D to inactive metabolites, resulting in diminished 25D concentrations [4, 33]. This interaction of calcium and vitamin D deficiencies is believed to be important in the rickets seen in the Asian immigrants to England (second wave) and might also play a role in nutritional rickets among toddlers in the United States [34, 35].

Non-nutritional calcipenic rickets

Vitamin D dependent rickets type 1 (VDDR-1), also known as pseudo-vitamin D deficiency rickets because of clinical similarities to very severe vitamin D deficiency, is caused by deficient calcitriol synthesis from an autosomal-recessive defect in 1-OHase [36]. Although it is generally quite rare, it is most common in the French-Canadian population from the Charlevoix–Saguenay–Lac-Saint-Jean region in Quebec. Affected people appear normal at birth, indicating little need for calcitriol in utero. Subsequently, they develop hypocalcemia and rickets, usually more rapidly than infants with vitamin D deficiency. Most clinical manifestations are similar to those of nutritional rickets, with weakness and hypotonia being more pronounced. Hypocalcemia can cause seizures, tetany and enamel hypoplasia. Although initially treated with high doses of vitamin D (prior to the discovery of calcitriol), it is best treated with physiological calcitriol replacement. The radiographic findings are nonspecific and similar to those in severe nutritional rickets including prominent signs of 2° HPTH (Fig. 13).

A rare autosomal-recessive defect in the intracellular receptor for calcitriol (VDR) that is essential for interacting with DNA also results in absent vitamin D signaling [37, 38]. It presents in infancy with severe rickets similar to VDDR-1 and was initially designated as VDDR-2. However, it does not respond to any form of vitamin D therapy, and hence is better designated as calcitriol-resistant rickets (CRR). With at least 34 mutations of the gene for VDR, CRR is a clinically heterogeneous condition. Some patients also have partial or total alopecia, believed to be a direct result of the VDR defect in

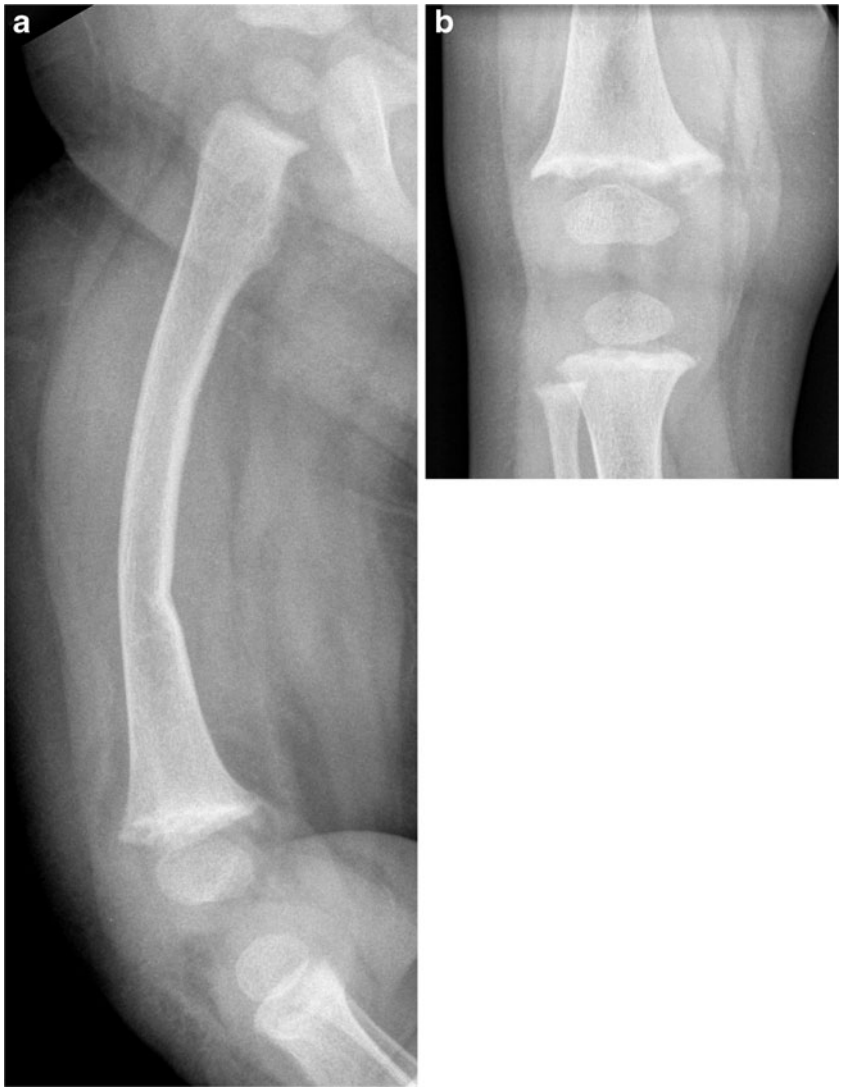

Fig. 10 Vitamin D deficiency rickets in a child age 1 year 2 months who presented with left thigh pain after falling out of bed and had 25D below detectable levels. **a** Lateral view radiograph of a nondisplaced left mid to distal femoral fracture. The frontal view suggested rickets, prompting a radiograph of the right knee (**b**), which shows moderate rickets in the distal femur and minimal rickets in the proximal tibia. In a case such as this, it is unclear to what extent metabolic bone disease contributed to bone fragility. No additional fractures were found on skeletal survey

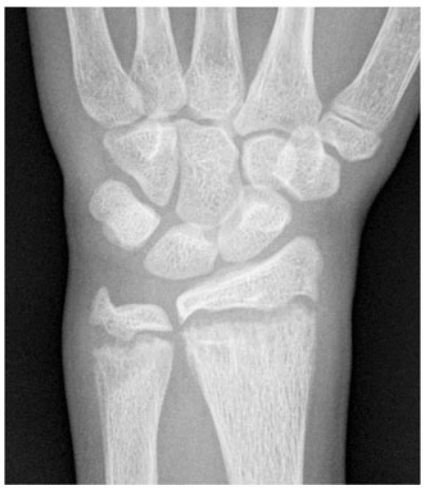

Fig. 11 Vitamin D deficiency rickets in an older child, a 10.6-year-old strict vegan with 25D below detectable levels. Radiograph of the wrist shows physeal widening, loss of definition of the ZPC and adjacent metaphyseal demineralization can be seen in all regions

hair follicles, unrelated to calcitriol signaling or mineral ion concentrations [38]. As in VDDR-1, patients with CRR have hypocalcemia and 2° HPTH. However, in CRR calcitriol levels are quite high, in response to the 2° HPTH, although ineffective because of the receptor defect. Treatment of CRR is difficult compared to VDDR-1. In most cases, all forms of vitamin D are ineffective in increasing intestinal transport of calcium. Rather, calcium needs must be met in a manner independent of calcitriol. Although not as effective for calcium absorption as active transport requiring calcitriol, some absorption occurs by passive diffusion that is independent of vitamin D. In some cases, with enough calcium administered, adequate calcium absorption can be achieved. Otherwise, intravenous infusion of calcium is needed. With sufficient calcium administration, all of the clinical manifestations of CRR are reversed other than alopecia.

Table 1 Thacher radiographic scoring system [26]

	Wrist: use worst wrist, score radius and ulna separately
Score	Findings
1	Wide growth plate, irregular metaphyseal margin, no cupping/concavity
2	As above plus metaphyseal cupping/concavity
	Knee: use worst knee, score femur and tibia separately
Score	Degree of lucency and widening of zone of provisional calcification
1	Partial lucency, smooth margin of metaphysis visible
2	Partial lucency, smooth margin of metaphysis not visible
3	Complete lucency, epiphysis appears completely separated from metaphysis
Multiplier	0.5 if only 1 femoral condyle or tibial plateau involved 1 if both condlyes or plateaus involved

Phosphopenic rickets

In this major group of rickets, hypophosphatemia results from phosphate wasting not caused by 2° HPTH, distinguishing it from calcipenic rickets where 2° HPTH and hypophosphatemia are compensatory effects. The three categories within this group include: (1) hereditary disorders of phosphate wasting, (2) tumor-induced rickets and osteomalacia (TIRO) and (3) intrinsic renal tubular diseases.

Although phosphate homeostasis is not as well understood as calcium homeostasis, major advances in our understanding of disorders of phosphate metabolism during the last two decades have centered around recognition of fibroblast growth factor 23 (FGF-23) as a major phosphaturic hormone and understanding its actions and roles in various phosphate disorders [39–41]. Briefly, FGF-23 is produced by osteocytes and acts on renal tubular cells to inhibit reabsorption of phosphate, leading to phosphate loss. Hence, increased FGF-23 signaling causes excessive renal tubular phosphate excretion leading to hypophosphatemic rickets whereas deficient FGF-23 signaling causes renal tubular phosphate retention and hyperphosphatemia. The clinical disorders of increased FGF-23 signaling include hereditary forms of hypophosphatemic rickets and TIRO. Alternatively, hyperphosphatemia from deficient FGF-23 signaling is seen in tumoral calcinosis and hyperostosis hyperphosphatemia syndrome, which are likely manifestations of the same disorder [42–44]. FGF-23 also downregulates renal 1-OHase. Therefore, with hypophosphatemic rickets from excessive FGF-23, calcitriol levels are either low or inappropriately not elevated in the face of hypophosphatemia. Similarly, with the hyperphosphatemic conditions from decreased FGF-23 signaling, calcitriol is either elevated or inappropriately not suppressed in the face of hyperphosphatemia.

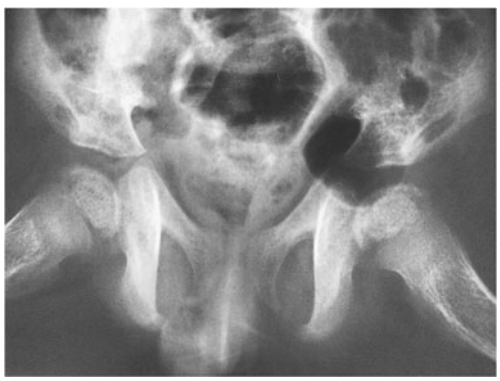

Fig. 12 Treated rickets in 4.3-year-old. Image shows hazy mineralization between trabecular bone of the metaphysis and the physis as well as surrounding the epiphysis, regions that were previously lucent. This gives a misleading impression of epiphyseal growth and maturation. The arrest of endochondral development in rickets involves a defect in chondrocyte apoptosis that can be corrected by therapy and is distinct from true maturation, which regulates chondrocyte hypertrophic differentiation. This case was described in Caffey's Pediatric Diagnostic Imaging, 11th edn

Hereditary disorders of phosphate wasting include XLH and autosomal-dominant and recessive variants. XLH is the most common form of phosphopenic rickets, with an incidence of 1:20,000 and complete penetrance; approximately one-third of cases are caused by new mutations. In XLH, a mutation of the PHEX gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) leads to increased levels of FGF-23 and hence phosphate wasting, although the mechanism by which deficiency of the PHEX endopeptidase leads to excessive FGF-23 remains unknown. XLH usually presents within the first 2 years of life. Because the major abnormality in XLH is phosphate wasting rather than impaired calcium absorption, there is usually no hypocalcemia or 2° HPTH. However, FGF-23 also downregulates renal 1-OHase, and thus if XLH is treated with only phosphate replacement, calcitriol insufficiency might be unmasked, leading to 2° HPTH. Bone mineralization is also often better preserved with XLH than vitamin D deficiency rickets in which 2° HPTH contributes significantly to diffuse demineralization. Additionally, XLH is a lifelong condition, thus affecting patients older and more ambulatory than many of those with nutritional rickets, and increased weight-bearing can contribute to

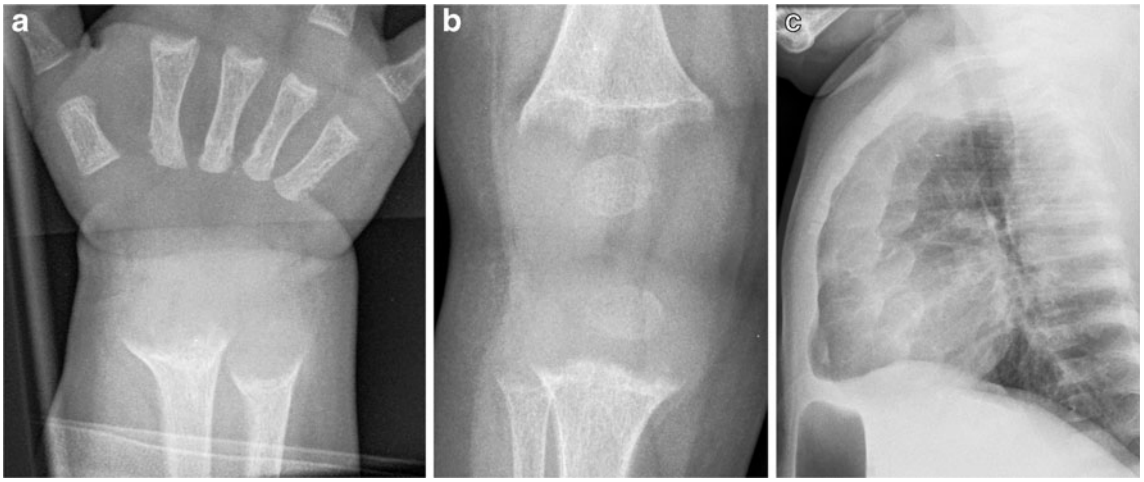

Fig. 13 VDDR-1. Radiographs of the hand (**a**), knee (**b**) and chest (**c**) in a 10-month-old show severe rickets. There is subperiosteal resorption involving the distal radius and ulna and metacarpals indicative of HPTH. Prominent rachitic involvement of the anterior rib ends is seen on a chest radiograph, best demonstrated on the lateral view (**c**). Despite a normal to high level of 25D, calcitriol was below detectable. Total and ionized calcium were low and PTH was elevated. The rickets healed promptly with calcitriol therapy

maintenance of skeletal mineralization. The major clinical features of XLH include short stature and bowing, particularly of the lower extremities. Weakness and hypotonia are absent, supporting a direct role of vitamin D for muscle function, which is not impaired in XLH. Swischuk and Hayden [27] have emphasized disproportionate involvement of the lower extremities compared to the upper extremities in XLH. Since genu varum is common in XLH, the distal femoral and proximal tibial physes are often more affected medially than laterally (Figs. 14 and 15). The prominent bowing in XLH, largely caused by osteomalacia, might reflect the chronicity of the disease. Other clinical and radiographic findings of osteomalacia in older children and adults include bone pain, insufficiency fractures, a coarse trabecular pattern, deformities and Looser zones. Looser zones, also called Milkman pseudofractures, are focal regions of lucency composed of nonmineralized osteoid extending through the cortices in osteomalacia (Fig. 16). These typically occur at sites of stress that increase bone turnover. With osteomalacia, the newly formed bone in these regions is poorly mineralized, resulting in focal lucency. Looser zones are often bilateral and symmetrical with sites of involvement including the lateral border of the scapula, posterior aspect of the olecranon process, ribs, pubic ramus and medial border of the proximal femur. Dental findings in XLH include delayed dentition and dental abscesses that are associated with enlargement of the pulp chamber and poorly mineralized dentin that can trap microorganisms [45]. Craniosynostosis, usually sagittal, might be mediated via interaction of FGF-23 with FGF receptors 2 and 3 in the cranial sutures [46, 47]. Bone mineral studies in adults and children have shown that demineralization involves mostly the appendicular skeleton and that bone mineral density in the axial skeleton might be increased [48–50]. In adults, enthesopathic calcifications resembling diffuse idiopathic skeletal hyperostosis can occur and osteoarthritis, especially in the knee, can result from altered mechanics from the lower extremity deformity [7]. Treatment of XLH with phosphate and calcitriol is effective in healing rickets, decreasing bowing deformity, and improving growth [51]. However, hypercalcemia, hypercalciuria, nephrocalcinosis and renal calculi might result from excessive calcitriol, whereas insufficient calcitriol or excessive phosphate can lead to 2° HPTH. Hence, treatment requires biochemical monitoring; US imaging is also used to monitor for nephrocalcinosis.

Although autosomal-dominant hypophosphatemic rickets (ADHR) is quite rare compared to XLH, it is known for its role in the discovery of the function of FGF-23 in phosphate homeostasis when it was shown to be caused by a mutation that prevents FGF-23 degradation, thereby increasing FGF-23 signaling [52]. Although many of the features of ADHR are similar to those of XLH, it has incomplete penetrance and the age of onset is variable but usually older than in XLH.

In tumor-induced rickets and osteomalacia (TIRO), phosphaturia and hypophosphatemia result from a phosphaturic factor, usually FGF-23, secreted by the culpable tumor [53, 54]. Removal of the tumor, if feasible, cures the biochemical abnormality and rickets. The tumors responsible for TIRO are most often small mesenchymal tumors, with many of these currently classified as “phosphaturic mesenchymal tumor, mixed connective tissue variant” [55]. Additionally, processes such as fibrous dysplasia and epidermal nevus syndrome can produce FGF-23 and are included within the spectrum of TIRO. Because the tumors responsible for TIRO are often quite small and might have no other clinical

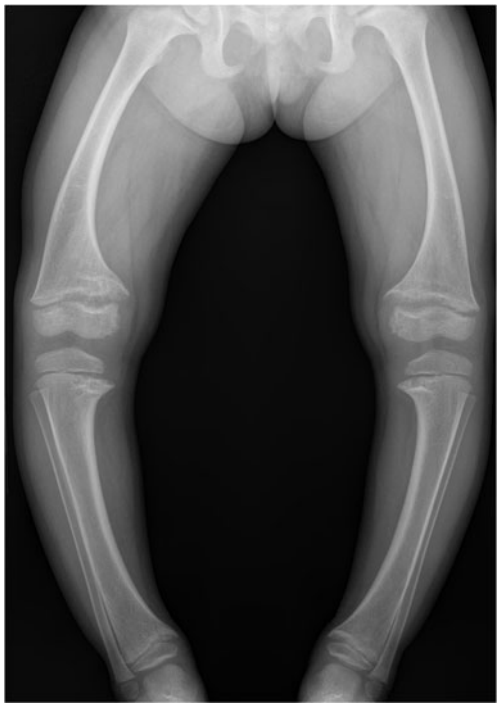

Fig. 14 XLH in a 3.9-year-old. Note the typical bowlegs with varus bowing of femurs and tibias. The rickets is more severe medially than laterally for the distal femurs and proximal tibias

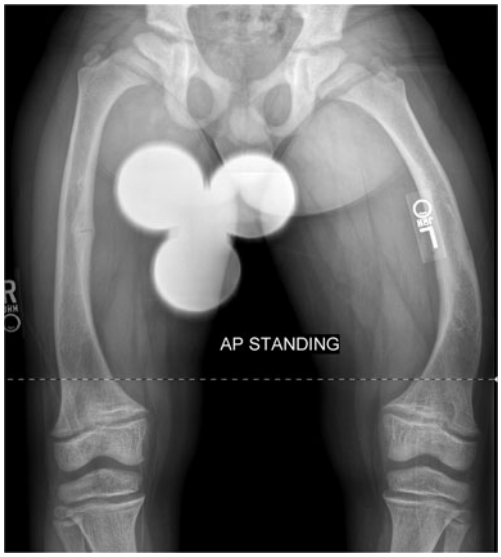

Fig. 16 XLH with Looser zone in a 9.9-year-old. Note the varus bowing of both femurs, left greater than right, and rickets at the physes. A well-defined Looser zone is present in the medial cortex of the right mid femur

manifestations, imaging has a role in their detection. Many of these tumors express somatostatin receptors and hence In-111 octreotide imaging might be useful [56]. [F-18]2-fluoro-2-deoxyglucose (FDG) PET/CT imaging has also been suggested, particularly for tumors that are not octreotide-avid [57]. When imaging studies show more than one suspicious site, selective venous sampling for determination of FGF-23 levels is helpful in determining which of these corresponds to the culpable tumor [58].

Hypophosphatemic rickets from renal tubular phosphate wasting might also be seen in many renal tubular disorders. In most of these, global tubular dysfunction causes the Fanconi syndrome with excessive tubular loss of phosphate, glucose, amino acids and bicarbonate. This might be an isolated

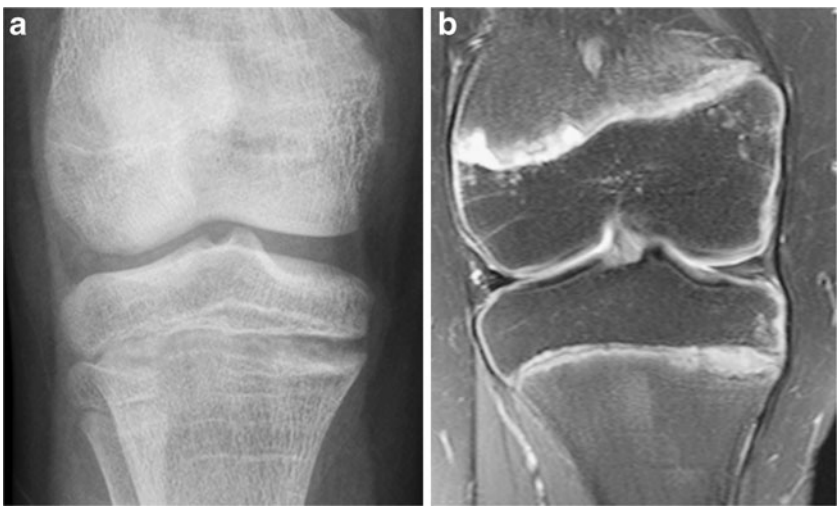

Fig. 15 XLH in a 15-year-old. **a** AP radiograph shows widening of the proximal tibial physis medially; the distal femoral physis is not well projected on this view. **b** Coronal T2-weighted MR image with fat suppression shows greater involvement of the proximal tibia medially than laterally as well as involvement of the lateral aspect of the distal femoral physis. Evaluation of the proximal tibial physis shows that laterally the ZPC is partly visualized as a thin dark line with bright cartilage of the growth plate between it and the epiphysis. The high signal between the ZPC and metaphyseal trabecular bone represents residual incompletely ossified hypertrophic cartilage. Medially, the ZPC is absent and there is greater accumulation of rachitic hypertrophic cartilage. In the distal femur, tongues of rachitic cartilage are most prominent laterally. (Case courtesy of Soroosh Mahboubi, MD, Children's Hospital of Philadelphia, Philadelphia, PA)

disorder or secondary to other conditions such as cystinosis, galactosemia, tyrosinemia, Lowe syndrome, Wilson disease or toxins. The radiographic findings in these conditions are not distinguishable from those in other causes of rickets.

The etiolological classification of rickets is summarized in Table 2, with pathophysiology and treatment for the major entities given in Table 3.

Rickets in special circumstances

Renal osteodystrophy

Renal osteodystrophy (ROD), which is being renamed "chronic kidney disease—mineral bone disorder," refers to the many skeletal abnormalities that are caused by chronic renal insufficiency or failure [59–62]. Although sometimes referred to as "renal rickets," this is inaccurate because some of the rachitic-appearing features do not always represent true rickets. With diminishing glomerular filtration, phosphate retention and hyperphosphatemia cause the circulating ionized calcium level to fall slightly, triggering HPTH to restore a normal calcium level. This 2° HPTH is the major metabolic abnormality in ROD. With advancing renal insufficiency and declining renal mass, the ability of the kidneys to produce sufficient calcitriol might also be impaired, causing true rickets and osteomalacia, although this is often minor compared to the 2° HPTH.

The major radiographic features of HPTH are those of increased osteoclastic bone resorption. Subperiosteal resorption, the most specific type, has many target sites such as the radial aspects of the index and middle finger middle phalanges [61]. Other types of bone resorption include intracortical resorption, endosteal resorption, and subligamentous resorption. Of particular interest, HPTH can also cause resorption of bone adjacent to physeal cartilage, a form of subchondral resorption. This produces a radiographic appearance that is quite similar to the appearance of rickets, with loss of definition of the ZPC and adjacent metaphyseal lucency [63]. However, the pathophysiology and pathoanatomy is quite different. In rickets, with failure of endochondral ossification and mineralization, this lucent zone is composed of nonmineralized cartilage and osteoid. However, HPTH is characterized by osteoclastic bone resorption and bone replacement by lucent peritrabecular fibrosis (osteitis fibrosa). Although similar-appearing radiographically, these

Table 2 Rickets classification by etiology

- Calcipenic rickets
  - Vitamin D abnormalities
    - Low 25D from precursor deficiency
      - Vitamin D deficiency
        - Nutritional
        - Malabsorption
          - Bowel disease
          - Biliary disease, especially biliary atresia
    - Low 25D not from precursor deficiency
      - Hepatic disease (rarely)
      - Drug-induced hepatic catabolism to inactive forms
    - Low calcitriol from renal 1-OHase deficiency (VDDR type 1)
    - Calcitriol nonresponsiveness (CRR, mostly from VDR defect)
  - Dietary calcium deficiency
- Phosphopenic rickets
  - Caused by increased FGF-23 signaling
    - Hereditary hypophosphatemia
      - XLH
      - AD and AR variants
    - Tumor-induced rickets and osteomalacia
  - Not caused by increased FGF-23 signaling
    - Renal tubular disease (Fanconi syndrome)
      - Isolated
      - Secondary: cystinosis, tyrosinemia, Lowe syndrome, toxins, etc.

Table 3 Mechanisms and treatment

Type	Cause of hypophosphatemia	Vitamin D levels	Treatment
Dietary vitamin D deficiency	2° HPTH	25D L; calcitriol L, N, H	Vitamin D replacement
VDDR-1	2° HPTH	25D N; calcitriol very L	Calcitriol
CRR	2° HTPH	25D N; calcitriol H	Calcium supplementation, oral or IV if needed
Dietary calcium deficiency	2° HPTH	25D N or L; calcitriol L, N, H	Dietary modification. Note that calcium deficiency might uncover vitamin D deficiency
Hereditary hypophosphatemic rickets (XLH and AD and AR variants)	FGF-23 caused by mutations in PHEX (XLH) FGF-23 (ADHR) DMP1 (ARHR)	25D N; calcitriol L or inappropriately not H	Oral phosphate replacement Calcitriol
Tumor-induced rickets	FGF-23 produced by tumor	25D N; calcitriol L or inappropriately not H	Tumor removal
Renal tubular disease	Tubular defect	25D N; calcitriol N until renal disease advanced	Oral phosphate replacement and other metabolic corrections as needed

N normal, *L* low; *H* high

processes differ not only in their pathophysiology but also in consequence. The fibrous tissue of osteitis fibrosa is weaker than the nonmineralized cartilage and osteoid of rickets and at greater risk of mechanical disruption. Hence, slipped epiphyses are a major clinical problem in children with ROD but are not seen as a complication of true rickets [64, 65].

Rickets with osteopetrosis

An interesting situation is rickets complicating infantile malignant osteopetrosis (Fig. 17), a sclerosing bone dysplasia in which failure of osteoclastic bone resorption results from defects in the enzymes needed to acidify extracellular fluid in the resorption pit [66–69]. This resorption defect blocks the ability to mobilize mineral from bone when needed for normal homeostasis. Hence, even though whole-body calcium and phosphate stores are large, these minerals are sequestered in bone and are not available to replenish the circulation [4, 68]. Hypocalcemia then causes 2° HPTH. While mobilization of mineral from the skeleton is blocked in osteopetrosis, the kidneys are normally responsive to PTH and increase phosphate excretion causing hypophosphatemia, the common pathway to rickets [3].

Differential diagnoses

The two major disorders to be considered in the differential diagnosis of rickets are hypophosphatasia and metaphyseal chondrodysplasias. Metaphyseal changes in many other metabolic, infectious and traumatic disorders might also have features suggestive of rickets.

Hypophosphatasia

Hypophosphatasia also involves defective mineralization of the skeleton, although this is caused by insufficient activity of tissue-nonspecific alkaline phosphatase (TNAP) rather than abnormality of mineral ion concentrations [70, 71]. Hydroxyapatite crystals are initially formed in matrix vesicles of

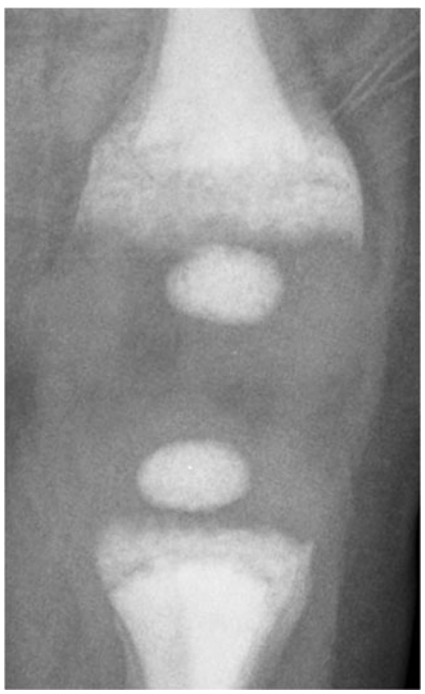

Fig. 17 Infantile malignant osteopetrosis complicated by rickets in a child age 6 months. The ossified bones including the epiphyses are abnormally sclerotic. The ZPCs are not visualized. The rachitic hypertrophic cartilage has considerable mineralization but has not undergone differentiation to bone

chondrocytes and osteoblasts that accumulate calcium, phosphate and TNAP. Following exocytosis, these vesicles rupture, releasing hydroxyapatite crystals that continue to grow extracellularly. In hypophosphatasia, initial crystal formation is normal, but extracellular crystal growth is impaired because of an inhibitory effect of inorganic pyrophosphate (PPi). TNAP acts at the cell surface to break down PPi. Its insufficiency in hypophosphatasia leads to excessive accumulation of PPi, which inhibits crystal growth, accounting for the mineralization defect [71].

Although there are autosomal-dominant and recessive mutations of the gene for TNAP, classification remains clinical. The perinatal lethal form is characterized by severely deficient skeletal mineralization in utero and is lethal either at or shortly after birth. The infantile form presents between birth and 6 months with lethargy, poor feeding and failure to thrive, clinical features that are quite nonspecific but can be seen with rickets. Rachitic findings might be particularly prominent in the ribs, and associated rib fractures might lead to pneumonia. Because of calvaria demineralization, the sutures appear wide even though craniosynostosis is common. The prognosis for this group is quite variable. Progressive skeletal disease in approximately half portends a poor prognosis, with death usually from pneumonia; the other half improve spontaneously. Survivors show improvement in skeletal mineralization and many clinical manifestations, although they often encounter craniosynostosis and premature loss of deciduous teeth from hypoplasia of the dental cementum. The childhood form has many similar features but is milder, and the adult form mimics osteomalacia clinically with metatarsal stress fractures and thigh pain from femoral pseudofractures. Accumulation of PPi also leads to calcium pyrophosphate dihydrate deposition, causing pseudogout. Adults with hypophosphatasia often have a history of rickets during childhood or early tooth loss but then become asymptomatic for decades. Biochemical distinction between rickets and osteomalacia is most easily made on the basis of a low rather than elevated serum alkaline phosphatase.

Radiographically, the mineralization defect of the perinatal form is profound, with apparent absence of mineralization of several portions of the skeleton, an appearance not at all reminiscent of rickets and also more severe than osteogenesis imperfecta. In the infantile and childhood forms, the metaphyses are often described as "rachitic," although the appearance often differs from true rickets. The mineralization defects of hypophosphatasia do not involve the metaphyses as uniformly as in rickets but rather are often more focal and patchy, particularly in the childhood form, appearing as "punched out" metaphyseal defects (Fig. 18). The adult form simulates osteomalacia radiographically with a coarse trabecular pattern, metatarsal stress fractures, and Looser zones.

Metaphyseal chondrodysplasias

Metaphyseal chondrodysplasias (MCD) also enter into the differential diagnosis of rickets. Although not often confused with rickets, Jansen MCD can appear rachitic very early in life, and is also of interest because of its pathophysiology. Of the MCDs that present later in life, type Schmid is most often confused with rickets, although some of the others have a similar appearance.

In Jansen MCD, an activating mutation of the combined PTH/PTHrP receptor causes increased PTH and PTHrP signaling even in the absence of those substances [72]. PTHrP normally prevents differentiation of proliferating to

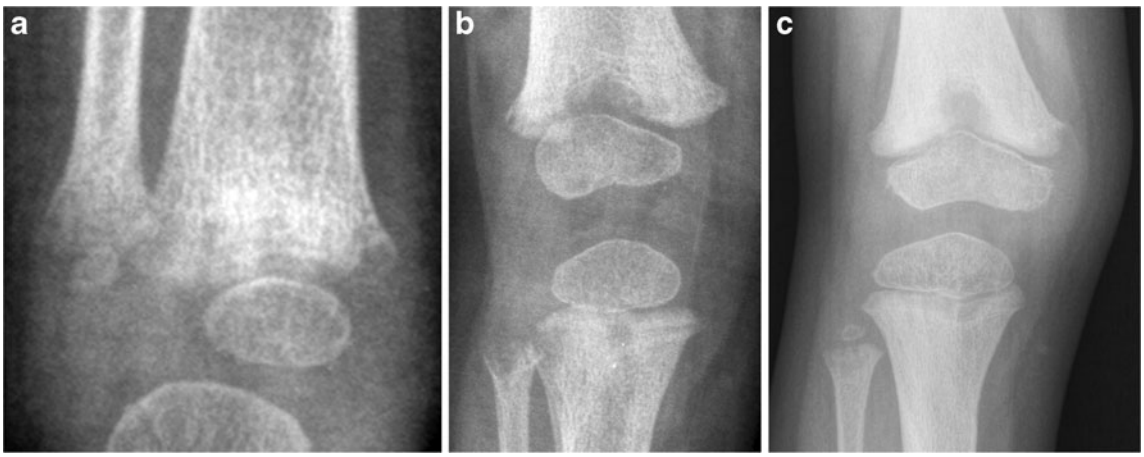

Fig. 18 Hypophosphatasia. Symmetrical radiographic findings (only right shown). **a** Initial radiograph in a 14-month-old shows rachitic appearance of the ankle. **b** At the knee, the proximal fibula has a typical rachitic appearance, but involvement of the distal femur and to a lesser extent the proximal tibia is more focal, suggestive of hypophosphatasia. **c** At 2 years 10 months, the focal defects in the distal femoral metaphysis are more prominent and quite typical of childhood hypophosphatasia. The proximal tibia and fibula remain involved

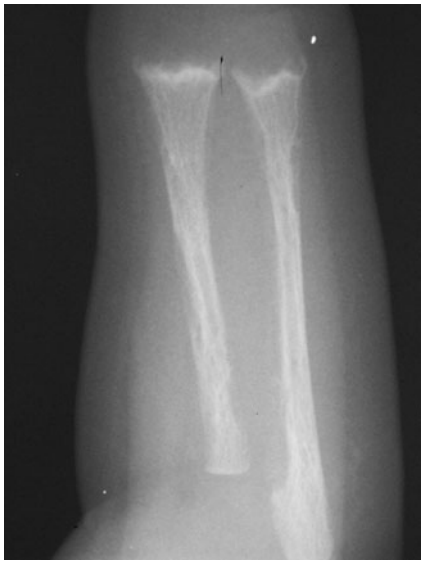

Fig. 19 Metaphyseal chondrodysplasia type Jansen in a 5-day-old with severe hypercalcemia simulating HPTH. There are extensive demineralization and subperiosteal resorption from increased PTH signaling caused by inherent activation of PTH/PTHrP receptor. The physes appear rachitic from a defect in endochondral ossification caused by excessive PTHrP signaling. This eventually leads to such a large zone of nonossified cartilage between the shaft and the end of the bone that it no longer appears rachitic (Reprinted from Caffey's Pediatric Diagnostic Imaging, 11th edn with permission from Elsevier)

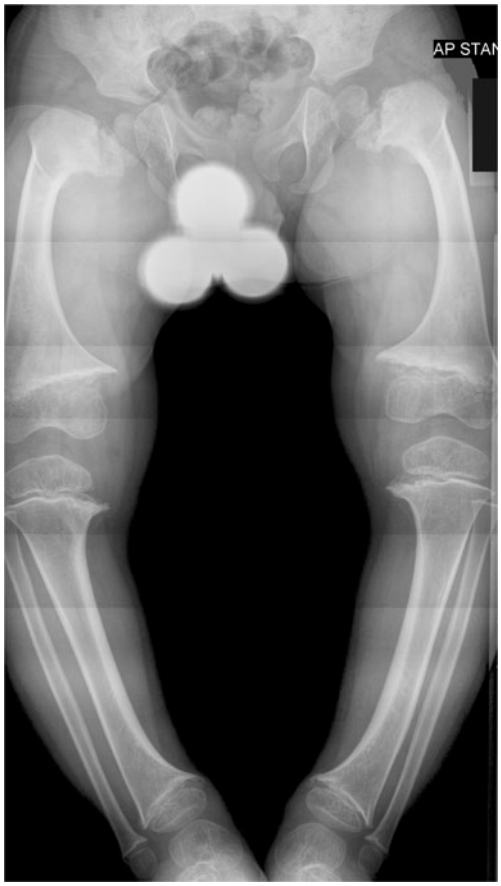

Fig. 20 Metaphyseal chondrodysplasia type Schmid in a child who presented at 2 years 4 months with bowlegs and clinically evident rachitic rosary. Initial radiographs (not shown) demonstrated rachitic findings of the major metaphyses, but biochemical studies were normal. A lower-extremity radiograph at 3 years 6 months shows bilateral bowlegs and widening and irregularity of the distal femoral and proximal tibial and distal tibial physes, more pronounced medially than laterally. There are also marked coxa vara and fragmentation of the proximal femoral metaphyses. Although the bowing and appearance of the knees is similar to what is seen in XLH, the coxa vara and proximal femoral fragmentation strongly suggest that this is MCD type Schmid rather than XLH

hypertrophic chondrocytes [31]. Hence, excessive PTHrP signaling retards endochondral ossification with accumulation of excessive proliferative cartilage, a defect earlier in the process of endochondral ossification than hypertrophic chondrocyte apoptosis, which is impaired in rickets. Activation of the PTH/PTHrP receptor also increases PTH signaling with typical biochemical and radiographic findings of HPTH. In the neonatal period, the findings of HPTH are particularly prominent, with severe hypercalcemia, subperiosteal bone resorption and bone demineralization. The metaphyses also appear rachitic, because of the arrest of endochondral ossification (Fig. 19). Beyond the neonatal period, the metaphyseal ossification defect is so severe that it no longer appears rachitic. Rather, lucent zones of nonossified proliferative cartilage develop between the epiphyses and the ossified portions of the shafts that are much larger than the widened growth plates of rickets. These regions eventually ossify in a dysplastic manner.

MCD type Schmid (Fig. 20), caused by an autosomal-dominant mutation for type 10 collagen, usually presents with genu varum and short stature, features that also typify XLH. Similar to rickets, the physeal widening and adjacent metaphyseal irregularity are most prominent in the most rapidly growing bones, particularly the distal femur, with involvement of proximal femur and tibia less pronounced. The anterior rib ends are also constantly involved. The femoral heads might be enlarged and coxa vara is frequently seen, but not invariable, findings that point away from rickets [73]. Overall the metaphyses are better mineralized than in rickets, although many patients with XLH also appear fairly well mineralized. Small spikes of bone projecting into the physis from the metaphysis have been described in Schmid MCD [7]. Schmid MCD and XLH have several clinical and radiographic similarities. Looser zones, if present, clearly indicate osteomalacia from XLH rather than Schmid MCD. Standard biochemical testing is effective in sorting these out, with elevated serum alkaline phosphatase and low phosphate in XLH and normal findings in Schmid MCD. Other MCDs that might be confused with rickets include MCD type McKusick (cartilage hair hypoplasia) and MCD Schwachman (Schwachman-Diamond dysplasia).

Vitamin D deficiency/nonaccidental trauma controversy

A topic of particular importance for the pediatric radiologist is whether the "epidemic of vitamin D deficiency" can be invoked to account for otherwise unexplained fractures in infants as has been suggested by Keller and Barnes [74]. There was considerable debate over that publication in the pages of *Pediatric Radiology* in 2008–2009 that will not be reiterated. Rather, the focus will be on evaluating some of the studies that have been presented since that time and their potential contributions to the vitamin D deficiency/nonaccidental trauma (VDD/NAT) controversy.

Gordon et al. [75] provided data regarding the prevalence of vitamin D deficiency and associated radiographic findings from a cross-sectional study of 365 well infants and toddlers (ages 8–24 months) seen for routine primary care in Boston [75]. Vitamin D deficiency (25D ≤ 20 ng/mL) was found in 44 of 365 (12.1%). Of those, 40 returned for additional evaluation. Only one had any clinical manifestation of rickets (genu varum). Radiographs of the wrists and knees in these 40 children were initially reported to show rickets in three and demineralization in 13. Subsequently, the same radiographs were re-evaluated using three instead of two readers [76]. Data analysis in the second publication was complex and many cases were scored as not having majority agreement for the presence or absence of rickets or demineralization. Rickets was considered present in two children but there was no majority agreement in four cases. Demineralization using high-threshold criteria was deemed present in only two, with no agreement in two others. With low-threshold criteria, demineralization was present in six, with no agreement in 16. No fractures of the knees or wrists were found. They concluded that rickets and demineralization were uncommon in healthy infants and toddlers with vitamin D deficiency, each present in two of the 40 infants (5%, high-threshold criteria used for demineralization) [75]. The discordance between this conclusion and the initial report that 13 (32%) were demineralized attests to known difficulty with radiographic assessment of skeletal mineralization. How the data from these publications affects the VDD/NAT debate depends on what issues are being addressed. Their data clearly demonstrate that rickets and probably demineralization are relatively uncommon in infants with 25D ≤ 20 ng/mL. However, we also know that vitamin D deficiency rickets with significant bone disease is not rare; the resurgence of rickets does not imply that much will be found on a cross-sectional study of 365 infants. Although no fractures were found, if they had found a single fracture (of the knees or wrists) in such a cross-sectional study of 40 children it would have implied a considerable fracture risk for those with low vitamin D levels. If we wanted to know whether a mild degree of bone fragility were present for this group, a much larger study would be needed.

Schilling et al. [77] examined 25D levels in 118 infants younger than 2 years of age with fractures, of whom 60% were considered accidental, 31% abusive and 9% indeterminate. The overall incidences of vitamin D deficiency and insufficiency in this Philadelphia study (25D <20 ng/mL and 20-29 ng/mL, respectively) were 8% and 31%, percentages considered similar to those found in the Boston study described above (12% with 25D ≤ 20 ng/mL and 28% 20–29 ng/mL). There was no evidence of either rickets or radiographically identifiable demineralization in any of the Schilling subjects. No correlation was found between 25D levels and multiple fractures, rib fractures, metaphyseal fractures, or diagnosis of NAT. How do these data help the vitamin D deficiency/NAT debate? If the claim from those suggesting that vitamin D deficiency might mimic NAT were that vitamin D deficiency causes more of a predisposition for fractures suggestive of abuse than other fractures, then this study would refute such a claim. However, the more likely claim is that vitamin D deficiency might be a cause of increased bone fragility and hence predispose to any fracture, i.e. single fractures, multiple fractures, ordinary-appearing fractures and fractures considered to be suspicious for NAT. For this more important question, the study also argues against such causality by showing that the frequencies of vitamin D deficiency and insufficiency were similar in those with fractures and in a control population without fractures. Unfortunately, for this most important aspect of their study, which evaluates whether vitamin D deficiency/insufficiency is associated with an increased fracture risk, the critical comparison is made with a control population taken from the literature. The absence of their own control population, matched for geographic location, demographic features, season and year, is a significant limitation. There have been many studies of the prevalence of vitamin D deficiency in children with somewhat variable findings. Was the Boston study selected as a single control population because it was particularly well matched demographically with the Philadelphia population? It is also not indicated whether this particular literature control population was selected prior to or following determination of the prevalence of vitamin D deficiency/insufficiency in the subjects of Schilling et al. [77].

Chapman et al. [78] evaluated the types of fractures occurring in 40 infants with rickets between 2 and 24 months of age, 32 of whom had nutritional rickets. Fractures were found in 7 of the 40 infants with rickets, all in mobile infants and toddlers and all in children with "severe overtly evident rickets," although no data were provided systematically comparing the severity of rickets in those with and without fractures. Radiographically, 38 of the 40 were considered to

be osteopenic. Fracture types included diaphyseal, metaphyseal, anterior rib and anterior-lateral rib fractures. Unlike the classic metaphyseal lesions (CMLs) of NAT, the metaphyseal fractures in the Chapman study were more remote from the physis and generally did not have the other findings of CMLs. There was one metatarsal fracture but no posterior rib, spine, skull, scapular or metacarpal fractures. These are important data for at least two groups of patients. For infants with fractures suggestive of NAT, particularly CMLs and posterior rib fractures, and no overt evidence of rickets, it is exceedingly unlikely that such fractures would be caused by vitamin D insufficiency because they are not even seen with severe rickets. Additionally, for those infants with fractures suggestive of NAT and rickets, the Chapman [78] data argue that rickets would not explain all of the findings and hence that rickets and NAT likely co-exist. The absence of fractures in nonmobile infants in their study also appears to argue against considering fractures in nonmobile infants with or without obvious rickets to be caused by metabolic bone disease, although the number of nonmobile children in their study is not indicated. The group not addressed in the study is infants with ordinary-appearing fractures for whom NAT is suspected based on lack of reasonable explanation or other clinical considerations.

Before summarizing how these studies affect the VDD/NAT controversy, it is worth considering the issues of what low vitamin D levels imply, what kind of diagnosis rickets is, and what constitutes bone disease caused by vitamin D deficiency. Low vitamin D levels alone are not diagnostic of rickets or any clinical or physiological condition. The amount of vitamin D needed to support physiology follows a normal distribution. The 2011 IOM panel selected a 25D level of 20 ng/mL to indicate a laboratory cut-off for vitamin D sufficiency because it considered that level to meet the needs of 97% of the population. However, 16 and 12 ng/mL meets the needs of 50% and 3% of the population, respectively. Rather, physiological vitamin D deficiency for an individual implies a functional disturbance caused by insufficient vitamin D, ultimately resulting from impaired intestinal absorption of calcium.

Rickets is a disorder of ossification and mineralization at the physis caused by insufficient mineral ion concentrations. However, the question remains as to whether it is a clinical, biochemical, radiologic or pathological diagnosis. Rickets does have clear histopathological findings, and hence is ultimately a histopathological entity, although the diagnosis is almost never made this way. Pettifor [6] states that rickets is a clinical syndrome resulting from physeal abnormalities. In concordance with considering rickets a clinical syndrome, patients are usually referred to as having "rickets" as an overall diagnosis, even though we have carefully distinguished the pathophysiological processes of rickets, osteomalacia, and 2° HPTH, all of which are present simultaneously in patients with rickets as overall diagnosis [4]. It has been indicated that "rickets is not a subclinical diagnosis," which is an attractive statement particularly because it was used specifically to indicate that the relatively large number of individuals with low 25D levels should not be labeled as having "subclinical rickets" [77]. Indeed, a low 25D level in the absence of other biochemical, radiographic or clinical findings does not indicate rickets or any disorder. However, as rickets is ultimately a pathological entity, it is too dogmatic to suggest that subclinical rickets does not exist. In reviewing Georg Schmorl's 1909 autopsy series showing a higher incidence of rickets histopathologically than in clinical series we would not suggest that only those with clinical manifestations truly had rickets. Although histology is rarely available, there are biochemical indicators of when skeletal pathophysiology has developed secondary to vitamin D deficiency, recognizing that a wide range of normal values in growing children might complicate interpretation in some patients [79]. In the pathophysiological progression of rickets, if there is only hypocalcemia (a relatively rarely identifiable stage), then there is physiological evidence of abnormal mineral metabolism secondary to vitamin D deficiency but no evidence of bone disease. When PTH and alkaline phosphatase become abnormal, then bone disease, as indicated by Parfitt's [4] designation of "hypovitaminosis D osteopathy," is present. Whether this term or "rickets" is used is less important than understanding the difference between a low 25D level with no physiological effect and the presence of abnormal skeletal physiology. These considerations might be useful in helping the reader decide when the term "rickets" is appropriate and whether positive radiographic findings are required.

Given these considerations and the studies described above, what conclusions can be drawn and what issues remain unanswered regarding VDD/NAT?

There are now good data that rickets is not associated with the types of fractures that are considered to have high specificity for NAT. Hence, neither rickets nor hypovitaminosis D osteopathy without apparent rickets is a plausible explanation for these types of fractures.

For patients with vitamin D deficiency and ordinary fractures in which the possibility of NAT is raised by lack of appropriate history, the issue of increased bone fragility becomes more problematic. One end of the spectrum of children with vitamin D deficiency is clear; with florid rickets and severe demineralization, there is likely significant structural skeletal insufficiency. Whether such skeletal insufficiency accounts for the findings depends on the entire clinical picture. At the other end are those with 25D levels in a mildly deficient range, no biochemical indicators of hypovitaminosis D osteopathy, and radiographically normal

bones. These are likely children whose 25D levels are classified in the "deficient" range but meet their physiological needs, and hence bone fragility is unlikely. However, we do not have a good way of assessing potential bone fragility for those between these two ends of the spectrum. There is some information concerning the entire cross-section of children with 25D levels below 20 ng/mL. This group includes some who are physiologically vitamin D sufficient, some with mild vitamin D deficiency, and a smaller number with more severe vitamin D deficiency. For this entire population of infants with low vitamin D levels, the absence of a significantly increased fracture risk is suggested by the similarity of low vitamin D levels in Schillng's infants with fractures [77] compared to Gordon's cross-section of healthy infants [75], recognizing the problem of relying on a literature comparison group for this determination. However, failure to find demonstrable bone fragility in this population might be because most of the children had 25D levels that were only mildly low, and for many that level might have been physiologically sufficient. Indeed, in Gordon's Boston cross-sectional study, only 7 (1.9%) were classified as severely deficient (25D $\leq$ 8 ng/mL), and even those children showed little rickets [75]. Rather, the group that needs more evaluation is those with evidence of skeletal abnormality related to vitamin D insufficiency, recognized either by biochemical tests or radiographic findings, without diluting the data by including those with no identifiable bone disease. Even this group comprises a spectrum of severity with corresponding effects on mechanical sufficiency. Ultimately, our goal must be to be able to assess bone strength for individual children in order to answer the question as to whether increased bone fragility can explain fractures in the setting of suspected NAT.

Summary

Part II of the review of rickets details the pathophysiology, pathoanatomy and resultant clinical and radiographic findings of vitamin D deficiency rickets. Understanding the pathophysiology of rickets helps clarify important conceptual distinctions between low levels of vitamin D metabolites, physiological vitamin D deficiency, and varying degrees of hypovitaminosis D osteopathy that range from subtle changes of HPTH to florid rickets. Low levels of 25D alone do not establish a diagnosis of rickets or any disorder, as there is individual variability regarding vitamin D requirements.

The major controversial issue with respect to vitamin D concerns how much vitamin D is needed by humans (Part I). This has been a matter of intense scientific debate, with failure to resolve this issue likely related to the enormous amount of data from various sources available for review. The VDD/NAT issue is quite different. For this there are relatively few data. Our scientific goal should be to be able to determine whether and to what extent increased bone fragility is present in individuals with evidence of hypovitaminosis D osteopathy.

Rickets is often considered to be the tip of the iceberg of vitamin D deficiency, referring to the many potential health benefits of vitamin D that extend beyond the prevention of rickets and osteomalacia [13]. Accordingly, considerable work has addressed multiple health effects of various levels of vitamin D and the effects of vitamin D supplementation for people who do not have rickets or osteomalacia. The issue of how much vitamin D is required by humans must be settled for a rational recommendation to be made on the need for vitamin D supplementation, which has considerable public health implications. Notwithstanding the importance of these issues, the argument can be made that attention to "vitamin D insufficiency" has distracted attention from the less frequent problem of clinically evident vitamin D deficiency. As Parfitt [4] has indicated, despite its multiple effects on nontraditional tissues, the major role of vitamin D remains the prevention of rickets and osteomalacia. Rickets remains a significant and preventable clinical problem in both developing and developed countries. Attention also needs to be focused on its elimination, a task that is independent of debate about whether healthy individuals need 25D levels of 20 ng/mL or 30 ng/mL.

Conflict of interest The authors have no conflicts of interest to report.

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