Rickets

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Abstract

Worldwide, rickets is the most common form of metabolic bone disease in children. Despite the concept that it is a rare disease, it is on the increase in many regions, including Western Europe and the USA, and in many ethnic subgroups that have immigrated to temperate regions. Vitamin D deficiency is the main cause of rickets, though nutritional deficiency of calcium and phosphorous generates the same clinical picture. Rickets also occurs when the metabolites of vitamin D are deficient. This may be due to an inherited cause or secondary to disorders of the gut, pancreas, liver or kidney from disruption of vitamin D metabolism.

Keywords 1,25-dihydroxyvitamin D; 25-hydroxyvitamin D; hypophosphataemic rickets; osteomalacia; rickets; vitamin D; vitamin D-dependent rickets

Clinical features

Accelerated changes in body composition, bone growth and dental development during infancy and adolescense,[1] associated with an increase in calcium and phosphate demands,[2,3] exaggerate the detrimental affects of vitamin D deficiency. This is particularly important in adolescence, when peak bone mass is achieved.[4,5] Rickets typically presents at 4–18 months of age in nutritional vitamin D deficiency and X-linked hypophosphataemic rickets (XLH). Preterm infants develop rachitic changes from 7 weeks of age if their diet is inadequate. The clinical signs of calcium deficiency rickets occur up to 2 years later. Vitamin D deficiency during adolescence usually results in osteomalacia.

Skeletal effects of vitamin D deficiency

The earliest radiological sign is the loss of demarcation between the growth plate and the metaphysis. This progresses until the classical radiological features of rickets (metaphyseal cupping, fraying and splaying (Figure 1a) best seen at the wrists, knees or ankles) are evident.

The widening of the space between the epiphysis and the metaphysis is due to expansion of the layer of hypertrophic chondrocytes in the growth plate. As healing begins, a thin white line of calcification appears at the junction of the growth plate and the metaphyseal area that becomes denser and thicker as calcification proceeds. Unmineralised osteoid causes the periosteum to appear separated from the diaphysis. Osteomalacia appears on radiography as generalised osteopenia with visible coarsening of trabeculae due to secondary hyperparathyroidism.

Once the child is walking, bowing of the legs due to tibial and femoral softening occurs (Figures 1b and 2). Genu varum with an intercondylar distance of more than 5 cm is suggestive of rickets and is the commonest bony deformity in infants and young children; genu valgum and windswept deformities are more often seen in older cases.

Diffuse bone pain is a feature of both rickets and osteomalacia.

Through prolonged mechanical stress on softened vertebrae in severe rickets, kyphoscoliosis may develop in children over the age of 2 years. The anteroposterior diameter of the pelvis can shrink resulting in a ‘triradiate’ or ‘flat’ pelvis. These changes may cause obstructed labour with associated maternal and infant morbidity.

The costochondral junctions become swollen after 1 year of age, leading to an appearance termed ‘rickety rosary’. The development of Harrison’s groove and pectus carinatum result from muscles pulling on weakened bones. Cartilaginous swellings are also evident in a bracelet conformation around the wrist and the ankles. The main distinction is from normal-sized wrist bones that become more prominent secondary to muscle wasting in malnourished children.

Craniotabes is softening of the skull bones due to failure of intramembranous ossification.[6] It is usually seen in early infancy, and may occur before 2 months age in nutritionally deficient preterm babies. Although present in rickets, it is not pathognomonic of this disorder.[7]

Expansion of the cranial vault relative to the facial skeleton causes frontal bossing. This clinical appearance occurs in both rickets and hydrocephalus and has been given the term ‘rickets hydrocephalus’.

Other associated cranial problems include delayed closure of the anterior fontanelle and benign intracranial hypertension.[8,9] Craniosynostosis may be seen in XLH.[10]

Fibrous-cystic osteitis (brown tumour) secondary to hyperparathyroidism may be present, but is extremely rare.[11] On radiography, it appears as single or multiple radiolucencies within the bone.

Dental features

Dental features of rickets include enamel hypoplasia and delayed tooth eruption due to failure of tooth ‘mineralisation’.[12,13] These are more pronounced in hereditary forms[13] of rickets and may present as a feature of maternal vitamin D[14] deficiency. Root abscesses are a particular problem in XLH.

Non-skeletal effects of vitamin D deficiency

Hypocalcaemic seizures occur typically in infants under 6 months, usually before radiological features are apparent. Tetany, apnoea and stridor are also seen in these cases.

Reduced serum calcium levels may affect left ventricular contraction producing left ventricular hypertrophy and dilatation or, in extreme cases, dilated or hypertrophic cardiomyopathy. Cardiac pathology resolves once treatment is instigated.[15,16]

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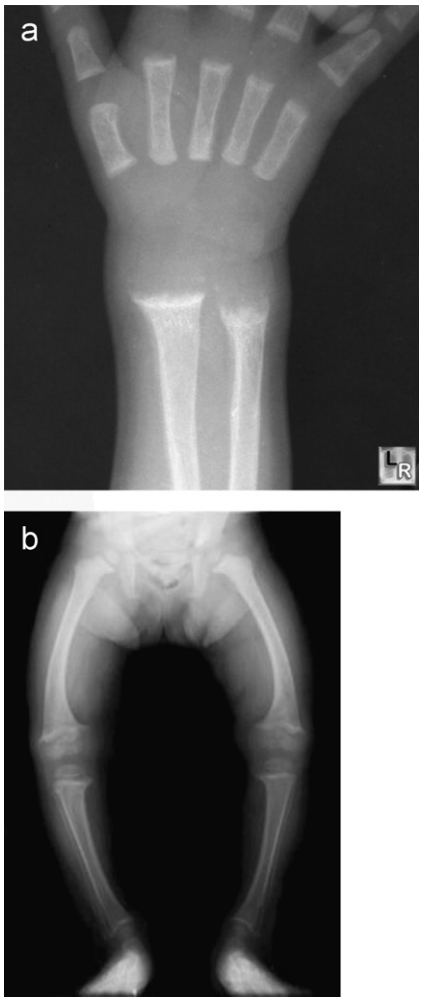

Figure 1 (a) Radiograph of metaphyseal cupping, fraying and splaying at the distal radius and ulna. (b) Radiograph of tibial and femoral bowing due to bone softening in rickets.

Figure 2 Femoral and tibial bowing seen in rickets once the child is walking. ©Biophoto Associates/Photo Researchers, Inc.

Hypocalcaemia can result in prolongation of the QTc interval, arrhythmias, hypotension and heart failure. Cardiac changes are usually confined to early infancy.

Children may also present with muscle weakness secondary to proximal myopathy[17,18] or carpopedal spasm as an early manifestation of tetany secondary to hypocalcaemia.

Rickets may also be associated with myelofibrosis[19,20] with associated anaemia or, in the most severe cases, pancytopenia. This complication is rare.

Pathogenesis

The process of depositing new bone where bone did not previously exist is termed 'modelling'. Remodelling is the process by which previously formed bone is resorbed and replaced with new bone at the same site. Rickets is defined as a failure to mineralise newly formed osteoid during modelling or remodelling before epiphyseal fusion. These changes are typically seen both at the growth plate and in the shape of long bones on radiographs. Once the growth plates have fused, most bone formation activity is associated with remodelling; at this stage, the term 'osteomalacia' is more correctly used.

During endochondral ossification in the developing fetus, mesenchymal cells aggregate to form a pre-chondrogenic condensation, initiating the process of skeletal development.[21–23] Following condensation, the mesenchymal cells differentiate into chondroblasts and then chondrocytes, and produce a cartilage matrix. During bone growth, chondrocytes differentiate through a series of well-defined morphological zones within the epiphyseal growth plate (Figure 3).[24] The hypertrophic chondrocytes calcify the surrounding matrix before undergoing apoptosis, forming a primary ossification centre. Blood vessels then penetrate the calcified matrix, supplying osteoclasts and osteoblasts. Similar secondary ossification centres form within the epiphyses and remain until epiphyseal fusion has occurred, marking the end of longitudinal growth.

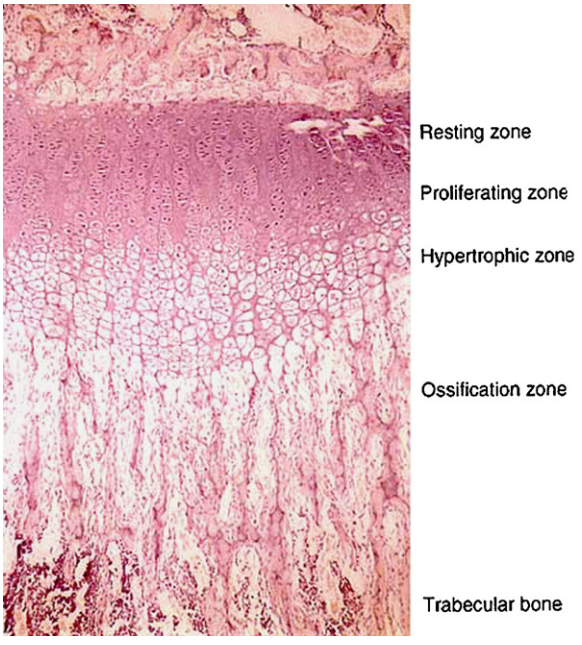

Figure 3 Endochondral ossification at the epiphyseal plate (H&E stain).

In rickets, there is expansion of the late chondrocytic layer secondary to impaired apoptosis of hypertrophic chondrocytes. Maturation of the growth plate is dependant on phosphate-regulated apoptosis of hypertrophic chondrocytes via activation of the capase-9-mediated mitochondrial pathway.[25]

In response to the decline in blood calcium levels, parathyroid hormone (PTH) is produced and exerts effects to maintain calcium within the range required for normal nerve and muscle function. At the renal level, calcium retention and phosphate excretion occur. Initial increased production of 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) in concert with PTH releases both calcium and phosphate from bone via increased osteoclastic bone resorption. 1,25(OH)D also acts at the level of the small intestine to increase calcium uptake. In the face of continuing poor supply of vitamin D, $1,25(OH)_2D$ production in the proximal tubules diminishes gradually, and this may also contribute to the rise in PTH through lack of feedback at the level of PTH gene transcription.

Serum levels of 25-hydroxyvitamin D (25OHD; calcidiol) are typically less than 12.5 nmol/litre (<5 ng/millilitre) in infants and children with rickets.

Management

Ergocalciferol (vitamin D, calciferol) is used to treat nutritional vitamin D deficiency. Simple deficiency should not be treated with vitamin D analogues such as alfacalcidol (1α-hydroxyvitamin D) and calcitriol ($1,25(OH)_2D$). As vitamin D requires hydroxylation to its active form by the kidney and liver, the hydroxylated derivative alfacalcidol or calcitriol should be prescribed when a patient with severe liver or renal impairment requires vitamin D therapy. Alfacalcidol is generally preferred in children. Calcitriol is unlicensed for paediatric use and is reserved for those with severe liver disease.

Nutritional vitamin D deficiency

- Treat acute vitamin D deficiency with ergocalciferol 6000 IU (150 μg) p.o. daily for 2–4 months in older infants, toddlers and children.
- Doses of up to 10,000 IU can be used in adolescents. A reduced dose of 3000 IU is used in infants aged 1–6 months.
- Continue after with a prophylactic dose of 400–600 IU as part of a multivitamin preparation or as ergocalciferol tablets.
- If there are concerns about compliance, a single dose of 100,000 IU (2500 μg) p.o. can be safe and effective.
- Nutritional deficit may also be treated with oral calcium supplementation (infants, 1–2 mmol/kg in divided doses; toddlers and schoolchildren, 25 mmol (1000 mg) daily). Phosphate supplementation is not necessary, as phosphate is abundant in the diet.
- Calcium levels should be monitored during the treatment of severe nutritional deficiency.
- Ergocalciferol is contraindicated in renal impairment.

Hypophosphataemic rickets

Treatment of hypophosphataemic rickets is with high doses of oral phosphate and hydroxylated vitamin D preparations to optimise bone mineralisation and growth. Under the age of 12 years, alfacalcidol is given at a daily dose of 25–50 ng/kg (maximum 1 μg) p.o. or i.m. This is increased to 1 μg once daily in adolescents.

Hypocalcaemic seizures and neonatal rickets

Neonatal rickets is usually the result of maternal vitamin D deficiency or prematurity. Evidence of frank rickets in the baby should be confirmed by knee and wrist radiography. Evidence of maternal osteomalacia in the form of raised alkaline phosphatase should also be sought and maternal vitamin D levels should be checked.

Neonatal hypocalcaemic seizures should be controlled with calcium gluconate 10% in a single dose of 0.11 mmol/kg (0.5 millilitre/kg) given by intravenous infusion over 30–60 minutes. A maintenance infusion can be used at a rate of 0.5 mmol/kg over 24 hours. Switch to the oral route as soon as possible due to the risk of extravasation injury. Oral calcium can be given at a dose of 0.25 mmol/kg in four daily divided doses. In neonates, ergocalciferol 100 IU (25 μg) daily also helps to elevate serum calcium.

The plasma calcium concentration usually increases within 72 hours, but may take up to 10 days. Once plasma calcium has normalised, treatment is withdrawn slowly. Thereafter, prophylactic vitamin D can be used, increasing the dose to 3000 IU (75 μg) after 4 weeks.

In neonates, it is important to save the baby's serum so that, if the hypocalcaemia persists, the pre-treatment 25OHD concentration can be checked.

Types of rickets

Nutritional rickets

Sun exposure: appropriate exposure to sunlight is vital for the production of vitamin D. Darker skin requires longer exposure, as melanin competes with 7-dehydocholesterol for UV-B photons.[26] However, darker skin has the same capacity as lighter skin to synthesise vitamin D.[27]

The estimated level of suberythemal UV sunlight[28] exposure required to maintain serum 25OHD concentrations above the lower limit of the normal range (11 ng/millilitre) is 30 minutes per week for an infant wearing only a nappy or 2 hours per week fully clothed without a hat.[29] However, vitamin D synthesis in the skin is dependent on both season and latitude.[30–32]

Factors that may limit sun exposure in children include use of sunscreens[33,34] increased indoor activities, industrial pollution, inadequate skin exposure due to dress codes or customs,[35] migration of immigrants to temperate regions[36] and seasonal variation.[30] Use of a sunscreen with a sun protection factor of 8 reduces the cutaneous production of vitamin D by 97.5%.[33,34]

A serum 25OHD concentration of at least 80 nmol/litre are needed for optimal bone health, on the basis of studies of older white subjects living in Europe and the USA.[37]

Dietary intake: dietary intake of vitamin D becomes a dependent source when there is inadequate exposure to sunlight. In the UK, dietary intake of vitamin D is markedly below the recommended amount, despite fortification of foods. Consequently, children are dependent on sunlight exposure or vitamin D supplementation to achieve the reference nutrient intake (RNI), though less than 50% receive supplementation.[38–41]

Rickets is often seen in children whose mothers also have low levels of vitamin D. During the second and third trimesters, there is a twofold increase in calcium absorption in the mother.[42] Mothers with osteomalacia provide low levels of vitamin D *in utero* to the baby, resulting in early rickets.[43,44] This problem is exacerbated by breast-feeding, as breast milk is low in vitamin D. If breast-feeding is prolonged, the use of fortified weaning foods and cereals may be delayed, compounding the problem. Use of soy-based milks as an alternative milk source may also lead to vitamin D deficiency.[45]

With the introduction of solid foods, cereals and yellow fat spread are the significant sources of vitamin D. Fatty fish such as salmon, mackerel, tuna and sardines contain 3–8 μg (120–320 IU) of vitamin D per 100 kcal, but are usually not present in infant diets.

There appears to be a need to supplement the diets of school-age children with vitamin D until the pubertal growth spurt has finished, to optimise bone health. In the UK, the Committee on Medical Aspects of Food Policy (COMA) recommends that all infants should receive 7–8.5 μg (280–340 IU) of vitamin D in a multivitamin preparation or fortified formula milk.[38] It also recommends that pregnant and lactating mothers should receive 10 μg (400 IU) of vitamin D daily.

In the UK, plasma vitamin D levels below 25 nmol/litre have been reported in almost one-third of Asian toddlers,[46] even in children taking vitamin D supplements.[47] Explanations for this could include reduced exposure to the sun, late weaning, high phytate consumption, darker skin colouring, reduced calcium intake and possibly underlying genetic differences in vitamin D biosynthesis.[48] One-half of Asian children in the UK also have iron-deficiency anaemia.[49] Treatment with iron in this group results in an increase in vitamin D concentration – evidence that these two disorders may be related. COMA recommends that Asian children should be encouraged to take vitamin D supplements during their first 5 years.[38]

Calcium intake is also important for bone health in children. Calcium is relatively low in breast milk and infant formulas, but is sufficient on a daily basis.[50] In children and adolescents, however, there appears to be a reduction in the amount of milk consumed in preference to soft drinks, which may be detrimental to bone health.[51,52] In the UK, the calcium intake of pubertal boys (781 mg) falls below the RNI of 1000 mg.[41]

Some foods containing phytates (e.g. cereals, certain breads) limit calcium absorption.[53] In some developing countries, the use of phytases in weaning foods to improve mineral absorption is being explored.[54] After infancy, cows' milk is an important source of dietary calcium (80 mg/100 kcal, 120 mg/100 millilitre). Diets high in broccoli, spring onion, watercress, parsley and canned fish would improve calcium intake in children. However, these foods are less popular with children, and fortified foods remain an important dietary source of vitamin D. Increased exposure to sunlight, especially in ethnic groups at risk of vitamin D deficiency, would constitute a far more successful therapy.

Vitamin D deficiency

Vitamin D metabolism: vitamin D tightly regulates calcium levels, permitting normal muscular and neuronal function and ensuring adequate bone mineralisation. Initially, provitamin D (7-dehydrocholesterol) is derived from cholesterol through an oxidation step. Previtamin D is obtained from the skin, through initial photoconversion of 7-dehydrocholesterol by ultraviolet light (270–300 nm).[55] Provitamin D equilibrates with previtamin D by thermal rearrangement of the B sterol ring over 24–48 hours.[56] Direct dietary intake of vitamin D provides an alternative source. Excessive sunlight exposure promotes conversion of previtamin D to lumisterol and tachysterol. Vitamin D-binding protein (VDBP) has a strong affinity for vitamin D, but does not bind lumisterol or tachysterol.[57] Transport of vitamin D, 25OHD, and $1,25(OH)_2D$ is by VDBP.[58]

In the liver, vitamin D undergoes 25-hydroxylation by 25-hydroxylase, one of several cytochrome P450-containing enzymes (CYPs) involved in vitamin D metabolism.[59] CYP2R1 currently seems the most likely candidate to be the primary 25-hydroxylase, given its high affinity and specificity for vitamin D.[60]

25OHD is the major circulating metabolite of cholecalciferol. It increases in proportion to vitamin D production, and is used as a clinical indicator of vitamin D status. The enzyme 25-hydroxyvitamin D-1α-hydroxylase (CYP27B1/CYP1α), which is found in both the proximal[61] and the distal[62] tubules of the kidney and in the cortical and medullary part of the collecting ducts,[62] is responsible for 1α-hydroxylation to the active $1,25(OH)_2D$) during periods of calcium and phosphate depletion.

The 25-hydroxylation step in the liver is constitutive, whereas CYP27B1 is under tight regulation in the kidney by PTH[63] and calctonin.[64] An abundance of calcium leads to degradation of 25OHD through a 24-hydroxylation step by the enzyme 25-hydroxyvitamin-D3-24-hydroxylase (CYP24) to 24,25-dihydroxyvitamin D ($24,25(OH)_2D$). CYP24 closely regulates the amount of circulating 1,25OHD by conversion to calcitroic acid, which is excreted in bile,[65,66] and $1\alpha,25(OH)_2D$-26,23-lactone.[67] CYP24 is found in the kidney,[68] the intestine and bone,[69] as well as in other vitamin D target organs. PTH also closely regulates the expression of CYP24 in the presence of $1,25(OH)_2D$ to control circulating vitamin D levels.[70]

Vitamin D receptor (VDR): the biological action of $1,25(OH)_2D$ results from its interaction with a high-affinity VDR that acts as a ligand-activated transcription factor. After binding of $1,25(OH)_2D$ to the VDR, heterodimerisation occurs between the VDR and the retinoid X receptor in the cytosol.[71] Following transport to the nucleus, the heterodimer binds to a specific DNA sequence termed the 'vitamin D response element' (VDRE) on the promoter region of $1,25(OH)_2D$-regulated genes, resulting in a conformational change of the DNA and subsequent gene transcription.[72] Binding of $1,25(OH)_2D$ to the VDR also produces a conformational change in the carboxyl (COOH) terminus of the VDR that allows it to interact with transcription co-activators known as vitamin D receptor-interacting proteins,[73] resulting in DNA conformational change and up-regulation of transcription activity.[74]

$1,25(OH)_2D$ down-regulates *CYP27B1* gene expression via negative VDREs. Thus $1,25(OH)_2D$ autoregulates its own production.[75]

Vitamin D and calcium homeostasis: $1,25(OH)_2D$ promotes calcium absorption in the small intestine through its interaction

with the VDR.[76] In vitamin D deficiency, 10–15% of dietary calcium is absorbed by the gastrointestinal tract. However, with adequate vitamin D, adults absorb approximately 30% of dietary calcium.[77] During pregnancy, lactation and the adolescent growth spurt, circulating concentrations of $1,25(OH)_2D$ increase, thereby increasing the efficiency of intestinal calcium absorption by as much as 50–80%.[77] $1,25(OH)_2D$ also increases the efficiency of dietary phosphorus absorption, especially in the jejunum and ileum. Approximately 60% of dietary phosphorus is passively absorbed in the small intestine, and $1,25(OH)_2D$ actively increases dietary phosphorus absorption by an additional 15–20%.[77]

If dietary calcium is insufficient, $1,25(OH)_2D$ interacts with the VDR in osteoblasts, stimulating the production of surface receptor-activated NFκB-ligand (RANKL). Pre-osteoclasts have a RANK receptor for RANKL on their cell membrane. Signal transduction through RANK induces pre-osteoclasts to become mature osteoclasts.[78,79] Osteoclasts mobilise calcium stores from bone to maintain serum calcium concentrations within the normal range.

Vitamin D pathway defects: gene defects of *CYP27B1* on chromosome 12q13.1-q13[80,81] result in failure of the 1α-hydroxylation of 25OHD. This results in vitamin D-dependent rickets type 1 (VDDR1), also termed 'pseudovitamin D-deficiency rickets.[81] Patients with this autosomal-recessive inherited gene defect[82] exhibit severe rickets with marked hypocalcaemia leading to convulsions and tetany. Other serum changes include markedly decreased serum $1,25(OH)_2D$, normal serum 25OHD, aminoaciduria and hyperparathyroidism.[83] Bone changes in VDDR1 are more pronounced. Patients also show delayed tooth eruption and enamel hypoplasia. In some mutations, partial CYP27B1 activity remains, resulting in a milder presentation of VDDR1 despite *CYP27B1* mutations on both alleles.[84] The mainstay of treatment of VDDR1 is supplementation with calcitriol.

Mutations in the VDR[85] result in either a defect in the ligand-binding domain that binds $1,25(OH)_2D$, the so-called 'receptor-negative' subclass,[86] or downstream changes in the DNA-binding domain – the 'receptor-positive' subclass.[87,88] Both of these disorders are rare and are inherited as autosomal recessives. They lead to a severe form of rickets known as vitamin D-dependent rickets type 2 (VDDR2) that is resistant to vitamin D and its derivatives. Receptor-positive subclass VDDR2 is often associated with alopecia.[89,90] The biochemical findings are increased circulating $1,25(OH)_2D$, normal 25OHD, undetectable $24,25(OH)_2D$, hypocalcaemia, secondary hyperparathyroidism, hypophosphataemia, hyperphosphatasaemia and generalised aminoaciduria.[91–93]

Children with defects in the ligand-binding domain may be treated with very large doses of calcitriol (5–60 μg/day). Children with alopecia rarely respond[94] and typically need calcium infusions at high doses (2 mmol/kg/day for up to 2 years, 2–7 g/day p.o. thereafter).[95,96]

Defects in phosphate metabolism

Phosphate plays a critical role in skeletal integrity and mineral metabolism. Phosphate homeostasis is largely regulated by proximal renal tubular absorption. This role is performed by the type IIa sodium-dependent phosphate co-transporter (NPT2a).[97] Expression of NPT2a is regulated by PTH and $1,25(OH)_2D$.[97] Abnormalities of NPT2a are seen in three forms of hypophosphataemic rickets: XLH, and autosomal-dominant and tumour-induced hypophosphataemic rickets. Hypophosphataemia should promote an increase in circulating $1,25(OH)_2D$, but all three disorders show inappropriately normal or low levels. Abnormal CYPB21 and CYP24 activity underlie this paradox.[98]

In these diseases, there is no intrinsic abnormality in NPT2a. Instead, the abnormality lies in the regulation of renal phosphate transport by the *PHEX* gene (phosphate-regulating gene with homologies to endopeptidases on the X chromosome) on Xp22.2-p22.[99] *PHEX* has been isolated from bone, teeth, brain, muscle, testis, ovary and parathyroid glands, but not from the kidney.[100–104] Consequently, the actions of PHEX protein must occur indirectly, promoting renal phosphate resorption by limiting the phosphaturia promoted by molecules generally called phosphatonins.

Matrix extracellular phosphoglycoprotein (MEPE) and fibroblast growth factor 23 (FGF23) were candidates proposed as 'phosphatonins' in XLH.[105] Transfer of MEPE deficiency onto a PHEX-deficient Hyp (XLH) mouse background failed to correct hypophosphataemia and serum $1,25(OH)_2D$ levels. Increased FGF23 levels in Hyp mice were not affected by superimposed MEPE deficiency. In addition, MEPE-deficient Hyp mice retained defective bone mineralisation. This suggests that XLH is not the result of uninhibited MEPE action.[106] Current evidence suggests that FGF23 causes hypophosphataemia, possibly by acting directly on NPT2a via fibroblast growth factor receptor 3C.[107,108] PHEX limits the phosphaturic action of FGF23 by proteolysis. FGF23 injected into mice induces phosphaturia by reduction in the expression of NPT2a protein, but also reduces $1,25(OH)_2D$ by down-regulation of CYP27B1 and up-regulation of CYP24. This pathway is independent of the effects of PTH on NPT2a. In contrast to the lack of phenotypic rescue in the double knockout PHEX/MEPE mouse model, PHEX/FGF23 double knockouts have a normal skeletal phenotype.[106]

The commonest inherited form of rickets is XLH, which is caused by mutations in *PHEX*. FGF23 action is uninhibited, resulting in reduced expression of NPT2 and accelerated phosphate loss. Mutations in the gene encoding FGF23 that create the PHEX cleavage-resistant form of FGF23 result in a similar clinical presentation.[109] Similarly, in tumour-induced osteomalacia, primitive mesenchymal tumours (haemangiopericytomas, fibromas, angiosarcomas) produce high circulating levels of FGF23 that result in phosphaturia.[110] This process is reversed following tumour resection.

In contrast to XLH, autosomal-dominant hypophosphataemic rickets shows incomplete penetrance, variable age at onset (childhood to adult), and resolution of the phosphate-wasting defect in rare cases.[111]

Rickets of prematurity

Peak calcium and phosphate accretion into the skeleton *in utero* occurs in the third trimester at 2.5–3.0 and 2.0 mmol/kg, respectively.[112] To match this calcium intake in breast milk, babies would need 400 millilitre/kg of milk every day. Consequently, preterm babies are at significant risk of developing rickets of prematurity secondary to inadequate milk intake.

Immobilisation of preterm infants resulting in generalised osteopenia further exacerbates rickets. Subsequent abnormalities in bone modelling and reduced linear growth[113] may persist through infancy and childhood.[114,115] In the first 2 weeks, there is a decrease in serum phosphate, with a subsequent 3–5-fold increase in serum alkaline phosphatase in the next 4–8 weeks. These biochemical changes do not predict the total body bone mass at the time of discharge,[116] though post-natal studies suggest that they may predict cortical bone mass.[117]

Preterm formula milks provide 3.0 mmol of calcium and 2.5 mmol of phosphate for every 100 ml. This amount approximates to *in utero* exposure,[112] and phosphate supplementation is now routinely used in many units. Use of mineral-enriched formula milk post-discharge can result in greater mineral accretion 9 months later.[118] This is important, as failure of supplementation during the period of rapid growth in early infancy may result in cortical thinning predominantly at the diaphysis, possibly due to increased endosteal resorption.[119]

Immobilisation-induced osteopenia may respond to physiotherapy.[120]

Conclusion

Nutritional rickets is once again emerging as a problem in Western society. Measures such as adequate sunlight exposure and dietary supplementation are simple but effective in reducing this disease. It is important to target culturally vulnerable groups and pregnant women. Although inherited forms of vitamin D deficiency are rare, they may present in populations where nutritional rickets and consanguinity occur. ◆

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Practice points

- Nutritional rickets is increasing in developed countries. Adequate sun exposure and dietary intake of vitamin D through simple education can prevent this disease
- Vitamin D supplementation may prevent rickets in vulnerable subgroups such as Asian toddlers and pregnant women
- Large single doses of vitamin D may be used safely to treat rickets where compliance may be a significant issue
- Preterm infants are at a significant risk of rickets of prematurity. Phosphate supplementation ensures adequate bone accretion during a period of rapid growth