



Rickets

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Rickets, historically referred to as “the English disease”, is common worldwide. Absence of phosphate at the growth plate and mineralising bone surfaces due to inadequate vitamin D supply either from sunlight exposure or diet is the main cause. Inherited disorders causing hypophosphataemia have shown the intricacies of phosphate metabolism. Present advice about the provision of vitamin D to young infants needs to be clarified; the existing guidance is fragmentary and contradictory, and will not help to eradicate the disease.

Introduction

A century ago rickets affected more than 25% of children in the UK.² Nowadays, rickets is one of the most common non-communicable diseases of children in the developing world,³ and is thought to be on the rise again in the UK,⁴ although recent reliable data showing the extent of the increase are scarce. Rickets is characterised by bony deformity and stunted growth. Lower limb deformities such as bow-legs, knock-knees, or windswept changes can cause pronounced disability, and girls with pelvic deformity can die during obstructed labour.⁵ Long-term effects on skeletal health can occur with reduced bone size and mass predisposing to osteoporotic fracture later in life.

The pathological definition of rickets, the failure to mineralise newly-formed bone, means that preformed osteoid is unmineralised (osteomalacia) and endochondral calcification at the growth plate is absent or reduced, with associated growth-plate deformity.⁶ These features are the result of vitamin D deficiency in most cases, usually with an easily discernible clinical history (panel) and associated characteristic biochemical (table 1) and radiological changes. What remains unclear is whether an absolute threshold for vitamin D exists, below which rickets is inevitable; rickets can also occur when vitamin D is within the range associated with maximum calcium absorption, but calcium intake is low.⁷

Search strategy and selection criteria

The overriding aim was to provide an update summarising the advances and controversies that have arisen in the decade since the previous Seminar published in *The Lancet* in 2003.¹ Particular attention has been paid to the issue of defining vitamin D deficiency, the difficulties measuring vitamin D, rachitic fractures, the role of phosphate, and public health policy with regard to supplementation. We searched Medline, Embase, CINAHL, AMED, Health Business Elite, and HMC with the keywords “rickets”, “hypophosphatemic”, “vitamin D”, “vitamin D dependent rickets”, and “vitamin D resistant rickets” with many subsearches done for smaller, related topics. We selected papers based on our opinion of their scientific or historic importance. Research published since 2008 was given particular attention as it could be less well known to the reader. To reduce the number of references up-to-date review papers were used. We excluded book chapters and abstracts where possible.

In rare cases, abnormalities that mainly affect phosphate metabolism or bone-tissue mineralisation might be the cause. Our understanding of the intricacies of phosphate homeostasis is still evolving. This Seminar will address these issues and other areas of controversy, such as the contribution of low vitamin D to fractures in infancy.

Historical context

The original description of rickets is attributed variously to Whistler or Glisson, both practising in England in the mid-1600s.⁶ The origin of the word itself is unclear, possibly relating to the German “wricken” meaning twisted. Glisson clearly differentiated rickets from

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See [Editorial](#) page 1609

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Panel: Clinical history and examination for vitamin D deficiency-induced rickets

History

- Dark skin colour
- Reduced skin exposure
- No vitamin D supplementation during pregnancy
- Prolonged exclusive breastfeeding
- No vitamin D supplementation of infant
- Use of foods high in phytates
- Iron deficiency

Skeletal features

- Slowing linear growth
- Metaphyseal swelling at long-bone ends
- Rickety rosary
- Bowing deformity of long bones
- Frontal bossing
- Craniotables
- Persistent anterior fontanelle
- Harrison’s sulci

Non-skeletal features

- Hypocalcaemic convulsions
- Hypocalcaemic cardiac failure
- Hypotonia
- Delayed motor milestones
- Carpopedal spasm
- Enamel hypoplasia
- Delayed dentition
- Failure to thrive
- Fractious, irritable child
- Bone pain

	Serum biochemistry							Urine biochemistry		Other features
	Phosphate	Calcium	PTH	25OHD	1,25OH,D	FGF23	Alk phos	Phosphate	Calcium	
Hypocalcaemic vitamin D pathway defects										
Vitamin D deficiency	Low	Variable	High	Low	Might be increased	NA	Increased	Increased	Low	Variable aminoaciduria
VDDR1B	Low	Low	High	Very low	Variable	NA	Increased	Increased	Low	25OHD does not increase after vitamin D dosing
VDDR1A	Low	Low	High	Normal or high	Very low or ND	NA	Increased	Increased	Low	25OHD does increase after vitamin D dosing
VDDR2A	Low	Low	High	Normal or high	High	NA	Increased	Increased	Low	..
VDDR2B	Low	Low	High	Normal or high	High	NA	Increased	increased	Low	..
Hypophosphataemic rickets with raised FGF23										
XLX	Low	Normal	Normal or slightly high	Normal	Low	High	Increased	Increased	Variable	Urine calcium:creatinine used in monitoring therapy
ADHR	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	..
ARHR1	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	..
ARHR2	Low	Normal	Normal	Normal	Low	High	Increased	Increased	Variable	..
Hypophosphataemic rickets without raised FGF23										
Dent's disease*	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	Low molecular weight proteinuria
HHRH	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	High	No loss of low molecular weight protein
αKlotho mutation	Low	Normal	Normal	Normal	Normal	Normal	Increased	Increased	Variable	..
Other inherited rachitic disorders										
HPP (severe)	High	High	Low	Normal	normal	Normal	Very low	Normal or high	High	Raised concentrations of mineralisation inhibitors
HPP (mild)	Normal or high	Normal or high	Low or normal	Normal	Normal	Normal	Low	normal	Variable	Raised concentrations of mineralisation inhibitors

PTH=parathyroid hormone. 25OHD=calcidiol. 1,25OH,D=calcitriol. FGF23=fibroblast growth factor 23. Alk phos=alkaline phosphatase. NA=data not available. VDDR1B=vitamin D dependent rickets due to defects in CYP2R1 encoding vitamin D 25-hydroxylase. VDDR1A=vitamin D dependent rickets due to defects in CYP27B1 encoding 25-hydroxyvitamin D-1 alpha hydroxylase. ND=not detected. VDDR2A=vitamin D dependent rickets due to defects in VDR encoding the vitamin D receptor. VDDR2B=vitamin D dependent rickets due to defects in HNRNPC encoding hNRNPC1 and hNRNPC2. XLH=X-linked hypophosphataemic rickets due to mutations in PHEX. ADHR=autosomal dominant hypophosphataemic rickets due to mutations in FGF23. ARHR1=autosomal recessive hypophosphataemic rickets due to mutations in DMP1. ARHR2=autosomal recessive hypophosphataemic rickets due to mutations in ENPP1. HHRH=hereditary hypophosphataemic rickets with hypercalciuria, due to mutations in SLC34A3. HPP=hypophosphatasia. *Dent's disease is due to mutations in CLCN5.

Table 1: Biochemical changes in rickets

infantile scurvy on the basis of post-mortem observations, although his suggested treatment of lamb's wool ligatures to the legs was clearly inappropriate. In 1861–62, Trousseau⁸ identified absence of sunlight and poor nutrition as probable causes of rickets and suggested appropriate remedies, including cod-liver oil. In 1890, Palm⁹ commented on the relation between increasing latitude (and hence decreased sunlight exposure) and rickets. Hess and Unger¹⁰ in 1916 did a randomised controlled study and showed the positive effects of cod-liver oil on clinical rickets in the Columbia district of New York, predating the classic work of Mellanby¹¹ who created and then cured rickets in sunlight-deprived dogs fed porridge. Hess and Unger¹² also cured children's rickets through exposure to sunlight. Infants fed cod-liver oil in addition to their normal diet were noted by Daniels and colleagues¹³ to grow more quickly than those receiving the same diet alone.

In 1932, Windaus chemically characterised vitamin D₂ and vitamin D₃, which was succeeded by clinical studies by Jeans and Stearns¹⁴ in American orphanages in which wet-nursed infants received different doses of vitamin D₂ or vitamin D₃. Figure 1 shows the conversion factors for vitamin D therapy and measurements. Infants given 8.5–10 µg (340–400 units) of vitamin D daily were on average 2 cm longer at 1 year of age than infants fed 1.5–3.4 µg (60–135 units). Infants on the lower dose exposed to sunlight grew more quickly than those on the higher dose who were not exposed to sunlight.¹⁴ In subsequent studies, infants who received doses of greater than 45 µg per day (1800 units per day) grew less quickly, and their growth rate improved when the dose was reduced to 10–15 µg per day (400–600 units per day).¹⁵ Recent studies have not shown slower growth at these higher doses.¹⁶ The original dose regimens are echoed

in the present recommended daily intakes for the UK (table 2).

Vitamin D metabolism and actions

Vitamin D₂ (ergocalciferol) is obtained only from diet, whereas vitamin D₃ (cholecalciferol) is found in cod-liver oil and oily fish and is the form synthesised in skin. Sunlight, specifically ultraviolet B in the 290–315 nm range, converts 7-dehydrocholesterol to previtamin D₃.^{17,18} At normal skin temperature, previtamin D₃ thermally isomerises during a period of hours to vitamin D₃. Although increased biological effects of the natural form (vitamin D₃) might be expected, in the 1930s Jeans and Stearns¹⁴ added either form to milk and both were equally effective at preventing rickets and improving linear growth, and both have equivalent effects at raising serum 25-hydroxyvitamin D (calcidiol, 25OHD) concentrations.¹⁹

Vitamin D binds to vitamin D binding protein and is transported to the liver for 25-hydroxylation (the main enzyme is CYP2R1)²⁰ and then to the kidney. The vitamin D binding protein-25OHD complex is excreted and then reabsorbed in the proximal tubule through the endocytic receptors megalin and cubilin,²¹ where it undergoes 1-hydroxylation by CYP27B1 resulting in the active metabolite 1,25-dihydroxyvitamin D (calcitriol, 1,25(OH)₂D). Absence of the CYP27B1 enzyme results in vitamin D-dependent rickets type 1A²² and treatment requires the use of calcitriol or 1 α -calcidol.

1,25(OH)₂D binds to the vitamin D receptor, which heterodimerises with the retinoic acid receptor, to form a ligand-receptor complex that targets specific response elements on the genome. Mutations in the ligand-binding domain of vitamin D receptor resulting in rickets can be overcome in some instances with high-dose calcitriol therapy; however, mutations in the DNA-binding domain do not usually respond to this treatment.²³ Affected infants present with hypocalcaemia and severe rickets, and are typically alopecic. Such children need high-dose intravenous calcium infusions daily until 2 years of age, and then high oral doses of calcium. Rare cases have been described with intact vitamin D receptor but abnormal interacting proteins preventing or reducing transcription.²⁴ Both 1,25(OH)₂D and 25OHD are degraded initially by the vitamin D 24-hydroxylase enzyme, coded for by CYP24A1, absence of which can cause idiopathic infantile hypercalcaemia.²⁵ Figure 2 shows the vitamin D pathway.

The primary action of 1,25(OH)₂D is to increase gut calcium absorption by upregulating the calcium channel TRPV6, the intracellular transporter calbindin D, and the calcium pump PMCA1b to move calcium up the concentration gradient from enterocytes to serum.²⁶ Calcium absorption reduces by 70–75% in animals without the vitamin D receptor;^{23,27} however, the extent to which there is a threshold of either 25OHD or 1,25(OH)₂D for reduced calcium absorption is unclear. Fractional calcium absorption in children with low 25OHD

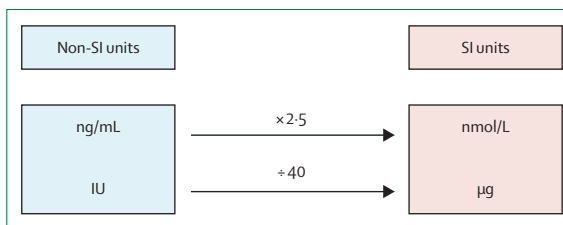


Figure 1: Conversion factors for vitamin D therapy and measurements

	Regimen*	Calciferol (ergocalciferol or cholecalciferol)
1–6 months†	Treatment	75 µg (3000 units) daily
6 months–12 years	Treatment	150 µg (6000 units) daily
12–18 years	Treatment	250 µg (10 000 units) daily
12–18 years (for concerns about probable poor adherence)	Stosstherapy	7500 µg (300 000 units) as supervised oral single dose or two divided doses over 12 h
Neonate	Supplement	10 µg (400 units) daily
Child 1 month–18 years	Supplement	10–15 µg (400–600 units) daily

*Following completion of 8–12 weeks treatment children should receive a supplementation dose until completion of linear growth. †Babies receiving 500 mL or more of formula milk per day do not require supplementation after treatment.

Table 2: Treatment and supplementation doses of vitamin D-deficient rickets according to age as advised by the British National Formulary for Children guidelines 2013

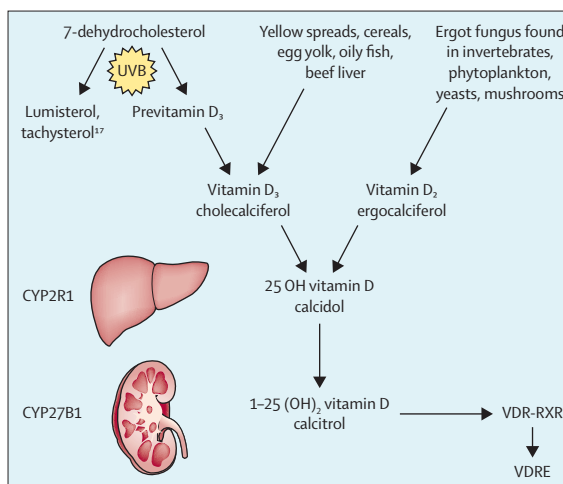


Figure 2: Vitamin D pathway

UVB=ultraviolet B. VDR-RXR=vitamin D receptor-retinoid X receptor complex. VDRE=vitamin D response element.

concentrations (25–50 nmol/L) is 0.34 compared with 0.28 at high 25OHD concentrations (50–80 nmol/L)²⁸—ie, more dietary calcium is absorbed at lower 25OHD concentrations than at the higher concentrations. Need and colleagues²⁹ reviewed the records of 319 adults with comprehensive calcium absorption and bone profile data and concluded that calcium absorption does not fall until 25OHD concentration is less than 10 nmol/L; however, since similar work has not been done in the paediatric population and the adult calcium requirement is lower than it is in children, how this extrapolates to growing

children is unclear. Additionally, $1,25(\text{OH})_2\text{D}$ acts in concert with osteoblast-derived factors to increase osteoclastic bone resorption. Thus, the role of vitamin D in skeletal homeostasis seems mainly to keep serum calcium concentrations greater than the threshold below which neuromuscular abnormalities occur.

Pathophysiology

Absence of phosphate results in the characteristic growth plate changes seen in rickets. Sabbagh and colleagues³⁰ investigated different mouse models (dietary depletion, x-linked hypophosphataemic, and vitamin D receptor knockout) and showed that the unifying defect was failure of the hypertrophic chondrocyte to undergo apoptosis, a process that is dependent on phosphorylation of caspase 9 in those cells. In vitamin D deficiency, fasting phosphate is low, with phosphate lost from the kidney as parathyroid hormone rises in response to the falling supply of calcium.

Some of the genetically determined forms of hypophosphataemic rickets (table 3) lose phosphate as a result of inhibition of the renal sodium-phosphate cotransporter. In these forms of rickets, there are raised circulating concentrations of fibroblast growth factor 23 (FGF23), a member of the endocrine fibroblast growth factors that have no heparin sulphate binding domains, and hence are not restricted to the extracellular matrix.³¹ FGF23 binding to fibroblast growth factor receptors requires the presence of αklotho ; absence of either αklotho or FGF23 in man results in hyperphosphataemia and ectopic calcification. FGF23 secretion is stimulated by increased phosphate intake, by $1,25(\text{OH})_2\text{D}$ and by parathyroid hormone in some studies.³² In turn, FGF23 downregulates the renal CYP27b1 enzyme that creates $1,25(\text{OH})_2\text{D}$ and upregulates the 24-hydroxylase that destroys $1,25(\text{OH})_2\text{D}$.³² Although phosphate is required for healing of the growth plate, osteomalacia and bowing deformity of long bones in children with hypophosphataemic rickets requires $1,25(\text{OH})_2\text{D}$ to resolve.³³

At bone remodelling sites, where new bone replaces old bone, and at the periosteal bone surface, absence of phosphate results in failure of mineralisation of the fibrous component of bone, the osteoid. The balance of

mineralisation inhibitors, such as pyrophosphate and phosphate, in the initiation and propagation of mineral crystal deposition into the bone matrix is thought to be under local control. Members of the SIBLING (small integrin-binding ligand, N-linked glycoprotein) family of proteins, that includes dentine matrix protein 1, have major roles in regulating bone tissue mineralisation through the balance of phosphate and mineralisation inhibitors at the bone surface.³⁴ Mutations of dentine matrix protein 1 result in autosomal recessive hypophosphataemic rickets type 1. However, with the exception of this protein, altered SIBLING proteins do not produce a rachitic phenotype in man. The SIBLING proteins all contain an acidic serine aspartate-rich matrix extracellular phosphoglycoprotein (ASARM) motif or cleavable peptide moiety.³⁵ The ASARM peptide binds strongly to hydroxyapatite, can directly inhibit bone mineralisation, can provoke hypophosphataemia through inhibition of the renal sodium-phosphate cotransporter, and might be a substrate for *PHEX*.³⁶

The similarity between the clinical and biochemical phenotypes in X-linked hypophosphataemic rickets and autosomal recessive hypophosphataemic rickets type 1 suggest that *PHEX* and dentine matrix protein 1 act in the same pathway to regulate FGF23 expression.³⁵ Dentine matrix protein 1 and FGF23 are primarily expressed in osteocytes embedded deep within bone and *PHEX* in osteoblasts sitting on bone surfaces. The process of osteoid mineralisation affects the envelopment of osteoblasts that will become osteocytes.³⁷ The processes underpinning the interactions are thus spatially and temporally complex and might affect other aspects of bone structure. Notably, radiographs of bones from patients with inherited hypophosphataemic rickets often show sclerosis rather than osteopenia typical of the vitamin D pathway forms of the disease.

Infantile hypophosphatasia, in which absence or severe deficiency of tissue non-specific alkaline phosphatase results in failure to clear pyrophosphate and other mineralisation inhibitors, presents with a severe rachitic phenotype in the first days and months of life; the perinatal and infant forms have a mortality rate exceeding 50%. Recombinant bone-targeted enzyme replacement therapy is reported as having some benefit.³⁸

	History	Features
Oncogenic osteomalacia	Weakness, bone pain, fractures	Very high fibroblast growth factor 23 leads to phosphaturia, suppression of vitamin D metabolism
Metabolic bone disease of prematurity	Usually less than 28 weeks gestation, with reduced mineral substrate intake plus illness-induced immobility	Rachitic features typically appear from 10 weeks; increased risk of fracture with prolonged intravenous feeding, conjugated hyperbilirubinaemia, and prolonged oxygen requirement
GNAS1 activating mutation (McCune Albright syndrome)	Polyostotic fibrous dysplasia	Features of fibrous dysplasia plus phosphaturia
Fanconi renal tubular syndrome	Polydipsia and polyuria; some patients develop rachitic features	Phosphaturia, glycosuria, and aminoaciduria

Table 3: Other hypophosphataemic disorders with rickets

Rickets in infants born prematurely

Rickets has been repeatedly described in infants born prematurely. Clearly, inadequate supply of mineral substrates, rather than vitamin D deficiency, is the root cause.³⁹ Most infants affected are born at less than 28 weeks of gestation or have had many difficulties resulting in delay in the establishment of enteral feeding, and some might have chronic lung disease that necessitates the use of steroids and diuretics causing hypercalciuria. Infants with such a history, and particularly those who develop conjugated hyperbilirubinaemia, are at increased risk of fracture.^{40,41} The risk of fracture is probably further increased in such infants by periods of immobilisation associated with illness during their time in hospital. Fractures of the ribs can be occult and result from physiotherapy. The prevalence of such fractures at discharge is unclear because exit (from the neonatal unit) chest radiographs are not a routine part of care; however, recent data suggests that around 2% have rib fractures in the first year of life.⁴¹ Table 4 shows the history and clinical features of other hypophosphataemic disorders with rickets.

Rickets, low vitamin D, and fractures in infants born at term

The extent to which reduced osteoid mineralisation diminishes bone strength in the early stages of rickets is unclear. Cases of one fracture but not several have been

reported in infants and children with rickets.⁴² No association has been reported between low vitamin D in the absence of rickets and increased fracture risk during infancy. Childhood data for the frequency of clinical rickets in infants who present with vitamin D deficiency-induced hypocalcaemia are scarce, and data for their subsequent fracture risk are absent. These important issues should be clarified. Such data are needed both to advise parents about the handling of infants potentially at increased risk of fracture, and to better clarify the extent to which biochemical measures such as isolated low 25OHD concentration need to be taken account of in cases of suspected child abuse.⁴³

Working definition of vitamin D deficiency

The consensus is that, as the circulating form of vitamin D with the longest half-life, serum 25OHD is the most appropriate marker of vitamin D status.⁴⁴ Controversy continues, however, about the definition of thresholds in 25OHD for vitamin D sufficiency and deficiency. What is regarded as normal depends on the clinical endpoint of interest, and thresholds from 25 to 100 nmol/L have been proposed. The value might differ in consideration of optimum general health and good bone health⁴⁵ or that needed to prevent rickets and osteomalacia. Most studies seeking optimum vitamin D status for good health have been done in adults and the childhood value is likely to differ and vary with age.⁴⁶ We do not know the absolute

	Genetic defect	Clinical history	Features
Vitamin D pathway defects			
Vitamin D 25-hydroxylase deficiency, autosomal recessive	CYP2R1	Consanguinity, later onset washed out bones	Bowing deformities
25-hydroxy vitamin D 1 α -hydroxylase deficiency, autosomal recessive	CYP27B1	Consanguinity, early onset hypocalcaemia	Severe rickets, signs as for vitamin D deficiency
Hereditary vitamin D-resistant rickets, autosomal recessive	Vitamin D receptor	Consanguinity, early onset hypocalcaemia	Severe rickets, signs as for vitamin D deficiency; alopecia in defects where DNA-binding domain affected
Hypophosphataemic rickets with raised FGF23			
X-linked dominant hypophosphataemic rickets	PHEX	Bowing deformity appearing around or slightly before walking; boys worse than girls	Usual rickets features plus craniosynostosis and tooth root abscesses
Autosomal dominant hypophosphataemic rickets	FGF23	Bone pain, fatigue, weakness, fractures and pseudofractures, tooth abscesses	Variable, rachitic features prominent in those presenting at a younger age
Autosomal recessive hypophosphataemic rickets type 1	DMP1	Lower limb bowing deformity, dental caries, back pain, joint stiffness in later life	Skull base osteosclerosis, sensorineural hearing loss
Autosomal recessive hypophosphataemic rickets type 2	ENPP1	Might present as infantile arterial calcification, treat with bisphosphonate	Rachitic features appear at usual time if arterial calcification survived
Hypophosphataemic rickets without raised FGF23			
X-linked recessive hypophosphataemic rickets	CLCN5	Nephrocalcinosis might result in renal failure in adulthood	Usual rickets features, small kidneys reported in one family
Hypophosphataemic rickets with hypercalciuria-autosomal recessive	SLC34A3	Early onset bowing deformity and rachitic features	Treatment with phosphate alone effective, vitamin D analogues can cause nephrolithiasis
Other inherited rachitic disorders			
Hypophosphatasia, autosomal dominant (mild); autosomal recessive (severe)	ALPL	Age at presentation shows severity, neonates and infants can die	Perinatal or infant forms—severe rickets, respiratory failure, failure to thrive, craniosynostosis, motor delay. Childhood forms; motor impairment, mild rickets, bone pain.

FGF23=fibroblast growth factor 23.

Table 4: Genetic origin, clinical history, and examination of inherited forms of rickets

25OHD concentration that unequivocally confers either good general or good bone health in children. Clearly, as vitamin D falls, so the risk of ill-health rises, but there are many examples of very low 25OHD concentrations with no evidence of rickets.

Among paediatricians in the UK, there seems to be emerging agreement that a serum 25OHD of less than 25 nmol/L represents deficiency with an increased likelihood of rickets, whereas less than 50 nmol/L represents insufficiency.^{43,47-51} Worldwide, there is support for a higher cutoff but different organisations advocate various definitions. The 2011 Endocrine Society Clinical Practice Guideline (USA) defines greater than 72.5 nmol/L as optimum, less than 50 nmol/L as deficient, and concentrations inbetween as insufficient.⁵² The Institute of Medicine (USA) regard concentrations of 25OHD less than 30 nmol/L as deficiency,⁵³ cutoffs supported by both the US and Canadian Governments, and similarly the Lawson Wilkins Paediatric Endocrine Society, now the Pediatric Endocrine Society, define deficiency as less than 37.5 nmol/L and insufficiency between 37.5 nmol/L and 50 nmol/L.⁵⁴ Some physicians advocate identification of concentrations of serum 25OHD that indicate increased risk of adverse events rather than defining deficiency.⁵⁵ The absence of consensus shows both the importance of considering covariates, such as calcium intake, and the absence of contemporary large-scale controlled studies showing benefit of administered vitamin D either to bone or general health in children of differing ages.

Cause of vitamin D-deficient rickets

Fetal vitamin D is acquired entirely from the mother and concentrations are dependent on maternal vitamin D status, which is often low in women of childbearing age.⁵⁶ Maternal 25OHD crosses the placenta and undergoes placental conversion to 1,25(OH)₂D.⁵⁷ At birth, the 25OHD concentrations in cord blood closely correlate to maternal concentrations and range from 68% to 108%.⁵⁸ Vitamin-D-replete mothers give birth to vitamin-D-replete infants, and rare cases of congenital rickets in babies born to osteomalacic mothers occur.⁴⁷ Breast milk is a poor source of vitamin D, containing less than 1.5 µg/L (60 IU/L),^{59,60} unless mothers are taking near-pharmacological doses of 100 µg per day (4000 units per day) of vitamin D.⁶¹ Babies born to vitamin-D-replete mothers will have serum vitamin D concentrations consistent with deficiency after only 8 weeks of exclusive breastfeeding.⁵⁷

Exposure to sunlight is reduced by living at latitude, because negligible vitamin D synthesis occurs at latitudes greater than 35° in the northern hemisphere⁶² and greater than 32° in the southern hemisphere during winter months.⁶³ Covering up for religious or cultural customs and as a sun protective measure substantially reduces skin exposure to ultraviolet B light, as does the use of sunscreen. Atmospheric pollution in rapidly industrialising

nations⁶⁴ might recapitulate the problems of the UK from a century ago. The same amount of vitamin D synthesis requires increased sunlight exposure in dark skinned compared with light skinned individuals.⁶⁵

The pathophysiology of rickets is such that it is most apparent, and therefore clinically most often seen, at periods of peak growth, in particular in the first 2 years of life but also during the adolescent growth spurt. The most typical presentation for a child with rickets is in the context of maternal insufficiency due to dark skin colour, covering up without supplementation during pregnancy, and long-term breastfeeding without supplementation of the infant.

Hypocalcaemia and vitamin D deficiency

The earliest presentation is of neonatal hypocalcaemia (early less than 1 week of age, late 2–4 weeks), which can result in jitteriness or progress to full-blown convulsions. Maiya and colleagues⁶⁶ reported a series of 16 infants with life-threatening heart failure secondary to hypocalcaemia and presumed vitamin D deficiency. In an 11-year retrospective case study of 126 children presenting with vitamin D deficiency (<50 nmol/L) or rickets to paediatric centres in Sydney, Australia, hypocalcaemic seizures were the most common presentation, seen in a third of cases.⁶⁷ In the west midlands in the UK, Callaghan and colleagues⁴⁸ reported a quarter of presentations with symptomatic vitamin D deficiency were due to hypocalcaemic convulsions, although bowed legs were common (46%).

Measurement of vitamin D status

Although 1,25(OH)₂D is the active product of vitamin D synthesis, its quantification is hampered by its presence in picomolar quantities (25OHD circulates in nanomols) and a substantially shorter half-life than 25OHD. Additionally, as the rate-limiting step in vitamin D synthesis, the concentration of 25OHD needs to be substantially reduced before there is any effect on serum 1,25(OH)₂D concentrations, which might be misleadingly normal or even high because of secondary hyperparathyroidism.⁶⁸

Measurement of 25OHD is analytically challenging. Until recently, no reference methods or standard reference materials had been made, resulting in much interlaboratory variability.⁶⁹⁻⁷² Nowadays, the gold standard technique for measurement of vitamin D status, allowing separate measurement of total 25OHD, 25OHD₂, and 25OHD₃, is isotope dilution liquid chromatography–mass spectrometry (LC–MS/MS).⁶⁸ The LC–MS/MS method is not without its flaws. Different laboratories use various methods, causing high interlaboratory variability, with data from the International Vitamin D External Quality Assurance System showing both over-estimations and under-estimations. Additionally, present extraction techniques do not remove 3-epi-25OHD (not usually detected by immunoassays), which was initially thought to be present in only 22.7% of infant samples (contributing 8.7–61.1% of the total 25OHD),⁷³ but more recently

reported to be contributing about 5% of the total 25OHD (range 0–25.5%) in 99% of samples from patients of all ages.⁷⁴ The biological activity of 3-epimer is unclear.⁷⁵

Incidence and prevalence

Accurate incidence and prevalence data are undermined by the absence of a robust screening instrument, no global consensus for a vitamin D deficiency cutoff, and confusion about the difference between vitamin D deficiency and rickets. Worldwide, incidence of rickets seems to be rising, although good up-to-date data are not available.^{48,63,76,77} Previously published prevalence values range from 70% in Mongolia, to 42% in Ethiopia, 9% in Nigeria, 3.3% in The Gambia, and 2.2% in Bangladesh.⁷⁸ In northwest England, 1.6% of a predominantly Asian population were reported to have rickets.⁷⁹ In Hokkaido, northern Japan, an estimate of rickets incidence was nine children per 100 000 between 1999 and 2004 for children younger than 4 years.⁸⁰ In Denmark, the average incidence during 20 years was 2.9 cases per 100 000 children per year, and 5.8 cases per 100 000 children per year in those younger than 3 years.⁸¹ In eastern Turkey, the prevalence of rickets in children presenting to paediatric outpatient clinics was 0.1%.⁸²

An Australian surveillance study estimated the overall incidence of vitamin D deficiency and rickets in children younger than 15 years of age as 4.9 cases per 100 000 children per year, 98% of whom were intermediate or dark skinned.⁸³ The UK National Diet and Nutrition Survey 2011 measured serum 25OHD in

160 young people aged 11–18 years and reported a mean of 44.6 nmol/L for boys and 42.2 nmol/L for girls showing widespread insufficiency and probable deficiency.

The apparent increase in rickets has been seen worldwide. The occurrence of vitamin D-deficient rickets in areas of the tropics where cultural and religious custom do not preclude adequate sunlight exposure has led to the suggestion of a casual role for a high phytate, low calcium diet.^{7,84} A recent case-control study done in India showed no difference in 25OHD concentrations, but much lower calcium and higher phytate dietary intakes in the group with rickets.⁸⁵ Lower concentrations of calcium have been noted in the breastmilk of mothers of rachitic children.⁸⁶ Radiological and biochemical rachitic changes seen in vitamin D sufficient (>25 nmol/L) hypocalcaemic children have been reported to resolve rapidly with calcium supplementation as opposed to with vitamin D alone, although the combination of both was most effective.^{7,87}

The rise in cases in high-income countries is probably because of increased movement of darker skinned individuals to more temperate climates, because individuals of Afro-Caribbean and Asian origin in Europe and African-Americans in North America are generally cited in published case series.⁶³ Numbers of immigrants continue to rise in the UK, with data from the 2011 census showing that 13% of the UK population is now foreign born, with the greatest numbers coming from India, Poland, and Pakistan.⁸⁸

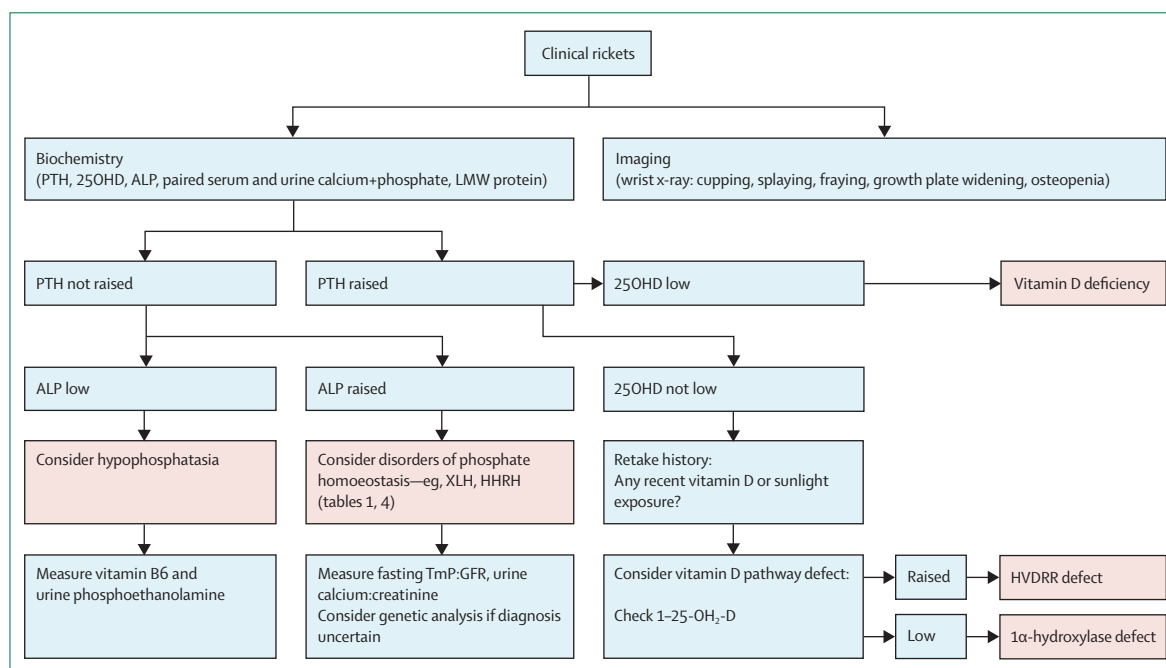


Figure 3: Management algorithm of rickets

PTH=parathyroid hormone. 25OHD=calcidiol. ALP=alkaline phosphatase. LMW=low molecular weight. XLH=X-linked hypophosphataemic rickets. HHRH=hereditary hypophosphataemic rickets with hypercalcaemia. TmP:GFR=ratio of renal tubular reabsorption rate of phosphate to glomerular filtration rate. HVDRR=hereditary vitamin D-resistant rickets.

Treatment

Figure 3 shows the management algorithm of rickets. The treatment of vitamin D deficiency-induced rickets is simple and cost effective and usually entails an oral preparation of vitamin D with calcium supplementation in children with poor dietary intake or evidence of hypocalcaemia. Choice of vitamin D preparation, ergocalciferol or cholecalciferol, and dose regimen are contentious issues. Concerns have arisen about the effectiveness of ergocalciferol compared with cholecalciferol, both in terms of its ability to raise 25OHD concentrations and the precipitate fall in serum concentrations after completion of treatment.⁸⁹ Others have reported the rise in 25OHD after administration of both forms to be equivalent,⁹⁰ including two studies in paediatric populations.^{91,92} Most consensus statements and supplement or treatment guidelines do not recommend one form over the other. Other than the 80-year-old studies by Jeans and Stearns,^{14,15} no data exists for the functional outcome that compares the two forms.

The British National Formulary for Children⁹³ recommends either form of calciferol at treatment dose for 8–12 weeks after which supplemental doses should be used, which we recommend continuing until completion of linear growth (table 2). In practical terms, vitamin D deficiency will take longer to correct with reduced vitamin D intake; as a result, a sliding scale of vitamin D treatment is suggested that takes some account of age-related changes in body size and rate of growth (table 2). Vitamin D insufficiency (<50 nmol/L but >25 nmol/L) is usually treated with supplement doses rather than treatment doses. The British National Formulary for Children recommends all patients receiving pharmacological doses to have serum calcium checked initially once or twice a week and when the child has nausea or vomiting.⁹² Our local practice is not to monitor asymptomatic patients and do a bone profile and 25OHD shortly after completion of treatment.

In the USA, dealing with a population of diverse ethnic origins, the Endocrine Society Clinical Practice Guidelines⁵² recommend use of either vitamin D₂ or vitamin D₃ at a dose of 2000 IU per day or 50 000 IU per week for 6 weeks in infants aged 0–1 years followed by maintained intake of 400 IU per day; the same schedule is recommended for children aged 1–18 years but with a maintenance dose of 600 IU per day.

We do not recommend administration of vitamin D as an intramuscular injection as a routine measure in children. Stosstherapie (from the German “push”) with 600 000 units of vitamin D can result in hypercalcaemia and nephrocalcinosis.⁹⁴ There is no place for the routine use of 1 α -hydroxylated preparations, such as alfalcidol or calcitriol, in the treatment of rickets caused by vitamin D deficiency. These drugs are used in the treatment of hypophosphataemic rickets with raised FGF23 and rare vitamin D pathway defects; they could also have a place in the acute treatment of hypocalcaemic cardiomyopathy.⁶⁶

Treatment of hypophosphataemic rickets

In the forms of hypophosphataemic rickets associated with raised serum FGF23, replacement of phosphate is required alongside the use of either calcitriol or 1 α -calcidiol. Regular review in a specialist paediatric metabolic bone clinic is needed to monitor growth, bony deformity, and complications associated with these disorders and their treatment, including root abscesses, craniosynostosis, nephrocalcinosis, and parathyroid gland hyperplasia. Balancing the intake of phosphate with 1 α -calcidiol can be difficult especially during periods of rapid growth. Bowing deformity resulting in genu varum with an intercondylar distance of more than 12 cm is likely to require surgical intervention; such intervention should be done only when the bone disease is under control. A good clinical management guideline was published in 2010.⁹⁵

Anti-FGF23 antibody therapy has been assessed in the murine model of X-linked hypophosphataemic rickets (the HYP mouse) and was shown to correct both hypophosphataemia and restore conversion of 25OHD to 1,25(OH)₂D, and restore longitudinal growth and improving osteomalacia.⁹⁶ A phase 1 single-dose escalation trial in adults has been completed but not yet reported (NCT00830674).

Prevention

Prevention of rickets can be summarised as adequate exposure to sunlight and dietary intake. However, these methods are complicated by high-profile public health campaigns advising sunlight avoidance, the need for different culturally sensitive strategies for groups at risk, and varying international guidance for the recommended daily intake of vitamin D. Population screening is not a viable option because of an absence of consensus about diagnostic cutoff and a test with appropriate levels of sensitivity and specificity, and the few long-term data for the sequelae of low serum 25OHD.

The exhortations to expose skin to adequate sunlight fail because they are either counter-cultural, at odds with skin cancer campaigns, or inappropriate because of latitude or season. Strong epidemiological evidence linking sun exposure and skin cancers has led the American Paediatric Association to support the guidance restricting exposure to sunlight in children and promotion of vitamin D supplementation throughout childhood.⁹⁷ Studies of adults living in northwest England (latitude of 53·5°N) have shown that sunlight exposure at recommended levels (15 min unshaded noon-time exposure 3 times per week with 35% skin surface exposed), while improving 25OHD concentrations and being adequate for white skinned individuals, left South Asian participants (n=15) vitamin D insufficient (<50 nmol/L).⁹⁸ Increasing exposure three-fold achieved sufficiency in only a quarter of the South Asian cohort showing that sun exposure advice needs to be tailored to the degree of skin pigmentation and might remain inadequate for a large proportion of the population.⁹⁹

Improvements in air quality enhance access of ultraviolet B to the skin. The Clean Air Act of 1956 in the UK is thought to have contributed to a reduction in cases of rickets thereafter and similar government interventions in rapidly industrialising nations might improve population 25OHD values.

Worldwide guidance and recommended vitamin D intakes during pregnancy vary (table 5). Advised supplementation doses are between 5 and 100 µg per day (200–4000 IU per day), many advising bodies recently increased from the typical 5–10 µg per day (200–400 IU per day), which have proved inadequate to achieve an optimum blood concentration of 80 nmol/L (32 ng/mL).¹⁰⁴

The upper limit regarded as safe for pregnant and lactating women was increased in Europe after a large randomised control trial in which 100 µg per day (4000 IU per day) was noted to be the most effective dose in achieving sufficiency in the absence of any adverse events.^{61,105} The upper level of intake advised by the Institute of Medicine in the USA is similarly 100 µg per day (4000 IU per day).⁵³ A randomised controlled trial assessing supplementation with higher doses is underway (NCT01060735). The long-term effects of such supplementation on the exposed fetal skeleton remain to be established.

Although concerns remain about poor adherence to supplementation programmes, reductions in the prevalence of rickets¹⁰⁶ and symptomatic vitamin D deficiency have been shown after targeted and universal supplementation campaigns.¹⁰⁷

WHO recommends exclusively breastfeeding infants until 6 months of age. A 3.5 kg baby taking 150 mL/kg per day of breastmilk would therefore receive slightly more than 0.75 µg per day vitamin D (30 IU per day), less than the intake noted to be inadequate to support normal linear growth in the Jeans and Stearns studies¹⁴ (inadequate 1.5–3.4 µg per day [60–135 IU per day]; adequate 8.5–15 [340–600 IU per day]). To increase the vitamin D concentration sufficiently in breastmilk, maternal supplementation would need to be in the range of 100–160 µg per day (4000–6400 IU per day), but these doses have been trialled only in pilot studies¹⁰⁸ and therefore supplementation of breastfeeding infants is recommended.

The advice from the UK Department of Health, based on the 2007 position statement by the Scientific Advisory Committee on Nutrition,⁴⁴ is to start supplementation of breastfed infants from age 6 months. In 2012, a letter from the UK Chief Medical Officers to family doctors, health visitors, pharmacists, and practice nurses stated that “breast fed infants may need to receive drops containing vitamin D from one month of age if their mother has not taken vitamin D supplements throughout pregnancy”.¹⁰⁰ Adequate intake will not be achieved by breastfeeding without supplementation in the absence of adequate sun exposure and therefore the advice is inconsistent with the original published data and confusing for health-care practitioners.

Overdosing with vitamin D will cause hypercalcaemia and nephrocalcinosis. Serum calcium rises with increasing 25OHD; hypercalcaemia occurs when 25OHD exceeds 200 nmol/L. In the UK, the tolerable upper intake concentration for vitamin D for infants and children up to age 10 years is set at 25 µg per day (1000 units per day). The European Food Safety Authority recently revised their limits to a tolerable upper intake of 25 µg per day (1000 IU per day) in infants, 50 µg per day (2000 IU per day) for children younger than 10 years, and 100 µg per day (4000 IU per day) for children older than 10 years.¹⁰⁵ In North America, the same limits are set by the Institute of Medicine for infants younger than 6 months, 37.5 µg per day (1500 IU per day) from 6 months to 1 year, and 62.5 µg per day (2500 IU per day) from 1 to 3 years, 75 µg per day (3000 IU per day) from 4 to 8 years and 100 µg per day (4000 IU per day), the tolerable upper limit, thereafter.⁵³

In most countries, infant formula milk is fortified to give a concentration of vitamin D of 10 µg/L (400 IU/L). In the USA, milk and breakfast cereals are fortified and in Canada, milk and margarine are.¹⁰⁹ After deaths from idiopathic infantile hypercalcaemia in the 1950s in the UK, the Department of Health banned food fortification with the exception of yellow spreads (margarines), cereals, and infant formula milks. Fortification of chapati flour to target low vitamin D status in the Asian community also in the UK proved effective but was not universally introduced, although fortified flour is available.¹¹⁰

Advice	
Pregnant and breastfeeding women	
UK Department of Health 2012 ¹⁰⁰	All pregnant and breastfeeding women to take a daily supplement containing 10 µg per day of vitamin D
NICE 2008 (CG62)	Supplementation in at risk groups
American Academy Of Pediatrics 2008 ⁹⁷	Measure maternal vitamin D status and supplement if found to be “insufficient”
WHO 2012 ^{*101}	Call for rigorous randomised controlled trials to evaluate the benefit and safety of routine vitamin D supplementation in pregnancy
Canadian Paediatric Society 2007 ¹⁰²	50 µg per day for pregnant and lactating women, especially during winter months
Institute of Medicine 2010 ⁵³	Recommended dietary allowance 15 µg per day. Upper level intake 100 µg per day
Breastfed infants	
UK Department of Health 2012 ¹⁰⁰	If mother has not taken supplements throughout pregnancy baby might need to receive drops from 1 month of age
Canadian Paediatric Society 2007 ¹⁰²	5 µg per day (200 IU per day) for premature infants, 10 µg per day (400 IU per day) until 1 year of age, but 20 µg per day (800 IU per day) during winter and for those living at more northern latitudes than the 55th parallel or between 40 and 55th parallel with additional risk factors
Institute of Medicine 2010 ⁵³	10 µg per day (400 IU per day) during first year of life
Children and adolescents	
American Academy Of Pediatrics 2008 ⁹⁷	Universal supplementation of 10 µg per day (400 IU per day), greater doses for at risk groups
UK Department of Health 2012 ¹⁰⁰	7–8.5 µg per day (280 IU per day) in all children aged 6 months until the age of 5 years
*Advice based on conclusions from Cochrane meta-analysis. ¹⁰³	

Table 5: Summary of global supplementation advice by advising bodies

Summary

Rickets is a preventable disease and prevention should start in pregnancy. The simplest measure for prevention is adequate sunlight exposure; however, in populations where this is impracticable or implausible, vitamin D supplementation should be instituted. No global consensus on the amount of vitamin D offered in supplementation exists. Guidance in the UK from the Department of Health is fragmentary and confusing. Vitamin D 400 IU per day is sufficient to maintain vitamin D status in the range in which adverse skeletal consequences are very unlikely, suggesting that a daily supplement ensures that irrespective of skin colour, latitude, sunlight exposure, pollution, and societal or cultural pressures to cover up, the growing skeleton will get what it needs. We believe that until growth ceases supplementation at 10 µg per day (400 IU per day) in all individuals, except those with a known contraindication (eg, hypercalcaemia or sarcoidosis) should be recommended and that, without such a programme of supplementation and concurrent public health campaign, the incidence of rickets will probably continue to rise.

Contributors

Both authors contributed equally to the writing of the Seminar.

Conflicts of interest

We declare that we have no conflicts of interest.

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