Seminar

Rickets

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Rickets, once thought vanquished, is reappearing. In some less developed countries it hardly went away. This seminar reviews the effects of genes, stage of development, and environment on clinical expression of the disease. Rickets can be secondary to disorders of the gut, pancreas, liver, kidney, or metabolism; however, it is mostly due to nutrient deficiency and we concentrate on this form. Although calcium deficiency contributes in communities where little cows' milk is consumed, deficiency of vitamin D is the main cause. There are three major problems: the promotion of exclusive breastfeeding for long periods without vitamin D supplementation, particularly for babies whose mothers are vitamin D deficient; reduced opportunities for production of the vitamin in the skin because of female modesty and fear of skin cancer; and the high prevalence of rickets in immigrant groups in more temperate regions. A safety net of extra dietary vitamin D should be re-emphasised, not only for children but also for pregnant women. The reason why many immigrant children in temperate zones have vitamin D deficiency is unclear. We speculate that in addition to differences in genetic factors, sun exposure, and skin pigmentation, iron deficiency may affect vitamin D handling in the skin or gut or its intermediary metabolism.

Although rickets had been well known for many years, it was described medically in the mid-17th century by Whistler (an Englishman studying in Leiden), Boate (a Dutchman working in Dublin), and Glisson and other fellows of the Royal College of Physicians, London. Since that time, the importance of rickets has waxed, waned, and waxed again. Events in the cycle have included the therapeutic use of cod-liver oil[1] and sunlight or ultraviolet light;[2] the demonstration that either approach was effective;[3] the observation that vitamin D improved growth and weight gain;[4] the unravelling of the metabolism and mechanism of action of vitamin D uniting the dietary and sunlight aetiologies;[5] fortification of foods with vitamin D; and hypercalcaemia due to overuse of vitamin D.[6] In recent years, however, despite the better understanding and a wide choice of preventive and therapeutic strategies, rickets is reappearing, not only in temperate zones with limited sunshine (eg, Canada, New Zealand, the UK)[7–9] but also in sunnier climates (eg, Australia, the USA, Ethiopia, Saudi Arabia).[10–12] Indeed, rickets is more common in some sunny countries than in temperate ones. An old problem of nutritional child health, once thought vanquished, has resurfaced.

What is rickets?

Endochondral ossification is the process by which cartilage is transformed into bone. The cartilage matrix produced by hypertrophic chondrocytes is calcified before being reabsorbed and replaced with woven bone, which in turn is removed and replaced with mature lamellar bone. During these processes, there is extensive deposition of new unmineralised bone tissue, known as osteoid. Rickets is the failure to mineralise this newly formed osteoid. Bones grow longer during childhood, and they must also become wider and alter their shape. The alteration process, in which bone is formed at one site and later removed at a different site, is called modelling. Finally, worn-out bone is replaced by bone-resorbing and bone-forming cells in a process called remodelling. Demineralised osteoid can accumulate at the sites of modelling and remodelling (osteomalacia).[13] These pathological changes result in the typical appearances at the growth plate and in the gradual softening of bone, which leads to deformity in association with weight-bearing. Osteomalacia can occur in adults deficient in calcium, phosphate, or vitamin D. Rickets can occur only before fusion of the epiphyses.

Although rickets has several osseous clinical signs (panel 1), a requirement for diagnosis is a radiograph of a long bone showing cupping, splaying, and fraying of the metaphysis (figure 1). Of the non-osseous effects of vitamin D deficiency (panel 2), the most important is symptomatic hypocalcaemia with convulsions, tetany, or cardiac failure in rare cases. Biochemical abnormalities reflect the causes and effects of rickets (panel 3).

Search strategy

The first aim was to examine the effects of genes, stage of development, and environment on rickets, and to relate these influences to clinical and public-health concerns. Literature searches of PubMed were done with the keywords "rickets" or "vitamin D" alone and then with "genes, or genetics", specified ages, "sun", "treatment", "prevention", and specific countries, with subsearches as necessary (eg, "weaning + calcium + phytate"). The choice of papers to quote was related to their historical or scientific importance, in our view. Publications since Jan 1, 2000, were given more attention since they might be less well known than older papers. To limit the total number of references cited, a recent paper on a topic that quoted many earlier papers was favoured over multiple citations. We cited few chapters in books, since many are difficult to retrieve, or papers appearing only as abstracts, since many do not subsequently appear in peer-reviewed journals or are altered substantially.

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Panel 1: **Signs of rickets in osseous tissues**

Craniotabes in newborn baby and young infant
Softening of skull bones may be present but is not pathognomonic of rickets.[14]

Frontal bossing in early infancy
Expansion of cranial bones relative to facial bones; hydrocephalus also causes this disparity ("rickets hydrocephalus").[15]

Fontanelle
Delayed closure, but normal time of closure varies; occasionally intracranial hypertension.[16]

Big wrists
An apparent bracelet of bone around the wrist (specificity 81%[17]) but normal-sized wrist bones may appear large if there is muscle wasting due to protein-energy deficiency.

Rickety rosary
Swollen costochondral junctions of ribs (specificity 64%[17]).

Skeletal deformities
Particularly "bow legs" once the child is walking; genu valgum is generally not due to rickets. Spinal curvature occurs in occasional cases, but causes other than rickets are more likely. Narrowed pelvic outlet used to cause obstructed labour.

Brown tumour
Fibrous-cystic osteitis associated with the secondary hyperparathyroidism (rare).[18]

Limb pain
Bone pain and pseudoparalysis are uncommon in rickets;[17,19] osteomalacia and the subperiosteal haematoma of scurvy are more likely causes of pain.

Delayed eruption of teeth
Deciduous incisors not present by 9 months and first molars by 14 months, but normal eruption varies by 2–3 months and other factors affect eruption.

Enamel hypoplasia
Greater susceptibility to caries in the first dentition.

Bone imaging
Cupping, splaying, and fraying of the metaphysis well seen in the ulna and radius at 1 year. A scoring method for severity has been described.[20] Periosteal reaction, in association with rickets in preterm infants, probably represents accumulation of unmineralised osteoid on the periosteal bone surface, rather than occult fracture.[21] The metaphysis does not have "rubbed out areas"; these suggest acute or chronic infection.
Swollen costochondral junctions. Fractures are rare[22] except in very preterm babies and are very uncommon beyond age 6 months.

Simple nutrient deficiency, particularly of vitamin D from sunlight, diet, or both, is the most common cause of rickets. However, genetic or acquired disorders of the gut, liver, kidney, and metabolism can present with rickets (figure 2). Panel 4 shows factors that suggest that rickets in an individual child is unlikely to be due to the usual simple deficiency of vitamin D. We recommend other authoritative recent reviews and commentaries on vitamin D and rickets.[39–41] Our seminar focuses on "simple" rickets, not secondary to gastrointestinal, hepatic, renal, or metabolic disease. As with any nutritional disorder, the aetiology, presentation, and effects depend on genes, stage of development, and environment.

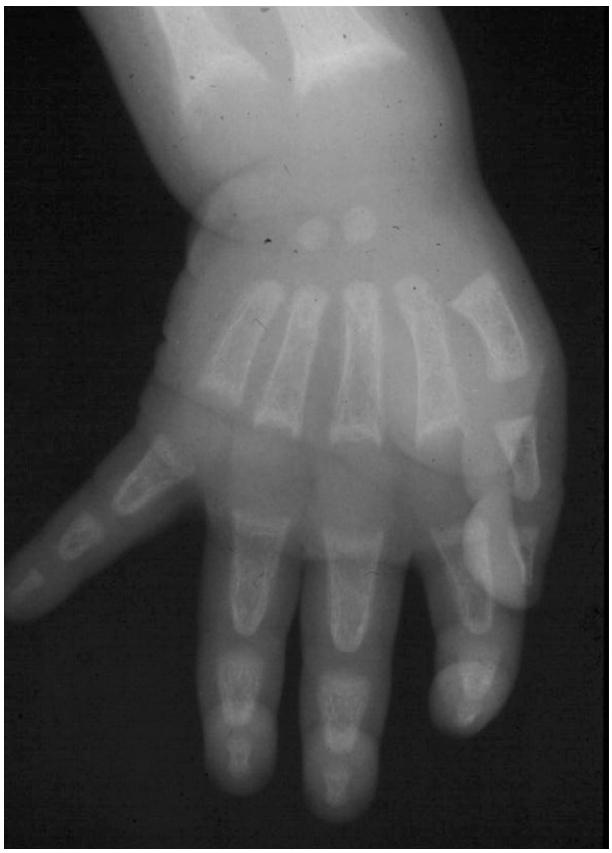

Figure 1: **Radiograph of wrist showing rickets**
Classic features of rickets include cupping, fraying, and splaying of the metaphysis. The ulna (which grows more quickly at its distal end) is more severely affected. Widening of the growth plates is not shown because the secondary ossification centres of the radius and ulna are not yet apparent.

Genetics and molecular biology

There is little evidence of any specific genetic predisposition to nutritional rickets. Polymorphisms of the vitamin D receptor (VDR) have been studied extensively in adults, but less so in children. Fischer and colleagues reported an increased frequency of the VDR *FF* genotype in Nigerian children with rickets.[42] Paradoxically, the *FF* genotype is thought to encode a "better functioning" receptor. However, Nigerian children are at risk of calcium-deficiency rickets rather than that caused by vitamin D deficiency.

Adults of Asian origin have higher activity than white adults of calcidiol-24-hydroxylase in cultured skin fibroblasts stimulated with calcitriol. This difference implies more rapid degradation of calcidiol to a less active metabolite.[43] Doxiadis and colleagues[44] reported that in six of 21 infants whose rickets healed after treatment with 4000 IU vitamin D daily, aminoaciduria persisted for at least 8–12 weeks after alkaline phosphatase activity had returned to normal. Of nine parents whose infants showed persistent aminoaciduria, five also showed aminoaciduria. The researchers suggested that this finding indicated a genetic predisposition to rickets that was associated with aminoaciduria. However, alkaline phosphatase activity and other measures of vitamin D sufficiency were not assessed in the parents, so the issue of whether the tendency to clinically apparent rickets and osteomalacia within families reflects an underlying genetic predisposition or shared environmental factors remains unclear. There are several disorders of phosphate and vitamin D metabolism that give rise to rickets.

Panel 2: **Non-osseous effects of vitamin D deficiency**

Symptomatic hypocalcaemia with convulsions
Particularly in young infants (<6 months old) of mothers who have untreated, in many cases subclinical, osteomalacia.

Myopathy
Proximal myopathy in infants and adolescents. Heart failure simulating cardiomyopathy with severe hypocalcaemia, responding to treatment for rickets and inotropes.[23]

Myelofibrosis
With pancytopenia or microcytic hypochromic anaemia, returning to normal when treated with vitamin D.[24]

Other disorders
Finnish infants receiving supplements of vitamin D 50 µg daily had a lower than normal incidence of type 1 diabetes during first 10 years of life.[25] Some studies suggest links between early vitamin D deficiency and other disorders in later life—eg, multiple sclerosis, some cancers, schizophrenia, and heart disease.[26–28]

Intrauterine and infant growth
Some, but not all, studies have shown that vitamin D supplements in the last trimester of pregnancy improve growth in utero and during infancy.[29]

Panel 3: **Normal biochemical values[30] and abnormalities in rickets before treatment**

Calcium
(Normal values 2·3–2·7 mmol/L; as low as 1·9 mmol/L in neonatal period)
Near lower limit of normal since it is maintained by a secondary rise in parathyroid hormone; sometimes this mechanism is insufficient and calcium concentration falls.

Phosphate
(Normal values vary with age: 1·2–2·1 mmol/L; higher in the neonatal period, 1·6–3·0 mmol/L; lower in adolescence, 0·9–1·5 mmol/L)
Initially normal. Later, slightly low because parathyroid hormone increases renal excretion; high or very low concentrations ma iy indicate renal rickets.

Parathyroid hormone
(Normal values vary with age and method: 1–6 pmol/L)
Higher than normal (roughly in inverse proportion to the concentration of calcidiol) to maintain serum calcium. Concentrations can be monitored to assess adequacy of treatment.[9]

Alkaline phosphatase
(Typical values <500 IU/L in neonatal period, <1000 IU/L up to 9 years, falls after puberty)
Higher than normal. May be normal if accompanied by protein-energy malnutrition; also raised when serum direct bilirubin is raised. Range varies depending on method used.

Calcidiol (25-hydroxycholecalciferol)
(Normal values >25 nmol/L)
Below 10 nmol/L in most cases of radiologically proven rickets. In adults parathyroid hormone concentrations do not reach a nadir until calcidiol concentration is as high as 70 nmol/L.[31] In children concentrations below 25 nmol/L are definitely deficient. Different assays give different results.[32]

Calcitriol (1,25-dihydroxycholecalciferol)
(Normal values 43–139 pmol/L, up to 250 pmol/L in preterm babies)
Normal or high in most cases of nutritional rickets. Not commonly measured.

Other
Excretion of hydroxyproline peptides and pyridinium cross links (from collagen) is increased; serum concentrations of osteocalcin from osteoblasts are normal or raised.[33] These measurements are rarely made.

Vitamin D metabolism

Failure to convert calcidiol to calcitriol causes rickets. Such failure is caused by a defect in the gene encoding vitamin D 1α-hydroxylase, which is expressed in the mitochondria of proximal tubular and, to a lesser extent, collecting-duct cells of the kidney. This enzyme is regulated by calcium, phosphate, parathyroid hormone, calcitonin, calcitriol, and intracellular vitamin-D-binding protein 1.[45] The clinical picture with this gene defect is one of severe rickets with hypocalcaemia commonly causing convulsions. Tooth eruption is delayed, and the enamel is hypoplastic. Frontal bossing, craniotabes, and a widely patent anterior fontanelle are found. Serum calcitriol concentrations are low but not zero in untreated patients,[46] so some enzyme activity remains. Before calcitriol became available, some patients were successfully treated with large doses of vitamin D.

The VDR is a nuclear steroid hormone receptor. Mutations in the receptor give rise to severe rickets. These mutations can lead to a change in the ligand-binding domain (which binds calcitriol) or in the DNA-binding domain (binding to DNA activates transcription). Some children with defects in the calcitriol-binding domain can be successfully treated with very large doses of calcitriol. Alopecia is associated with lack of response to calcitriol.[47] Children with defects in the DNA-binding domain may initially need to have calcium infused at very high doses.[48] Both disorders are autosomal recessive. Awareness of these disorders is important despite their rarity, because consanguinity rates are high among some populations in which nutritional rickets is common.[49]

Phosphate

Studies of three different disorders of phosphate metabolism have advanced the concept of a circulating factor (or factors) that might have a role in regulating phosphate homoeostasis.[38] The commonest inherited form of rickets is X-linked hypophosphataemic rickets, which is caused by mutations in *PHEX* (Phosphate-regulating gene with Homologies to Endopeptidases, on the X chromosome). *PHEX* is predominantly expressed in osteoblasts. Individuals with this disorder have higher than normal urinary losses of phosphate, due partly to lowered activity of the sodium-phosphate cotransporter in the proximal tubular epithelium. Autosomal dominant hypophosphataemic rickets is also characterised by excessive urinary phosphate losses. Mutations in the gene encoding fibroblast growth factor 23 (FGF23) render the factor insensitive to cleavage by a cell-membrane-anchored enzyme, PHEX. Oncogenic osteomalacia is characterised by very high circulating concentrations of FGF23, which fall after the tumour is removed, and by increased urinary phosphate losses; serum concentrations of the active metabolite of vitamin D (calcitriol) are low or even undetectable.[50] Serum calcitriol concentrations are also "inappropriately low" in many individuals with X-linked hypophosphataemic rickets, which suggests that FGF23 may have a role in vitamin D metabolism.

The clinical observations in these three disorders help to fill in some gaps in our understanding of phosphate metabolism, a crucial element in the pathogenesis of rickets.

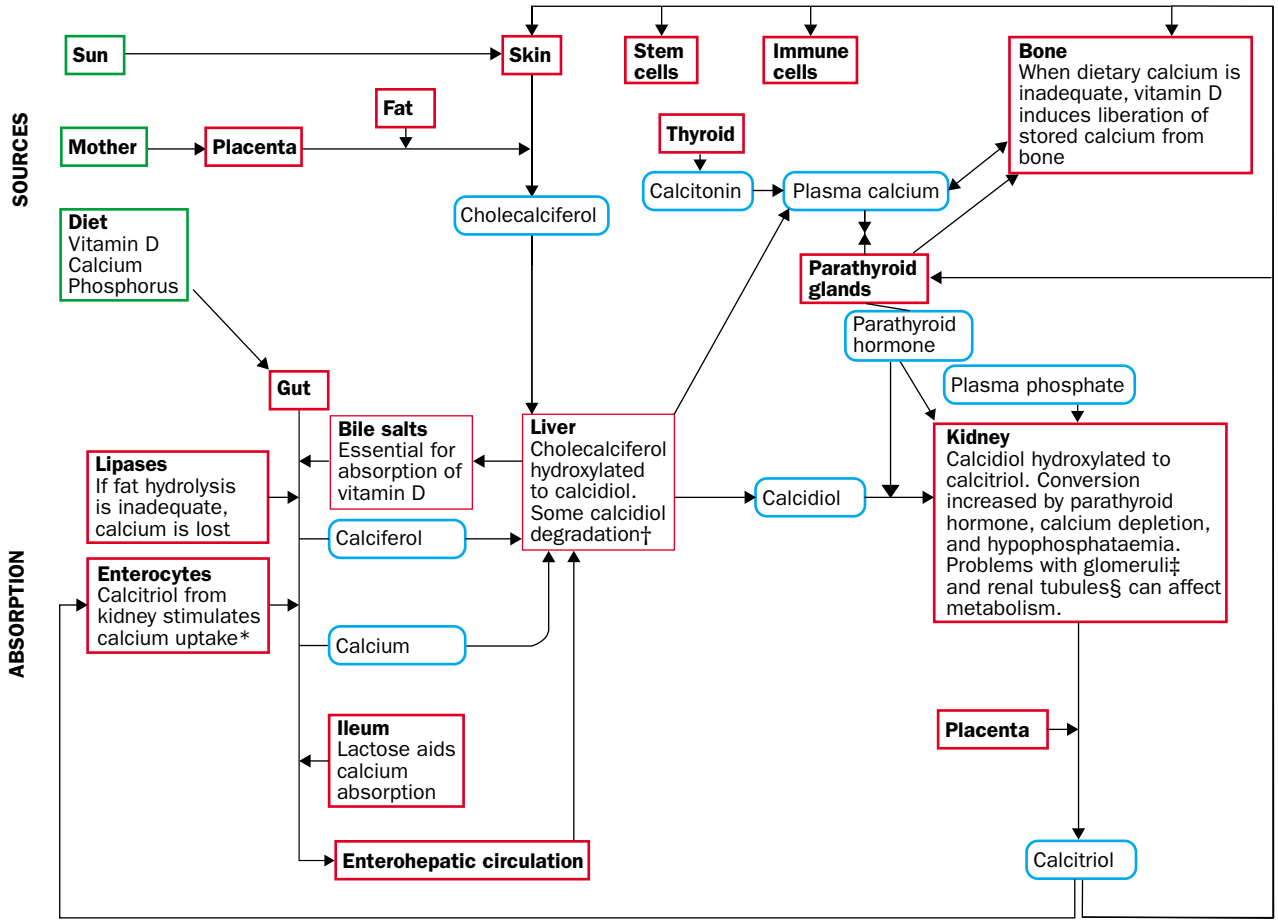

Figure 2: **Nutritional handling of calcium, phosphorus, and vitamin D, and the causes of rickets**

*Enterocyte abnormality (eg, coeliac disease) can inhibit vitamin D and calcium absorption; transport out of the cell is reduced if carrier proteins are inadequate (eg, abetalipoproteinaemia or hypobetalipoproteinaemia[34]). †Degradation of calcidiol is increased by certain anticonvulsants and in hyperparathroidism (primary or secondary to limited amounts of absorbed calcium[35]) via the action of calcitriol. Hepatic/bile-duct disease limits bile-acid secretion.[36] ‡Any cause of glomerular failure leads to retention of phosphorus with reciprocal hypocalcaemia and secondary hyperparathyroidism.[37] §Tubular disorders can lead to excessive phosphaturia.[38] Substances produced by some tumours induce phosphaturia leading to rickets before the tumour is clinically obvious.

However, evidence that FGF23 acutely and directly regulates serum phosphate concentrations is lacking at present.[38]

Stages of development

Three components of development are relevant to rickets: growth, body composition, and biological events. Figure 3 explains why simple rickets is most common in infancy and at puberty and emphasises the importance of later fetal life and infancy for events affecting bones and teeth subsequently.[51–56]

Growth is rapid in late fetal life (slowing somewhat during the last 2–3 weeks) and early infancy. The rate falls in the toddler years then rises for the prepubertal growth spurt before a further deceleration. Changes in body composition (tissue increments of calcium and phosphorus mainly into bone) show a similar qualitative pattern, but the amount of calcium deposited per gram of extra weight gain rises. Osseous mineral is about 2% of bodyweight in later infancy and increases to 4% in adolescent boys.

The biological events are the formation of deciduous teeth (figure 3) and puberty. Events in utero include tooth-germ and dentine formation. During infancy, enamel deposition of the deciduous teeth is completed, with the laying down of an insoluble calcium phosphate, $Ca_{10}(PO_4)_6(OH)_2$, similar to the rock hydroxyapatite. Calcium disturbances in pregnancy and early infancy therefore lead to enamel hypoplasia.[57]

The prepubertal growth spurt includes bone growth, so the risk of rickets increases. Secretion of gonadal hormones rises, stimulating the closure of epiphyses, after which rickets does not occur. The rate of skeletal maturation speeds up in teenagers. Protein-energy deficiency delays skeletal maturity more than rickets does. The daily accumulation of calcium in adolescents near their peak growth velocity is about a third higher than that during the long time periods shown in figure 3.[58]

Low-birthweight babies

Preterm infants are at risk of metabolic bone disease during the initial period in hospital owing to an inadequate supply of phosphorus and calcium. Rickets of prematurity[59,60] is characterised by biochemical evidence of disturbed mineral metabolism, followed by reduced bone mineralisation, abnormal bone remodelling, and reduced linear growth.[61] The most profound disturbances have been in the most immature infants receiving the diets lowest in mineral, such as unsupplemented human milk. Typically, serum phosphate concentrations fall over the first 2 weeks of life, and there is a rise in serum alkaline phosphatase activity at 4–8 weeks. Serum concentrations of alkaline phosphatase more than five times the upper limit for adults are associated with reduced linear growth in the neonatal period and at age 18 months, with the deficit persisting up to 12 years later.[62,63] Neither mean serum phosphate concentration nor peak serum alkaline phosphatase activity

Panel 4: **Factors suggesting that rickets may not be due to simple vitamin D deficiency**

Age

Below 6 months—Radiological bone changes are unusual at this age except in very-low-birthweight babies; in such cases calcium and phosphorus deficiency should also be considered. Vitamin D deficiency generally presents as hypocalcaemia, is accompanied by maternal osteomalacia, and only occasionally has the classic radiographic signs of rickets.

3–10 years—The risk of toddler rickets has passed and the increased demands of the prepubertal growth spurt and adolescence are not yet apparent.

Radiographs

Show a periosteal reaction, motheaten metaphysis, or both, rather than only the classic cupping, splaying, and fraying.

Plasma biochemistry

Urea >7 mmol/L (5 mmol/L in newborn infant). Creatinine >100 µmol/L. Alkaline phosphatase not raised. Phosphorus >2·0 mmol/L (2·5 mol/L in newborn infant) or less than 1·2 mmol/L (1·5 mmol/L in newborn infant). Plasma calcidiol not low, so long as early treatment can be excluded. Very high or very low plasma calcitriol. Vitamin D metabolites rarely measured in a routine case.

Geography

Child in tropical or subtropical Africa and Turkey, where calcium deficiency may have a role.

Response to treatment

Oral calciferol is not followed by radiographic evidence of some healing after 2–4 months. Early biochemical signs of success are an initial rise to well above normal concentrations of alkaline phosphatase and calcitriol then a gradual fall, and a rise to normal concentrations of calcidiol; however, this monitoring is not necessary in most cases.

during the neonatal period is predictive of total body bone mass at the time of discharge.[64] However, in postdischarge studies these biochemical indices predicted bone mineral content in the forearm at a site largely consisting of cortical bone.[65]

Preterm infants have low bone mass at discharge from hospital with catch-up during infancy and childhood.[66–68] The use of a mineral-enriched postdischarge formula milk was associated with a higher rate of mineral accretion up to age 9 months post term.[69] Radiographic measurement of the humerus after discharge suggests thinning of the cortex during the rapid growth of early infancy,[70] which could explain the preponderance of diaphyseal fractures (including rib fractures) in affected infants, and also their timing; fractures are unusual after 6 months corrected postnatal age.[71]

Frank rickets is, however, uncommon nowadays. The widespread use of breastmilk fortifiers and preterm formulas enriched with minerals and nutrients is generally believed to have led to the attenuation of bone disease in infants born prematurely. Mineral accretion in utero reaches a peak during the third trimester of pregnancy; typical daily calcium accretion into the skeleton is 2·5–3·0 mmol/kg and that of phosphate 2 mmol/kg.[72] To match this calcium intake from breastmilk (with assumed 50–60% absorption) would require a daily milk intake of 400 mL/kg, twice the maximum generally provided in a neonatal nursery. Supplementation is now routine in most nurseries, and the final mineral content of the milk can be as much as 3·0 mmoles calcium and 2·5 mmoles phosphate for every 100 mL. Preterm formulas can provide similar amounts of mineral.

Nevertheless, some investigators have recorded little improvement in bone mass at discharge from hospital, despite high supplementation rates.[73] Immobilisation-induced osteopenia may contribute to skeletal ill-health in these infants, interacting with the rachitic process. Gentle exercise can help to maintain bone mass in premature infants.[74]

Young infants

Deficiency of vitamin D at this age is closely related to the vitamin D status of the child's mother. Inadequate vitamin D status in pregnant women contributes to hypocalcaemia and rickets in their babies.[11,75–77] It may result in hypocalcaemia, rachitic bone changes, and slower growth.

Healthy term infants born to mothers with good vitamin D status have serum concentrations of total vitamin D metabolites that correlate with those of their mothers, with total concentrations of calcidiol and calcitriol typically lower in cord blood than maternal blood at delivery.[78] However, concentrations of free calcidiol and calcitriol in cord blood are either greater than or equal to those in maternal blood. Importantly, vitamin D metabolites in breastfed infants born to vitamin-D-replete mothers fell to concentrations consistent with vitamin D deficiency within 8 weeks of delivery in the absence of vitamin D supplementation.[78]

Some years ago, hypocalcaemia in infants was precipitated by the high phosphate intake from unmodified cows' milk. Now that more babies are breastfed and infant formulas have low concentrations of phosphate, this cause has almost disappeared and late-onset hypocalcaemia is more likely to indicate poor antenatal vitamin D status[75] than an unsuitable postnatal diet. Less commonly it is due to congenital hypoparathyroidism, calcium-sensing-receptor defects, or osteopetrosis. In infants with hypocalcaemia due to vitamin D deficiency, serum parathyroid hormone concentrations commonly remain inappropriately low and parathyroid hypoplasia may be mistakenly diagnosed. Hypocalcaemia accompanied by a raised serum parathyroid hormone concentration is also seen in pseudohypoparathyroidism; other clinical features should be sought in all cases. Treatment is with calcium, sometimes magnesium, and vitamin D (panel 5). Preparations of calciferol alone, without other nutrients, are not universally available, and pharmacists may have to arrange supplies directly with a manufacturer.

Frank rachitic changes in the bones may be seen in infants born to mothers who are severely malnourished or have malabsorption, in particular coeliac disease.[79] Rickets presenting at this age in the absence of apparent maternal vitamin D deficiency or malnutrition should raise the possibility of an inherited form of rickets. Treatment is calciferol (panel 5).

Vitamin D also promotes growth, as intervention trials of vitamin D have shown. During pregnancy, supplemented mothers had higher plasma concentrations of vitamin D and in one study gained more weight. Their babies had significantly higher plasma calcium concentrations and grew better in the first year. Symptomatic hypocalcaemia did not occur, and dental enamel hypoplasia was much less common than in babies of unsupplemented mothers.[29,57] Postnatal supplementation of vitamin D was shown 70 years ago[4] to increase length and weight velocity in healthy infants; those who received 135 IU vitamin D grew more slowly than those who received 340 IU.

Supplementation during infancy of exclusively breastfed infants resulted in a higher bone mineral content and higher serum calcidiol concentrations at 12 weeks.[80] Long-term follow-up of children in a retrospective cohort study[81] suggested that vitamin D supplementation in infancy is

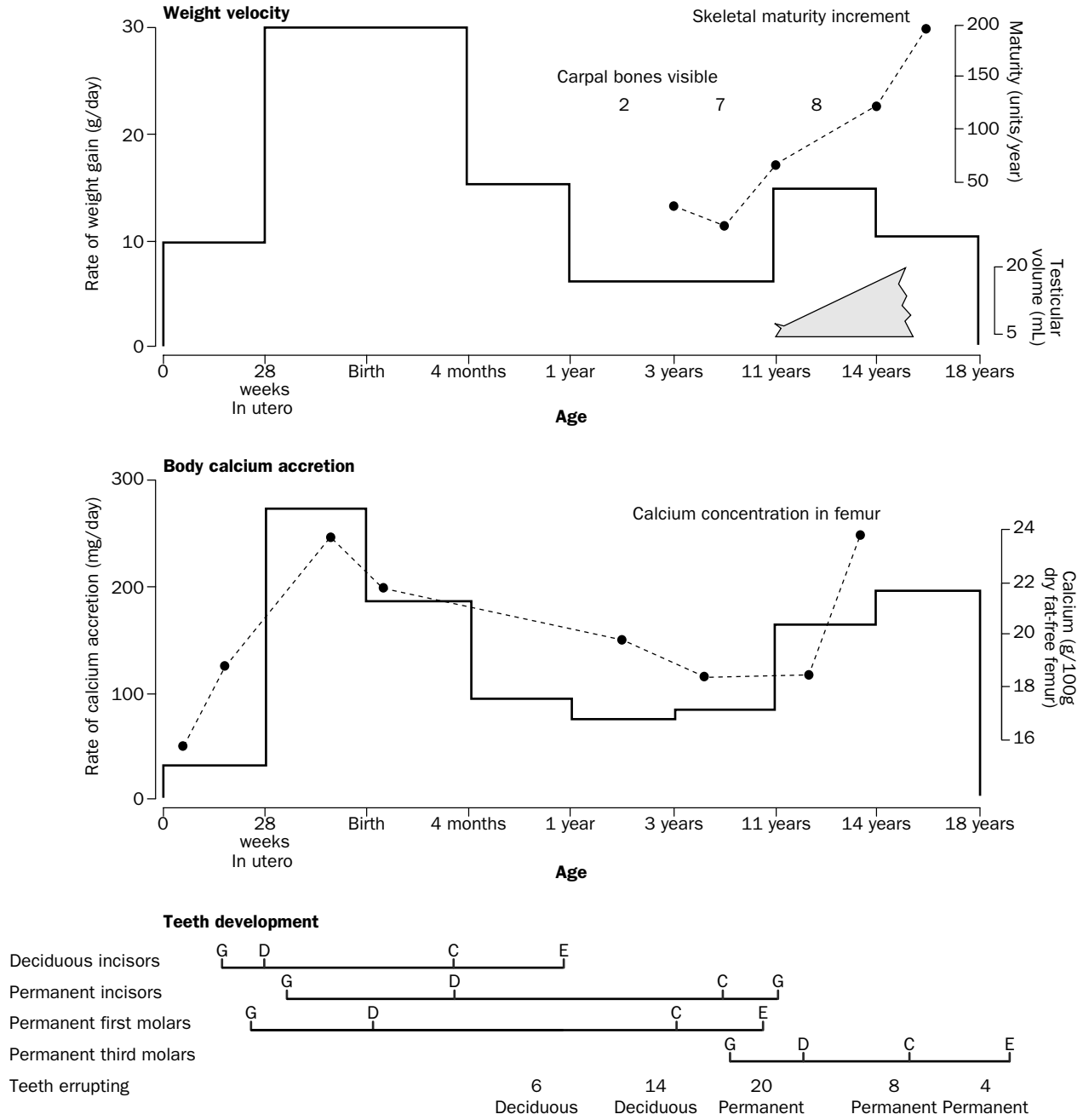

Figure 3: **Developmental changes in boys (conception to 18 years) relevant to mineralised tissues**
Note that age scale is not continuous. For teeth development: G=tooth germ fully formed; D=dentine formation begins; C=crown formation complete; E=eruption. Abstracted from various sources: weight velocity,[51] skeletal maturity,[52] body calcium accretion,[53,54] calcium concentration in femur,[55] tooth development.[56]

associated with increased bone mineral density in later childhood (median age 8 years).

Unless there is adequate sunlight exposure, there is an argument for ensuring adequate dietary vitamin D for mothers and their infants by supplementation with vitamin drops or from fortification of common foods. Infant formulas and some weaning foods are fortified with vitamin D (1·5–2·0 μg per 100 kcal, 40–53 IU/100 mL) but there is little vitamin D in human milk.

Older infants and toddlers

The cause of rickets at this age is simple vitamin D deficiency in almost all cases, but in a sunny climate, in a community drinking little milk, calcium deficiency is possible. Presentation in infancy is generally as the "wrist bracelet" sometimes with deformity, irritability, delayed walking, or tetany.[82] In older infants and toddlers, bowed legs are a common reason for referral to an orthopaedic surgeon or paediatrician.

Perinatal events may still play a part. Many mothers of children with rickets have poor vitamin D status.[11] A mother with osteomalacia, typically undiagnosed, gives her baby a low endowment of vitamin D. Her breastmilk provides little of the vitamin, and vitamin supplements are not given.[83] Fear of sun in sunny climates or inclement weather in higher latitudes leads to limited exposure, so cutaneous conversion is limited. Weaning foods are given late and contain only limited amounts of vitamin D; indeed few of the commonly used foods provide much of the vitamin unless fortified commercial foods are used.

Panel 5: **Treatment and management of hypocalcaemia and 'simple rickets'**

EARLY INFANCY (for very-low-birthweight babies, see that section)

Hypocalcaemia[30]

- To control continuing seizures, diluted 10% calcium gluconate can be given intravenously over 30–60 min, though it is rarely necessary. In the newborn infant, intramuscular magnesium sulphate can be added if necessary. The objective is to halt seizures rather than increase serum calcium.
- Oral calcium (3 mmol/kg bodyweight daily), given as a buffered solution in divided doses NOT with feeds.
- Calciferol orally (most preparations are ergocalciferol) 25 µg (1000 IU) daily (75 µg [3000 IU] daily over age 4 weeks) particularly in Asian babies, since in most the hypocalcaemia reflects poor maternal and fetal vitamin D status. Save baby's serum (at –20°C) so that if the hypocalcaemia persists, the pretreatment calcidiol concentration can be checked.
- Seek evidence of frank rickets in the baby; radiograph of knee and wrist.
- Seek circumstantial evidence of maternal osteomalacia–eg, plasma alkaline phosphatase raised.
- Plasma calcium concentration usually rises within 72 h, but may take up to 10 days. If not, consider other causes. Treatment is slowly withdrawn when plasma calcium is normal. Thereafter continue prophylactic vitamin D.

Rickets without hypocalcaemia

- Calciferol orally 75 µg (3000 IU) daily for 2-4 months.[9]

OLDER INFANTS, TODDLERS, AND ADOLESCENTS

- Calciferol orally 150 µg (6000 IU) daily for 2–4 months[9] treats the acute deficiency and replenishes stores. Continue afterwards with usual prophylactic doses. If compliance might be poor, one single oral dose (2500 µg [100 000 IU]) is effective and unlikely to be toxic. Simple deficiency should not be treated with vitamin D analogues such as alphacalcidol or calcitriol.
- If dietary deficiency may be a factor, add oral calcium (Infants 1–2 mmol/kg bodyweight daily, given as a buffered solution in divided doses not with feeds; toddlers and schoolchildren 25 mmoles [1000 mg] daily. The tolerable upper intake [www.nap.edu] is as high as 60 mmoles [2400 mg] but should not be necessary.)
- Phosphorus is abundant in the diet so supplementation is not needed in simple rickets. It is necessary for very preterm babies and in the phosphate-wasting causes of rickets.

Possible reasons for the increasing prevalence of rickets in older infants and toddlers include: prolonged exclusive breastfeeding without vitamin D supplementation of non-white children in higher latitudes;[84] extensive use of sunscreens; increased use of day-care facilities where children stay indoors much of the time; unusual diets (eg, macrobiotic diets and soy health-food beverages) that provide little vitamin D and calcium or interfere with calcium uptake;[85] migration of darker-skinned people to less sunny climates;[7–9,86] and increasing atmospheric pollution.[87]

Panel 6: **Factors modifying effectiveness of sun in production of vitamin D**

Latitude and season

Conversion becomes less effective and the effect of season becomes greater with increasing distance from the equator.[109–111] There is striking seasonal variation in measurements of vitamin D status in pregnant women and children in many locations.[107,112,113]

Exposure to sun

Length—The time of exposure needed to maintain satisfactory vitamin D concentrations in older infants varies with latitude; in Cincinnati (38°N), 20 min exposure per day of hands and face was sufficient, but in Beijing, only a little further north (40°N) 2 h exposure was necessary during September to October.[113,114]

Atmosphere—Complete cloud halves the energy of the radiation and shade reduces it by 60%. Industrial pollution is associated with rickets.[87]

Indoor living—Many children stay indoors to play. Disabled children may not receive the summertime boost of vitamin D.[115] Window glass blocks ultraviolet radiation.

Skin exposure—Adverse weather may limit exposure even in summer; as will dress codes and customs.

Safety—Measures to prevent sunburn, dehydration, and skin cancer lead to less exposure; use of sunscreens can lower vitamin D concentrations.[117]

Skin colour

Darker skin pigmentation limits conversion.[118–120]

The association of low plasma vitamin D concentrations with iron deficiency has been shown in some studies.[88,89] If one deficiency is suspected, the other should be considered. A third of Asian children with anaemia in the UK were also vitamin D deficient; half of children with vitamin D deficiency were also anaemic. Treatment with iron alone was followed by a rise in vitamin D concentrations, evidence that iron deficiency causes vitamin D deficiency.[90] Case studies in Turkey, France, and Pakistan showed that myelofibrosis can occur in rickets, evidence that vitamin D deficiency causes anaemia.[24]

Many European centres have reported a higher prevalence of vitamin D deficiency or rickets in the children of immigrants from Asia and Africa. For example, in the UK, plasma vitamin D concentrations below 25 nmol/L were found in 20–34% of Asian toddlers[88] but in a much smaller proportion of white toddlers. Similar data from national studies in the USA are difficult to interpret because people living in northern latitudes were studied in the summer and those in the south in the winter.[91]

Why rickets and low plasma vitamin D concentrations are so much more common in immigrant children than the white indigenous children is not clear, but this pattern is seen not only in northern Europe (eg, Scandinavia and the UK) but also in sunnier countries such as Spain.[86] Possible explanations are: genetic differences in vitamin D handling; behavioural differences leading to less exposure to sun, perhaps related to religious dress codes; less effective response in the skin to ultraviolet light; childhood nutritional deficiencies, particularly of iron (we speculate that iron deficiency modifies vitamin D handling in the skin or gut or its intermediary metabolism); and possible effects of mineral substrate depletion, particularly of calcium.[92]

Even in sunny countries rickets is common. Besides bone changes, pneumonia is commonly present, perhaps reflecting the effect of vitamin D on the immune system or softened ribs reducing the efficiency of breathing and coughing to clear a lung infection.[93] Three further factors

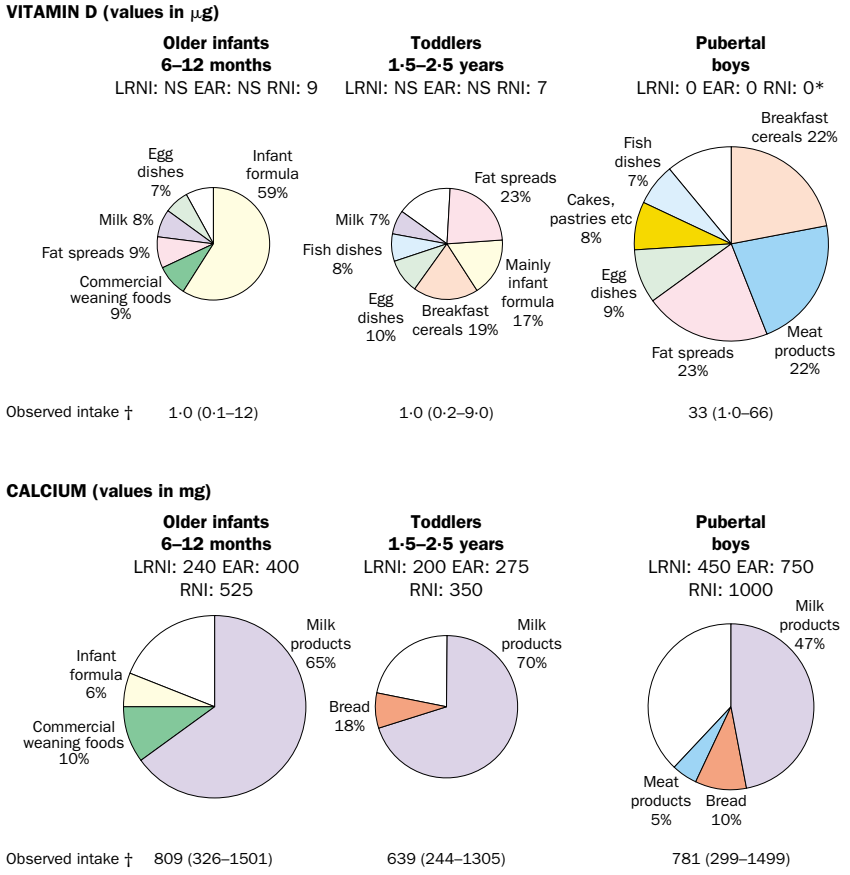

Figure 4: **Dietary reference values (DRV), observed intakes, and food contributions to these intakes of vitamin D and calcium in older infants, toddlers, and pubertal boys in the UK**

DRV=dietary reference values from UK Department of Health report 1991.[123] LRNI=lower reference nutrient intake (values below this are almost certainly inadequate for most individuals). EAR=estimated average requirement. RNI=reference nutrient intake (intakes above this amount will almost certainly be adequate for almost all individuals). NS=not stated. White segments indicate all other sources. *Over age 3 years RNI in the UK for vitamin D is stated as 0 for "a normal lifestyle"; if "confined indoors" the reference nutrient intake is 10 μg. †Observed intakes, median (3rd–97th centile), abstracted from various UK government reports on representative national samples of the population.[124–126]

are poor use of sunlight, poverty, and accompanying nutritional deficiencies. There are perceived dangers from the sun or "the evil eye"[12] and less opportunity for playing outside as urbanisation increases. In Ethiopia and Nigeria, factors associated with high rates of rickets were: large families; not being cared for by the mother during the day; unmarried mothers; low education of the care-giver; and not belonging to the area.[94,95] In Ethiopia, six times more children with rickets than controls were marasmic (protein-energy deficient),[96] and even in affluent Kuwait, children with rickets were lighter and shorter than average.[97] Deficiency of dietary calcium contributes to rickets and osteomalacia in Nigeria, Turkey, and South Africa.[98–101] In Nigeria, rickets healed in more children who received both calcium and vitamin D (61%) or calcium alone (59%) than in those who received vitamin D only (19%).[101] A combination of calcium and vitamin D was more effective than vitamin D alone in Turkish children aged 6–30 months.[100] The Nigerian and South African children are a little older than is the common age of presentation in Europe, so the disorder may be slightly different.[102] It occurred more commonly in siblings of affected children, and the vitamin D receptor *FF* genotype differed from that of controls.[42] Iron deficiency has been discussed.

Puberty

Two factors moderate the presentation of simple rickets during puberty—physical changes (figure 3) and behavioural changes. Sports enthusiasts and sunbathers have greater exposure to sunlight. In many countries, girls become more covered from about 11 years of age as a rite of passage heralding womanhood. In traditional societies, these young women would receive sunlight in the inner courtyards of their houses where they were free to expose more skin. Many now live in apartments without gardens, and the opportunity for exposure to sun with modesty is limited. However, rickets also occurs in boys in these communities.[12]

Wrist signs are not obvious but leg deformity, carpopedal spasm, and limb pain occur.[103] Fractures complicate rickets in very-low-birthweight infants[71] but also occur in pubertal young people—eg, in three of 42 cases in Saudi Arabia and in 20 individuals with cerebral palsy and rickets in South Africa.[104,105]

In white children with rickets a screening test for coeliac disease is worthwhile. Coeliac disease is less common in other races but is reported sufficiently frequently, particularly in Punjabi people, for it to be excluded if there is even slight suspicion (eg, alkaline phosphatase not raised, red-blood-cell folate low, anaemia).

Many adolescents have low serum vitamin D concentrations in the winter: in 45% of Beijing girls (<12·5 nmol/L), 25% in Paris (<15 nmol/L), and 14% in Turku, Finland (<20 nmol/L).[106–108] In Beijing, girls with the lowest winter values also had low values in the previous summer, which suggests they had made less use of sunlight. The French researchers suggested one dose of oral vitamin D 2500 μg (100 000 IU) during the winter season for all adolescents. In the Finnish girls, sunlight exposure in the summer was more effective than vitamin D supplements of 20 μg (800 IU). A low calcium intake was also found in the Beijing girls and schoolchildren in rural areas of South Africa.[102]

Environment

Sunlight

The contribution of the sun to vitamin D synthesis depends on latitude, season, exposure to direct sunlight, and skin colour (panel 6). Ultraviolet B radiation of wavelength 290–310 nm leads to the conversion (photolysis) of 7-dihydrocholesterol in the skin to precholecalciferol, which then undergoes thermally induced rearrangement of its double bonds to form cholecalciferol (vitamin D3).

There may be wider evolutionary concepts. The clinical gradation of skin colour could be related to levels of ultraviolet radiation and represent a compromise between photoprotection and vitamin D synthesis. A dark epidermis protects against injury to sweat glands and photolysis of

folate. As hominids migrated outside the tropics, depigmentation evolved to permit synthesis of vitamin D.[121]

Diet

Some countries publish observed dietary intakes from nationally representative samples of people, which can be compared with recommended dietary intakes (as shown for the UK in figure 4).[122–126] Diet becomes an important source of vitamin D only when there is inadequate exposure to sunshine. Recommended intakes vary. Figure 4 shows the very low intakes of UK children. Even though much of the observed intake is from fortified foods, most children would need supplements to achieve the reference nutrient intake or would have to rely extensively on skin synthesis for an adequate supply. Less than half take supplements, and children living in the north of the country are less likely to receive them than those in the south, even though they obtain less vitamin D from sun exposure.[127]

Breastmilk contains little vitamin D. Infant and follow-on formulas and some weaning cereals are fortified (up to 2 μg/100 kcal (100 kcal=420 kJ; 1·3 μg [52 IU] per 100 mL formula). After infancy, fortified foods such as breakfast cereals and yellow fat spreads are significant sources (about 1 μg [40 IU]/100 kcal). Unfortified foods provide little. Fatty fish such as salmon, pilchards, sardines, and tuna contain 3–8 μg (120–320 IU) per 100 kcal, but they are uncommon items in the diet of many children.

Calcium

Milks consumed during infancy contain limited amounts of calcium (breastmilk 50 mg/100 kcal or 35 mg/100 mL; infant formula 70 mg/100 kcal or 43 mg/100 mL) but the proportion absorbed and retained (about a third) meets requirements except in preterm babies. After infancy, cows' milk (calcium 180 mg/100 kcal or 120 mg/100 mL) and milk products are major sources of calcium. Children who do not like milk or are on a therapeutic diet with milk restriction have much lower intakes. In societies without a tradition of milk drinking, calcium intake is often below 300 mg daily. Even in the UK, with such a tradition, median calcium intake of pubertal boys (781 mg) was well below the reference nutrient intake (1000 mg; US recommended daily allowance 1300 mg). But adaptation to low calcium intakes by increasing the proportion retained is well established. Some foods have a much higher calcium/energy ratio than milk (eg, fish of which the bones are eaten, such as canned sardines and pilchards, broccoli tops, spring onion, parsley, and watercress) but only small quantities of these foods are eaten. The net absorption of calcium and other minerals is limited by other food substances, such as phytate, present in most cereals. High-extraction flour (eg, for wholemeal bread) contains more calcium and phosphorus than low-extraction flours but also more phytate, so absorption is less. Therefore, the amount of calcium absorbed from a diet containing little milk and a lot of phytate is likely to be low. In some less developed countries, the addition of phytase to weaning foods is being explored, to improve mineral absorption by use of animal husbandry technology.[128] This approach will also improve the dietary zinc/phytate ratio, which is low in many of these countries.

Phosphorus

Phosphorus is abundant in most diets but there may not be sufficient in rapidly growing low-birthweight babies (see above). Phosphate may be precipitated in the stomach by antacids.[129]

Panel 7: Methods to combat nutritional deficiency

Screening
Unlikely to be relevant to rickets; radiographs are justified only when the disorder is suspected. The proportion of children with low serum calcidiol concentrations who go on to have frank rickets is unknown; moderately raised alkaline phosphatase could be due to rapid but normal growth.

Health education
Exhortations to make more use of sunlight fail because of latitude/season, modesty, or safety. Policies to reduce exposure to sunlight are aimed at reducing the incidence of skin cancers, though some argue that the potential benefits of exposure (in mental health, coronary-artery disease, and rickets) could outweigh the reduction in skin cancers.[25–28,130] Foods naturally rich in vitamin D are not popular. Fortified foods make a substantial contribution to intake.
Dietary calcium intake is below international recommendations if little or no milk is drunk, but there is adaptation to low intakes.

Fiscal measures
Free or subsidised food could include vitamin D supplements or vitamin-D-fortified foods.

Supplements
Many countries have a supplementation policy but indications for prescription and actual uptake are variable.[131] Few obstetricians prescribe vitamin D supplements to pregnant women.[132] 10 μg (400 IU) daily is the most common dose; single large doses are used in France for pregnant women and for adolescents.[107,133]

Fortification of foods
Infant milks/formulas and many weaning foods are fortified with vitamin D, so it is easy to target at-risk infants. After infancy, fortified foods include many manufactured breakfast cereals and table spreads such as margarine. In North America, most milk for people of all ages is fortified,[134] but rickets is reappearing there[7,10] and plasma calcidiol is low in many black women.[135] In less developed countries, fortification programmes for other nutrients are increasing, but few for vitamin D.[136] Efficacy of fortification with calcium of low-extraction flours is disputed.

Prevention

Methods of prevention are the same as for any other nutrient deficiency, plus the need to promote exposure to sunlight. The parts played by the methods listed in panel 7 will vary according to country depending on the physical environment, cultural factors, diet (including national policies on food fortification), and socioeconomic factors (access to health services including policies for and provision of supplements).

Pregnancy and infancy

The aim should be that all pregnant women living outside the tropics receive a supplement of 10–25 μg (400–1000 IU) of vitamin D daily during the second and third trimesters of pregnancy. The reviewers in the Cochrane collaboration might not support this opinion,[137] which underlines the need for a large placebo-controlled double-blind trial of vitamin D supplements in pregnancy.

Exclusively breastfed children of Asian and black mothers living outside the tropics should receive vitamin D supplements (7–10 μg or 280–400 IU; national policies vary). The same may also apply to breastfed children of white mothers, although that is not the policy of the

American Academy of Pediatrics or the UK Department of Health. A baby might go some months without developing vitamin D deficiency if the mother had adequate vitamin D status during pregnancy and the baby received reasonable exposure to sunlight. However, it is difficult to be sure of all these safeguards, and in our opinion the only safe policy is to give vitamin D supplements to all breastfed infants. Human beings have evolved with little vitamin D in breastmilk so perhaps we should be wary of giving infants a chemical they would not receive in "natural" circumstances in their diet. However, and importantly, supplementation could be seen as replacing a chemical babies should have received from their mothers who were living in the tropics. The need for extra dietary vitamin D is the price of successful migration of human beings from the tropics to more temperate areas. In any case, this caution seems overruled by the public-health problem of rickets. Some advise supplements in all Asian or black infants even if they are receiving a fortified infant formula.[9] The American Academy of Pediatrics has lately revised its vitamin-supplement policy so that all breastfed infants (and bottle-fed infants receiving less than 500 mL formula daily) should receive 200 IU (5 μg) vitamin D daily.[138]

These approaches should also apply to women and babies in the tropics who receive inadequate exposure to sunlight.

Toddlers and schoolchildren

Vitamin D supplements should be given to all children until after the pubertal growth spurt unless the health professional adviser (of the individual child, or of the whole population via a policy of the national health-care system) is confident that there is likely to be an adequate supply from sunlight or the diet. With this policy many children in temperate areas would receive supplements. Since most non-Muslim children living in tropical countries show no evidence of rickets (either clinically or on radiographs taken for other reasons such as for trauma or a chest infection), universal vitamin D supplementation for them does not seem indicated. However, if there is already a system for the supplementation of vitamin A or iodine, the need for, and logistical possibility of adding vitamin D to the supplements, could be explored. An adequate supply from the diet means consumption of fortified foods.

For calcium in the diet of children there is particular concern in communities where little milk is drunk and cereals consumed are high extraction and therefore contain much phytate. There is limited experience of intervening on these matters, however, and the introduction of non-traditional foods would be difficult.

Policies on sun exposure

The dangers of excessive sun exposure, particularly in adolescents, are well known.[120] Nevertheless, advice on prevention of skin cancer should also ensure that mothers and infants receive adequate solar radiation in the summer, since this is likely to be at least as effective as winter supplements in maintaining adequate plasma concentrations of calcidiol.[93,132] Adequate exposure is not easily defined and few studies have measured the necessary duration and time of day at specific latitudes to achieve satisfactory calcidiol concentrations. "Sun bingeing" should be avoided to prevent skin cancer, and excessive sunbathing does not continue to boost vitamin D since 7-dehydrocholesterol is converted to non-active lumisterol and tachysterol.[139]

Fiscal measures

Schemes promoting the consumption of subsidised unfortified foods, mostly milk, should be reviewed. Deficiencies of micronutrients are common in the target populations and these micronutrients should be added to the chosen subsidised food. The approach will vary from country to country depending on the foods subsidised and the local prevalence of micronutrient deficiencies.

Conflict of interest statement

BAW has advised the UK Department of Health, European Union, WHO, and food companies on various issues in child nutrition, which have included rickets and vitamin D supplementation and fortification. Fees for advice or opinions on nutritional child health have been received from WHO and food companies. NJB advises Proctor and Gamble and Novartis on bone disease in children and undertakes research sponsored by these companies to assess the safety and efficacy of drugs for children with osteoporotic disorders.

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