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Title:

Rickets

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Abstract

Rickets, the English Disease, remains common worldwide. Lack of phosphate at the growth plate and mineralising bone surfaces due to inadequate vitamin D supply either from sunlight exposure or diet remains the principal cause. Inherited disorders causing hypophosphataemia have cast light recently on the intricacies of phosphate metabolism. Current advice regarding the provision of vitamin D to young infants needs to be clarified - the existing guidance is fragmentary and contradictory, and will not facilitate the eradication of the disease.

Introduction

A century ago rickets affected over 25% of children in the UK. Today, rickets remains one of the commonest non-communicable diseases of children in the developing world and has been thought to be on the rise again in the UK,[1] although reliable recent data indicating the extent of the increase nationally is lacking. Rickets is characterised by bony deformity and stunted growth. Lower limb deformities such as bow-legs, knock-knees, or windswept changes can cause significant disability and pelvic deformity in girls can kill because of obstructed labour.[2] There may be longer-term consequences for skeletal health with reduced bone size and mass predisposing to later osteoporotic fracture.

The pathological definition of rickets, the failure to mineralise newly-formed bone, means that preformed osteoid remains unmineralised (osteomalacia) and there is a lack of, or reduced, endochondral calcification at the growth

plate, with associated growth plate deformity.[3] These features are the result of vitamin D deficiency in most cases, usually with an easily discernable clinical history and associated characteristic biochemical 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 maximal calcium absorption, but calcium intake is low.[4]

In rare cases, abnormalities that primarily affect phosphate metabolism or bone tissue mineralisation may 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 practicing in England in the mid 1600s.[3] The origin of the word itself is unclear, possibly relating to the German “wricken” meaning “twisted”. Glisson clearly differentiated rickets from infantile scurvy based on post-mortem observations although his suggested treatment of lamb’s wool ligatures to the extremities was wide of the mark. Trousseau in 1861-2 identified lack of sunlight and poor nutrition as likely causes of rickets and suggested appropriate remedies, including cod-liver oil.[5] Palm commented on the relationship of increasing latitude (and hence decreased sunlight exposure) and rickets in 1890.[6] Hess and Unger undertook a randomised controlled study demonstrating the positive effects of cod-liver oil on clinical rickets in the

Columbia district of New York in 1916,[7] predating the classic experiments of Mellanby who created and then cured rickets in sunlight-deprived dogs fed porridge.[8] Hess and Unger also cured children's rickets through exposure to sunlight.[9] Infants fed cod liver oil in addition to their normal diet were observed by Daniels to grow more quickly than those receiving the same diet alone.[10]

The chemical characterisation of vitamin D_2 and vitamin D_3 by Windaus in 1932 was succeeded by the clinical studies of Jeans and Stearns in American orphanages in which wet-nursed infants received different doses of vitamin D_2 or D_3.[11] Infants fed 8·5-10 µg (340-400 units) of vitamin D daily were on average 2 cm longer at one 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.[11] Infants who received doses of over 45 µg/day (1800 units/day) in subsequent studies grew less quickly, and their growth rate improved when the dose was reduced to 10-15 µg/day (400-600 units/day).[12] More recent studies have not shown slower growth at these higher doses.[13] The original dosing regimens are echoed in the current recommended daily intakes for the UK (table 1).

Vitamin D metabolism and actions; also see figure 1

Vitamin D_2 (ergocalciferol) is obtained solely from diet whereas D_3 (cholecalciferol) is found in cod liver oil and oily fish and is the form synthesised in skin. Sunlight, specifically Ultraviolet-B (UVB) in the 290-315 nm range, converts 7-dehydrocholesterol to previtamin D_3.[14, 15] At normal skin temperature this thermally isomerises over a period of hours to vitamin D_3. Whilst increased biological effects for the "natural" form (vitamin D_3) might be expected, addition of either form to milk in the 1930s studies of Jeans and

Stearns appeared equally effective at preventing rickets and improving linear growth,[11] and there is an equivalence of effect in raising serum 25-hydroxy vitamin D (calcidiol, 25OHD) concentrations.[16]

Vitamin D binds to vitamin D binding protein (VDBP) and is transported to the liver for 25-hydroxylation (the main enzyme is CYP2R1)[17] 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,[18] where it undergoes 1-hydroxylation by CYP27B1 resulting in the active metabolite 1,25-dihydroxyvitamin D (calcitriol, $1,25(OH)_2D$). Lack of the CYP27B1 enzyme results in vitamin D-dependent rickets type 1A[19] and treatment requires the use of calcitriol or 1α-calcidol.

The $1,25(OH)_2D$ binds to its cognate receptor (VDR), which heterodimerises with the retinoic acid receptor (RXR) to form a ligand-receptor complex that targets specific response elements on the genome. Mutations in the ligand-binding domain of the VDR resulting in rickets can be overcome in some instances using high dose calcitriol therapy; mutations in the DNA-binding domain do not usually respond to this.[20] Affected infants present with hypocalcaemia and severe rickets, and are typically alopecic. Such children require high dose intravenous calcium infusions daily until two years of age, and then high oral doses of calcium. Rare cases have been described with intact VDR but abnormal interacting proteins preventing or reducing transcription.[21] Both $1,25(OH)_2D$ and 25OHD are degraded initially by the vitamin D 24-hydroxylase enzyme, coded for by CYP24A1, lack of which can cause idiopathic infantile hypercalcaemia.[22]

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 needed to move calcium up the concentration gradient from enterocytes to serum.[23] Calcium absorption reduces by 70-75% in animals lacking the vitamin D receptor,[20, 24] 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 at lower 25OHD levels (25-50 nmol/l) is 0.34 compared to 0.28 at higher 25OHD concentrations (50-80 nmol/l),[25] i.e. relatively more dietary calcium is being absorbed at these lower 25OHD concentrations. Need and colleagues reviewed the records of 319 adult subjects with comprehensive calcium absorption and bone profile data and concluded that calcium absorption does not fall until 25OHD is below 10nmol/l;[26] however, as similar work has not been performed in the paediatric population and the adult calcium requirement is lower, it is unclear how this extrapolates to growing children. In addition $1,25(OH_2)D$ acts in concert with osteoblast-derived factors to increase osteoclastic bone resorption. Thus vitamin D's role in skeletal homeostasis seems primarily to keep serum calcium above the threshold below which neuromuscular abnormalities occur.

Pathophysiology of rickets

It is lack of phosphate that results in the characteristic growth plate changes in rickets. Elegant experiments by Sabbagh and colleagues using different mouse models (dietary depletion, x-linked hypophosphatemic and vitamin D receptor knock-out) showed that the unifying defect was the failure of the

hypertrophic chondrocyte to undergo apoptosis, a process dependent upon phosphorylation of caspase-9 in those cells.[27] In vitamin D deficiency, fasting phosphate is low with phosphate lost from the kidney as parathyroid hormone (PTH) rises in the face of the falling supply of calcium.

Some of the genetically determined forms of hypophosphataemic rickets (panel 1) lose phosphate as a result of inhibition of the renal sodium-phosphate co-transporter. In these forms of rickets, there are elevated circulating levels of FGF23, a member of the "endocrine" fibroblast growth factors (FGFs) that lack heparin sulfate binding domains, and are hence not restricted to the extracellular matrix.[28] FGF23 binding to FGF receptors requires the presence of αklotho; the absence of either αklotho or FGF23 in humans results in hyperphosphataemia and ectopic calcification. FGF23 secretion is stimulated by increased phosphate intake, by $1,25(OH)_2D$ and by PTH in some studies. In turn, FGF23 down-regulates the renal CYP27b1 enzyme that creates $1,25(OH)_2D$ and upregulates the 24-hydroxylase that destroys $1,25(OH)_2D$.[29] Whilst phosphate is required for the healing of the growth plate, the osteomalacia and bowing deformity of long bones in children with hypophosphataemic rickets requires $1,25(OH)_2D$ to resolve.[30]

At bone remodeling sites, where new bone replaces old bone, and at the periosteal bone surface, lack of phosphate results in a 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 bone matrix is thought to be under local control. Members of the SIBLING family of proteins, that includes dentine matrix protein 1 (DMP1), have major roles in regulating bone tissue

mineralisation through the balance of phosphate and mineralisation inhibitors at the bone surface.[31] DMP1 mutations result in autosomal recessive hypophosphataemic rickets type 1 (ARHR1). However, with the exception of DMP1, altered SIBLING proteins do not produce a rachitic phenotype in humans. The SIBLING proteins all contain an acidic serine asparate-rich MEPE (ASARM) motif or cleavable peptide moiety.[32] The ASARM peptide binds strongly to hydroxyapatite, can directly inhibit bone mineralisation, can provoke hypophosphataemia through inhibition of the renal sodium-phosphate co-transporter, and may be a substrate for PHEX.[33]

The similarity of the clinical and biochemical phenotypes in X-linked hypophosphataemic rickets (XLH) and ARHR1 suggest that PHEX and DMP1 act in the same pathway to regulate FGF23 expression.[34] DMP1 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.[35] The processes underpinning the interactions are thus spatially and temporally complex and may affect other aspects of bone structure. It is notable that radiographs of bones from patients with inherited hypophosphataemic rickets often show sclerosis rather than the osteopenia typical of the vitamin D pathway forms of the disease.

Infantile hypophosphatasia (HPP), in which lack 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 exceeding 50%.

Recombinant bone-targeted enzyme replacement therapy is reported as having some benefit.[36]

Rickets in infants born prematurely

Rickets has been described repeatedly in infants born prematurely. It is clear that inadequate supply of mineral substrates, rather than vitamin D deficiency, is the root cause.[37] Most of those affected are born at less than 28 weeks of gestation, have had many difficulties resulting in delay in the establishment of enteral feeding, and some may 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.[38, 39] The risk of fracture is likely further increased in such infants by periods of immobilization associated with illness during the period of their hospitalization. Fractures of the ribs can be occult and result from physiotherapy. The prevalence of such fractures at discharge is unclear as exit (from the neonatal unit) chest x-rays are not a routine part of care; however recent data suggests that around 2% suffer rib fractures in the first year of life. [39]

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. Single but not multiple fractures have been reported in infants and children with rickets.[40] There is no reported association of low vitamin D, in the absence of rickets, with increased fracture

risk during infancy and childhood. There is limited data regarding the frequency of clinical rickets in infants who present with vitamin D deficiency-induced hypocalcaemia, and none regarding their subsequent fracture risk. Further research is needed to clarify these important issues. Such data are needed both to advise parents regarding their handling of infants potentially at increased risk of fracture, and to better clarify the extent to which biochemical parameters such as an isolated low 25OHD need to be taken account of in cases of suspected child abuse.[41]

Working definition of vitamin D deficiency

There is consensus that, as the circulating form of vitamin D with the longest half-life, serum 25OHD is the most appropriate marker of vitamin D status.[42] Controversy continues, however, about the definition of thresholds in 25OHD for vitamin D sufficiency and deficiency. What is "normal" depends on the clinical endpoint of interest and thresholds from 25-100 nmol/l have been proposed. The value may be different when considering optimal general health, good bone health[43] or that needed to prevent rickets and osteomalacia. The majority of studies seeking the optimal vitamin D status for good health have been done in adults and the childhood value is likely to be different and to vary with age.[44] We do not know the absolute 25OHD level that unequivocally confers either good general or good bone health in children. It is clear that as vitamin D falls, so the risk of ill-health rises, but there are numerous of examples of very low 25OHD levels with no evidence of rickets.

Amongst UK paediatricians there seems emerging agreement that a serum 25OHD of <25 nmol/l represents deficiency with an increased likelihood of rickets and <50 nmol/l insufficiency.[41, 45-49] Worldwide there is support for a higher cut off but different bodies advocate different definitions. The Endocrine Society (USA) 2011 Clinical Practice Guideline defines >72·5 nmol/l as optimal, <50 nmol/l deficient and levels in-between as insufficient.[50] The Institute of Medicine (USA) consider levels of 25OHD <30 nmol/l as deficiency[51], cut offs supported by both the US and Canadian governments, and similarly the Lawson Wilkins Pediatric Endocrine Society define deficiency as <37·5 nmol/l and insufficiency between 37·5-50-nmol/l.[52] Some advocate levels of serum 25OHD that indicate an increase risk rather than define deficiency.[53] The lack of consensus reflects both the importance of considering covariates such as calcium intake and the lack of contemporary large scale controlled studies demonstrating benefit of administered vitamin D either to bone or general health in children of differing ages.

Aetiology of vitamin D deficient rickets

Fetal vitamin D is acquired entirely from the mother and levels are dependent on maternal vitamin D status which is frequently low in women of child-bearing age.[54] Maternal 25OHD crosses the placenta and undergoes placental conversion to $1,25(OH)_2D$.[55] At birth the 25OHD level in cord blood closely correlates to maternal levels and ranges from 68-108%.[56] Vitamin D-replete mothers give birth to vitamin D replete infants and there are rare cases of congenital rickets in babies born to osteomalacic mothers.[57] Breast milk is a poor source of vitamin D containing less than 1·5 µg/l (60 IU/l)[58, 59] unless

mothers are taking near-pharmacological doses of 100 µg/day (4000 units/day) of vitamin D.[60] Babies born to vitamin D-replete mothers will have serum vitamin D levels consistent with deficiency after only eight weeks of exclusive breast feeding.[55]

Exposure to sunlight is reduced by living at latitude as negligible vitamin D synthesis occurs at latitudes greater than 35° in the northern hemisphere[61] and greater than 32° in the southern hemisphere during the winter months.[62] Covering up for religious or cultural custom and as a sun protective measure substantially reduces skin exposure to UVB light, as does the use of sunscreen. Atmospheric pollution in rapidly industrialising nations[63] may recapitulate the problems of the UK from a century ago. The same amount of vitamin D synthesis requires more sunlight exposure in dark as opposed to light skinned individuals.[64]

The pathophysiology of rickets is such that it is most apparent, and therefore clinically most frequently seen, at periods of peak growth, in particular in the first two 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 darker skin colour and/or covering up without supplementation during pregnancy, and prolonged breast-feeding without supplementation of the infant.

Hypocalcaemia and vitamin D deficiency

The earliest presentation is of neonatal hypocalcemia (“early” – less than 1 week of age; “late” 2-4 weeks), which may result in jitteriness, or progress to full-blown convulsions. A series of 16 infants with life-threatening heart failure

secondary to hypocalcaemia and presumed vitamin D deficiency has been reported.[65] 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.[66] In the West Midlands, Callaghan and colleagues reported a quarter of presentations with symptomatic vitamin D deficiency as due to hypocalcaemic convulsions although bowed legs were more common (46%).[46]

Measuring vitamin D status

Although 1,25$(OH)_2$D is the active product of vitamin D synthesis its quantification is hampered by its presence in picomolar quantities (25OHD circulates in nanomols) and a considerably shorter half-life compared with 25OHD. Additionally as the rate-limiting step in vitamin D synthesis, the levels of 25OHD need to be considerably reduced before there is any affect on serum 1,25$(OH)_2$D levels, which may be misleadingly normal or even high due to secondary hyperparathyroidism.[67]

The measurement of 25OHD is analytically challenging. Until recently there had been no reference methods or standard reference materials, resulting in considerable inter-laboratory variability.[68-71]

The current gold standard technique for measurement of vitamin D status, enabling total 25OHD, $25OHD_2$ and $25OHD_3$ to be measured separately, is isotope dilution LC-MS/MS.[67] The LC-MS/MS method is not without its flaws. Different laboratories employ different LC-MS/MS methods causing high inter-laboratory variability with data from DEQAS (international vitamin D External

Quality Assurance System) demonstrating both over- and under-estimations. In addition current extraction techniques do not remove 3-epi-25OHD (not usually detected by immunoassays), initially only thought to be present in 22·7% of infant samples (contributing 8·7-61·1% of the total 25OHD),[72] but more recently reported to be contributing approximately 5% of the total 25OHD (range 0 to 25·5%) in 99% of samples from patients of all ages.[73] The biological activity of the 3-epimer is unclear.[74]

Incidence and Prevalence of rickets – a global perspective

Accurate incidence and prevalence data are undermined by the lack of a robust screening tool, with no global consensus for a vitamin D deficiency cut off and confusion over the difference between vitamin D deficiency and rickets. There appears to be an increasing incidence of rickets worldwide, although good, up-to-date data are not available.[57, 62, 75, 76] Previously published prevalence figures range from 70% in Mongolia, 42% in Ethiopia, 9% in Nigeria, 3·3% in The Gambia to 2·2% in Bangladesh.[77] In NW England 1·6% of a predominantly Asian population were found to have rickets.[78] In Hokkaido, Northern Japan, an estimate of rickets prevalence was 9/100,000 for under four year-olds.[79] In Denmark the average incidence over a twenty year period was 2·9/100,000 per year, with 5·8/100,000 per year in the under three year-olds.[80] In Eastern Turkey the incidence of rickets in children presenting to paediatric outpatient clinics was 0·1%.[81]

An Australian surveillance study has estimated the overall incidence of vitamin D deficiency and rickets in children under 15 years of age to be 4·9/100,00/year, 98% of whom were intermediate or dark skinned.[82] The UK's

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 indicating 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 significant aetiological role for a high phytate, low calcium diet.[4, 83] A recent case-control study conducted in India has added further credence to this by demonstrating no difference in 25OHD levels but significantly lower calcium and higher phytate dietary intakes in the group with rickets.[84] Lower concentrations of calcium have been found in the breast milk of mothers of rachitic children.[85] Radiological and biochemical rachitic changes observed in vitamin D sufficient (>25 nmol/l) hypocalcaemic children have been seen to resolve rapidly with sole calcium supplementation as opposed to with only vitamin D, although the combination of both was most efficacious.[4, 86]

The increase in cases in industrialised countries is likely due to increased movement of darker skinned individuals to more temperate climes, as individuals of Afro-Caribbean and Asian origin in Europe and African-Americans in North America are generally cited in published case series.[62] Immigrant numbers continue to rise in the UK, with data from the 2011 census showing that 13% of the UK population is now foreign born, the greatest numbers coming from India, Poland and Pakistan.[87]

Treatment

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 of dosing regimen, are contentious issues. There have been concerns about the efficacy of ergocalciferol, both in terms of its ability to raise 25OHD and the precipitate fall in serum levels compared with cholecalciferol after completing treatment.[88] Others have found the rise in 25OHD after administration of both forms to be equivalent[89] including two studies in paediatric populations.[90, 91] Most consensus statements and supplement/treatment guidance do not recommend one form over the other. Other than the 80 year-old Jeans and Stearns studies, there is no data on functional outcome comparing the two forms.

The British National Formulary for Children (BNFc) recommends either form of calciferol at treatment dose for 8-12 weeks after which supplemental doses should be employed, which we recommend continuing until completion of linear growth (table 1).[92] In practical terms, vitamin D deficiency will take longer to correct with lower vitamin D intake; consequently 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 1). Vitamin D insufficiency (<50 nmol/l but >25 nmol/l) is usually treated with supplement doses rather than treatment doses. The BNFc recommends all patients receiving pharmacological doses to have serum calcium checked initially once or twice weekly and when the child has nausea or vomiting.[92] Our local practice is not

to monitor asymptomatic patients and perform a bone profile and 25OHD shortly after completion of treatment.

In the United States, dealing with an ethnically diverse population, the Endocrine Society Clinical Practice Guideline[50] recommends the use of either vitamin D_2 or D_3 in a dose of 2,000 IU/day or 50,000 IU/week for 6 weeks in infants aged 0-1 years followed by maintenance intake of 400 IU/d; the same schedule is recommended for children aged 1-18 years but with a maintenance dose of 600 IU/d.

We do not recommend administration of vitamin D as an intramuscular injection as a routine measure in children. Stosstherapy (from the German "push") with 600,000 units of vitamin D may result in hypercalcaemia and nephrocalcinosis.[93] There is no place for the routine use of 1α-hydroxylated preparations such as alfacalcidol or calcitriol in the treatment of rickets caused by vitamin D deficiency; their role is in the treatment of hypophosphatemic rickets with raised FGF23 and the rare vitamin D pathway defects. They may have a place in the acute treatment of hypocalcaemic cardiomyopathy.[65]

Treating 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 1α-calcidol. Regular review in a specialist paediatric metabolic bone clinic is needed to monitor growth, bony deformity, and the complications associated with these disorders and their treatment including root abscesses, craniosynostosis, nephrocalcinosis and parathyroid gland hyperplasia. Balancing the intake of phosphate with 1α-calcidol can be difficult

particularly during periods of more 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 only be undertaken when the bone disease is under control. A good clinical management guideline was published in 2010.[94]

Anti-FGF23 antibody therapy has been assessed in the murine model of X-linked hypophosphataemic rickets, the HYP mouse, and shown to correct both the hypophosphataemia and restore conversion of 25OHD to $1,25(OH)_2D$, as well as restoring longitudinal growth and improving osteomalacia.[95] 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. This is complicated by high profile public health campaigns advising sunlight avoidance, the need for different, culturally sensitive, strategies for at risk groups and varying guidance internationally for the recommended daily intake of vitamin D. Population screening is currently not a viable option due to the lack of a consensus over a diagnostic cut-off, lack of a test with appropriate levels of sensitivity and specificity and paucity of long term data regarding the sequelae of low serum 25OHD.

Adequate sunlight exposure

The exhortations to expose skin to adequate sunlight fail because they are either counter-cultural, at odds with skin cancer campaigns, or inappropriate

due to latitude/season. The strong epidemiological evidence linking sun exposure and skin cancers has led the American Pediatric Association (APA) to support the guidance limiting exposure to sunlight in children and promotion of vitamin D supplementation throughout childhood.[96] Studies on adults living in North West England (latitude of 53.5°N) have shown that sunlight exposure at recommended levels (15 minutes unshaded noontime exposure 3 times/week with 35% skin surface exposed), whilst improving 25OHD levels and being adequate for white skinned individuals, left all South Asian participants (N=15) vitamin D insufficient (<50 nmol/l).[97] Increasing this exposure three-fold only achieved sufficiency in a quarter of the South Asian cohort demonstrating that sun exposure advice needs to be tailored to the degree of skin pigmentation and may remain inadequate for a significant proportion of the population.[98]

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

Vitamin D Supplementation (table 2)

Worldwide guidance and recommended vitamin D intakes during pregnancy vary (table 2). Advised supplementation doses are between 5-100 µg/day (200-4000 IU/day), many recently increasing from the typical 5-10 µg/day (200-400 IU/day), which have been shown to be inadequate to achieve an "optimal" blood concentration of 80 nmol/l (32 ng/ml).[99]

The upper limit considered safe for pregnant and lactating women was increased in Europe following a large randomised control trial (RCT) in which 100 µg/day (4000 IU/day) was found to be the dose most effective in achieving sufficiency in the absence of any adverse events.[60, 100] The upper level of intake advised by the Institute of Medicine (IOM) in the US is similarly 100 µg/day (4000 IU/day).[51] An RCT is currently underway looking at supplementation with higher doses (NCT01060735). The longer-term effects of such supplementation on the exposed fetal skeleton remain to be determined.

Although there remains concern about poor adherence to supplementation programmes, reductions in the prevalence of rickets[101] and symptomatic vitamin D deficiency have been demonstrated following targeted and universal supplementation campaigns.[102]

Supplementation in breastfed infants

The WHO recommends exclusively breastfeeding infants until 6 months of age. A 3.5 kg baby taking 150 ml/kg/day of breast milk would therefore receive little more than 0·75 µg/day vitamin D (30 IU/day), below the intake found to be inadequate to support normal linear growth in the Jeans and Stearns studies (inadequate 1·5-3·4 µg/day (60-135 IU/day); adequate 8·5-15 (340-600 IU/day)).[11] In order to increase the vitamin D concentration sufficiently in breast milk maternal supplementation would need to be in the range of 100-160 µg/day (4000-6400 IU/day) but these doses have only been trialled in pilot studies[103] and therefore supplementation of the breastfeeding infant is recommended.

The advice from the UK Department of Health (DH), based on the 2007 position statement by the Scientific Advisory Committee on Nutrition,[42] is to commence supplementation of breastfed infants from age 6 months. A letter in 2012 from the UK Chief Medical Officers to GPs, Health Visitors, Pharmacists and Practice Nurses stated "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".[104] It is clear that adequate intake will not be achieved by breastfeeding without supplementation in the absence of adequate sun exposure and the advice is therefore 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. The UK tolerable upper intake level for vitamin D for infants and children to age 10 is set at 25 mcg/day (1000 units/day). The European Food Safety Authority recently revised their limits to a tolerable upper intake of 25 mcg/day (1000 IU/day) in infants, 50 mcg/day (2000 IU/day) for children under 10 years and 100 mcg/day (4000 U/day) for children over 10 years.[100] In North America the limits set by IOM are the same for infants under six months, 37·5 µg/day (1500 IU/day) from six months to one year and 62·5 µg/day (2500 IU/day) from one to three years, 75 µg/day (3000 IU/day) from four to eight years and 100 µg/day (4000 IU/day), the tolerable upper limit, thereafter.[51]

Food fortification

In most countries infant formula milk is fortified to give a concentration of 10 µg/l (400 IU/l). In the US milk and breakfast cereals are fortified and in Canada milk and margarine.[105] Following deaths from Idiopathic Infantile Hypercalcaemia in the 1950s in UK the Department of Health banned food fortification with the exception of yellow spreads (margarines), cereals and infant formula milks. Fortification of chapatti flour to target low vitamin D status in the UK's Asian community was shown to be effective but was not universally introduced, although fortified flour is available.[106]

Summary/Take home messages

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. There is no global consensus on the amount of vitamin D offered in supplementation. The guidance in the UK from the Department of Health is fragmentary and confusing. Vitamin D 400IU/d is sufficient to maintain vitamin D status in the range where adverse skeletal consequences are very unlikely; suggesting 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. It is the view of the authors that supplementation until growth ceases with 10 mcg/day (400 IU/day) in all except those with a known contraindication (e.g. hypercalcaemia, sarcoidosis) should be recommended and that, without such a programme of supplementation and concurrent public health campaign, it is likely the incidence of rickets will continue to rise.

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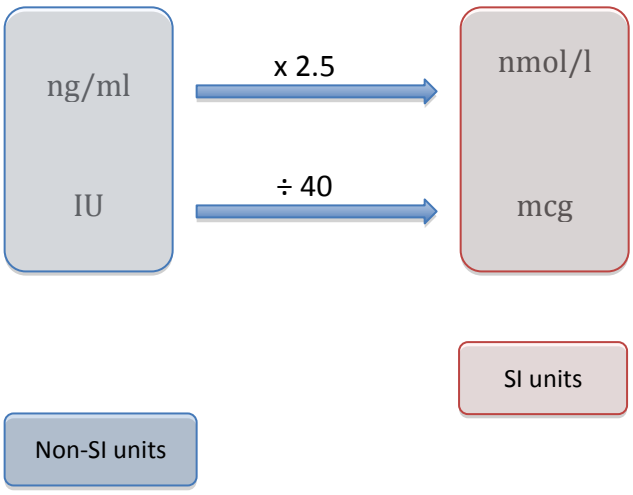
Inserts and Panels

Insert 1: *Search strategy*

The overriding aim was to provide an update summarising the advances and controversies that have arisen in the decade since the previous seminar in 2003 [107]. Particular attention has been paid to the defining vitamin D deficiency, the difficulties measuring vitamin D, rachitic fractures, the role of phosphate and public health policy with regard to supplementation. Literature searches were performed on Medline, Embase, CINAHL, AMED, Health Business Elite and HMIC with the keywords "rickets", "hypophosphatemic", "vitamin d", "vitamin d dependent rickets" and "vitamin D resistant rickets" with multiple sub-searches performed on smaller, related topics. The selection of quoted papers was based on our opinion of their scientific or historic importance. Research published since 2008 was given particular attention as they may be less well known to the reader. To reduce the number of references up-to-date review papers were used. Book chapters and abstracts were avoided where possible.

Insert 2: *SI unit conversion*



Panels

Panel 1: *Genetic origin, clinical history and examination in inherited forms of rickets*

Genetic origin	Clinical history	Features
Vitamin D pathway defects		
CYP2R1 – vitamin D 25-hydroxylase deficiency; autosomal recessive	Consanguinity; later onset, washed out bones	Bowing deformities
CYP27B1 – 25-hydroxy vitamin D 1α–hydroxylase deficiency; (PDDR) autosomal recessive	Consanguinity; early onset hypocalcaemia	Severe rickets, signs as for vitamin D deficiency
VDR – vitamin D receptor; (HVDRR) - autosomal recessive	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		
PHEX – X-linked dominant hypophosphataemic rickets (XLH)	Bowing deformity appearing around or just before walking; boys worse than girls	Usual rickets features plus craniosynostosis and tooth root abscesses
FGF23 – autosomal dominant hypophosphataemic rickets (ADHR)	Bone pain, fatigue, weakness, fractures and pseudofractures, tooth abscesses	Variable; rachitic features prominent in those presenting at a younger age
DMP1 - autosomal recessive hypophosphataemic rickets type 1 (ARHR1)	Lower limb bowing deformity, dental caries, back pain, joint stiffness in later life	Skull base osteosclerosis Sensorineural hearing loss
ENPP1 - autosomal recessive hypophosphataemic rickets type 2 (ARHR2)	May present as infantile arterial calcification – treat with bisphosphonate	Rachitic features appear at usual time if arterial calcification survived
Hypophosphataemic rickets without raised FGF23		
CLCN5 - X-linked recessive hypophosphataemic rickets	Nephrocalcinosis may result in renal failure in adulthood	Usual rickets features, small kidneys reported in one family
SLC34A3-Hypophosphataemic rickets with hypercalciuria (HHRH) - autosomal recessive	Early onset bowing deformity and rachitic features	Treatment with phosphate alone effective; giving vitamin D analogues can cause nephrolithiasis
Other inherited rachitic disorders		
TNSALP – hypophosphatasia – autosomal dominant (mild); autosomal recessive (severe)	Age at presentation reflects severity. Neonates and infants may die.	Perinatal/infant forms – severe rickets, respiratory failure, failure to thrive, craniosynostosis, motor delay. Childhood forms; motor impairment, mild rickets, bone pain.

Panel 2: *Other hypophosphataemic disorders with rickets*

Disorder	History	Features
Oncogenic osteomalacia	Weakness, bone pain, fractures	Very high FGF23 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 develop rachitic features	Phosphaturia, glycosuria, and aminoaciduria

Panel 3: *Clinical history and examination in vitamin D deficiency-induced rickets*

History	Skeletal features	Non-skeletal features
Darker skin colour Reduced skin exposure No vitamin D supplementation during pregnancy Prolonged exclusive breast feeding No vitamin D supplementation of infant Use of foods high in phytates Iron deficiency	Slowing linear growth Metaphyseal swelling at long bone ends Rickety rosary Bowing deformity of long bones Frontal bossing Craniotabes Persistent anterior fontanelle Harrison's sulci	Hypocalcaemic convulsions Hypocalcaemic cardiac failure Hypotonia Delayed motor milestones Carpopedal spasm Enamel hypoplasia Delayed dentition Failure to thrive Fractious, irritable child Bone pain

Panel 4. *Biochemical changes in rickets*

Type of rickets	***Serum Biochemistry***							***Urine biochemistry***		***Other features***
	Phosphate	**Calcium**	**PTH**	**25OHD**	**1,25OH_2D**	**FGF23**	**Alk Phos**	**Phosphate**	**Calcium**	
Hypocalcaemic vitamin D pathway defects										
Vitamin D deficiency	Low	Variable	High	Low	May be increased	N/A	increased	increased	low	Variable aminoaciduria
VDRR1B	Low	Low	High	Very low	Variable	N/A	increased	increased	low	25OHD does not increase after vitamin D dosing
VDRR1A	Low	Low	High	Normal/ high	Very low/ Not detected	N/A	increased	increased	low	25OHD does increase after vitamin D dosing
VDRR2A	Low	Low	High	Normal/ high	High	N/A	increased	increased	low	
VDRR2B	Low	Low	High	Normal/ high	High	N/A	increased	increased	low	
Hypophosphataemic rickets with raised FGF23										
PHEX	Low	Normal	Normal or slightly high	Normal	Low	High	increased	increased	Variable	Urine calcium:creatinine used in monitoring therapy
FGF23	Low	Normal	Normal	Normal	Low	High	increased	increased	Variable	
DMP1	Low	Normal	Normal	Normal	Low	High	increased	increased	Variable	
ENPP1	Low	Normal	Normal	Normal	Low	High	increased	increased	Variable	
Hypophosphataemic rickets without raised FGF23										
CLCN5	Low	Normal	Normal	Normal	Normal	Normal	increased	increased	High	Low molecular weight proteinuria
SLC34A3	Low	Normal	Normal	Normal	Normal	Normal	increased	increased	High	No loss of low molecular weight protein
αKlotho	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 levels of mineralisation inhibitors
HPP - mild	Normal or high	Normal or high	Low or normal	normal	normal	normal	Low	normal	Variable	

TABLES

Table 1: *Treatment and supplementation doses of vitamin D deficient rickets* as per BNFc 2013*

Age	Regime	Calciferol (ergo or chole)
1-6 months**	Treatment	75 mcg (3000 units) daily
6 months-12 years		150 mcg (6000 units) daily
12-18 years		250 mcg (10000 units) daily
12-18 years (for concerns over likely poor adherence)	Stosstherapy	7500 mcg (300,000 units) as supervised oral single dose or two divided doses over 12 hours
Neonate	Supplement	10 mcg (400 units) daily
Child 1 month-18 years		10-15 mcg (400-600 units) daily

* Following completion of 8-12 weeks treatment children should receive a supplementation dose *(table 2)* until completion of linear growth.

**Babies receiving 500 mls or more of formula milk per day do not require supplementation following treatment.

Table 2: *Summary of global supplementation advice*

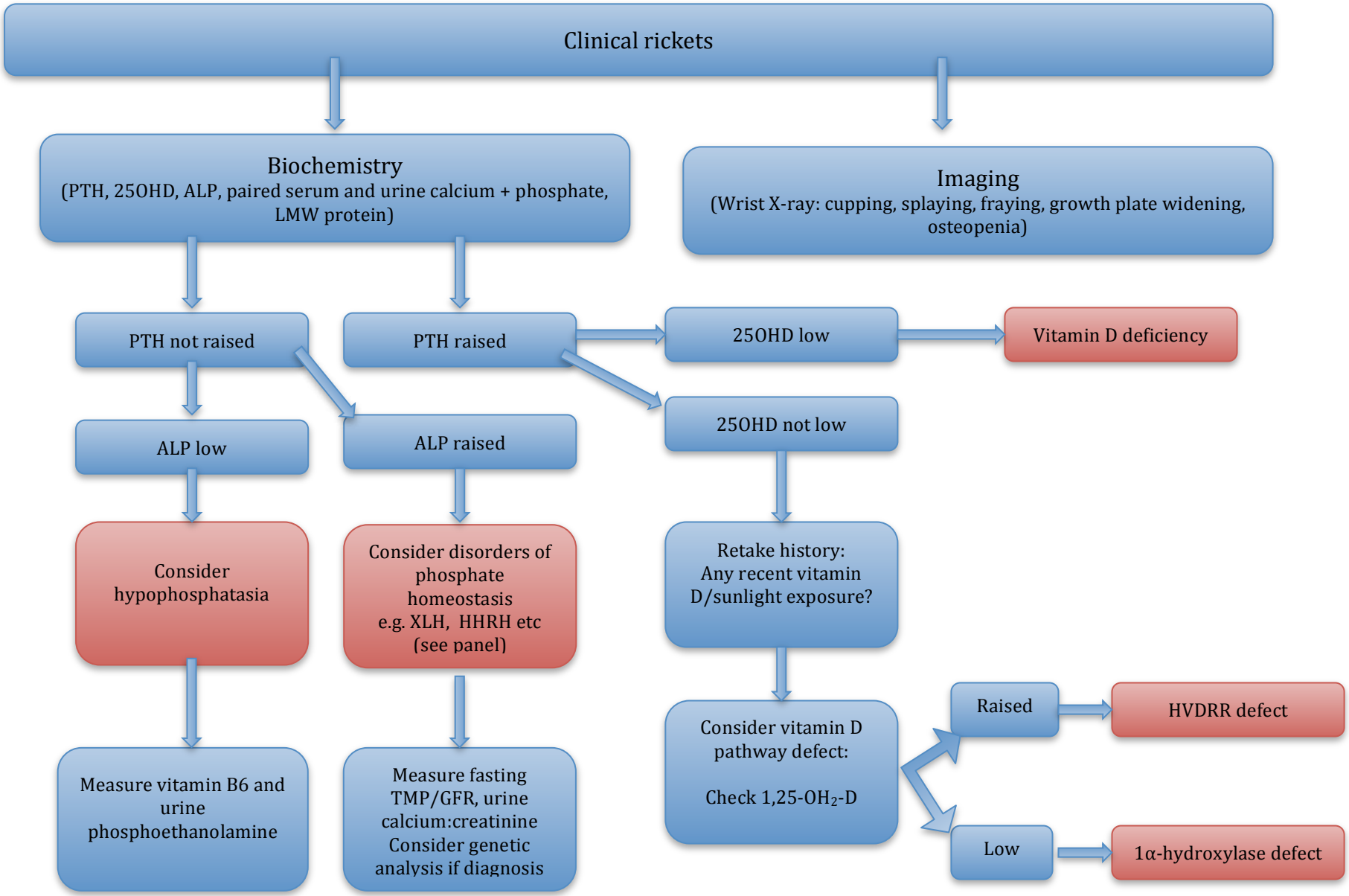
Supplemented group	Advising body	Advice
Pregnant and breastfeeding women	DoH 2012 [104]	All pregnant and breastfeeding women to take a daily supplement containing 10 µg/day of vitamin D
	NICE 2008	Supplementation in at risk groups

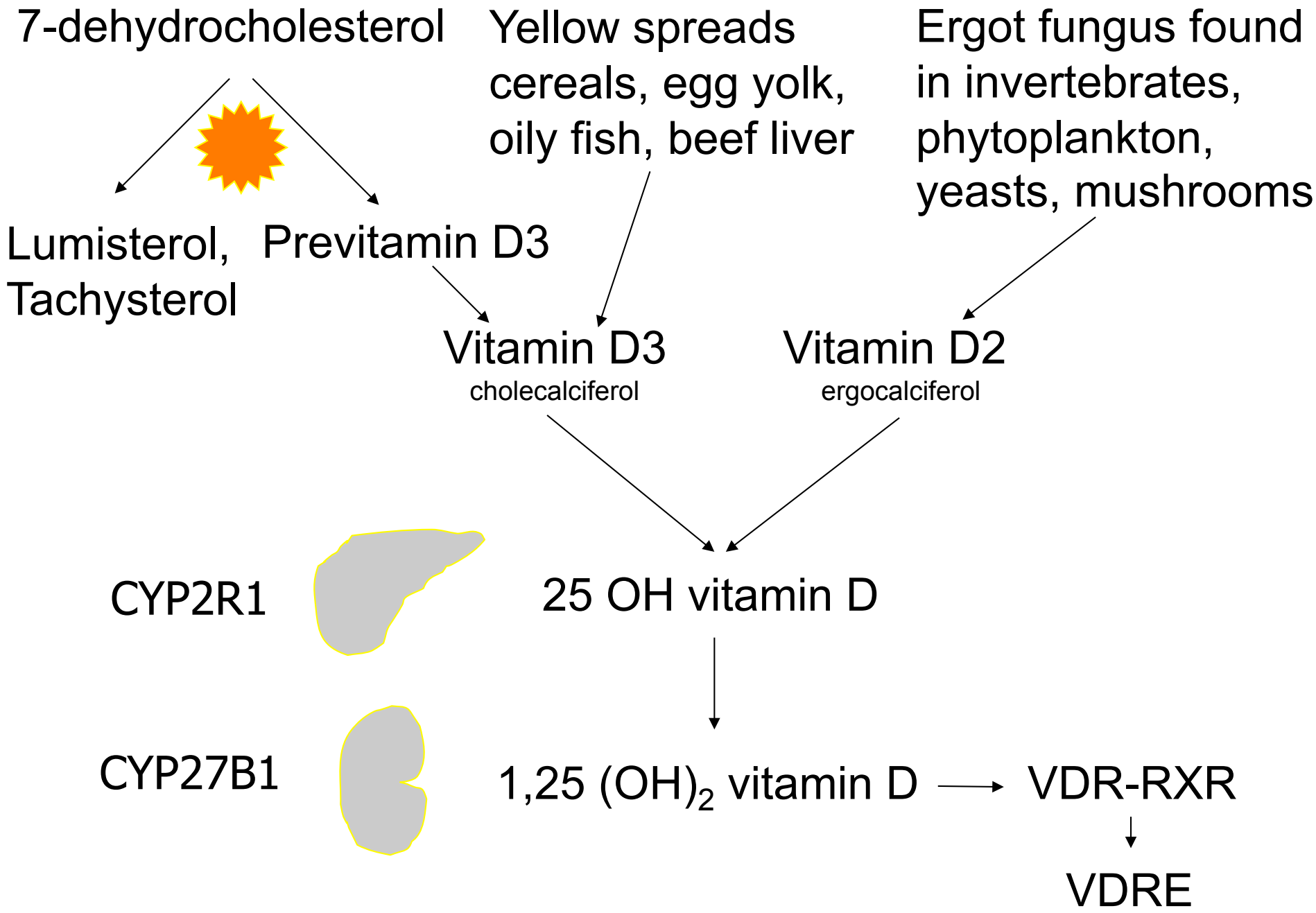
	(CG62)	
	APA 2008 [96]	Measure maternal vitamin D status and supplement if found to be “insufficient”
	WHO 2012* [108]	Call for rigorous RCTs to evaluate the benefit and safety of routine vitamin D supplementation in pregnancy
	Canadian Paediatric Society 2007 [109]	50 µg/day for pregnant and lactating women, especially during winter months
	Institute of Medicine 2010 [51]	Recommended dietary allowance - 15 mcg/day. Upper level intake 100 mcg/day
Breastfed infants	DoH 2012 [104]	If mother has not taken supplements throughout pregnancy baby may need to receive drops from one month of age
	Canadian Paediatric Society 2007 [109]	5 µg/day (200 IU/day) for premature infants, 10 µg/day (400 IU/day) until the first birthday but 20 µg/day (800 IU/day) during winter and for those living at more northern latitudes than the 55th parallel or between 40-55th parallel with additional risk factors.
	Institute of Medicine 2010 [51]	10 µg/day (400 IU/day) during first year of life
Children and adolescents	APA 2008 [96]	Universal supplementation of 10 µg/day (400 IU/day), more in at risk groups
	DoH 2012 [104]	7-8.5 mcg/day (280 IU/day) in all children aged

		6 months until the age of five years

- Advice based on conclusions from Cochrane meta-analysis [110]

Figure 2: *Rickets management algorithm*




7-dehydrocholesterol
Yellow spreads cereals, egg yolk, oily fish, beef liver
Ergot fungus found in invertebrates, phytoplankton, yeasts, mushrooms
Lumisterol, Tachysterol
Previtamin D3
Vitamin D3
cholecalciferol
Vitamin D2
ergocalciferol
CYP2R1
25 OH vitamin D
CYP27B1
1,25 (OH)2 vitamin D
VDR-RXR
VDRE