Review

Vitamin D in childhood and adolescence

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It is well-established that prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults. More marginal vitamin D deficiency is likely to be a significant contributing factor to osteoporosis risk. However, recent emerging data from studies of adults suggest that low vitamin D status (serum 25-hydroxyvitamin D levels <50 nmol/L) may be contributing to the development of various chronic diseases, including cardiovascular disease, hypertension, diabetes mellitus, some inflammatory and autoimmune diseases, and certain cancers. Adequacy of vitamin D status in children and adolescents has been the focus of a number of recent investigations, and these studies have shown a high prevalence of low vitamin D status during the winter (especially in adolescents), with lower prevalence during the summer. Therefore, consideration of potential corrective strategies to allow children and adolescents to maintain adequate vitamin D status throughout the year, even in the absence of adequate summer sun exposure, is warranted.

Vitamin D is essential for intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity. It is well-established that prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults. In addition, while the aetiology of osteoporosis is multifactorial, it is believed that secondary hyperparathyroidism as a result of a more marginal vitamin D deficiency is a significant contributing factor. There has also been a growing body of evidence for the contribution of poor vitamin D status (i.e., serum 25-hydroxyvitamin D (25(OH)D) levels below 50 nmol/L) to the development of various chronic diseases (for example, hypertension, cardiovascular diseases, diabetes mellitus, as well as some inflammatory and autoimmune diseases, and some forms of cancer) which are frequent in Western societies (for reviews, see Zitterman and Holick). This may be of major concern in light of the sizeable numbers of subjects in many countries with serum 25(OH)D levels below 50 nmol/L, especially during winter. However, much of this evidence is from studies in adults and whether poor vitamin D status in childhood is a risk factor for these chronic diseases is less well understood. Moreover, the biochemical definition commonly used to classify an adult as marginally vitamin D deficient, or vitamin D insufficient, may not be appropriate for use in children and adolescents. The present review will begin with a brief recap of the physiological roles of vitamin D, and then will briefly consider the issue of defining vitamin D status. Then it will review the data on prevalence of poor vitamin D status among children and adolescents, the likely underlying causes of poor vitamin D status, and comment on possible health implications, especially those beyond rickets. Some possible modes of addressing low vitamin D status in childhood and adolescence will be considered. The literature on vitamin D in childhood and adolescence in the present review was gathered from various sources, including, but not limited to, internet search engines and websites, electronic databases (in particular, Medline) and library resources.

Physiological effects of vitamin D

Upon exposure of skin to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol is converted to previtamin D3, which in turn is modified to vitamin D3 (cholecalciferol) at skin temperature. The vitamin D3 diffuses into the circulation and is transported protein-bound to the liver where it is hydroxylated to 25(OH)D3 (calcidiol). Dietary-derived vitamin D (as vitamin D3 and ergocalciferol (vitamin D2; from certain plants and fungi)) is also transported, via chylomicrons and the lymphatic system, to the liver for hydroxylation. Serum or plasma 25(OH)D3 is the most commonly used and appropriate biochemical marker of vitamin D status. In the kidney, 25(OH)D3 undergoes a further hydroxylation at the first carbon, catalysed by 25-hydroxylase, to form 1,25(OH)2D3 (calcitriol), which is the biologically most active form of vitamin D. Although 1,25(OH)2D3 represents the active form of the vitamin, due to a tight regulation of its production as well as a relatively short half-life (4-6 h), it is not a good indicator of vitamin D status.

The biological effects of 1,25(OH)2D3 can be grouped into two categories: the "classical actions", mainly affecting calcium homeostasis, and the "non-classical actions", which include functions unrelated to calcium metabolism, such as the regulation of cell differentiation and proliferation, cellular growth, the regulation of hormone secretion, among others.

Classical effects of vitamin D

The principal (classical) function of 1,25(OH)2D3 is to maintain serum calcium and phosphate concentration within the physiologically acceptable range. It is of utmost importance to maintain normal serum levels of calcium, as these are, in turn, critical for normal bone mineral density and fracture risk. Moreover, it is also important to maintain normal serum levels of phosphate, as these are critical for normal bone formation.

Abbreviations: 25(OH)D3, 25-hydroxyvitamin D3; BMD, bone mineral density; CT, calcitonic; PTH, parathyroid hormone; UVB, ultraviolet B.
turn, needed for the normal mineralisation of bone, muscle contraction, nerve conduction and many other cellular functions. This tight regulation of plasma calcium concentration is achieved through a complex physiological system comprising the interaction of the calcitropic hormones, such as 1,25(OH)₂D₃, parathyroid hormone (PTH) and calcitomin (CT), with specific target tissues (kidney, bone and intestine) which serve to increase or to decrease the entry of calcium into the extracellular space (fig 1). These well-established effects of 1,25(OH)₂D₃ on the three target tissues have been described elsewhere in detail. People with prolonged vitamin D deficiency tend to have chronic elevations in serum PTH, known as secondary hyperparathyroidism, which may have consequences for the bone health (see below). 1-3

NON-CLASSICAL (NON-SKELETAL) ACTIONS OF VITAMIN D
While the maintenance of calcium homeostasis and bone density are generally regarded as the main biological effects of 1,25(OH)₂D₃, studies have suggested other important roles of 1,25(OH)₂D₃ in various organs which may be independent of calcium concentration. In addition, the discovery that the vitamin D receptor is present in most tissues and cells of the body leads to the belief that 1,25(OH)₂D₃ has many biologic effects that are non-calcemic in nature. These include the regulation of cell differentiation and proliferation, cellular growth, and the regulation of hormone secretion, among others. It is also emerging that 1,25(OH)₂D₃ can be locally produced in several tissues that possess vitamin D receptors. Consequently, additional paracrine and autocrine roles have been proposed for 1,25(OH)₂D₃ apart from its calcium regulatory function.14

DEFINING VITAMIN D STATUS AND ITS ASSESSMENT
There is a general consensus that serum/plasma 25(OH)D should be used to assess vitamin D status as this reflects the amount ingested in the diet (including that from supplements and vitamin D-fortified food products) and that produced in the skin in response to sunlight (UVB) exposure. On the other hand, there is a lack of consensus on levels of 25(OH)D that define different stages of vitamin D status. In relation to low vitamin D status, one distinction that can be drawn is that of severe clinical vitamin D deficiency, leading to overt skeletal abnormalities, versus subclinical vitamin D deficiency in which serum 25(OH)D levels are low but there is no or less apparent skeletal or calcium abnormalities. It is clearly recognised that serum/plasma 25(OH)D₂ levels below 12.5 nmol/l can result in bone diseases, such as rickets in infants and osteomalacia in adults. There is also evidence that circulating 25(OH)D₃ levels below 20–25 nmol/l may result in rickets and osteomalacia in the longer term. In many cases, the low 25(OH)D₃ levels will be accompanied by elevated serum/plasma 1,25(OH)₂D₃, PTH and alkaline phosphatase levels, reduced serum phosphate and normal or reduced serum calcium levels.15

Definite cut-off levels for circulating 25(OH)D, which reflect subclinical vitamin D deficiency have not yet been fully defined. Low vitamin D status in adults which results in elevations in serum PTH has been described as mild to moderate vitamin D deficiency, with variable effects on bone. Moderate vitamin D deficiency, characterised by serum 25(OH)D levels >12.5 nmol/l but <25 nmol/l, is associated with 15–30% increases in serum PTH levels and high rates of bone turnover. Mild vitamin D deficiency (also referred to as vitamin D insufficiency) is characterised by serum 25(OH)D levels between 25–30 nmol/l, which may be associated with serum PTH elevations up to 15% and with normal to high bone turnover. Beyond deficiency, there is no international consensus on how to define optimal vitamin D status. Dawson-Hughes and colleagues have recently suggested that serum 25(OH)D concentration should exceed 70 nmol/l to achieve optimal status in adults. These authors considered a number of criteria by which to define optimal serum 25(OH)D, including maximal suppression of PTH, greatest calcium absorption, highest bone mineral density (BMD), reduced rates of bone loss, reduced rates of falling, and reduced fracture rates.16

Figure 1: Homeostatic regulation of serum calcium. CT, calcitomin; GIT, gastrointestinal tract; PTH, parathyroid hormone.
However, still others suggest that circulating 25(OH)D levels between 100–200 nmol/l can be regarded as adequate concentrations for optimum health, where body stores are replete, and therefore no disturbance in vitamin D-dependent body functions occurs.3,8

While a number of criteria can be considered, the serum 25(OH)D value at which a PTH plateau is considered by many to be the most appropriate criteria for defining adequate vitamin D status in adults is controversial.9 However, it is important to stress that while it is well recognised that in elderly subjects vitamin D deficiency elevates PTH which, in turn, increases bone turnover and bone loss, contributes to mineralisation defects and increases risk of hip and other fractures,10 its effects in children and adolescents are unclear. Elevated PTH concentrations may not be driven by the same mechanisms in adolescents as in adults, and may not necessarily be detrimental to bone health. For example, serum PTH concentrations are normally raised during adolescence.11,12 As the rate of bone remodelling and consolidation is at a peak. Therefore, the appropriateness of the various definitions used for the adult population, which are largely based on suppression of PTH, for children and adolescents might be questionable. Notwithstanding this issue, an inverse relationship between serum 25(OH)D, and PTH during adolescence has been shown in a number of studies.11,12 Collectively, these studies might suggest that high serum 25(OH)D, levels (at least >70 nmol/l) are required to suppress serum PTH levels in this age group, even though Outila et al failed to find a plateau in the relationship between serum 25(OH)D and PTH in Finnish adolescent girls.13

POSSIBLE HEALTH IMPLICATIONS OF LOW VITAMIN D STATUS DURING CHILDBOOTH/ADOLESCENCE

While prolonged and severe vitamin D deficiency leads to rickets in children, it is possible that a more marginal deficiency of vitamin D during early life may contribute to osteoporosis risk as well as potentially to the development of various other chronic diseases which are frequent in Western societies.

Vitamin D status and skeletal health in childhood/adolescence

Although an inadequate supply of vitamin D from sunlight, diet or both is the most common cause of rickets, nutritional deficiencies of calcium and/or phosphate, genetic or acquired disorders of the gut, liver, kidney and metabolism can also lead to rickets.14 Rickets is a disorder of mineralisation of the bone matrix (osteoid) in growing bone, involving both the growth plate (epiphyseal) and newly formed cortical and trabecular bone. It often develops in the early months of life with growth failure, lethargy and irritability often presenting as early symptoms.6 Clinical and laboratory manifestations include muscle weakness, tetany, bowing deformity of the long bones, indentation of lower ribs, deformities of the back, diffuse bone pain, decreased bone density and abnormal biochemistry (low serum calcium, phosphorus, vitamin D and high alkaline phosphatase, PTH). If untreated it may result in permanent dwarfing, gross bowing of the legs and a dislocated pelvis which could lead to obstructive complications for females in later life.6 Rickets, although most commonly seen in infancy, can also occur during the pubertal growth spurt and adolescence. In late, or adolescent, rickets, bowing of the legs, muscle weakness and lower limb pain and back pain are the most common symptoms.14

While the evidence base is much weaker at present, less severe vitamin D deficiency, which although not causing rickets, may prevent children and adolescents from reaching their genetically programmed height and peak bone mass.6 As adolescence is a critical developmental period for bone health, the effect of vitamin D status on PTH concentrations and BMD in adolescents could be of major importance. Recent results from studies in adolescents provide evidence of a possible adverse effect of vitamin D deficiency and insufficiency for bone health in children.15,16 For example, in a 3-year longitudinal study of Finnish girls, aged 9–15 years, Lehonen-Vernomas et al found that baseline 25(OH)D levels were positively correlated with unadjusted 3-year change in BMD at the lumbar spine and femoral neck.17 The difference from baseline-adjusted 3-year BMD accumulation between those with severe hypovitaminosis D (serum 25(OH)D <20 nmol/l) and those with a normal vitamin D status (serum 25(OH)D 20–35 nmol/l) was 4% at the lumbar spine in the girls with advanced sexual maturation.17 In another study from Finland, Outila et al showed that 13.5% and 62% of 14–16 year old girls had severe and marginal vitamin D deficiency, respectively.18 They also showed that subjects with serum 25(OH)D levels <40 nmol/l had low mean forearm BMD values at both the radial (p = 0.04) and ulnar (p = 0.08) sites.18 Of note, results from a recent 12-month vitamin D intervention study in adolescent Finnish girls shows that vitamin D supplementation led to bone mineral augmentation in the femur and lumbar spine.18

Vitamin D status and risk of cardiovascular disease, hypertension, diabetes, cancer and other chronic disease

While rickets and osteomalacia are the index diseases for severe vitamin D deficiency, there has been growing evidence that less severe deficiency, may also contribute to other chronic diseases, such as cardiovascular disease, hypertension, diabetes, cancer and other chronic disease. However, much of the evidence for this comes from epidemiologic studies of adults. These have been expertly reviewed by Holick and Zittermann.6 There is also some evidence that supplementation with vitamin D (usually high dose 20–2500 I.U/day) and in some cases in combination with calcium; low dose vitamin D supplementation did not appear to be effective) may beneficially influence muscle function, rheumatoid arthritis, blood pressure, blood glucose and insulin levels (reviewed by Zittermann).19 Unfortunately, again much of this evidence is from studies in adult or elderly populations. Far less is known of the effect of poor vitamin D status during childhood and adolescence on risk of these non-skeletal chronic diseases. However, in his recent review of childhood vitamin D deficiency, Holick highlights evidence that living at latitudes above 35° for the first 10 years of life increases risk of multiple sclerosis by 100%, as well as increasing the risk of several other autoimmune diseases.20 Children in Finland in the 1960s who received the recommended daily 2000 IU (50 μg) of vitamin D at least during the first year of life and followed for the next 31 years demonstrated a reduced risk of developing type 1 diabetes by 80%.21 Furthermore, children from the same cohort who were vitamin D deficient at 1 year of age had a 2.4-fold increased risk of type 1 diabetes.22

Prevalence of low vitamin D status in children and adolescence

Vitamin D deficiency, rickets, once thought vanquished, has in recent years made a resurgence in neonates and young children in some countries (see review by Holick).6 While the prevalence of this severe clinical vitamin D deficiency is relatively low, this is only the thin end of a much broader spectrum of low vitamin D status. As mentioned earlier, serum 25(OH)D levels <25 nmol/l and <50 nmol/l are regarded as subclinical vitamin D deficiency and insufficiency, respectively.23 Data from national surveys in the UK, USA and New Zealand show that the prevalence of low vitamin D status is less of a
Figure 3. The prevalence of vitamin D deficiency in children and adolescents in the UK. Row data from the National Diet and Nutrition Surveys of children (aged 1.5–4.5 years and 4–18 years) kindly provided by Dr Anne Prentice, MRC Human Nutrition Research, Cambridge, UK.

Is it on the basis that it is assumed that skin synthesis of vitamin D will generally ensure adequacy which depends on regular exposure to summer sunlight. If individuals have restricted sunlight exposure, then 10 μg/day is recommended.

However, vitamin D is rather sparsely represented in the diet, which might explain the low intakes in children and adolescents during winter, as mentioned earlier. oily fish such as salmon, mackerel and sardines contain high amounts of vitamin D. Cod liver oil is also an excellent source of vitamin D. Some meats may contain 25(OH)D. Fortified foods can also be a major contributor to dietary vitamin D. Vitamin D–fortified foods include some types of margarines, breakfast cereals, infant formulae, fruit juices, chocolates and milks, to name but a few. Use of vitamin D–containing supplements can also make a major contribution to mean daily intake of vitamin D in both adults and children. However, the proportion of the population that take vitamin D supplements can be low. For example, in Ireland only 15% of adults (aged 18–64 years) and 18% of children (aged 5–12 years) took a supplement containing vitamin D (E Walsh, University College Cork, personal communication, August 2006). Anderson et al recently showed that vitamin D supplement use was the only positive determinant of winter-time vitamin D status in a cohort of young adolescent girls from four different European countries.

CONCLUSION

While there is no doubt that severe vitamin D deficiency leads to rickets in childhood and adolescence, the impact of less severe vitamin D deficiency on health, especially non-skeletal health effects, is less clear. It has always been assumed that adolescents are at risk of low vitamin D status; however, a number of recent studies have shown this not to be the case, especially during winter. In contrast, younger children seem to have a lower prevalence of low vitamin D status. The reasons for the high prevalence of vitamin D insufficiency during adolescence are unclear. Dietary supply of vitamin D, including vitamin D–containing supplement use, is an important consideration in relation to improving vitamin D status during childhood and adolescence, especially during winter time. Without doubt, exposure to skin to summer sunshine is an extremely effective method of improving vitamin D status, but because of the fear of skin cancer there is still much debate among experts as to best practice. In the absence of sunshine exposure, dietary supply takes on a much more important role. Unfortunately, much research effort is still needed to identify what the optimal dietary recommendation for vitamin D should be. Such research should receive a high priority.

MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F))

1. The best biochemical indicator of vitamin D status is:
   (A) serum calcium
   (B) serum 25-hydroxyvitamin D3
   (C) serum 1,25-dihydroxyvitamin D3
   (D) serum alkaline phosphatase

2. What is the minimum sun protection factor (SPF) in suncreams which would essentially eliminate (ie, 98% reduction) dermal biosynthesis of vitamin D?
   (A) 8
   (B) 15
   (C) 30
   (D) 45

3. The cut-off level of circulating 25-hydroxyvitamin D which definitely places children at risk of rickets is:
   (A) <12.5 nmol/l
   (B) <25 nmol/l
   (C) <50 nmol/l
   (D) <80 nmol/l

4. What cut-off level of circulating 25-hydroxyvitamin D3 has been associated with increased risk of autoimmune diseases, cancers and cardiovascular disease?
   (A) <12.5 nmol/l
   (B) <25 nmol/l
   (C) <50 nmol/l
   (D) <80 nmol/l
5. The recommended dietary intake of vitamin D for children in the USA is
   (A) 2 µg/day
   (B) 5 µg/day
   (C) 10 µg/day
   (D) 15 µg/day

ACKNOWLEDGEMENTS
This research has been funded by the North-South Programme for Collaborative Research. Higher Education Authority, Dublin. The author would also like to thank Dr. Anne Premiet, Elsie Waldron-Lamerson, MRC Human Nutrition Research, Cambridge, UK for supplying the TNO’s raw data on prevalence of serum 25(OH)D levels below the two recommended values.

The author has no competing interests.

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