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.[1] It is well-established that prolonged and severe vitamin D deficiency leads to rickets in children and osteomalacia in adults.[2] 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.[3 4] There has also been a growing body of evidence for the contribution of poor vitamin D status (ie, serum hydroxyvitamin D_3 ($25(OH)D_3$) 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[5] and Holick[6]). This may be of major concern in light of the sizeable numbers of subjects in many countries with serum $25(OH)D_3$ 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/or 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 for poor vitamin D status, and comment on possible health implications, especially those beyond rickets. Finally, 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.

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PHYSIOLOGICAL EFFECTS OF VITAMIN D

Upon exposure of skin to solar ultraviolet B (UVB) radiation, 7-dehydrocholesterol is converted to previtamin D_3, which in turn is modified to vitamin D_3 (cholecalciferol) at skin temperature. The vitamin D_3 diffuses into the circulation and is transported protein-bound to the liver where it is hydroxylated to $25(OH)D_3$ (calcidiol).[2] Dietary-derived vitamin D (as vitamin D_3 and ergocalciferol (vitamin D_2; from certain plants and fungi)) is also transported, via chylomicrons and the lymphatic system, to the liver for hydroxylation.[2] Serum or plasma $25(OH)D_3$ is the most commonly used and appropriate biochemical marker of vitamin D status.[2 7] In the kidney, 25(OH)D undergoes a further hydroxylation at the first carbon, catalysed by 1,α-hydroxylase, to form $1,25(OH)_2D_3$ (calcitriol), which is the biologically most active form of vitamin D.[7] Although $1,25(OH)_2D_3$ 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.[2 8]

The biological effects of $1,25(OH)_2D_3$ 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.[6]

CLASSICAL EFFECTS OF VITAMIN D

The principal (classical) function of $1,25(OH)_2D_3$ 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

Abbreviations: $25(OH)D_3$, hydroxyvitamin D_3 (calcidiol); BMD, bone mineral density; CT, calcitonin; PTH, parathyroid hormone; UVB, ultraviolet B

turn, needed for the normal mineralisation of bone, muscle contraction, nerve conduction and many other cellular functions.[2] This tight regulation of plasma calcium concentration is achieved through a complex physiological system comprising the interaction of the calcitropic hormones, such as $1,25(OH)_2D_3$, parathyroid hormone (PTH) and calcitonin (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).[9] These well-established effects of $1,25(OH)_2D_3$ on the three target tissues have been described elsewhere in detail.[2 6] 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 10]

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 $1,25(OH)_2D_3$, studies have suggested other important roles of $1,25(OH)_2D_3$ in various organs which may be independent of calcium concentration.[2] In addition, the discovery that the vitamin D receptor is present in most tissues and cells of the body leads to the belief that $1,25(OH)_2D_3$ has many biologic effects that are non-calcaemic in nature.[11 12] These include the regulation of cell differentiation and proliferation, cellular growth, and the regulation of hormone secretion, among others.[6] It is also emerging that $1,25(OH)_2D_3$ can be locally produced in several tissues that possess vitamin D receptors.[2] Consequently, additional paracrine and autocrine roles have been proposed for $1,25(OH)_2D_3$ apart from its calcium regulatory function.[13]

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 could be drawn is that of severe clinical vitamin D deficiency, leading to overt skeletal abnormalities, versus subclinical vitamin D deficiency in which serum $25(OH)D_3$ levels are low but there is no or less apparent skeletal or calcium abnormalities.

It is clearly recognised that serum/plasma $25(OH)D_3$ levels below 12.5 nmol/l can result in bone diseases, such as rickets in infants and osteomalacia in adults.[14 15] There is also evidence that circulating $25(OH)D_3$ levels below 20–25 nmol/l may result in rickets and osteomalacia in the longer term.[16 17] In many cases, the low $25(OH)D_3$ levels will be accompanied by elevated serum/plasma $1,25(OH)_2D_3$, PTH and alkaline phosphatase levels, reduced serum phosphate and normal or reduced serum calcium levels.[18]

Definite cut-off levels for circulating $25(OH)D_3$ 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,[19] with variable effects on bone.[18 19] Moderate vitamin D deficiency, characterised by serum $25(OH)D_3$ 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.[19 20] Mild vitamin D deficiency (also refereed to as vitamin D insufficiency[5 18]) is characterised by serum $25(OH)D_3$ levels between 25–50 nmol/l, which may be associated with serum PTH elevations up to 15% and with normal to high bone turnover.[18 19]

Beyond deficiency, there is no international consensus on how to define optimal vitamin D status. Dawson-Hughes and colleagues have recently suggested that serum $25(OH)D_3$ concentration should exceed 70 nmol/l to achieve optimal status in adults.[21] These authors considered a number of criteria by which to define optimal serum $25(OH)D_3$, 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.[21]

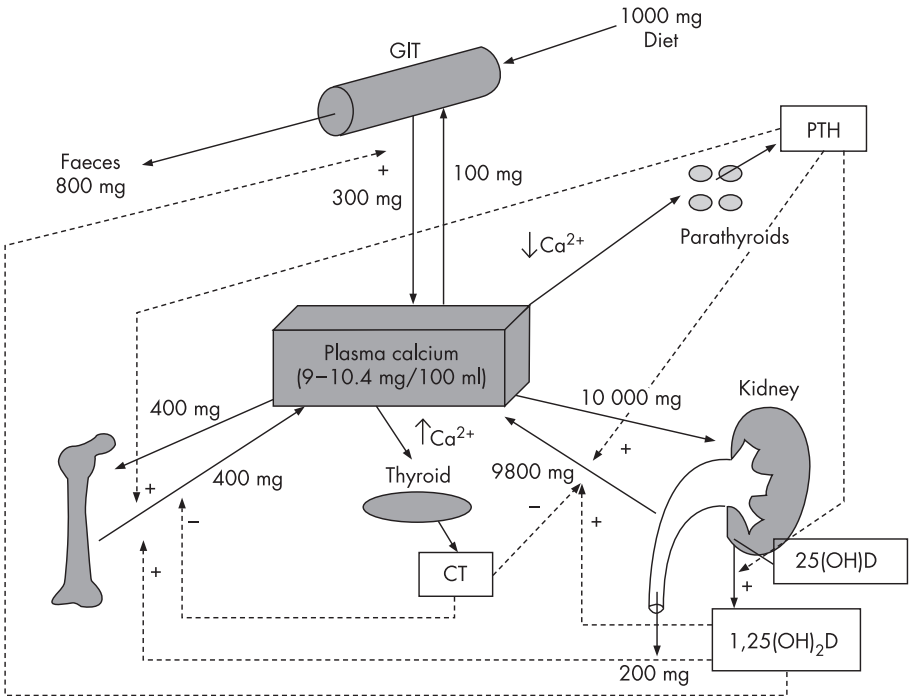

Figure 1 Homeostatic regulation of serum calcium. CT, calcitonin; GIT, gastrointestinal tract; PTH, parathyroid hormone.

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 disturbances in vitamin D-dependent body functions occur.[5 22]

While a number of criteria can be considered, the serum 25(OH)D value at which PTH plateaus is considered by many as the most appropriate criteria for defining adequate vitamin D status in adults.[4 20 23] 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,[4] its effects in children and adolescents are unclear. Elevated PTH concentrations may not be driven by the same mechanism in adolescents as in adults, and may not necessarily be detrimental to bone health. For example, serum PTH concentrations are normally raised during adolescence,[24 25] 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_3 and PTH during adolescence has been shown in a number of studies.[26–31] Collectively, these studies might suggest that high serum 25(OH)D_3 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.[29]

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

While prolonged and severe vitamin D deficiency leads to rickets in children,[2] 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.[32] Rickets is a disorder of mineralisation of the bone matrix (osteoid) in growing bone, involving both the growth plate (epiphysis) 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.[14] 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 distorted pelvis which could lead to obstetric complications for females in later life.[33] 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 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,[9] 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.[29 30 34] For example, in a 3-year longitudinal study of Finnish girls, aged 9–15 years, Lehtonen-Veromaa *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.[34] 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 ⩾35 nmol/l) was 4% at the lumbar spine in the girls with advanced sexual maturation.[34] 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.[29] 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.[29] Of note, results from a recent 12-month vitamin D intervention study in adolescent Finnish girls shows that vitamin D supplementation lead to bone mineral augmentation in the femur and lumbar spine.[35]

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 base for this comes from epidemiologic studies of adults. These have been expertly reviewed by Holick[6] and Zittermann.[5] There is also some evidence that supplementation with vitamin D (usually high dose (20–2500 μg/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[5]). 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.[18] 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 I diabetes by 80%.[36] 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 I diabetes.[36]

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[18]). 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_3 levels <25 nmol/l and <50 nmol/l are regarded as subclinical vitamin D deficiency and insufficiency, respectively.

Data from national surveys in the UK, USA and New Zealand show that the prevalence of low vitamin D status is less of a

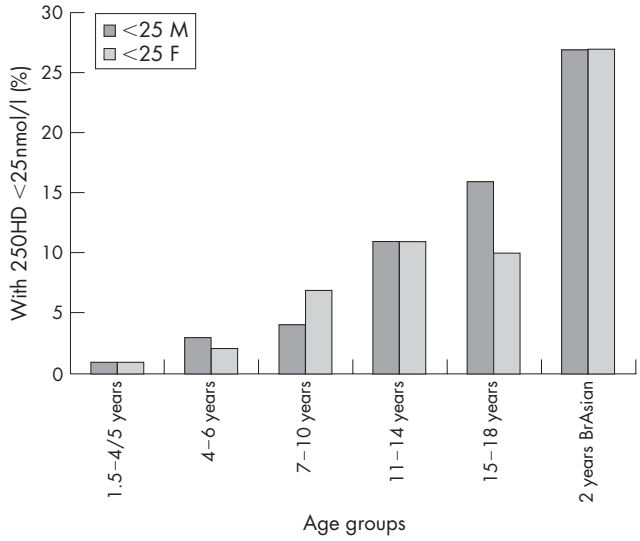

Figure 2 The prevalence of subclinical vitamin D deficiency in children and adolescents in the UK. Raw data from the National Diet and Nutrition Surveys of children (aged 1.5–4.5 years and 4–18 years) kindly provided by Dr Anne Prentice, MRC Human Nutrition Research, Cambridge, UK. <25 F, % females with serum 25(OH)D <25 nmol/l; <25 M, % males with serum 25(OH)D <25 nmol/l; BrAsian; British Asian.

concern for children than for adolescents.[2 37–39] The prevalence of low vitamin D status appears to increase with age in early life, with adolescents being the life-stage group in the UK young population with the highest prevalence of low vitamin D status (ie, deficiency and insufficiency) (figs 2 and 3). In particular, young children of Asian decent in the UK appeared to be at particular risk of low status compared to similarly aged children of Caucasian origin. This relates to the fact that an increase in skin melanin pigmentation can notably diminish production of vitamin D_3.[6 8] Generally, the prevalence of vitamin D deficiency (serum 25(OH)D_3 <25 nmol/l) in 1.5- to 10-year-old children in the UK is less than 7%, when subjects are sampled throughout the year (fig 2). On the other hand, 11–16% of adolescents in the UK (aged 11–18 years) have serum 25(OH)D <25 nmol/l throughout the year (fig 2). The prevalence of vitamin D deficiency could be almost twofold higher if sampling is limited to winter time only.[37] Of potential concern, the prevalence of vitamin D insufficiency (serum 25(OH)D_3 <50 nmol/l) in UK adolescents is in excess of 40% (fig 3).

The prevalence of low vitamin D status in adolescents in other parts of Europe,[29 30 40–43] the USA,[38 44 45] and elsewhere (New Zealand,[39] the Lebanon[28]) is also relatively high. While these different studies used different cut-off values of serum 25(OH)D_3 to define vitamin D deficiency/insufficiency (ranging from <30 to <50 nmol/l), estimates of its prevalence among the adolescents, especially during winter, were, in general, relatively high (46–92%). Our recent work in >1000 adolescents from Northern Ireland shows that even during summer and autumn, when serum 25(OH)D_3 levels should be at their highest, about 9–15% of 11- and 15-year-old boys and girls had serum 25(OH)D_3 levels <50 nmol/l.[43]

Underlying reasons for low vitamin D status in children and adolescents

The major causes of vitamin D deficiency rickets have been discussed in detail elsewhere,[18 33] and will not be dealt with in this review. The reasons for the high prevalence of subclinical vitamin D deficiency and insufficiency in early life, particularly in adolescents, are less clear. Dietary vitamin D (including vitamin D-containing supplement use) and summer sunshine exposure are important contributors to vitamin D status. Several European countries are located at relatively high latitudes (above 37°N) and, consequently, during the dark winter months, when sunlight is of insufficient intensity to stimulate dermal vitamin D synthesis, status would be expected to be low. It is also likely that the children and adolescents with vitamin D insufficiency during summer time have either low exposure to sunlight and/or use a sun cream with a sun protection factor ⩾15 (which essentially reduces dermal synthesis of vitamin D by more than 98%[6]).

Dietary intakes of vitamin D are less than the recommended level in many children, especially in many adolescents.[37 46–51] Low intakes of vitamin D in combination with low sun exposure during summer would certainly contribute to low vitamin D status in some children and adolescents. In addition, low intakes in winter would also largely determine those at risk of vitamin D deficiency.[52] Data from the National Diet and Nutrition Survey show that the mean daily intake of vitamin D for adolescents (aged 11–18 years) in the UK is 2.6 μg.[37] There is also some suggestion that intakes of vitamin D may be worse in females than males. For example, Moore *et al* reported that adolescent males in the USA were the group most likely to consume the adequate intake value for vitamin D, while adolescent females were about half as likely as males of corresponding age to meet their dietary reference intakes.[50] In addition, Moore *et al* estimates that only 50% and 32% of girls aged 9–13 years and 14–18 years, respectively, are meeting the dietary reference intake for vitamin D.[50] Suboptimal intakes of vitamin D in adolescent girls have also been confirmed in several other studies.[41 47 51]

A number of studies have reported a negative association between pubertal status and serum 25(OH)D,[27 28 47] which may contribute to higher prevalence of low vitamin D status in adolescents compared to younger children.

Addressing poor vitamin D status in early life

Rickets can be treated effectively with vitamin D supplementation.[18] In relation to addressing subclinical vitamin D deficiency and insufficiency, sun exposure and dietary vitamin D intake (including vitamin D fortified foods and supplemental vitamin D use) undoubtedly have important roles. However, the relative importance of these two routes of exposure differs from summer to winter for most people.

If sun exposure is sufficient, very little if any vitamin D is required from the diet during summer.[16] It is worth remembering, however, that the production of vitamin D in the skin during summer varies with the geographical location, atmospheric conditions, time spent outdoors, clothing, and skin pigmentation[53] as well as sunscreen use,[6] as mentioned earlier. According to Holick,[54] approximately 30 min of skin exposure (without sunscreen) of the arms and face to sunlight can provide all the daily vitamin D needs of the body. When sunlight exposure is limited, dietary intakes of vitamin D, if sufficient, can make a significant contribution to vitamin D status. In particular, at latitudes above 37°N, production of vitamin D_3 in winter is virtually zero, because the zenith angle of the sunlight increases in the autumn and winter and consequently, the amount of solar ultraviolet radiation that reaches the Earth's surface is substantially reduced.[6] Therefore, there is an increased reliance on dietary vitamin D for maintaining adequate vitamin D status during winter, and even in summer for those who avidly avoid sunshine exposure. While the US authorities recommend 5 μg vitamin D/day for children and adolescents (aged 1–18 years),[2] respectively, in the UK children aged 1–3 years are recommended 7 μg vitamin D/day while there is no dietary recommendation for vitamin D for subjects aged 4–64 years.[16] This lack of dietary recommendation

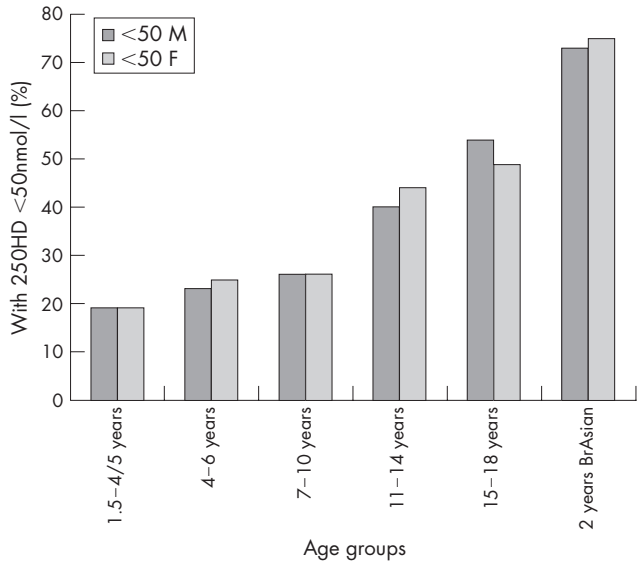

Figure 3 The prevalence of vitamin D insufficiency in children and adolescents in the UK. Raw data from the National Diet and Nutrition Surveys of children (aged 1.5–4.5 years and 4–18 years) kindly provided by Dr Anne Prentice, MRC Human Nutrition Research, Cambridge, UK. <50 F, % females with serum 25(OH)D <50 nmol/l; <50 M, % males with serum 25(OH)D <50 nmol/l; BrAsian; British Asian.

is 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.[16] 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_3. Fortified foods can also be a major contributor to dietary vitamin D.[2] 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[55]) and 18% of children (aged 5–12 years) took a supplement containing vitamin D (E Walsh, University College Cork, personal communication, August 2006). Andersen *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.[41]

CONCLUSION

While there is no doubt that severe vitamin D deficiency leads to rickets in childhood and adolescence, the impact of less severe vitamin deficiency on health, especially non-skeletal health effects, is less clear. It has always been assumed that adolescents are not 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 of 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.[6 56] 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.

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MULTIPLE CHOICE QUESTIONS (TRUE (T)/FALSE (F); ANSWERS AFTER THE REFERENCES)

1. The best biochemical indicator of vitamin D status is:

(A) serum calcium
(B) serum 25-hydroxyvitamin D_3
(C) serum 1,25-dihydroxyvitamin D_3
(D) serum alkaline phosphatase

2. What is the minimum sun protection factor (SPF) in sun creams 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 D_3 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

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ANSWERS

1. (A) F, (B) T, (C) F, (D) F
2. (A) F, (B) T, (C) F, (D) F
3. (A) T, (B) F, (C) F, (D) F
4. (A) F, (B) F, (C) T, (D) F
5. (A) F, (B) T, (C) F, (D) F