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Low levels of 25-hydroxyvitamin D in the pediatric populations: prevalence and clinical outcomes

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Abstract

Vitamin D deficiency is becoming increasingly common in the USA. In this review we provide estimates of the prevalence of deficiency, and review the risk factors and the evidence of clinical consequences of vitamin D deficiency. Vitamin D deficiency causes the pediatric disease rickets. In addition, there is some evidence that vitamin D deficiency may lead to other diseases including diabetes mellitus, hypertension, infections, asthma and dyslipidemia.

Keywords

asthma; bone mass; diabetes mellitus; hypertension; rickets; vitamin D

Vitamin D metabolism & sources of vitamin D

There are two naturally occurring forms of vitamin D – vitamin D₃ (cholecalciferol) and vitamin D₂ (ergocalciferol) – which have slightly different chemical structures. Cholecalciferol is made by the conversion of 7-dehydrocholesterol in the epidermis and dermis in humans upon exposure to UVB radiation [1]. Ergocalciferol is made in mushrooms and yeast and the synthetic form is often used to fortify foods and in dietary supplements. Few foods, mostly fatty fish, are naturally rich in vitamin D. Milk and other dairy products in the USA are fortified with vitamin D. After ingestion, vitamin D undergoes two separate hydroxylations. One in the liver to 25-hydroxyvitamin D (25[OH]D), the precursor hormone which is tested to evaluate for vitamin D status owing to its half-life of approximately 3 weeks [2,3]. The second hydroxylation is catalyzed by the 1- α hydroxylase enzyme, to the biologically active 1,25 dihydroxyvitamin D (1,25[OH]₂D) mainly in the kidney but also in other target tissues [4]. Other target tissues include the skin and vasculature and it is thought that 1- α hydroxylation at these sites facilitates autocrine and paracrine signaling and is responsible for the non-calcemic actions of vitamin D, which are detailed later in this review [5]. 1,25[OH]₂D interacts

with the vitamin D receptor (VDR) to affect physiological changes. The VDR has been found in tissues that are not directly involved in calcium metabolism, suggesting that vitamin D may play other important roles in the body [6-9]. Vitamin D becomes inactivated by the 25(OH) D-24-hydroxylase, which creates the biologically inactive 24,25-dihydroxyvitamin D.

Prevalence of vitamin D deficiency

Certain patient groups are more at risk for vitamin D deficiency, including obese and non-White children and adolescents. An analysis of 217 obese adolescents in Brooklyn, NY, USA, revealed that 55% of the patients were vitamin D deficient (defined as 25(OH)D levels <20 ng/ml) while 22% had levels below 10 ng/ml [10]. Another study showed that 52% of 307 Hispanic and African-American adolescents in Boston, MA, USA, had 25(OH)D levels below 15 ng/ml [11]. A study in 40 healthy, mostly Black, mother-infant pairs found that 50% of the mothers and 65% of the infants had 25(OH)D levels below 12 ng/ml [12]. A study of vitamin D levels in presumably healthy toddlers and infants attending a pediatrics clinic found that 12.1% (44 out of 365) of the children had levels below 20 ng/ml [13].

Recently, a couple of studies have used nationally representative data to evaluate the 25(OH) D status of the US pediatric population [14,15]. Both these studies revealed a high prevalence of 25(OH)D deficiency, defined as below 15 ng/ml, and insufficiency, defined as less than 30 ng/ml. In our study using a sample of 9757 children and adolescents in the National Health and Nutrition Examination Survey (NHANES) 2001–2004, we found that 9% of the US pediatric population had levels below 15 ng/ml while an additional 61% had levels between 15 and 29 ng/ml [15]. As in previous studies, certain groups were at higher risk for deficiency. We found that the prevalence of deficiency was highest amongst non-Hispanic Black adolescent girls where the prevalence was almost 60%. The lowest prevalence was amongst non-Hispanic White boys aged 1–6 years in whom prevalence was approximately 1%. Looker *et al.* showed that the prevalence of vitamin D deficiency in the USA has increased between 1988 and 1994 (the years of the NHANES III survey), and 2001 and 2004 (NHANES 2001–2004) [14].

Data from other countries suggest that low vitamin D levels are a worldwide problem. A study from Andhra Pradesh in India revealed that 62–82% of children had 25(OH)D levels below 20 ng/ml [16]. A study of infants of Pakistani, Turkish and Somali immigrants to Norway revealed that 47% of infants had 25(OH)D levels below 10 ng/ml [17]. In 93 children from northern Jordan (mean age 5 years), 39% of the children had 25(OH)D levels below 20 ng/ml [18]. Reports from other countries confirm low levels of 25(OH)D amongst children [19,20].

Risk factors for vitamin D deficiency

There is little consensus regarding what constitutes vitamin D deficiency in children and adolescents [21]. Different authors have used different definitions of deficiency, including less than 10 ng/ml [22-24], less than 15 ng/ml [11,25-27] and less than 20 ng/ml [10,13,28]. Most experts agree that whatever level one defines as deficiency, any 25(OH)D levels between the deficiency cut-off and 30 ng/ml constitutes vitamin D ‘insufficiency’. Levels above 30 ng/ml are considered, at least in adults, to be associated with the best outcomes [29].

Box 1. Common risk factors for vitamin D (25[OH]D) deficiency

Non-modifiable risk factors

- Age
- Female sex [15]

- Non-white race
- Non-white race
- Antiepileptic therapy [102]
- Malabsorption (inflammatory bowel disease and cystic fibrosis)
- Burns

Modifiable risk factors

- Obesity
- Less milk drinking
- Not taking vitamin D supplements
- Less outdoor physical activity
- Exclusive breast-feeding
- Sunscreen use
- Clothing

Non-patient factors

- Higher latitude
- Season of year
- Lower altitude
- More cloud cover

Common risk factors for 25(OH)D deficiency include those outlined above, non-White ethnicity and obesity, as well as other risk factors outlined in Box 1. Risk factors can be divided into non-modifiable risk factors such as age and skin color, modifiable risk factors such as sunscreen use and low vitamin D intake, and non-patient factors such as living at high latitude and low altitude (further away from the sun). In our analysis of NHANES 2001–2004, we found that older age, female sex, non-White ethnicity, obesity, less frequent milk drinking, and watching over 4 h of television, video or computer per day were associated with 25(OH)D levels below 15 ng/ml [15]. Vitamin D supplement use was associated with a lower risk for deficiency [15]. A study from Japan revealed that limited exposure to sunlight and a limited diet were the primary causes amongst 31 confirmed cases of rickets [30]. Children with inflammatory bowel disease have also been shown to have a high prevalence of 25(OH)D deficiency with almost 35% of 130 patients having 25(OH)D levels below 15 ng/ml [31]. Children with cystic fibrosis also have a high prevalence of inadequate vitamin D levels, in one recent study, 95% had levels below 30 ng/ml [32]. Another study recently demonstrated that the prevalence of vitamin D deficiency has increased over the past 10 years in patients with chronic kidney disease [33]. In summary, certain patient groups are at higher risk of vitamin D deficiency.

Vitamin D & rickets

There has recently been an increase in the number of case reports of rickets in the USA and other countries [30,34–43]. Inadequate intakes of either calcium or vitamin D or both can result in rickets. A recent analysis of 102 children with nutritional rickets in Denmark revealed two peaks in incidence, one at 0–4 years of age with a second peak during adolescence [43]. Symptoms included pain in the legs in 62% of adolescents, refusal to support weight on legs

in 33% of toddlers, skeletal pain in 29% of adolescents, epiphyseal swelling in 63% of toddlers, bowed legs in 52% of toddlers, rachitic rosary in 45% of toddlers and growth retardation in 39% of toddlers [43]. Of the toddlers, 23% experienced generalized seizures that brought them to medical attention. Those with seizures had much lower calcium levels compared with those without seizures [43].

Robinson *et al.* retrospectively analyzed 126 cases of rickets from 1993–2003 in Sydney, Australia. The median age of presentation was 15.1 months, with 25% presenting at less than 6 months of age. The most common presenting features were hypocalcemic seizures (33%) and bowed legs (22%). Males comprised 64% of the cases, and presented at a younger age, with a lower weight standard deviation score, and more often with seizures. Most of the cases were from recently immigrated children or first-generation offspring of immigrant parents, with the region of origin the Indian subcontinent (37%), Africa (33%), the Middle East (11%) and Australia (79%). A total of 11 cases (all aged <7 months) presented atypically with hyperphosphatemia [44].

It is important to remember that nutritional rickets has effects outside of the bone and muscle. Recent case reports of cardiomyopathies associated with low 25(OH)D levels and rickets highlight the need to add vitamin D deficiency to the differential diagnosis of cardiac dysfunction [45,46]. In addition, as mentioned previously, although classically rickets mostly affects children aged 6–24 months and up to 5 years old, case reports of rickets with hypocalcemic seizures in adolescents are emerging [47].

Vitamin D & bone mineral density

Low vitamin D levels have been associated with low bone mass, and therapy with vitamin D leads to higher growth velocity. In a study of 85 pediatric patients with primary or secondary osteoporosis, 21% had 25(OH)D levels below 20 ng/ml. In that study there was also a strong correlation between parathyroid hormone levels and 25(OH)D levels suggesting a physiologic impact to the low 25(OH)D levels [22]. Lack of sun exposure because of veiling in mothers is also associated with low bone mass in their children at adolescence [48]. A recent study showed that treatment of nutritional vitamin D deficiency with a 300,000 IU vitamin D3 injection in 40 children revealed a higher growth velocity standard deviation score after therapy compared with normal controls [49]. The children who were treated also showed a lowering of alkaline phosphatase and parathyroid hormone levels and increases in insulin growth factor-I levels. A study in 78 children and adolescents (10–18 years) on long-term therapy with anticonvulsants found similar increases in bone mineral density after a year of 400 IU/day or 2000 IU/day of vitamin D [50].

Vitamin D & high blood pressure

The antihypertensive actions of vitamin D are thought to be the result of suppression of the renin–angiotensin–aldosterone system [51–53], direct effects on vascular cells [54,55], effects on calcium metabolism [56] and the prevention of secondary hyperparathyroidism [57–59]. The VDR-knockout mouse develops hypertension [51].

There have been few studies in children that have evaluated the association between 25(OH)D levels and blood pressure. Smotkin-Tangorra *et al.* evaluated 25(OH)D levels in 217 obese children and found higher systolic blood pressure in those with levels below 20 ng/ml [10]. This study had only obese children and it is possible that obesity could be a potential confounding factor in determining the effects of low 25(OH)D levels on hypertension. Reis *et al.* performed a cross-sectional analysis of 3577 adolescents who participated in the 2001–2004 NHANES [60]. They found an adjusted odds ratio of 2.36 (1.33–4.19) for those in the lowest (<15 ng/ml) compared with the highest quartile (>26 ng/ml) of 25(OH)D for hypertension. Our

analysis of data from children and adolescents aged 1–21 years using the NHANES 2001–2004 database found significantly higher prevalence of hypertension and higher systolic and diastolic blood pressures in the vitamin D-deficient (<15 ng/ml) group. 25(OH)D deficiency was associated with higher systolic blood pressure (OR: 2.24 mmHg [0.98–3.50mmHg]). Hypertension was 2.5-times more likely in the vitamin D-deficient (<15 ng/ml) group when compared with those with levels above 30 ng/ml [15].

All the above pediatric studies are cross-sectional analyses, hence they only highlight associations and do not prove causality. Randomized, controlled trials of vitamin D supplementation and its long-term effects on blood pressure in children need to be undertaken to evaluate the effects of vitamin D on blood pressure.

Vitamin D & diabetes mellitus

Type 1 diabetes mellitus

Several experimental and epidemiological studies have demonstrated associations between vitamin D levels and diabetes mellitus. Type 1 diabetes mellitus (T1DM) is an autoimmune disease and vitamin D is thought to play a role in its pathogenesis by its immunomodulatory actions of reducing lymphocyte proliferation and cytokine production [61,62].

Strong evidence of a vitamin D effect on T1DM risk first came from experiments in the non-obese diabetic (NOD) mice. The NOD mouse experiences disease pathogenesis similar to the human, including autoimmune destruction of β cells. When 1,25(OH)₂D, the active form of the vitamin, was administered to NOD mice in pharmacologic doses, it prevented the development of diabetes [63]. NOD mice when raised in a vitamin D-deficient state were shown to develop diabetes at an earlier age than nondeficient NOD controls [64].

Type 1 diabetes mellitus has a 350-fold range of age-standardized incidence rates, from an average of 0.1 per 100,000 in males younger than 14 years of age in China to 37 per 100,000 in boys younger than 14 years in Finland [65]. This pattern follows a latitudinal gradient that is the inverse of the global distribution of UVB irradiance. Exposure of the skin to sunlight is the source of 80–95% [65] of circulating vitamin D and its metabolites; thus, availability and intensity of sunlight, which are highly related to latitude, are strong correlates of 25(OH)D. Mohr *et al.* explored the possible association between UVB irradiance in 51 regions worldwide and incidence rates of T1DM in children [66]. They analyzed the relationship between UVB irradiance and age-standardized incidence rates of T1DM in children, according to regions of the world. Incidence rates were generally higher at higher latitudes ($R^2 = 0.25$; $p < 0.001$). UVB irradiance adjusted for cloud cover was inversely associated with incidence rates ($p < 0.05$). Incidence rates of T1DM approached zero in regions worldwide with high UVB irradiance, adding new support to the concept of a role of vitamin D in reducing the risk of the disease.

There is evidence of lower plasma 25(OH)D levels at diagnosis of T1DM compared with controls [67]. A number of recent studies from different regions of the world have highlighted the high prevalence of 25(OH)D deficiency in children with T1DM. Greer *et al.* in Australia, found a three-times higher risk of having levels below 20 ng/ml in adolescents with newly diagnosed diabetes than in the controls [68]. Another study from Italy examined 25(OH)D levels in 88 children newly diagnosed with T1DM and 57 healthy age- and sex-matched controls. Levels of both 25(OH)D and 1,25(OH)₂D were significantly lower in the diabetic adolescents ($p < 0.01$ and < 0.03 , respectively) [69]. A recent study from Boston measured 25(OH)D levels in 128 children with established and newly diagnosed T1DM. A total of 24% had levels above 30 ng/ml, but 61% had levels between 21 and 29 ng/ml and 15% were deficient (<20 ng/ml) [70]. Bener *et al.* compared 25(OH)D levels in 170 age-, race- and sex-matched

T1DM cases and healthy controls in Qatar, a region with ample sunshine all year round. There was a high prevalence of deficiency/insufficiency (<30 ng/ml) in both the groups (90.6 vs 85.3%), but it was significantly higher ($p < 0.009$) in the diabetic children [71].

Epidemiological studies suggest that supplementation with vitamin D in infants might be important in conferring protection against the development of T1DM. A prospective study of vitamin D supplementation in infants and T1DM was published in 2001 by Hyppönen *et al.* A total of 12,055 pregnant women who lived in Northern Finland and 91% of their living children who had multiple assessments of vitamin D supplementation during their first year recorded by medical personnel at health examinations were enrolled in the study. Incident cases of diabetes over the subsequent 30 years were identified from national databases. Compared with children who were not given vitamin D supplements, the relative risk of developing T1DM was only 0.12 among children given vitamin D supplements regularly and 0.16 among children given them irregularly. Among infants who were given supplements regularly, risk of diabetes was lower at doses of over 50 µg/day or 2000 IU/day (relative risk 0.14) and exactly 50 µg/day (relative risk 0.22) compared with doses less than 50 µg/day. This large, well-designed, prospective study provides evidence that vitamin D supplementation of 50 µg/day (2000 IU/day) or more during infancy may reduce the risk for T1DM, at least in very northern parts of the world where sunlight is severely limited during a greater part of the year [72]. Zipitis *et al.* in a recent systematic review and meta-analysis of five studies [67,72-76] performed in Europe assessed the effect of vitamin D supplementation on the risk of developing T1DM. Five observational studies (four case-control studies and one cohort study) met the inclusion criteria. Meta-analysis of data from the case-control studies showed that the risk of T1DM was significantly reduced in infants who were supplemented with vitamin D compared with those who were not supplemented (pooled OR: 0.71; 95% CI: 0.60 to 0.84). The result of the cohort study was in agreement with that of the meta-analysis. There was also evidence of a dose-response effect, with those using higher amounts of vitamin D being at lower risk of developing T1DM [77].

Two observational studies found a higher risk of T1DM in children whose mothers had low oral intake of vitamin D during pregnancy: the EURODIAB study found that children whose mothers consumed vitamin D supplements during pregnancy had a lower risk of T1DM than those whose mothers did not (OR: 0.67; 95% CI: 0.53–0.86) [78], and a case-control study by Stene and colleagues found that the risk of diabetes in children of mothers who took cod liver oil during pregnancy was lower than in mothers who did not (OR: 0.30; 95% CI: 0.12–10.75) [79]. Neither study measured serum 25(OH)D in the participants.

In a cohort study performed in Colorado, intake of vitamin D during the third trimester of pregnancy was assessed in the mothers of 233 children. The children were followed for an average of 4 years. Maternal intake of vitamin D from food had a protective effect against the appearance of islet cell autoantibodies (multiple-adjusted HR: 0.37; 95% CI: 0.17–10.78) [80].

Although none of the above studies are randomized, controlled, clinical trials they provide intriguing evidence for a link between vitamin D levels and the development of T1DM.

Insulin resistance/Type 2 diabetes mellitus

Vitamin D is thought to improve insulin sensitivity by its effects on muscle mass, and possibly fat metabolism or direct islet cell effects. The efficacy of vitamin D to promote muscle growth is supported by laboratory experiments. Rodents receiving diets containing high levels of vitamin D for 12 weeks had 8% greater muscle mass compared with animals receiving suboptimal vitamin D levels [81]. In support of an important physiological role for 1,25(OH)₂D on muscle, vitamin D receptor (VDR)-null mice experience myopathy characterized

by smaller muscle fibers [82]. Several intervention studies also support the conclusion that improved vitamin D status improves muscle function [83-85]. In a meta-analysis that included five double-blind, randomized, controlled trials in elderly populations (mean age 60 years; n = 1237), vitamin D supplementation reduced the corrected odds ratio of falling by 22% compared with patients receiving calcium or placebo, independent of calcium supplementation [83].

Evidence that supports a link between vitamin D status and an increase in energy expended from a meal [86] provides a possible explanation of the role of vitamin D to reduce adiposity. In the Women's Health Initiative, women who were randomized to calcium and vitamin D experienced less weight gain compared with women on placebo [87]. These studies suggest that vitamin D and calcium may play a role in fat metabolism. 1,25(OH)₂D, via VDR-mediated modulation of calbindin expression, appears to control intracellular calcium flux in the pancreatic islet cells, which in turn affects insulin release [88].

The evidence regarding insulin resistance and T2DM in the pediatric population are mostly cross-sectional studies. A recent cross-sectional study of 51 adolescent girls (mean BMI 43 ± 9) revealed that 61% had 25(OH)D levels below 15 ng/ml and that low 25(OH)D levels were associated with a lower Matsuda index of insulin sensitivity [89]. Another cross-sectional study of 127 adolescents (mean age: 13 years) showed an inverse relationship between 25(OH)D levels and hemoglobin A1c levels [90]. Reis *et al.*, in their analysis of NHANES 2001–2004 data, showed an inverse relationship between 25(OH)D levels and plasma glucose concentrations [60]. In our analysis of the same data, we did not see an association between low 25(OH)D levels and diagnosed diabetes mellitus [15].

Vitamin D & lipid abnormalities

Low vitamin D levels have been associated with many risk factors for cardiovascular diseases. In addition to insulin resistance and hypertension, hypovitaminosis D has been associated with altered lipid profile in adults. Vitamin D is thought to be essential for maintaining adequate levels of ApoA-I, a major component of HDL cholesterol. Individuals with high 25(OH)D concentrations have the highest plasma ApoA-I concentrations, and there is a positive correlation between 25(OH)D and serum HDL cholesterol concentrations [91,92].

In 3577 adolescents, aged 12–19 years, from the NHANES 2001–2004 survey, there was a higher adjusted odds ratio for those in the lowest (<15 ng/ml) compared with the highest quartile (>26 ng/ml) of 25(OH)D for low HDL cholesterol 1.54 (0.99–2.39); hypertriglyceridemia 1.00 (0.49–2.04); and the metabolic syndrome 3.88 (1.57–59.58) [60]. In a study of 217 obese children, lower HDL cholesterol levels were associated with lower levels of 25(OH)D [10]. Our analysis of data from NHANES 2001–2004 found children with 25(OH)D deficiency (<15 ng/ml) to have lower HDL cholesterol levels (OR: −3.03 [−5.02 to −1.04]; p = 0.004) when compared with those with levels below 30 ng/ml.

Vitamin D, infections & asthma

Vitamin D has been shown to have important functions in innate immunity at the systemic and cellular level [93]. The association between rickets, low vitamin D levels and infections has long been recognized and was recently reviewed [94]. A recent case–control study from Canada showed that kids who had acute lower respiratory infections and were admitted to the intensive care unit were more likely to have low 25(OH)D levels than other children with lower respiratory infections and control patients without infections [95]. A retrospective analysis of vitamin D supplementation use and urinary tract infections in infants revealed that infants who received vitamin D and were formula fed had a higher risk of developing a urinary tract infection [96]. However, there is some controversy surrounding this report [97].

Evidence of a link between low vitamin D levels, intake and asthma and other allergic conditions has been emerging. A study of 1669 children in Finland correlated lower maternal vitamin D intake during pregnancy with a higher risk of asthma and allergic rhinitis in their offspring at 5 years of age [98]. Other studies have found similar [99,100] and divergent results [101], suggesting the need for further research in this field.

Conclusion

In summary, vitamin D deficiency is a common problem worldwide. Risk factors for vitamin D deficiency include darker skin, less vitamin D intake and less outdoor activity. Low vitamin D levels can cause rickets in children, classically effecting toddlers but with increasing case reports in adolescence. Low vitamin D levels are associated with a variety of poor health outcomes including hypertension, diabetes mellitus, low bone mass, infections, dyslipidemia and asthma. The studies that suggest these associations have primarily been observational in nature and, therefore, causality cannot be established. The field needs more focus on clinical trials of vitamin D supplementation to evaluate the effects of vitamin D on the above parameters.

Future perspective

Randomized clinical trials are needed in the pediatric population with vitamin D deficiency to evaluate outcomes including insulin resistance, blood pressure and others. No doubt in the next 5 to 10 years some of these trials will have been conducted and the field will have greater evidence about the associations described in this review.

Executive summary

- There are few natural dietary sources of vitamin D.
- Vitamin D deficiency, defined variously as less than 15 ng/ml or less than 20 ng/ml, is common in the US pediatric population.
- Risk factors for vitamin D deficiency include darker skin, older age, less milk drinking, less sun exposure, sunscreen use and no vitamin D supplement use.
- Vitamin D deficiency can cause rickets, a disease seen in toddlers and adolescents characterized commonly by bone pain, epiphyseal swelling and bowed legs, and less commonly by hypocalcemic seizures, infections and cardiomyopathy.
- Studies of vitamin D supplementation suggest higher growth velocity in children.
- Animal and adult studies are suggestive that low vitamin D levels may be a factor in the development of hypertension; further studies are needed in children.
- There is observational evidence suggesting a link between low vitamin D levels and both Type 1 diabetes mellitus, potentially immunologically mediated, and Type 2 diabetes mellitus, potentially through muscle, adipose tissue or direct islet cell effects.
- Low vitamin D levels and intake have been associated with lower HDL levels, higher triglycerides, infections, asthma and allergic rhinitis.
- Most of the data in this review are observational in nature and there is a need for randomized clinical trials to test these associations.

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