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REVIEW

Vitamin D deficiency and childhood obesity: interactions, implications, and recommendations

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Abstract: Vitamin D deficiency and childhood obesity have been classified as epidemics throughout the world, and both share some common risk factors including poor diet and inactivity. Observational and clinical studies show that vitamin D status and fat mass are inversely correlated. It is not clear whether vitamin D deficiency contributes to, or is a consequence of obesity, or whether there are regulatory interactions between excess adiposity and vitamin D activity. The effects of this deficiency in childhood obesity appear to have negative influences on overall health, including insulin resistance, inflammation, and impeded bone mineralization, as well as increased future risk of type 2 diabetes, cardiovascular disease, and osteoporosis. The rather ubiquitous distribution of the vitamin D receptor and the 25-hydroxyvitamin D 1α-hydroxylase throughout the body, including evidence for a role of vitamin D in adipogenesis and adipocyte metabolism, may in part explain these widespread effects. Most of the findings to date suggest that the vitamin D needs of obese children are greater than the nonobese. Although ultraviolet B-induced skin synthesis is a main source of vitamin D, its use is neither feasible nor prudent due to limited sun availability for many and concerns for skin cancer. Likewise, obtaining adequate vitamin D from natural food sources alone is generally not achievable, and even in countries that allow fortification, vitamin D intakes are low. Therefore, in obese children, vitamin D supplementation is warranted. Weight loss interventions using energy restriction and physical activity may also improve the poor vitamin D status associated with obesity. More research is needed to define optimal vitamin D status in this vulnerable population, including investigations to determine the efficacy of vitamin D supplementation in attenuating the conditions associated with childhood obesity, and to further elucidate the mechanisms by which vitamin D exerts its effects on health.

Keywords: cholecalciferol, childhood overweight, hypovitaminosis D

Introduction

Childhood obesity is a major global health crisis. A systematic analysis of 1,769 reports representing 188 countries reveals that the worldwide prevalence of childhood overweight and obesity rose by nearly 50% over a span of three decades.[1] Roughly 43 million children are estimated to be overweight or obese throughout the world, and another 92 million are at risk of overweight.[2] If this trend continues, the global prevalence of childhood obesity is predicted to reach 60 million by 2020.[2]

The implications of this crisis are numerous and far reaching, involving both the individual and society.[3] For a child, there are physical health and psychosocial and functional consequences across a lifetime as studies show that childhood obesity is accompanied by an increase in associated chronic conditions such as insulin resistance (IR),

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inflammation, hypertension, and dyslipidemia.[4] Moreover, childhood obesity can predict adult illness[5] and compromise longevity.[6]

One growing, active area of research is the association between vitamin D deficiency and childhood obesity. Individually, each has been classified as an epidemic throughout the world, and both share some common risk factors including poor diet and inactivity.[2,7] Further, observational and clinical studies show that vitamin D status and fat mass are inversely correlated,[8] and recent intervention trials indicate that correcting the poor vitamin D status associated with obesity may attenuate some of the comorbidities of obesity. The objective of this review is to discuss the recent literature on vitamin D and childhood obesity including their interactions and implications for health and disease.

Vitamin D: the hormone, the nutrient, and its action

Although classified as a nutrient (largely due to the timing of its discovery which coincided with the discovery of other fat-soluble vitamins), vitamin D is more fittingly described as a prohormone/hormone.[9] It exists in two forms: vitamin D_2 and vitamin D_3. Vitamin D_2, or ergocalciferol, is a photoproduct of the irradiation of ergosterol, a fungal sterol also known as provitamin D_2. Vitamin D_3, or cholecalciferol, is produced following the irradiation of provitamin D_3 (7-dehydrocholestrol) in the epidermis and dermis layers of the skin.[10] The term "vitamin D" without a subscript refers to vitamin D_2, vitamin D_3, or both. The primary source of vitamin D is from skin synthesis as there are few naturally occurring dietary sources.[11]

Both vitamin D_2 and vitamin D_3 are hydroxylated twice to become active and capable of binding to their vitamin D receptor (VDR). The first hydroxylation occurs in the liver via 25-hydroxylase, forming 25-hydroxyvitamin D (25(OH)D) (also known as calcidiol). This is the major circulating form of vitamin D and is the primary determinant of vitamin D status. The enzyme 25-hydroxyvitamin D 1α-hydroxylase (1α-OH-ase) converts 25(OH)D to its active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$, also known as calcitriol). Although this enzyme is classically identified in the proximal tubules of the kidney, 1α-OH-ase (CYP27B1) gene expression has been demonstrated in a wide range of extrarenal tissues, including, but not limited to, immune, brain, pancreatic, and adipose tissue.[12,13] Renal activation of 25(OH)D results in elevated levels of circulating $1,25(OH)_2D$, which subsequently binds to the VDR in target tissues. Extrarenal formation of $1,25(OH)_2D$ appears to act locally by binding to VDR present within the same or neighboring cells. These intracrine and autocrine/paracrine actions are thought to be regulated by cytokines and to be responsible for the effects of $1,25(OH)_2D$ on cell proliferation, differentiation, and apoptosis.[14]

Vitamin D and its metabolites are transported bound to and solubilized by plasma protein carriers. Vitamin D-binding protein (DBP), a protein primarily produced by hepatic parenchymal cells, is the major transport protein. It binds 85% of circulating 25(OH)D, while albumin and lipoproteins account for the remaining 15%.[15]

Once synthesized, from renal or local production, $1,25(OH)_2D$ is transported to nuclear VDR in target cells.[16] The human VDR plays a central role in the biological actions of vitamin D as it regulates the expression of numerous genes in a largely ligand-dependent manner.[16] VDRs, upon activation by $1,25(OH)_2D$, form a heterodimer with retinoid X receptors (RXRs). These VDR–RXR heterodimers bind to vitamin D response elements of multiple genes, which results in either the transactivation or repression of these genes.[17]

Throughout childhood, vitamin D plays important roles in calcium and phosphorus homeostasis and bone growth/mineralization. Vitamin D deficiency in childhood causes osteomalacia, leading to growth retardation and skeletal deformities (ie, rickets).[10] More common, however, is an insidious presentation of vitamin D deficiency, which may prevent children and adolescents from reaching peak bone mass and predicted height.[18]

There is evidence that vitamin D is necessary for many other cellular processes. In addition to the organs responsible for calcium/phosphate homeostasis, VDRs are expressed in a variety of tissues and cells such as the hepatocytes, myocytes, adipocytes, pancreatic β-cells, and several immune cells, all of which are associated with obesity and its associated metabolic complications.[16,19,20]

Vitamin D deficiency: reemergence, diagnosis, and prevalence in children

Rickets, first documented in approximately 120 AD by Sorano of Ephesus, is the most recognized disease of vitamin D deficiency as it has plagued humans throughout history.[21] It became especially problematic in Europe and North America during the Industrial Revolution with the related reduction in sun exposure for those living and working in urban environments. Advancements in the science of vitamin D in the mid-20th century led to public health initiatives such as food fortification, which eliminated rickets as a significant health problem in the countries that

implemented them.[7] However, in the last 10–15 years, evidence has surfaced for a reemergence of rickets in certain ethnic and minority groups in Europe and Australasia and an alarming prevalence of poor vitamin D status worldwide.[22] The factors speculated to contribute to this rise in vitamin D deficiency include lower intakes of vitamin D-fortified foods, use of sunscreens/blocks, reduced time spent in outdoor activities, and air pollution.[23] Moreover, our understanding of the role of vitamin D in human health has expanded into areas beyond bone and has subsequently put into question the definition of adequate vitamin D status.[23,24]

Diagnostic criteria

The best available indicator of vitamin D status is the serum concentration of 25(OH)D,[25] although the extent to which this measurement relates to or serves as a predictor of health outcomes has not been fully elucidated. Furthermore, there is no general agreement on the required serum 25(OH)D for adequate status. For example, the Institute of Medicine (IOM) defines vitamin D deficiency, or hypovitaminosis D, as a serum 25(OH)D concentration <50 nmol/L (20 ng/mL),[26] whereas the Endocrine Society has suggested that a 25(OH)D concentration between 75 nmol/L and 250 nmol/L (30–100 ng/mL) is required for sufficiency, with the intermediate concentration range of 52–72 nmol/L (21–29 ng/mL) classified as "insufficient".[27] Vitamin D status classifications within pediatric clinical practice guidelines are similarly controversial. The American Academy of Pediatrics (AAP)[28] cut-off values are identical to IOM with a 25(OH)D concentration >50.0 nmol/L considered to be "sufficient", while the Society for Adolescent Health and Medicine (SAHM)[29] considers a 25(OH)D serum concentration between 75–125 nmol/L (30–50 ng/mL) to be "sufficient" for the adolescent.

Childhood prevalence of vitamin D deficiency

Hypovitaminosis D is a significant problem among people of all ages around the world,[30] although there are large gaps of information on the pediatric populations of some countries.[31] The estimated worldwide prevalence of hypovitaminosis D in children and adolescents is rather wide, between 29% and 100%,[32] and surveys show it to be in part related to the degree of adiposity, with healthy weight at 21%, overweight at 29%, obese at 34%, and severely obese at 49%.[33] Thus, obese children are a particularly vulnerable group for poor vitamin D status, which in turn appears to exacerbate the effects of obesity alone on overall health.[31,33,34]

Interactions and implications of vitamin D deficiency in obese children

It is not clear whether hypovitaminosis D contributes to, or is a consequence of, obesity, or whether there are regulatory interactions between excess adiposity and vitamin D activity. Data from a prospective, population-based study following 1,226 adult participants over a decade showed that the odds of gaining more than 3.7 kg (75th percentile) between the second and third visits in those with 25(OH)D serum concentrations <42 nmol/L (17 ng/mL) was 2.37 times greater than those with higher 25(OH)D concentrations.[35] This suggests that the poor vitamin D status in the obese may not be secondary to obesity but may instead precede it. In support of this, a population-based longitudinal study of children in the Brazilian Amazon found the effect of the obesity-associated gene variation (FTO rs9939609) to be more pronounced among children with insufficient vitamin D status.[36] Conversely, a recent bidirectional Mendelian randomization analysis of multiple cohorts involving a total of more than 42,000 individuals provided evidence of obesity as a causal factor in the development of vitamin D deficiency but not vice versa.[37] This analysis revealed that the "body mass index (BMI) allele score" created by the investigators was associated with both BMI and 25(OH)D concentration among study participants, and each 10% increase in BMI leads to a 4.2% decrease in 25(OH)D concentration.[37] However, although both of the two "25(OH)D allele scores" were linked with serum 25(OH)D concentration, neither was associated with BMI.

Conditions in obese children affected by vitamin D status

IR and inflammation are commonly seen in overweight/obese children and are predictive of the development of metabolic syndrome, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and perhaps osteopenia/osteoporosis. For example, reports indicate that children with these two risk factors are significantly more likely to have T2DM and CVD 25–30 years later compared with their peers.[38,39]

The relationship between poor vitamin D status and IR, T2DM, and metabolic syndrome is the most well studied and was first observed in obese adults.[40] Similar observations have since been made in obese children. Most, although not all, show significant associations between circulating 25(OH)D concentration and indices of IR and blood glucose control; their findings have been covered in detail elsewhere.[41] The very few published intervention

trials using vitamin D supplementation to improve IR and impaired glucose tolerance in obese children or adolescents have yielded beneficial effects.[41] For example, results from our 6-month randomized controlled trial (RCT) of obese adolescents (age =14.1±2.8 years; BMI =39.8±6.1 kg/m^2) supplemented with 4,000 IU per day showed an attenuation of IR similar to results involving the use of the drug metformin.[42] By comparison, the results of a 2012 meta-analysis of the evidence on vitamin D supplementation and glycemic control in adults revealed a weak effect of vitamin D supplementation in reducing fasting glucose and improving IR in patients with T2DM or impaired glucose tolerance.[43] Much of this discrepancy can be attributed to differences in methods employed, such as vitamin D dose and outcome measures, and participant characteristics, most notably body weight/fat status, initial vitamin D status, and age. Further, it is speculated that the status of both vitamin D and parathyroid hormone (PTH) needs to be considered in evaluating the impact of vitamin D status on glucose metabolism.[44] More RCTs are warranted.

The biological mechanisms by which vitamin D influences glycemic control in obesity have yet to be determined but are thought to involve enhancement of peripheral/hepatic uptake of glucose, attenuation of inflammation, and/or regulation of insulin synthesis/secretion by pancreatic β-cells.[41] Moreover, data from one of the first reports to examine the association between vitamin D deficiency and IR in obese children indicated that the most clinically meaningful threshold of serum 25(OH)D concentration for the identification of IR and impaired glucose homeostasis in the obese is 50 nmol/L (20 ng/mL).[45] This is the cut-off used by the IOM in the definition of vitamin D deficiency.

A new systematic review of 35 studies evaluated the degree to which vitamin D and CVD risk factors are associated in obese children.[46] The cross-sectional studies included in the analysis showed a relationship between 25(OH)D and systolic blood pressure but not the prospective studies. The lone RCT in the review suggested a relationship between vitamin D status and arterial stiffness. There were no associations between 25(OH)D and diastolic blood pressure or low-density lipoprotein cholesterol, and the links with high-density lipoprotein cholesterol and triglycerides were capricious.

Anther condition related to childhood obesity and metabolic disturbances is nonalcoholic fatty liver disease (NAFLD). Since both NAFLD and serum 25(OH)D concentration are associated with adiposity and IR, interest in examining their potential pathogenic link has emerged. Pediatric NAFLD is a condition characterized by hepatic fat infiltration >5% hepatocytes, as assessed by liver biopsy, in the absence of viral, autoimmune, and drug-/alcohol-induced liver disease.[47] It is becoming one of the most common complications of childhood obesity and is strongly associated with the clinical features of IR, especially the metabolic syndrome and T2DM.[47] Two separate observational studies showed that compared with non-NAFLD obese children and teens, those with NAFLD had significantly lower serum concentrations of 25(OH)D, which was correlated with IR in those with NAFLD but not in those without NAFLD.[48,49] Another investigation showed that lower 25(OH)D concentration is associated with NAFLD, independent of adiposity, physical activity, and IR.[50] At odds with these findings, an earlier report using data on 1,630 children, aged 12–19 years, from the National Health and Examination Survey (NHANES) 2001–2004, found vitamin D status not to be independently associated with NAFLD.[51] It remains to be determined whether poor vitamin D status contributes directly to the risk of developing NAFLD or if this association is confounded by hepatosteatosis,[48] as the liver is a primary site of vitamin D activation.

The bone mass attained during growth is a critical determinant of the risk of osteoporosis later in life.[52] Those with higher peak bone mass after adolescence have a protective advantage during normal aging and menopause when significant bone loss occurs. Although it is known that peak bone mass is determined by genetics and lifestyle factors, the effects of obesity on bone mineral accretion are not fully discerned. In contrast with adults in whom overweight/obesity is protective to bones, there is evidence that obesity in children is a risk factor for low bone mass and fractures.[53] However, this phenomenon is not uniformly observed.[54] Efforts of new investigations have focused on addressing the reasons for the discrepancy, including distribution of body fat (abdominal obesity),[55] and/or the presence of comorbidities, such as IR,[56] metabolic syndrome,[57] and NAFLD.[58]

Factors thought to be responsible for the altered bone mass described in childhood obesity include changes in the hormonal milieu (eg, increased conversion of androstenedione to estrogen),[59] and the participation of adipokines (resistin, adiponectin, leptin, osteocalcin)[60] and adipose-derived inflammatory markers (interleukin-6 [IL-6] and tumor necrosis factor-α [TNF-α]) in bone remodeling.[58,61] Another likely contributor is the poor vitamin D status related to obesity, via its indirect (inflammation) and/or direct (calcium homeostasis/bone mineralization) skeletal effects.

Children have high demands for dietary calcium to support the mineralization of growing bone. It is well established that serum PTH concentration varies inversely with absorbed calcium and serum 25(OH)D concentration. It has been proposed that the point along the 25(OH)D continuum at which PTH becomes constant is an indication of the point at which calcium absorption becomes constant.[62] A study of young, healthy children in Canada demonstrated that a 25(OH)D concentration of 100 nmol/L was required to see a plateau in PTH.[63]

Adipose-endocrine response as an important link between vitamin D deficiency and obesity-related conditions

The effect of excess body fat is theorized to 1) increase the metabolic clearance of vitamin D and its metabolites through enhanced uptake, 2) decrease the bioavailability of vitamin D once deposited in adipocytes, and/or 3) create a volumetric dilution of vitamin D due to a larger body mass.[64,65] For comparison, the amount of total body fat mass of lean children (BMI for age ≤15th percentile) is described to be between 1.8 kg and 2.2 kg, 2.7 kg and 4.2 kg, and 6 kg and 10 kg, for children 3–5 years, 6–11 years, and 12–19 years of age, respectively, while the total body fat mass of overweight/obese children (BMI for age ≥85th percentile) of similar age is reported to be more than threefold greater.[66] Adipose tissue, the storage site of this excess body fat, was once thought to be inert but is now regarded as a highly metabolic endocrine organ.[67] It secretes more than 260 different proteins/peptides (adipokines, chemokines, cytokines) and is a major player in glycemic control.[68,69] Vitamin D appears to have a role in adipose tissue and its metabolic processes; however, the molecular basis of the interactions of 25(OH)D, $1,25(OH)_2D$, DBP, and VDR after sequestration in adipose tissue and their regulations are not well understood.

The genes for VDR and vitamin D-metabolizing enzymes (CYP27A1, CYP27B1) have been identified in both animal and human adipocytes.[19,70] Research demonstrates that both the active form, $1,25(OH)_2D$, and the parent molecule, vitamin D_3, influence several key adipogenic genes and transcription factors as well as lipid accumulation.[19,70] Yet, the specific function of vitamin D in the adipogenic process remains largely ambiguous, and often contradictory, with studies showing both stimulation and inhibition of adipogenesis.[67]

Vitamin D metabolites also influence adipokine production and the inflammatory response in adipose tissue.[67] There is convincing support for chronic inflammation as the causal link between obesity and its related metabolic conditions, such as IR, liver fat deposition, and poor bone mineralization. As adipocytes expand, they produce and secrete several inflammatory cytokines and chemokines such as TNF-α, IL-6, monocyte chemotactic protein-1, and leptin.[67] Observational studies have shown an inverse correlation between 25(OH)D concentration and several of these inflammatory cytokines.[71,72] Furthermore, multiple in vivo and in vitro studies have reported that 25(OH)D downregulates the production and secretion of multiple pro-inflammatory cytokines including IL-1, IL-2, IL-6, IL-12, C-reactive protein, TNF-α, and interferon-γ.[73,74]

Age and pubertal status confound the association between vitamin D and childhood obesity

From the literature on vitamin D and childhood obesity, age and pubertal status surface as significant confounders. A recent study of obese 2- to 6-year olds found an inverse relationship between child age and serum 25(OH)D concentration,[75] while another in older children reported the same finding.[76] Greater vitamin D intakes in younger children may provide an explanation. Data collected from NHANES 2003–2003 show that 76% and 78% of 1- to 3-year-old boys and girls, respectively, have total intakes (diet and supplements) above the IOM recommendations, while, in 14- to 18-year-old boys and girls, only 32% and 54%, respectively, have intakes above recommendations.[77] Greater sun exposure in younger children is another feasible explanation as they engage in more outdoor playtime than older children and adolescents.[78,79]

Excess adiposity during childhood may advance puberty in girls and delay puberty in boys.[80] Puberty is known to affect many of the metabolic conditions associated with obesity and vice versa. IR and compensatory hyperinsulinemia may represent a common thread contributing to many of the pubertal changes reported to occur with childhood obesity[81,82] Two studies designed to specifically examine the effects of puberty on the association between 25(OH)D serum concentration and IR show that it does not become significant until children reach puberty.[83,84] Further, an analysis of cross-sectional data of obese children required adjustments for puberty to reveal associations between vitamin D status and homeostatic model assessment - insulin resistance (HOMA-IR),[85] and the aforementioned report of very young obese children found no association between vitamin D status and IR.[75]

Effects of vitamin D status on weight loss and vice versa

Preliminary results in obese adults hinted at a more favorable response (greater body fat loss) to energy restriction

in those with adequate vitamin D status.[86] However, a 2014 meta-analysis of RCTs using vitamin D supplementation without imposing energy restriction revealed only a small effect of improved vitamin D status on BMI but not fat mass.[87] Interestingly, this meta-analysis also indicated that studies in older people and men were less likely to show an effect on BMI or fat mass. There is a paucity of data available on the effect of vitamin D supplementation on weight loss in children. In one study of overweight children undergoing diet counseling, high milk consumption (primary source of vitamin D in the USA) did not lead to greater weight loss but attenuated insulin action.[88] (Unfortunately, serum 25(OH)D was not measured, so associations with vitamin D status could not be assessed.) Likewise, in our RCT of obese adolescents also undergoing diet counseling, although vitamin D supplementation decreased IR, neither body weight or waist circumference changed over 6 months.[42] Of relevance, an earlier RCT of healthy girls, 10–17 years of age, found that premenarcheal participants given weekly oral doses of vitamin D for 1 year had significant increases in lean body mass and height, with no changes in body weight, suggesting a decrease in body fat (although not reported).[89] Despite these data, however, the overall evidence of positive effects of vitamin D on weight or fat loss is thus far underwhelming.

Reports have looked at the effect of weight loss on vitamin D status. In a cross-sectional study of obese children who achieved a reduction in overweight over a 1-year time period, serum PTH decreased, and serum 25(OH)D increased significantly compared to obese children without weight loss.[90] Similar observations have been described in adult weight loss studies.[91,92]

Recommendations for treating vitamin D deficiency in obese children

The IOM-recommended dietary allowance is 600 IU (15 μg) daily for children 1–18 years of age.[26] Recommendations of pediatric medical societies such as the AAP or the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition are below this dose,[93,94] while the Endocrine Society and SAHM guidelines suggest that this same age group may need up to 1,000 IU (15–25 μg) per day (Table 1).[27,29] This disagreement reflects different goals and views on current evidence.[95]

The above recommendations are generally intended for healthy populations and do not reflect the unique needs of disease groups or of those with diagnosed vitamin D deficiency.

Vitamin D needs and dose response in the obese

With the high prevalence of hypovitaminosis D among obese children, the requirements for most obese youth would likely

Table 1 Comparison of selected pediatric recommendations for vitamin D maintenance and treatment of deficiency

Organization	General recommendation (IU per day)*	Upper limit (IU per day)	Treatment strategy for vitamin D deficiency
Institute of Medicine (IOM)[26]	1–3 y: 600 4–8 y: 600 9–18 y: 600	2,500 3,000 4,000	N/A
American Academy of Pediatrics (AAP)[94]	1–18 y: 400	N/A	Children with serum 25(OH)D ≤37.5 nmol/L (15 ng/mL), 5,000 IU per day until stores are replenished
European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN)[93]	Healthy diet with vitamin D-containing foods and adequate outdoor activities	1–10 y: 2,000 11–18 y: 4,000	N/A
Society for Adolescent Health and Medicine (SAHM)[29]	Adolescents: 600–1,000	4,000	Adolescents with serum 25(OH)D ≤50 nmol/L (20 ng/mL), 50,000 IU weekly for 8 weeks or until serum 25(OH)D >50 nmol/L
Endocrine Society[27]	1–18 y: 600–1,000	4,000	Children with serum 25(OH)D ≤50 nmol/L, 2,000 IU per day or 50,000 IU weekly of vitamin D for at least 6 weeks or until serum 25(OH)D >50 nmol/L

Note: *40 IU = 1 μg.
Abbreviations: IU, international units; y, years; N/A, not available; 25(OH)D, 25-hydroxyvitamin D.

fall under a different set of recommendations. For children with documented deficiency (serum 25(OH)D ≤37.5 nmol/L [15 ng/mL]), the AAP recommends 5,000 IU (124 μg) per day until stores are replenished.[28] Findings from our study of obese adolescents support this higher dose. After 3 months of supplementation with 4,000 IU (100 μg), none of the participants were of vitamin D-"deficient" status, and after 6 months, 93% were of "sufficient" status (>75 nmol/L or 30 ng/L).[42] By comparison, the Endocrine Society guidelines recommend 2,000 IU (50 μg) per day or 50,000 IU (1,250 μg) weekly of vitamin D for at least 6 weeks or until serum concentrations of 25(OH)D are above 50 nmol/L (20 ng/mL).[27] A new report investigating 25,000 IU weekly vitamin D supplementation of deficient/insufficient obese 8- to 18-year olds over 9 weeks found that it was well tolerated and resulted in advancement to "sufficient" status in more than 84% of participants.[96] However, given the altered metabolism of vitamin D reported in the obese,[64,97] it is questionable whether the dose required for maintenance in nonobese is the same as that required by the obese.

The obese are approximately half as efficient in using vitamin D compared to their lean counterparts.[97,98] It has been estimated that 100 IU are required for every 2.5 nmol/L (1 ng/mL) increase in serum 25(OH)D concentration in the nonobese,[99] whereas, in our study of obese adolescents, it took approximately 205 IU – more than double – of vitamin D for the same incremental increase.[42] As further evidence of a higher dose required in obese children, a vitamin D supplementation study found that vitamin D deficiency persisted in 24% of obese versus 11% of nonobese African-American children given 400 IU per day for 4 weeks.[100] Collectively, these findings argue for a separate set of guidelines for obese children and adolescents.

Meeting vitamin D needs through sun, food, or supplement sources

Vitamin D synthesis in the skin depends on the photoconversion of 7-dehydrocholestrol to previtamin D_3 by ultraviolet B (UVB) light (wavelength =209–315 nm).[101] Once formed, previtamin D3 undergoes heat-induced isomerization to vitamin D_3.[10] Vitamin D toxicity from skin synthesis is highly unlikely as prolonged exposure to sunlight photodegrades previtamin D_3 to biologically inert isomers.[102,103] Several factors affect the skin's ability to produce vitamin D_3. Season, latitude, and time of day affect vitamin D_3 production by altering the absorption of UVB photons by the ozone layer.[101,102] In the winter, the solar zenith angle of the sun is more diagonal at high latitudes causing the total number of photons reaching the Earth's surface to diminish. During the day, UVB radiation is most intense when the sun is at its highest point, which occurs at midday. The application of sunscreen/block (sun protection factor as low as seven to eight blocks approximately 95% of previtamin D_3 production),[104] possessing greater amounts of melanin in one's skin (acting as a natural sunscreen),[105] and the use of clothing or other body covering also significantly decrease the production of vitamin D in the skin.[102,103,106]

UVB synthesis is one of the main sources of vitamin D in most populations tracked; however, due to the limited sun availability throughout the year in many locations and concerns for skin cancers, relying on this source for the treatment of vitamin D deficiency in childhood obesity is neither practical nor prudent. Likewise, obtaining adequate vitamin D from natural food sources alone is generally not achievable as only a limited number of foods naturally contain vitamin D. Among them, the most vitamin D rich are fish liver oils, fish, and organ meats, and to a lesser extent, egg yolks and sun-dried mushrooms.[107]

For those countries in which high levels of fish are not consumed, the only alternative to UVB light exposure is the use of fortified foods or dietary supplements. Commonly fortified foods include breakfast cereals, milk, milk products, grain products, pastas, margarine, and some brands of orange juice.[11] In the USA, most vitamin D intake from foods is provided through fortification.[108] In New Zealand, Australia, Canada, and the UK, fewer foods are fortified, and the prevalence of insufficiency is as low as or lower than observed in the USA.[11,109,110]

Even in countries that allow fortification, vitamin D intakes are low in those with dietary practices that limit the consumption of fortified foods.[109] For example, the consumption of milk, the most common vehicle for vitamin D fortification, generally declines with increasing age in children.[111] Therefore, in obese children, a population with apparently greater needs and prone to deficiency, vitamin D supplementation is warranted.

Both forms of the vitamin, D_2 or D_3, can be used as a food fortificant or dietary supplement, although D_3 dominates.[11] Some reports indicate that D_2 is not as effective as D_3, while others show no difference.[112,113] In the USA, dietary supplements are readily available as over-the-counter (OTC) preparations and can contain up to 5,000 IU per capsule (which is not the case universally, eg, Australia).[114] The D_3 content of OTC is highly variable with potencies ranging from 9% to 146% of label claims.[115] For medical use, prescription-grade supplements are available in the D_2 form only.[116] Intramuscular (IM)

vitamin D_2 is also used to treat low-vitamin D status. The oral route is more efficacious than IM, but administration method should be based on patient's choice, compliance, and availability as IM preparations are not available in all countries.[117]

Ingested vitamin D is presumed to follow the same fate as dietary lipids, although new data reveal that digestive and absorptive processes may be more complex than previously recognized as large interindividual variation in postprandial responses to vitamin D has been observed.[118,119] During digestion, vitamin D is transferred to the mixed micelles generated by the lipolysis of dietary fat.[120] Upon uptake through the brush border, vitamin D becomes incorporated into chylomicrons along with the other products of fat digestion, and approximately 80% is absorbed into the lymphatic system.[121] D_2 and D_3 forms are similarly absorbed by the enterocyte.[122–124] Total fat content of a meal does not appear to significantly alter vitamin D absorption;[125] however, several fat-soluble molecules including dietary cholesterol, phytosterols, and vitamins A, E, and K have been shown to inhibit or compete with vitamin D for absorption.[119,126,127] Further, any health conditions characterized by fat malabsorption can increase the risk for vitamin D deficiency.[128]

Vitamin D can accumulate throughout the body with adipose tissue as its primary storage site. It has a half-life of 4–6 weeks,[129] although higher doses can lead to a long residence time.[130,131] One laboratory performed a series of experiments to determine the relation between serum vitamin D_3 and vitamin D status, as measured by serum concentration of 25(OH)D, in healthy adults after the oral administration of vitamin D_3 across a broad range of intakes. Doses of 0–11,000 IU per day showed the increases in serum 25(OH)D to be biphasic: rapid conversion of vitamin D_3 to 25(OH)D at physiological doses and slower rate of conversion at higher doses.[132]

Monitoring for vitamin D toxicity

Although vitamin D toxicity, defined as a serum concentration of 25(OH)D ≥375 nmol/L (150 ng/mL), in children is rare, health care providers should monitor children receiving treatment doses exceeding the upper ranges currently recommended.[133] The IOM set a daily tolerable upper intake level of 2,500 IU (63 μg) for 1- to 3-year olds, 3,000 IU (75 μg) for 4- to 8-year olds, and 4,000 IU (100 μg) for 14- to 18-year olds,[26] while the SAHM and Endocrine Society have endorsed an upper limit of 4,000 IU for all childhood age groups.[27,29] There is insufficient evidence to guide the frequency of testing; however, it has been suggested that measurements of serum 25(OH)D be taken no more than every 6 months.[133] In children with serum 25(OH)D concentrations above 375 nmol/L (150 ng/mL), serum calcium concentrations should also be monitored.[133]

Conclusion

Vitamin D deficiency is prevalent in childhood obesity. Excess adiposity is linked with poor vitamin D status, and the effects of this deficiency during obesity appear to have several health implications, including IR, inflammation, and compromised bone growth/mineralization. The rather ubiquitous distribution of VDR and the 1α-OH-ase throughout the body, including evidence of a role of vitamin D in adipogenesis and adipocyte metabolism, may in part explain these widespread consequences. Whether poor vitamin D status is a cause or an effect of obesity is not known; however, most of the findings to date suggest that the vitamin D needs of obese children are greater than the nonobese, and that weight loss can improve vitamin D status. Further research is required to define optimal vitamin D status and corresponding intake recommendations in this deficiency-prone population. Other investigations should focus on determining the clinical efficacy of vitamin D supplementation on the attenuation of the metabolic symptoms and conditions associated with childhood obesity. Finally, work is needed on the elucidation of the mechanisms by which vitamin D exerts its effects on obesity/adipose tissue and health.

Disclosure

The author reports no conflicts of interest in this work.

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