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Metabolic and Immunological Consequences of Vitamin D Deficiency in Obese Children

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Abstract

Numerous studies highlighted the link between vitamin D deficiency and cardiovascular, autoimmune, metabolic diseases, and obesity. However, a clear role of vitamin D in these disorders is still unknown. Vitamin D deficiency in children can be a potential risk factor for developing diseases at a later age. Early prevention and vitamin D supplementation should become a public health priority. This review highlights the clinical implications of vitamin D deficiency in adults and children with obesity.

Keywords

Cardiovascular diseases • Children • Obesity • Metabolic syndrome • Vitamin D deficiency

1 Introduction

Obesity is a major, increasingly prevalent health problem affecting modern societies. Vitamin D deficiency is highly prevalent in patients with obesity and is strongly connected with its consequences (Vimeswaran et al. 2013; Earthman et al. 2012). Body mass index (BMI) is inversely associated with the 25(OH)D serum level in response to vitamin D supplementation. The relationship between obesity and 1,25 $(OH)_2D$, the active form of vitamin D, is less clear and this is due probably to the dynamic nature of the production and regulation of the active hormone.

In children, vitamin D has a major biological action in mineral homeostasis and regulation of bone remodeling. Moreover, severity and prolonged duration of vitamin D deficiency can potentially lead to cardiovascular and metabolic diseases in adolescence or in early adulthood. A major form of vitamin D in the circulation is 25 (OH)D and the measurement of its serum level can be used to evaluate vitamin D status. Vitamin D deficiency has been defined as 25(OH)D of less than 20 ng/ml (<50 nmol/l). In healthy

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children, vitamin D deficiency can be caused by a combination of inadequate intake of vitamin D-containing foods and insufficient exposure to sunlight. Seasonal variations of vitamin D level may occur, depending on the geographic latitude and sun exposure. There are several conditions, such as obesity and liver or kidney disorders, in which the risk of developing vitamin D deficiency is increased (Joergensen et al. 2010).

In Poland, a multidisciplinary group formulated recommendations for vitamin D supplementation in obese children and adolescents: 1,200–2,000 IU/day (30–50 μg) from September to April, depending on the BMI. These recommendations are based on the studies of healthy individuals, taking into consideration both serum 25(OH)D concentrations and vitamin D intakes.

2 Vitamin D in Adipogenesis

The regulation of adipogenesis is a key biological process that is required for both lipid storage and the development of endocrine adipocytes (Blumberg et al. 2006). The expression of vitamin D-metabolizing enzymes has been demonstrated in human adipose tissue (Wamberg et al. 2013). Plasma 25(OH)D increases by 27 % after weight loss in obese individuals; concomitantly, 25-hydroxylase CYP2J2 and 1-α-hydroxylase CYP27B1 decrease by 71 % and 49 %, respectively, in subcutaneous adipose tissue of obese subjects. These findings suggest that adipose tissue, which can be dynamically altered during obesity and weight loss, has the ability to metabolize vitamin D locally. Vitamin D status may regulate human adipose tissue growth and remodeling (Blumberg et al. 2006). Adipocyte precursor cells (preadipocytes) are present throughout life, and obesity may be partially mediated by stimulating the differentiation of preadipocytes into adipocytes or by fat accumulation in the differentiated adipocytes (Nimitphong et al. 2012).

Cellular action of $1,25(OH)_2D$ is mediated by the vitamin D receptor (VDR), a ligand-dependent transcription regulator molecule belonging to the superfamily of nuclear receptors. There are some reports concerning the modulatory effect of $1\alpha25(OH)_2D$ on adipocyte differentiation, but the molecular mechanism of $1\alpha25(OH)_2D$-induced modulation remains unclear and further studies are needed to clarify this problem (Blumberg et al. 2006).

Differentiation of 3T3-L1 and other types of preadipocytes is a process highly controlled through sequential induction of transcription factors that regulate the expression of adipocyte-specific markers. During adipogenesis, a series of cellular events begins with a rapid expression of CCAAT/enhancer-binding protein b (C/EBPb), followed by the expression of C/EBPa, PPARg, and sterolregulatory element-binding protein 1 (SREBP1) (Christy et al. 1989).

Blumberg et al. (2006) showed that liganded VDR downregulates both C/EBPa and PPARg *via* inhibition of C/EBPb expression and action. Liganded VDR is a potent inhibitor of adipogenesis; the unliganded receptor is not required for adipogenesis, but may play a role in some aspect of the process. These data suggest that the intracellular calcitriol plays a key role in adipocyte formation.

During adipogenesis, there is an increase in the expression of genes that produce the adipocyte phenotype, including genes for lipoprotein lipase and adipocyte lipid-binding protein 2; the latter being a late marker of adipogenesis (Christy et al. 1989). In the differentiation phase, expression of genes encoding lipogenic enzymes, such as fatty acid synthase, is highly induced and *de novo* fatty acid synthesis increases enormously.

Links between $1,25(OH)_2D$ and adipocyte lipogenesis has also been supported by other researchers who demonstrate that the hormone strongly increases mRNA levels of insulin-induced gene-2 (Insig-2), a factor blocking fatty acid synthesis in mature 3T3-L1 adipocytes and inhibits preadipocyte differentiation (Lee et al. 2005). Ochs-Balcom et al. (2011) in a recent study have also shown a positive

association between VDR polymorphisms and the markers of adiposity.

3 Vitamin D in Autoimmune Diseases

Deficiency of vitamin D is frequently observed in patients with autoimmune diseases. Children with diabetes mellitus, both obese and non-obese, can develop severe late onset complications at an older age. The potential risk can be much greater in patients with vitamin D deficiency. Autoimmune diseases are characterized by a loss of immune homeostasis resulting in impaired self-antigen recognition, followed by destruction of body tissue by autoreactive immune cells. A combination of genetic predisposition, and epidemiological and environmental contributors can lead to the development of autoimmune diseases. One important factor may be the availability of sufficient vitamin D levels, as various epidemiological studies suggest an association between vitamin D deficiency and the incidence of autoimmune diseases, such as type 1 diabetes (T1D), multiple sclerosis (MS), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), inflammatory bowel disease (IBD), and Graves' disease.

In a recent review, Hewison (2012) has proposed four potential mechanisms by which vitamin D may influence T cell function:

- direct, endocrine effects on T cells, mediated *via* systemic calcitriol;
- direct, intracrine conversion of 25(OH)D to calcitriol by T cells;
- direct, paracrine effects of calcitriol on T cells following conversion of 25(OH)D to calcitriol by monocytes or dendritic cells.
- indirect effects on antigen presentation to T cells mediated *via* localized antigen-presenting cells (APC) affected by calcitriol.

Antico et al. (2012) reviewed 219 published studies and concluded that vitamin D seems to play a beneficial role in the prevention of autoimmunity, but that randomized controlled clinical trials confirming this observation are still missing.

4 Vitamin D Deficiency and Its Effects on BMI, Lipid Metabolism, Diabetes Mellitus, and Cardiovascular Disorders in Obese Patients

Current research considers a reduced vitamin D concentration as a potential risk factor for cardiovascular disorders (Earthman et al. 2012), metabolic syndrome (Vimeswaran et al. 2013), hypertension (Larsen et al. 2012; Lind et al. 1988), diabetes (Kayaniyil et al. 2011; Hypponen et al. 2001), cancer (Garland et al. 2011), autoimmune and infectious diseases resulting from decreased immunity (Hewison 2012).

According to Earthman et al. (2012), obesity could contribute to low serum 25(OH)D *via* adipose sequestration of vitamin D. However, adipose tissue has the VDR and can synthesize 1,25 $(OH)_2D$, and there is evidence that vitamin D may regulate adipose tissue mass, differentiation, and metabolism; and thus, contributes to obesity. Vimeswaran et al. (2013) investigated the relationship between body mass index (BMI) and vitamin D status and inferred causality by using genetic variants, namely vitamin D-related single nucleotide polymorphism (SNPs) and allele scores, as instruments in bidirectional Mendelian randomization (MR) analyses. This meta-analysis was based on data from 21 studies of adult cohorts comprising 42,024 individuals. Twelve established BMI-related SNPs, such as melanocortin 4 receptor, transmembrane protein 18, and brain-derived neurotrophic factor, were selected for the analysis. Each unit (kg/m^2) increase in BMI was associated with 1.15 % lower concentrations of 25(OH)D. The inverse association between BMI and 25(OH)D was stronger in subjects from North America than those from Europe, and in women compared with men, while no variation was seen in relation to age or BMI. The authors also showed that higher BMI is connected with lower vitamin D level. Speliotes et al. (2010) expanded the Genetic Investigation of Anthropometric Traits (GIANT) consortium genome-wide association

studies of BMI, confirmed 14 known obesity susceptibility loci and identified 18 new loci associated with BMI. Some loci are located near key hypothalamic regulators of energy balance and one of these loci is located near an incretin receptor GIPR.

Olson et al. (2012) showed that the mean serum 25(OH)D level is significantly lower in children with a higher BMI and high body fat mass. Data from the National Health and Nutrition Examination Survey (NHANES) 2001–2004 show that obese children are more likely to have a low level of 25(OH)D (Kumar et al. 2009). Significantly lower seasonal variations of 25 (OH)D concentration are observed in obese children (Olson et al. 2012). The bioavailability of 25(OH)D is decreased due to of its deposition in adipose tissue. Obese children often have an indoor lifestyle with reduced sunlight exposure. Poor dietary habits also contribute to decreased vitamin D levels, as unhealthy high caloric food is usually low in minerals and vitamins. Skipping breakfast, soda, and juice intake also are associated with decreased vitamin D levels (Olson et al. 2012). It is crucial for obese children to develop healthy dietary habits to ensure an adequate intake of vitamin D and serum 25 (OH)D levels. Moreover a significant increase in serum 25(OH)D concentration has been found in obese children after weight loss.

4.1 Lipid Metabolism

Vitamin D plays a role in lipid metabolism in adipose tissue. $1,25(OH)_2D$ causes a significant increase in lipoprotein lipase activity in 3T3-L1 adipocytes. Fatty acid synthase, which facilitates adipocyte lipogenesis, is downregulated by $1,25(OH)_2D$ in 2T3-L1 cells and VDR can inhibit lipid metabolism. Mice without VDR are resistant to high-fat diet-induced obesity, due probably to increased fatty acid β-oxidation in white adipose tissue, increased expression of uncoupling proteins in brown fat, and overall energy expenditure (Wong et al. 2009).

The connection of 25(OH)D with the lipid profile in children shows a strong correlation between lower HDL-C, high LDL-C, and TAG, on the one side, and the decreased level of serum 25(OH)D on the other (Alfawaz and Abdel Megeid 2013). The positive correlation between serum 25(OH)D and HDL-C is likely caused by vitamin D, which maintains the level of apolipoprotein A-1, the main component of HDL. This observation corresponds well with another study reporting an inverse correlation between vitamin D and total cholesterol (Kardas et al. 2013).

4.2 Type 2 Diabetes

Low 25(OH)D levels are frequent in patients with both type 1 and type 2 diabetes mellitus. In children with vitamin D deficiency, the risk of type 1 diabetes increases by approx. 200 % (Hypponen et al. 2001). Vitamin D deficiency increases insulin resistance, decreases insulin production, and is associated with the metabolic syndrome. Maestro et al. (2002) suggest a potentially beneficial influence of vitamin D on insulin sensitivity. They have shown that $1,25(OH)_2D$ treatment increased insulin receptor mRNA levels and insulin-stimulated glucose transport in U-937 promonocytic cells. This effect is possibly achieved through the upregulation of phosphatidylinositol 3-kinase activity. Higher levels of 25(OH)D can predict a better β-cell function and a lower glucose level in patients at risk of type 2 diabetes (Kayaniyil et al. 2011). In adults at risk of type 2 diabetes, short-term supplementation with cholecalciferol improves β-cell function. Joergensen et al. (2010) conducted similar research in patients with type 2 diabetes and showed that the baseline level of 25(OH)D below the 10th percentile predicts an increased risk of all-cause and cardiovascular mortality in such patients, but does not predict micro- or macroalbuminuria. Those results are consistent with other studies conducted in the general population and in patients with chronic kidney disease without diabetes.

Kayaniyil et al. (2011) examined a large group of multiethnic subjects and confirmed that a low serum 25(OH)D was significantly associated with a high incidence of the metabolic

syndrome. Multivariate linear regression analysis showed significant adjusted inverse association of 25(OH)D with waist circumference, triglyceride level, fasting insulin, and alanine transaminase. A cross-sectional study including 13,331 participants from NHANES III found low vitamin D levels to be associated with all-cause mortality. Also, childhood obesity is a risk factor for the metabolic syndrome and type 2 diabetes. It is important to identify modifiable risk factors for metabolic disorders to prevent the development of chronic diseases. Several studies have investigated the correlation between serum 25 (OH)D and impaired glucose tolerance, diabetes mellitus, dyslipidemia, metabolic syndrome, cardiovascular disease risk, and hypertension. The results are sometimes contradictory. There is a negative association between the serum 25(OH) D concentration and the level of fasting glucose (Kardas et al. 2013), insulin concentrations, insulin resistance-HOMA-IR (*homeostasis model assessment-insulin resistance*), HbA1c, and a positive association between 25(OH)D and insulin sensitivity-QUICKY (*quantitative insulin-sensitivity check index*) (Roth et al. 2011). This is in agreement with the results of other investigations, which show that 25(OH)D is positively associated with insulin sensitivity and negatively with serum insulin levels, insulin resistance (HOMA-IR), and a 2-h glucose level in an oral glucose tolerance test in obese children (Olson et al. 2012). Moreover, the association between 25(OH)D and insulin sensitivity or insulin resistance persisted after adjustment for body mass. Low 25(OH)D concentrations may be directly related to insulin resistance, irrespective of body fat mass. Low serum 25(OH)D concentrations apparently play a role in the pathophysiology of impaired glucose tolerance in children.

The reports are, however, contentious. A report, examining vitamin D-deficient (<10 ng/ml) and insufficient (10–20 ng/ml) obese children, has demonstrated that insulin resistance did not statistically differ from that in vitamin D-sufficient group (>20 ng/ml). There was no correlation between vitamin D level and insulin resistance in obese children and adolescents either. Insulin resistance was highly affected by BMI, BMI-SDS, and BMI% but less so by 25 (OH)D concentration. Some investigators demonstrate a negative correlation between 25(OH)D levels and HbA1c, while others report no correlation (Olson et al. 2012).

4.3 Cardiovascular Disease

Vitamin D deficiency is an important factor implicated in the development of cardiovascular diseases. Its pleiotropic effect is achieved through the activation of VDR. Calcitriol inhibits proliferation of vascular smooth muscle cells, expressing vitamin D receptors *via* an acute influx of calcium into cells. It has been shown that vitamin D deficiency increases cardiovascular disease mortality rate. Vitamin D has cardiovascular and renoprotective effects, because it has been associated with suppression of the renin-angiotensin-aldosterone system (RAAS), inhibits vascular calcification and atherosclerotic-plaque formation, has anti-inflammatory and immunomodulatory actions. Calcitriol therapy reduces blood pressure, plasma renin activity, and angiotensin II levels. Vitamin D deficiency causes an increase in the serum parathyroid hormone (PTH), which may contribute to cardiovascular disease, increasing cardiac contractility and myocardial calcification. Low 25(OH)D may influence the activity of macrophages and lymphocytes in the atherosclerotic plaques, thus promoting chronic inflammation in the artery wall. The studies by Van den Berghe et al. (2003) showed that vitamin D supplementation reduces the serum level of CRP, interleukin-6, and tissue matrix metalloproteinases. Hypovitaminosis D and secondary hyperparathyroidism may promote the acute phase response and may help to explain how vitamin D deficiency may act as a risk factor for cardiovascular diseases.

Hypertension is related to disturbed calcium metabolism. Calcium levels are lower in patients with hypertension, because they tend to have lower dietary calcium intake and a higher renal calcium loss than those in normotensive subjects.

There is an inverse association between the serum 25(OH)D level and diastolic blood pressure. Larsen et al. (2012) conducted a randomized, placebo-controlled, double-blind study in 130 hypertensive patients to investigate the relationship between supplementation of cholecalciferol and blood pressure. The patients received 3,000 IU (75 μg) cholecalciferol per day for 20 weeks, a dose that was deemed to effectively increase vitamin D levels in the blood. In a subgroup of 92 patients with baseline 25(OH)D levels <32 ng/ml, a significant decrease in 24-h systolic and diastolic blood pressure was found during cholecalciferol supplementation.

In an earlier study, Lind et al. (1988) showed that calcium metabolism plays a key role in blood pressure regulation. That prospective, double-blind, placebo-controlled study included 65 subjects with impaired glucose tolerance. The findings were that alphacalcidol supplementation (0.75 μg daily) over 12 weeks in patients with blood pressure of 150/90 mmHg or greater caused a significant reduction in both systolic and diastolic; the effect correlated with a reduction of PTH serum levels. Normal intracellular calcium levels help maintain normal blood pressure. This relation can explain the therapeutic effects of calcium-channel blockers in patients with hypertension. Low adenylate cyclase activity can lead to a decreased calcium re-uptake into the sarcoplasmic reticulum, an accumulation of intracellular free calcium, and an increase in vascular reactivity and blood pressure. The activity of this enzyme is calcitriol-dependent. An enhancement of adenylate cyclase activity may reduce intracellular calcium concentration. In children, the link between low 25(OH)D levels and elevated systolic and diastolic blood pressure has been confirmed (Kardas et al. 2013). However, another study reported no correlation between the level of vitamin D and blood pressure in a pediatric population (Olson et al. 2012).

Adiponectin gene expression may be upregulated by vitamin D. It has been reported that adipokine synthesis is regulated by 1,25 $(OH)_2D$. A recent study by Kardas et al. (2013) showed that adiponectin levels are lower in obese children (aged 10–16 years) and negatively associated with BMI. Moreover, adiponectin is strongly associated with HOMA index and fasting glucose. These results suggest that a low level of adiponectin is crucial in the development of insulin resistance and diabetes.

Further clinical investigations are warranted to examine the role of vitamin D in obesity and to determine the optimal mode of vitamin D supplementation, especially in obese children.

Conflicts of Interest No conflicts of interests were declared by the authors in relation to this article.

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