SUPPLEMENTATION OF VITAMIN D IN CHILDREN WITH OBESITY AND VITAMIN D DEFICIENCY - REVIEW OF OUTCOMES IN TERMS OF OBESITY PARAMETERS AND COMORBIDITIES

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Abstract:
In recent years, vitamin D deficiency and obesity in paediatric population have reached epidemic levels worldwide as crucial health concerns with far-reaching consequences. There has been a substantial growth in studies dedicated to these two public health issues over the last years. Numerous studies have confirmed that excess body weight has negative impact on vitamin D metabolism, leading to a higher risk of low levels of this essential vitamin, among individuals who are overweight or obese. Vitamin D deficiency may play a role in the development of obesity-related conditions as insulin resistance, type two diabetes, NAFLD and cardiovascular disease due to anti-inflammatory properties, impact on the endocrine system and metabolic functions of this vital nutrient. Vitamin D supplementation seems to be a beneficial addition to pharmacology and lifestyle changes during obesity treatment.

Keywords: children, obesity, vitamin D, vitamin D deficiency

Introduction and purpose:
In the past years the childhood obesity has grown to become a worldwide medical issue [1]. It is known that overweight in childhood and adolescence is an important risk factor for obesity in adulthood, as well as for the development of comorbidities. The factor contributing to obesity in children is a positive energy balance due to caloric intake in excess of caloric expenditure combined with a genetic predisposition for weight gain. The increasing prevalence of childhood obesity is associated with emergence of comorbidities previously considered to be diseases found mostly in adults, including type 2 diabetes mellitus [2], hypertension [3], non-alcoholic fatty liver disease [4], obstructive sleep apnoea [5], and dyslipidaemia [6].

Vitamin D is important regulator of calcium and phosphorus metabolism. Apart from its role in maintaining physiological condition of skeleton health, the results of previous studies have suggested that it also regulates influences glucose metabolism, hormone secretion and supports immune system functions [7-9]. Vitamin D deficiency is common health issue worldwide, especially in paediatric population [10]. Insufficient blood concentrations of vitamin D in childhood is associated with impaired bone mineralization but also with many other conditions, including increased risk of cardiovascular disease.
and metabolic disorders like insulin resistance, impaired glucose tolerance or type 2 diabetes [11,12].

Obese children are particularly prone to low blood concentrations of vitamin D (25(OH)D). The relationship between this hypovitaminosis and obesity has been widely studied in the general population [13,14]. Vitamin D deficiency and excess body fat have mutual negative effects, resulting from metabolic processes that generate accumulation of inactive forms and decreased vit D bioavailability, in addition to decreased tissue secretion and sensitivity to insulin. There is no consensus as to why vitamin D levels are lower in obese individuals. The main hypothesis may be the impaired absorption of vitamin D, which is fat soluble, by the excessive adipose tissue. Moreover, it could be related to reduced sun exposure because of less outdoor activities and incorrect eating habits practising by obese children [15].

The aim of this review is to assess the impact of vitamin D supplementation in obese children with deficiency of this vitamin on the parameters of obesity and its complications.

**Description of state of knowledge:**

**Obesity parameters**

Currently, in the paediatric population, the use of body mass index (BMI) is recommended to assess the degree of overweight and obesity. A child or adolescent with a BMI percentile between the 85th and 94th is considered overweight, while above the 95th percentile is considered obese. Determining the body weight, waist circumference and skin fold thickness also can be helpful to establish the degree of the problem.

Some studies shows that vitamin D supplementation may lead to modest reductions in body weight and body fat in obese children and adolescents, although the evidence is mixed. A triple-blind randomized controlled trial published in 2020 in BMC Pediatrics indicated that high dose of vitamin D (50,000 IU weekly) connected with dietary and physical modification during 24 weeks of treatment helps to improve anthropometric and body composition parameters in obese Sri Lankan children with vitamin D deficiency compared with low-dose and placebo group [16].

In another similar study published in 2020 different conclusion was established. The reduction in the level of BMI was not statistically significant between study and placebo group but in this trial the weekly dose of vitamin D was lower than in previous cited study [17].

These results may suggest that supplementation higher doses of vitamin D can act synergistically with dietary changes and physical activity to reduce obesity parameters in vitamin D deficient and obese individuals. Nevertheless, more randomized controlled trials are needed to determine the benefits of vitamin D supplementation in this group.

**Insulin resistance and impaired glucose metabolism**

Obesity, particularly the accumulation of visceral fat, is strongly associated with development of insulin resistance, characterized by a diminished response of cells in the
body to the effects of insulin, leading to inadequate glucose uptake. Both excess body weight and insulin resistance are major risk factor for developing type 2 diabetes [18].

The most common methods for assessment of carbohydrate metabolism in paediatric and adult population include biochemical parameters like fasting plasma glucose (FPG), haemoglobin A1c (HgbA1c) and serum insulin. The oral glucose tolerance test (OGTT) is also commonly used to indicate conditions such as impaired glucose tolerance or diabetes. The state of insulin resistance (IR) in studies is most often calculated using the homeostasis model assessment (HOMA-IR) [19,20].

Several studies indicated the correlations between low levels of vitamin D, insulin resistance and impaired glucose metabolism in obese children. [21,22]. In addition, a meta-analyse published in 2021 demonstrated a positive effect of vitamin D supplementation on lowering fasting glucose and triglycerides [23]. What is more, in randomized controlled trial from 2020 vitamin D3 supplementation led to reductions in fasting plasma glucose concentration and enhancement in insulin sensitivity in children with overweight or obesity [24].

The most probably clarification for this correlation is thesis where vitamin D may directly stimulate the secretion of insulin from pancreatic beta cells, but also enhance the sensitivity of insulin receptors in peripheral tissues [25,26]. Furthermore, vitamin D deficiency has been shown to increase inflammation in the body, which is a key factor in the development of insulin resistance [27,28].

These results submit that maintaining adequate vitamin D levels may be important for preventing or managing insulin resistance or even type 2 diabetes in this population.

**Non-alcoholic fatty liver disease**

NAFLD is a condition characterized by the accumulation of excess fat in the hepatic cells, which can progress to more severe forms of liver diseases. It is caused by different factors than alcohol consumption. Furthermore, this disease is commonly associated with excess body weight, insulin resistance and metabolic syndrome. Obesity is one of the most considerable risk factors for the development and progression of NAFLD. Studies have consistently exhibited that individuals who are overweight or obese are more likely to develop NAFLD compared to people with a normal weight in paediatric as well as in adult population [29,30].

Serum levels of clinically approved markers of hepatic steatosis include biochemical parameters like aspartate-aminotransferase (AST), alanine-aminotransferase (ALT) and glutamate-pyruvate-transaminase (GGT). Moreover, ultrasound scan (USS), liver biopsies and magnetic resonance imaging (MRI) are commonly used to assess the severity of NAFLD [31].

Study published in Journal of Gastroenterology and Hepatology in 2014 showed noticeable association between low serum 25-hydroxyvitamin D concentration and NAFLD in adolescents, regardless of insulin resistance and obesity [32]. A meta-analysis from 2019 also indicated this correlation [33]. Presumably, deficiency in vitamin D may contribute to the development or progression of NAFLD through impact this vitamin on
insulin sensitivity and inflammatory processes, which are important factors in the pathogenesis of hepatic steatosis [34].

Moreover, the results of a randomized controlled trial on adults with NAFLD and vitamin D deficiency demonstrated a significant reduction in serum ALT and an increase in beneficial adiponectin levels after 6 months of lifestyle modification and vitamin D supply compared to control group (only with lifestyle modification) [35].

Therefore, vitamin D supplementation seems to have potential benefits in treatment of non-alcoholic fatty liver disease in children. However, the studies have mainly shown associations, but not necessarily a direct cause-and-effect relationship and long-term efficacy of intervention with vitamin D in treatment NAFLD in this population. In this subject more randomized-controlled trials on children and adolescent are needed to better assess the effectiveness of vitamin D supplementation of therapy in NAFLD.

**Cardiovascular diseases**

Another metabolic dysfunction observed in obesity includes dyslipidaemia which is abnormal lipid profile characterized by elevated levels of triglycerides (TG), low-density lipoprotein cholesterol (LDL-C) with small dense low-density lipoprotein-cholesterol (sdLDL-C) and decreased levels of high-density lipoprotein cholesterol (HDL-C). What is more, obese and overweight individuals are more prone to develop hypertension, marked by persistently elevated systolic blood pressure above 140 mmHg and/or diastolic blood pressure above 90 mm Hg. These lipid and vascular abnormalities contribute to an increased risk of cardiovascular diseases, including atherosclerosis, coronary artery disease and stroke [36,37].

Several studies have indicated a potential link between low serum 25-hydroxyvitamin D level and higher risk of cardiovascular diseases, but the exact mechanisms of the relationship are still not fully understood [38-40]. One of proposed explanation is the role of vitamin D in suppressing of renin production which is a key component of the renin-angiotensin-aldosterone system. Thus, adequate level of this vitamin may potentially reduce blood pressure and the risk of hypertension [41]. It is also suggested that vitamin D due to its numerous receptors, including in liver and adipose tissue may influence lipid metabolism by regulating the expression of genes involved in cholesterol metabolism [42]. Furthermore, vitamin D and its anti-inflammatory properties may modulate the immune response, potentially reducing inflammation and protecting against damage in the vascular wall [43,44].

Nevertheless, studies directly examining the effects of vitamin D supplementation on markers of cardiometabolic risk in paediatric population with obesity have yielded inconsistent results. A meta-analysis published in 2021 have established that vitamin D supplementation ≥200,000 IU demonstrated a positive impact on reducing fasting glucose and triglycerides levels. Nonetheless, there was no significant effect observed on other cardiometabolic risk factors, such as HDL-C, LDL-C, TC, blood pressure, and waist circumferences [23]. Another meta-analysis of randomized controlled trials from 2022 has shown similarly, no significant improvement in cardiometabolic and bone-metabolic indicators after vitamin D intervention. However, the authors suggest that vitamin D
supplementation at higher daily doses, (>4000 IU per day), may have the potential to decrease CRP (C-reactive protein) levels, increase HDL levels and improve insulin sensitivity in overweight or obese children [45].

These results provide a thesis that maintaining sufficient vitamin D levels may have potential, modest benefits for cardiovascular health in paediatric patients with obesity. Importantly, further research, including clinical trials, are needed to better understand the relationship between vitamin D levels and cardiovascular diseases and to determine whether vitamin D supplementation can effectively reduce the risk of cardiovascular diseases.

**Summary**

In conclusion, maintaining an adequate level of vitamin D seems to have a beneficial impact on preventing and supporting the treatment of obesity-related diseases. Therefore, vitamin D supplementation has the potential as an promising addition in the obesity treatment in children with a deficiency of this vitamin. However, it is important to notice that the most crucial strategy in managing obesity and its comorbidities is weight loss through dietary changes and physical activity. Medications and supplements should only support this process. Nevertheless, additional research is necessary to establish the precise role of vitamin D in pathogenesis of obesity-related diseases in children and to determine optimal doses of vitamin D in this population.

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