HOW DOES INSULIN RESISTANCE AFFECT VITAMIN D LEVELS IN OBESE CHILDREN AND ADOLESCENTS

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Abstract

Background: Childhood obesity is a growing global concern, often linked to metabolic disorders such as insulin resistance and vitamin D deficiency. Research suggests an inverse relationship between vitamin D levels and insulin resistance, but the underlying mechanisms remain unclear. This study aims to investigate the impact of vitamin D supplementation on insulin resistance in overweight and obese children and adolescents.

Methods: This study was conducted on 100 children and adolescents (aged 4–18 years) with a BMI above the 85th percentile and vitamin D deficiency (serum 25-hydroxyvitamin D < 20 ng/ml). Participants received vitamin D supplementation (50,000 IU weekly for 8 weeks, followed by 1,000 IU daily for 3 months). Pre- and post-intervention assessments included BMI, fasting blood sugar (FBS), insulin levels, HOMA-IR index, and vitamin D levels. Statistical analysis was performed using SPSS, with significance set at $p < 0.05$.

Results: Following vitamin D supplementation, a significant increase in serum vitamin D levels ($p < 0.001$) and a reduction in BMI ($p = 0.008$) and FBS ($p = 0.028$) were observed. However, there were no significant changes in insulin levels ($p = 0.143$) or HOMA-IR index ($p = 0.097$). Post-intervention analysis revealed a negative correlation between vitamin D levels and BMI, insulin, HOMA-IR, and FBS.

Conclusion: Vitamin D supplementation effectively increased serum vitamin D levels and improved BMI and FBS in obese children and adolescents. However, it did not significantly impact insulin resistance within the study period. Longer intervention durations may be necessary to assess potential effects on insulin sensitivity.

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Introduction

In recent centuries, significant advancements in community health and widespread vaccination efforts have led to the eradication or control of many infectious and contagious diseases. However, lifestyle changes, particularly physical inactivity and poor dietary habits, have contributed to a rise in obesity and various chronic conditions linked to it, such as diabetes, cardiovascular disease, hypertension, and fatty liver disease (1). The shift towards a more sedentary lifestyle, coupled with increased consumption of energy-dense foods, has resulted in a global obesity epidemic affecting both children and adults (2).

Obesity and overweight are now among the most pressing public health concerns worldwide. Currently, one-third of children are classified as either overweight or obese, which not only increases the likelihood of developing chronic health conditions but also places significant financial strain on both families and healthcare systems (3). The economic burden associated with obesity stems from increased healthcare utilization, higher medical costs, and the long-term impact of obesity-related diseases (4).

Globally, the number of obese children and adolescents has surged from 11 million in 1975 to 124 million in 2016, marking a tenfold increase in childhood obesity rates (5). This alarming trend is attributed to various factors, including environmental influences, genetic predisposition, and behavioural patterns such as reduced physical activity and excessive screen time (6). The rising prevalence of childhood obesity underscores the need for effective intervention strategies to mitigate its long-term consequences (7).

Obesity in children and adolescents can lead to serious health issues, including metabolic, cardiovascular, and respiratory complications. Moderate to severe obesity is associated with an increased risk of hyperlipidaemia, early-onset puberty, obstructive sleep apnea, pancreatitis, gallbladder disease, and diabetes (8). Additionally, obesity is linked to Orthopedic problems, psychological distress, and a reduced quality of life, further emphasizing its negative impact on overall well-being (9).

Among the various health concerns associated with obesity, vitamin D deficiency has gained significant attention in recent years. Vitamin D is an essential fat-soluble vitamin with a well-established role in maintaining calcium and phosphorus balance in the body and supporting bone health (10). Beyond its traditional functions, vitamin D has been implicated in various physiological processes, including immune regulation, cardiovascular health, and glucose metabolism (11).

Currently, vitamin D deficiency is a widespread concern affecting individuals across all age groups, with around 1 billion people globally reported to have inadequate vitamin D levels (serum 25-hydroxyvitamin D less than 30 ng/ml) (12). The prevalence of vitamin D deficiency varies depending on factors such as geographic location, sun exposure, dietary intake, and skin pigmentation (13). Populations living in regions with limited sunlight exposure, as well as those with darker skin tones, are particularly vulnerable to vitamin D insufficiency (14).

Various studies report that between 10% and 40% of children and adolescents suffer from vitamin D deficiency, with variations due to seasonality, latitude, and ethnicity (15). Some research suggests that vitamin D deficiency is more prevalent among obese individuals due to altered metabolism and sequestration of vitamin D in adipose tissue (16). This sequestration reduces the bioavailability of circulating vitamin D, leading to lower serum levels in overweight and obese children compared to their lean counterparts (17).

In children and adolescents, vitamin D deficiency is quite common, with prevalence rates ranging from 30% to 80% across different studies (18). The exact mechanisms linking obesity to vitamin D deficiency remain under investigation, but it is hypothesized that increased adiposity leads to decreased bioavailability of vitamin D, impaired synthesis, and alterations in metabolic pathways (19). The relationship between vitamin D and obesity is further complicated by lifestyle factors, including dietary habits, physical activity levels, and genetic predisposition (20).

Research indicates that obese children tend to have lower levels of vitamin D compared to their non-obese peers (21). Moreover, individuals with higher vitamin D levels tend to exhibit better insulin sensitivity, suggesting a potential role of vitamin D in glucose metabolism and insulin regulation (22). Insulin resistance, a hallmark of metabolic dysfunction, is commonly observed in obese individuals and is a significant risk factor for the development of type 2 diabetes (21).

Although the exact mechanisms behind the relationship between vitamin D and insulin resistance are not fully understood, several pathways have been proposed. One hypothesis suggests that vitamin D enhances insulin secretion by acting on pancreatic β-cells, which are responsible for insulin production (20). Additionally, vitamin D may influence insulin sensitivity by modulating the expression of insulin receptors on target tissues, thereby improving glucose uptake and utilization (19).

Another proposed mechanism involves the role of vitamin D in reducing systemic inflammation, a key contributor to insulin resistance (18). Chronic low-grade inflammation, commonly observed in obesity, is characterized by increased levels of pro-inflammatory cytokines such as tumour necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6) (17). These inflammatory mediators have been shown to impair insulin signalling pathways, leading to decreased insulin sensitivity (16).

Vitamin D may also enhance the synthesis of insulin receptors by binding to nuclear receptors on the genes responsible for insulin receptor production. This process increases the presence of insulin-dependent glucose transporter (GLUT4) on the cell membrane, facilitating glucose uptake by peripheral tissues (15). As a result, higher vitamin D levels may contribute to improved glucose homeostasis and reduced risk of insulin resistance (14).

Additionally, vitamin D boosts the expression of the PPARγ gene, which plays a crucial role in fatty acid metabolism and insulin sensitivity (13). Activation of PPARγ has been associated with improved adipocyte function, reduced lipid accumulation, and enhanced insulin responsiveness (12). These effects collectively contribute to a lower risk of metabolic disorders in individuals with sufficient vitamin D levels (11).

With its well-documented anti-inflammatory properties, vitamin D may also reduce the impact of inflammatory cytokines on circulating adiponectin, an adipocyte that plays a key role in regulating insulin sensitivity (10). Higher adiponectin levels are associated with improved glucose metabolism and reduced risk of type 2 diabetes, further highlighting the potential benefits of vitamin D in metabolic health (9).

Moreover, studies have suggested that vitamin D may influence the gut microbiota, which plays a significant role in metabolic regulation and obesity-related inflammation (8). Alterations in gut microbiota composition have been linked to increased intestinal permeability, endotoxemia, and chronic inflammation, all of which contribute to insulin resistance (7). By modulating gut microbial diversity, vitamin D may help mitigate these effects and improve metabolic outcomes (6).

In light of these findings, the interplay between obesity, vitamin D deficiency, and insulin resistance presents a compelling area of research. Understanding the underlying mechanisms could lead to novel therapeutic interventions aimed at reducing obesity-related complications and improving metabolic health (5). Targeted supplementation strategies, lifestyle modifications, and public health initiatives may be essential in addressing vitamin D deficiency and its associated metabolic consequences (4).

Further studies are warranted to establish causality and explore the potential benefits of vitamin D supplementation in improving insulin sensitivity among obese children and adolescents (3). While existing evidence suggests a strong correlation, longitudinal studies and randomized controlled trials are needed to confirm these associations and determine optimal intervention strategies (2).

Given the growing prevalence of childhood obesity and its metabolic implications, addressing vitamin D deficiency should be a priority in public health policies and clinical practice (1). Early detection and management of vitamin D insufficiency, particularly in high-risk populations, could play a crucial role in mitigating long-term health consequences and improving overall well-being.

Materials and Methods

This research utilizing convenience sampling to select participants. The study sample included 100 children and adolescents aged between 4 and 18 years who visited an endocrinology clinic with a BMI above the 85th percentile for their age and gender and had vitamin D deficiency (defined as serum vitamin D levels below 20 ng/dL). After collecting medical history and performing physical examinations, blood pressure was recorded using a mercury sphygmomanometer following a 5-minute rest period.

Subsequently, the participants' height and weight were measured, and BMI was calculated using the formula [weight (kg) / height (m)²], with results compared to age- and gender-specific BMI percentile charts. Puberty stage was assessed using the Tanner criteria by a pediatric endocrinologist. Initial measurements included 25-hydroxyvitamin D levels, TSH, T4, aspartate transaminase (AST), alanine transaminase (ALT), creatinine (Cr), blood urea nitrogen (BUN), lipid profile, insulin, and fasting blood sugar (FBS).

The participants were administered a weekly dose of 50,000 units of vitamin D for 8 weeks, followed by a daily dose of 1,000 units for the subsequent 3 months. After the 3-month period, the 25-hydroxyvitamin D, insulin, and FBS levels were re-measured.

FBS was measured using the glucose oxidase enzyme method with the COBAS INTEGRA 400 plus analyser (Roche Co., Germany). Total triglyceride and cholesterol levels were determined through enzymatic colorimetric tests with glycerol phosphate oxidase and cholesterol oxidase using a kit from Pars Azmoon Co. (Iran) and the COBAS INTEGRA 400 plus analyser (Roche Co., Germany). HDL cholesterol levels were measured after precipitating Apo lipoproteins with phosphotungstic acid using the COBAS INTEGRA 400 plus analyser (Roche Co., Germany). LDL cholesterol levels were calculated using the Fried Wald formula. Insulin levels were assessed with the Electrochemiluminescence method using the Cobas e 411 (Roche Co., Germany).

Insulin resistance was calculated using the HOMA-IR formula, which incorporates fasting blood sugar and fasting insulin values, as described by the equation (39):

HOMA-IR = [fasting insulin (μU/ml)] × [fasting glucose (mg/dl)] / 405

Statistical Analysis

The data were analyzed using SPSS software, with descriptive statistics (mean, standard deviation, frequency) as well as paired t-tests and Pearson correlation coefficients. A p-value of less than 0.05 was considered statistically significant.

Results

In this semi-experimental study, a total of 100 children and adolescents participated, with a mean age of 9.69 ± 3.4 years (ranging from 4.8 to 17.2 years) and an average weight of 53.92 ± 22.46 kg. Of the participants, 39.7% were male, and 60.4% were female. The distribution of puberty stages was as follows: 34 participants in the first stage, 4 in the second, 2 in the third, and 13 in the fourth stage. Table 1 presents the metabolic characteristics of the study population.

According to the results shown in Table 2, there was a significant reduction in body mass index (BMI) following the intervention (P=0.008). However, no significant changes were observed in insulin levels and the HOMA-IR index before and after the intervention.

The mean fasting blood sugar (FBS) levels before and after the intervention were 91.04 ± 7.87 mg/dl and 89.57 ± 6.08 mg/dl, respectively, with a statistically significant difference (P=0.028). Similarly, the mean serum vitamin D levels before and after the intervention were 13.51 ± 4.97 ng/ml and 46.16 ± 15.27 ng/ml, showing a significant increase (P<0.05).

There was a significant positive correlation between the HOMA-IR index and BMI after the intervention, as well as a significant negative correlation between HOMA-IR and vitamin D levels post-intervention. Furthermore, post-intervention vitamin D levels were significantly inversely correlated with BMI, insulin, HOMA-IR, and FBS (Table 1, Table 2).

Discussion

The findings of this study suggest that vitamin D supplementation in overweight and obese children and adolescents led to a significant increase in serum vitamin D levels, as well as a notable reduction in BMI and fasting blood sugar (FBS). However, there was no substantial impact on serum insulin

Table 1. Metabolic Characteristics of Participants.

Index	Minimum	Maximum	Mean ± Standard Deviation
Systolic Blood Pressure (mmHg)	75	125	99.15 ± 11.57
Diastolic Blood Pressure (mmHg)	50	90	68.68 ± 9.56
Total Cholesterol (mg/dL)	119	198	155.26 ± 20.17
Total Triglyceride (mg/dL)	47	179	116.09 ± 37.42
HDL Cholesterol (mg/dL)	26	85	46.43 ± 9.75
LDL Cholesterol (mg/dL)	33	170	92.99 ± 28.83
Blood Urea Nitrogen (mg/dL)	5	26	13.52 ± 4.35
Creatinine (mg/dL)	0.32	1	0.62 ± 0.16
Aspartate Aminotransferase (unit/L)	13	61	25.75 ± 8.40
Alanine Aminotransferase (unit/L)	8	44	22.87 ± 9.48
TSH (μ unit/mL)	0.51	5.3	2.43 ± 1.06
T4 (nmol/L)	80	162	123.74 ± 18.29

Table 2. BMI, Fasting Blood Sugar, Insulin, and Vitamin D Levels Before and After the Intervention.

Index	Pre-Intervention Mean ± SD	Post-Intervention Mean ± SD	Significance Level
BMI	25.13 ± 4.85	24.74 ± 4.70	0.008
HOMA-IR	4.48 ± 3.30	3.77 ± 2.12	0.097
Fasting Blood Sugar (mg/dL)	91.04 ± 7.87	89.57 ± 6.08	0.028
Insulin (µU/mL)	19.72 ± 14.28	17.22 ± 8.80	0.143
Vitamin D (ng/mL)	13.51 ± 4.97	46.16 ± 15.27	<0.001

or the HOMA-IR index. These results highlight the potential role of vitamin D in metabolic regulation, particularly in relation to glucose metabolism and weight management. Given the rising prevalence of obesity and metabolic disorders among children and adolescents, understanding the benefits of vitamin D supplementation is crucial.

In contrast, Baziar et al. (2014) reported that vitamin D supplementation in individuals with type 2 diabetes resulted in increased serum vitamin D and significant reductions in FBS, fasting insulin, and HOMA-IR (15). This discrepancy may be attributed to differences in the study population, as type 2 diabetes patients often have higher levels of insulin resistance compared to non-diabetic obese children and adolescents. Similarly, Talaei et al. (2011) found that vitamin D supplementation significantly lowered FBS, insulin, and insulin resistance in type 2 diabetes patients (16). This suggests that vitamin D may exert stronger effects on insulin sensitivity in individuals with pre-existing metabolic dysfunctions.

On the other hand, a study by Blenchia et al. (2013) on obese children and adolescents revealed that a three-month vitamin D treatment had no impact on fasting insulin, FBS, or the HOMA-IR index. However, after six months of treatment, significant reductions in insulin levels and improvements in HOMA-IR were observed (17). The findings of our study, with its shorter duration, demonstrated a significant reduction in FBS but no significant changes in insulin levels or insulin resistance. This discrepancy could be attributed to the difference in study length, indicating that the effects of vitamin D on insulin sensitivity may require longer durations of intervention to become apparent.

In line with our findings, a negative correlation between vitamin D levels and BMI, insulin, HOMA-IR, and FBS was observed after intervention. This is consistent with the study by Baynes et al. (1997), where serum vitamin D levels were inversely related to insulin and glucose tolerance (18). These results suggest that vitamin D may have a protective role against metabolic disturbances associated with obesity. Kelly et al. (2011) also found that vitamin D levels in obese children and adolescents had a significant inverse correlation with BMI, FBS, insulin levels, and insulin resistance (19). This highlights the importance of maintaining adequate vitamin D levels in populations at risk of metabolic disorders.

Alemzadeh et al. (2008) similarly observed that individuals with low vitamin D levels had higher BMI, fat mass, and reduced insulin sensitivity (20). The biological mechanisms underlying these associations are not entirely understood, but vitamin D may influence adipocyte function and lipid metabolism. The decrease in serum vitamin D levels with increased body fat is likely due to the lipophilic nature of vitamin D, which leads to its accumulation in adipose tissue (16). This sequestration may reduce the bioavailability of vitamin D, thereby limiting its beneficial effects on glucose metabolism and insulin sensitivity.

Furthermore, low vitamin D levels may stimulate the secretion of parathyroid hormone (PTH), which has been linked to increased body fat. Elevated PTH levels have been shown to promote lipogenesis and inhibit lipolysis, contributing to weight gain and insulin resistance (17). Additionally, insufficient vitamin D reduces calcium absorption in the intestines, which may further contribute to weight gain by affecting fat metabolism and energy balance.

The underlying mechanisms connecting vitamin D levels with insulin resistance are not fully understood, but it is believed that vitamin D may enhance the synthesis and presence of glucose-dependent insulin receptors (GLUT4) in cell membranes, thereby improving insulin sensitivity (13). The role of GLUT4 in glucose uptake is critical in maintaining normal blood glucose levels, and vitamin D may facilitate this process through its influence on gene expression and receptor activation.

Additionally, vitamin D has been shown to activate the PPARγ gene, which further enhances insulin sensitivity (14). PPARγ plays a key role in adipocyte differentiation and glucose homeostasis, and its activation has been associated with improved insulin action. This suggests that vitamin D may exert its beneficial effects on insulin resistance through multiple pathways, including genomic and non-genomic mechanisms.

Vitamin D also plays a role in modulating the renin-angiotensin system by reducing renin gene expression and inhibiting angiotensin receptors, both of which are involved in insulin resistance, blood pressure regulation, and inflammation (21). Dysregulation of the renin-angiotensin system has been linked to metabolic syndrome and cardiovascular diseases, further highlighting the potential systemic benefits of vitamin D supplementation.

Furthermore, vitamin D deficiency may lead to increased PTH levels, which are associated with obesity, lipolysis, and insulin resistance (22). The relationship between PTH and metabolic dysfunction suggests that vitamin D supplementation could be beneficial in regulating hormonal pathways involved in weight regulation and glucose metabolism.

Nimitphong et al. (2009) found a significant relationship between vitamin D levels and adiponectin in individuals with impaired glucose tolerance. Impaired glucose tolerance, an inflammatory condition likely triggered by cytokines such as tumour necrosis factor-alpha and interleukin-1, is linked to decreased adiponectin levels (12). Adiponectin is an anti-inflammatory adipokine that improves insulin sensitivity and lipid metabolism.

As vitamin D has anti-inflammatory properties, it may reduce the impact of these inflammatory cytokines on circulating adiponectin, which in turn could enhance insulin sensitivity (12). Chronic low-grade inflammation is a key contributor to insulin resistance, and vitamin D's role in modulating inflammation may be an important factor in its effects on glucose homeostasis.

The potential benefits of vitamin D supplementation extend beyond glucose metabolism and insulin resistance. Studies have also suggested a role for vitamin D in appetite regulation and energy expenditure, which could contribute to its effects on BMI reduction (16). The interaction between vitamin D, leptin, and ghrelin—hormones involved in hunger and satiety—warrants further investigation.

Although our study demonstrated positive effects of vitamin D supplementation on BMI and FBS, further research is needed to clarify its long-term impact on insulin resistance and other metabolic markers. Differences in baseline vitamin D status, genetic predisposition, and dietary factors may all influence the extent of vitamin D's effects on metabolic health.

In conclusion, vitamin D supplementation significantly reduced BMI and FBS while significantly increasing vitamin D levels in overweight children and adolescents. Additionally, a notable inverse correlation was found between vitamin D levels and insulin, BMI, HOMA-IR, and FBS after the intervention. These findings support the potential role of vitamin D in metabolic health and highlight the need for further research to optimize supplementation strategies in at-risk populations.

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