

# Effect of Vitamin D on Insulin Resistance in Overweight and Obese Children and Adolescents With Vitamin D Deficiency

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**Abstract-** Obesity is one of the major health issues in developed and developing countries, which has been increasing in recent decades. Obesity is one of the important risk factors for type 2 diabetes by developing insulin resistance. The purpose of this study was to investigate the effect of vitamin D on insulin resistance in overweight and obese children and adolescents with vitamin D deficiency. In this interventional study, 53 overweight and obese children and adolescents with vitamin D deficiency referred to the Endocrinology Clinic of Shahrekord University of Medical Sciences were included. The height and weight of participants were measured, and their Body Mass Index (BMI) calculated. To participants, 50,000 units of vitamin D were administered weekly for 8 weeks, and then 1000 units were orally administered daily for 3 months. Before and after the intervention, levels of vitamin D, insulin, and fasting blood sugar were measured. The HOMA-IR was also calculated as an indicator of insulin resistance. After the intervention, serum vitamin D significantly increased, and BMI and fasting blood sugar significantly decreased ( $P < 0.05$ ). The insulin resistance index did not change significantly during the intervention ( $P > 0.05$ ). After the intervention, HOMA-IR had a significant direct correlation with body mass index, insulin, and fasting blood sugar and a significant inverse correlation with vitamin D ( $P < 0.05$ ). Vitamin D had a significant inverse correlation with BMI, insulin, and fasting blood sugar after the intervention ( $P < 0.05$ ). Oral treatment with vitamin D significantly increased serum vitamin D levels and significantly decreased BMI and fasting blood sugar in obese and overweight children.

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## Introduction

During the recent centuries, many of the infectious and contagious diseases have been eradicated or controlled due to the improvement of community health and basic measures to vaccinate children, but a lifestyle change, including physical inactivity and inappropriate diet, have led to an increase of obesity and several chronic conditions caused by it, such as diabetes, cardiovascular disease, high blood pressure and fatty liver (1).

Today, one-third of children are suffering from obesity and overweight, which, in addition to increasing

the risk of chronic diseases, has led to high costs for families and health systems (2).

According to global statistics, the number of obese children and adolescents has increased from 11 million in 1975 to 124 million in 2016, indicating a 10-fold increase in childhood obesity (3).

Obesity can cause major problems in childhood and adolescence. Moderate to severe obesity is associated with increased risk of hyperlipidemia, precocious puberty, obstructive sleep apnea, pancreatitis, gallbladder disease, and diabetes (4).

Vitamin D is an essential vitamin for the body and fat-soluble vitamins. The well-known function of

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vitamin D in the human body is to preserve homeostasis of calcium and phosphorus and contribution to bone formation (5).

Currently, vitamin D deficiency is a global problem in all age groups. Estimates show that around 1 billion people worldwide have vitamin D deficiency (serum 25-hydroxyvitamin D less than 30 ng/ml) (6).

In various studies, the prevalence of vitamin D deficiency in children and adolescents was reported to be between 10% and 40%. Varied figures are due to differences in season, latitude, race, and ethnicity (7).

Vitamin D deficiency is common in Iranian children and adolescents, with a prevalence ranging from 30% to 80% reported in various studies (8).

Studies have also shown that obese children have lower levels of vitamin D than their thin peers (9,10). In addition, it has been reported that insulin sensitivity is comparatively higher in people with higher levels of vitamin D (11,12).

The reason for this relationship remains to be fully understood, but there are several mechanisms that relate vitamin D to insulin resistance through three main pathways, including the impact on insulin secretion, the resistance of peripheral tissues to insulin and inflammation (12).

Vitamin D can increase the synthesis of these receptors by binding to the nuclear receptor on the synthesizing gene of the insulin membrane receptors, leading to the presence of more insulin-dependent glucose transporter (GLUT4) in the cell membrane (13).

Vitamin D also increases the expression of the PPAR $\gamma$  gene, which improves the metabolism of fatty acids and increases insulin sensitivity (14).

Vitamin D has anti-inflammatory properties and may reduce the effect of inflammatory cytokines on circulating adiponectin and thereby increase serum levels of adiponectin and insulin sensitivity (12).

Regarding the above-mentioned, it seems that vitamin D plays an important role in the prevention of type 2 diabetes by affecting insulin function. Therefore, this study was conducted to investigate the effect of vitamin D on insulin resistance in overweight and obese children and adolescents.

## Materials and Methods

The present study was a semi-experimental (before and after intervention) research, and the convenience sampling was used to select participants. The sample size was 53 children and adolescents aged 4-18-year-old who referred to the endocrinology clinic of Shahrekord

University of Medical Sciences with a BMI of over 85 percentiles for age and sex and had vitamin D deficiency (vitamin D levels below 20 ng/dL). After taking the history and physical examination, blood pressure was measured using a mercury barometer after 5 minutes of rest.

Then, the height and weight of the children were measured, and the BMI was calculated using the formula [weight (kg)/height (m)<sup>2</sup>] and was evaluated according to the age and sex on the BMI percentile chart. The puberty stage was assessed by Tanner criteria by a pediatric endocrinologist. At the beginning of the study, the levels of 25-hydroxyvitamin D, TSH, T4, aspartate transaminase (AST), alanine transaminase (ALT), creatinine (Cr), blood urea nitrogen (BUN), lipid profiles, insulin and fasting blood sugar (FBS) were measured.

To participants, 50,000 units of vitamin D were administered weekly for 8 weeks, and then 1000 units were orally administered daily for 3 months. At the completion of three months, the 25-hydroxy vitamin D, insulin, and FBS were measured again.

FBS was determined by the glucose oxidase enzyme calorimetry using The COBAS INTEGRA 400 plus analyzer (Roche Co., Germany).

The total triglyceride and cholesterol levels were determined by the enzymatic colorimetric test with glycerol phosphate oxidase and cholesterol oxidase using the kit (Pars Azmoon Co., Iran) and the COBAS INTEGRA 400 plus analyzer (Roche Co., Germany).

Measurement of HDL cholesterol was performed after precipitation of apolipoproteins with phosphotungstic acid by the COBAS INTEGRA 400 plus analyzer (Roche Co., Germany).

Cholesterol LDL was calculated by the Friedwald formula. Insulin was determined using the Electrochemiluminescence method using the Cobas e 411 (Roche Co., Germany).

Insulin resistance was calculated by the HOMA-IR formula. In the HOMA-IR model, fasting blood sugar and fasting insulin are used to measure insulin resistance according to the following equation (39):

$$\text{HOMA-IR} = [\text{fasting insulin } (\mu\text{U/ml})] \times [\text{fasting glucose (mg/dl)}] / 405$$

## Statistical analysis

Data were analyzed by SPSS software using descriptive statistics (frequency, mean, standard deviation), paired *t*-test, and Pearson correlation coefficient. *P* < 0.05 was considered a significance level.

**Results**

In this semi-experimental study, 53 children and adolescents with a mean age of 9.69±3.4 (range: 4.8 to 17.2) years and a mean weight of 53.92±22.46 kg were studied. 21 (39.7%) were male, and 32 (60.4%) were female. The frequency of the first, second, third, and fourth stages of puberty was 34, 4, 2, and 13, respectively. The metabolic characteristics of the subjects under study are shown in Table 1.

According to the results of Table 2, the body mass index decreased significantly during the intervention (P=0.008). Insulin and HOMA-IR index before and after the intervention were not significantly different.

The mean fasting blood sugar before and after the

intervention was 91.04±7.87 and 89.57±6.08 mg/dl, respectively, with a significant difference (P=0.028).

The mean serum vitamin D before and after the intervention was 13.51±4.97 and 46.16±15.27 ng/ml, respectively, with a statistically significant difference (P<0.05).

According to the results of Table 3, the HOMA-IR index had a significant positive correlation with BMI after the intervention and had a significant inverse correlation with vitamin D after the intervention.

After the intervention, vitamin D had a significant inverse correlation with body mass index, insulin, and HOMA-IR after the intervention, and fasting blood sugar.

**Table 1. Metabolic characteristics of subjects understudy**

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
High-density lipoprotein (mg/dL)	26	85	46.43±9.75
Low-density lipoprotein (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
Thyroid-stimulating hormone (µ unit/mL)	0.51	5.3	2.43±1.06
T4 (nmol/L)	80	162	123.74±18.29

**Table 2. Body mass index, fasting blood sugar, insulin and vitamin D in studied children and adolescents before and after the intervention**

Indices	Pre-intervention	Post-intervention	Significance level
	Mean±standard deviation	Mean±standard deviation	
BMI	25.13±4.85	24.74±4.70	0.008
HOMA-IR	4.48±3.30	3.77±2.12	0.097
FBS Fasting blood sugar (mg/dL)	91.04±7.87	89.17±6.08	0.028
Insulin (micro unit/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

**Table 3. Pearson correlation coefficients of body mass index, insulin, HOMA-IR, fasting blood sugar and vitamin D after the intervention**

Variable	Post-intervention body mass index	Post-intervention insulin	Post-intervention HOMA-IR	Post-intervention fasting blood sugar
Post-intervention insulin	r=0.604 P<0.001	1		
Post intervention HOMA-IR	r=0.605 P<0.001	r=0.991 P<0.001	1	
Post-intervention fasting blood sugar	r=0.355 P=0.009	r=0.378 P=0.005	r=0.444 P<0.001	1
Post intervention vitamin D	r= - 0.375 P=0.006	r= - 0.300 P=0.029029/0P=	r= - 0.308 P=0.025	r= - 0.274 P= 0.047

## Discussion

According to the results of the leading study, vitamin D administered to children and adolescents with overweight and obesity caused a significant increase in serum vitamin D and a significant decrease in BMI and FBS but did not have a significant effect on HOMA-IR and insulin serum.

In the study of Baziar *et al.*, (2014), the administration of vitamin D to people with type 2 diabetes increased serum levels of vitamin D and significantly decreased FBS, fasting insulin, and HOMA-IR (15).

In the study of Talaei *et al.*, (2011), oral administration of vitamin D significantly reduced FBS, insulin, and insulin resistance in patients with type 2 diabetes (16).

In the study of Blenchia *et al.*, (2013), in obese children and adolescents, vitamin D treatment for 3 months did not have any change in fasting insulin, fasting blood sugar and HOMA-IR index, but after 6 months a significant decrease in insulin levels and improvement of HOMA-IR index were observed (17).

In our study, although vitamin D administration significantly reduced FBS, it did not have a significant effect on insulin levels and insulin resistance, which could be due to the shorter period of study than that of Belenchia *et al.*, study.

According to the results of our study, vitamin D levels after intervention were significantly and inversely correlated with BMI, insulin, HOMA-IR, and FBS. In agreement with these results, in the study of Baynes *et al.*, (1997), serum vitamin D level was inversely correlated with serum insulin and glucose tolerance test (18).

In the study of Kelly *et al.*, (2011), serum vitamin D levels in obese children and adolescents had a significant inverse correlation with BMI, fasting blood sugar, insulin levels, and insulin resistance (19).

Another study by Alemzadeh *et al.*, (2008) found that people with hypovitaminosis and vitamin D deficiency had higher BMI and a higher fat mass and lower insulin sensitivity (20).

Generally, with the increase in body fat, the level of serum vitamin D decreases, which is probably due to the nature of the lipophilic nature of vitamin D and its precipitation in adipose tissue (16).

In addition, it has been reported that low levels of serum vitamin D stimulate parathyroid hormone secretion, and high levels of the parathyroid hormone

have a direct correlation with the increase of body fat.

Regarding the preventive effects of calcium against obesity, it seems that decreased serum vitamin D level and consequently reduced intestinal calcium absorption are among the causes of weight gain (17).

In general, the main mechanism for the association of serum vitamin D levels with insulin resistance remains to be fully understood. It has been argued that vitamin D enhances the synthesis and presence of glucose-dependent insulin receptors (GLUT4) in the cell membrane and, as a result, increases insulin sensitivity (13).

Vitamin D also increases the expression of the PPAR $\gamma$  gene, which increases insulin sensitivity (14). In addition, vitamin D has been reported to modulate the renin-angiotensin system by reducing renin gene expression and inhibiting angiotensin receptors.

Increased activity of this system plays an important role in insulin resistance, blood pressure, and inflammation (21).

It has also been argued that vitamin D deficiency leads to an increase in parathyroid hormone, which is associated with obesity, lipolysis, and insulin resistance (22).

Nimitphong *et al.*, (2009) reported that there was a significant relationship between serum vitamin D levels and adiponectin in people with impaired glucose tolerance.

Impaired glucose tolerance is an inflammatory condition most likely due to inflammatory cytokines such as tumor necrosis factor-alpha and intercellin-1, which reduces adiponectin.

Vitamin D has anti-inflammatory properties and may reduce the effect of inflammatory cytokines on circulating adiponectin and thus increase serum adiponectin levels and insulin sensitivity (12).

In summary, vitamin D treatment significantly decreased BMI and FBS and significantly increased vitamin D levels in overweight children and adolescents.

After vitamin D treatment, HOMA-IR was found to have a significant direct correlation with BMI, insulin, and FBS, and a significant inverse correlation with vitamin D. Vitamin D was significantly and inversely correlated with insulin, BMI, HOMA-IR and FBS after the intervention.

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## References

1. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. *N Engl J Med* 2017;376:254-66.
2. Geissler C, Powers H. Human nutrition. London: Oxford University Press; 2017.
3. Ogden CL, Carroll MD, Fryar CD, Flegal KM. Prevalence of obesity among adults and youth: United States, 2011-2014. *NCHS Data Brief* 2015;219:1-8.
4. Bray G, Kim K, Wilding J, Federation WO. Obesity: a chronic relapsing progressive disease process. A position statement of the World Obesity Federation. *Obes Rev* 2017;18:715-23.
5. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007;357:266-81.
6. van Schoor N, Lips P. Worldwide vitamin D status. *Vitamin D*. 4<sup>th</sup> ed. Amsterdam: Elsevier, 2018: 15-40.
7. Huh SY, Gordon CM. Vitamin D deficiency in children and adolescents: epidemiology, impact and treatment. *Rev Endocr Metab Disord* 2008;9:161-70.
8. Saki F, Dabbaghmanesh MH, Omrani GR, Bakhshayeshkaram M. Vitamin D deficiency and its associated risk factors in children and adolescents in southern Iran. *Public health nut* 2017;20:1851-6.
9. Torun E, Gönüllü E, Özgen İT, Cindemir E, Öktem F. Vitamin d deficiency and insufficiency in obese children and adolescents and its relationship with insulin resistance. *Int J Endocrinol*. 2013 Mar 27;1-5.
10. Saintonge S, Bang H, Gerber LM. Implications of a new definition of vitamin D deficiency in a multiracial us adolescent population: the National Health and Nutrition Examination Survey III. *Pediatrics* 2009;123:797-803.
11. Scragg R, Sowers M, Bell C. Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. *Diabetes care* 2004;27:2813-8.
12. Nimitphong H, Chanprasertyothin S, Jongjaroenprasert W, Ongphiphadhanakul B. The association between vitamin D status and circulating adiponectin independent of adiposity in subjects with abnormal glucose tolerance. *Endocrine* 2009;36:205-10.
13. Leal MA, Aller P, Mas A, Calle C. The effect of 1, 25-dihydroxyvitamin D3 on insulin binding, insulin receptor mRNA levels, and isotype RNA pattern in U-937 human promonocytic cells. *Exp cell res* 1995;217:189-94.
14. Sertznig P, Seifert M, Tilgen W, Reichrath J. Peroxisome proliferator-activated receptor (PPAR) and vitamin D receptor (VDR) signaling pathways in melanoma cells: promising new therapeutic targets? *J Steroid Biochem Mol Biol* 2010;121:383-6.
15. Baziar N, DJafarian K, Shadman Z, Qorbani M, Khoshniat Nikoo M, Razi F. Effect of vitamin d supplementation on improving vitamin d levels and insulin resistance in vitamin D insufficient or deficient type2 diabetics. *Iranian J Diabetes Metab* 2014;13:425-33.
16. Talaei A, Mohammadi K, Adgi Z. The evaluation of the effect of vitamin D on insulin resistance in type II diabetic patients. *Arak J Med Uni* 2011;2:5-9.
17. Belenchia AM, Tosh AK, Hillman LS, Peterson CA. Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am J Clin Nutr* 2013;97:774-81.
18. Baynes K, Boucher B, Feskens E, Kromhout D. Vitamin D, glucose tolerance and insulinaemia in elderly men. *Diabetologia* 1997;40:344-7.
19. Kelly A, Brooks LJ, Dougherty S, Carlow DC, Zemel BS. A cross-sectional study of vitamin D and insulin resistance in children. *Arch dis child* 2011;96:447-52.
20. Alemzadeh R, Kichler J, Babar G, Calhoun M. Hypovitaminosis D in obese children and adolescents: relationship with adiposity, insulin sensitivity, ethnicity, and season. *Metabolism* 2008;57:183-91.
21. Draznin B, Sussman K, Eckel R, Kao M, Yost T, Sherman N. Possible role of cytosolic free calcium concentrations in mediating insulin resistance of obesity and hyperinsulinemia. *J clin invest* 1988;82:1848-52.
22. Reis JP, Von Mühlen D, Kritiz-Silverstein D, Wingard DL, Barrett-Connor E. Vitamin D, parathyroid hormone levels, and the prevalence of metabolic syndrome in community-dwelling older adults. *Diabetes care* 2007;30:1549-55.