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The Relationship between 25-Hydroxyvitamin D3 and CRP Levels in Obese Adolescents with Insulin Resistance

Huseyin Dag[1], Okan Dikker[2]

[1]*University of Health Sciences, Istanbul Okmeydani Training and Research Hospital, Department of Pediatrics, Istanbul, Turkey.*
[2]*University of Health Sciences, Istanbul Okmeydani Training and Research Hospital, Department of Medical Biochemistry, Istanbul, Turkey.*

***Corresponding Author:** Dr. Huseyin DAG, University of Health Sciences, Istanbul Okmeydani Training and Research Hospital, Department of Pediatrics, Istanbul, Turkey.*

ABSTRACT

***Background:** Vitamin D3 has been shown to be useful in the prevention of cancer, autoimmunity, cardiovascular disease and infections as well as bone development. Decreased levels of vitamin D3 have been associated with many non-skeletal diseases, including inflammation, insulin resistance, and diabetes. Obesity has a low-grade inflammation and is associated with decreased vitamin D3 levels. CRP is the most widely studied biomarker of low-grade systemic inflammation. In our study; we aimed to evaluate 25-hydroxyvitamin D3 levels in obese adolescents with insulin resistance and to evaluate its effects on CRP levels.*

***Method:** A total of 70 adolescents were included in our study, with age ranging from 10 to 16 years. Among study participants 38 were obese with insulin resistance, and 32 of them were healthy and having normal-weight. The adolescents having body mass index (BMI) on 95% percentile and over according to their age and sex were defined as obese. Obese adolescents with a homeostatic model of assessment- insulin resistance (HOMA-IR) value of over 2.5 were regarded as obese adolescents with insulin resistance; while healthy control group consisted of normal weight adolescents without insulin resistance and obesity. The obese adolescents with insulin resistance were divided into two groups according to 25-hydroxyvitamin D3 levels as 0-20 ug / L and > 20 ug / L. Laboratory tests, gender, age and BMI were statistically compared between groups.*

***Results:** BMI, HbA1c, ALT, CRP, triglyceride, insulin and HOMA-IR levels of the obese group were found to be significantly higher than the control group ($p < 0.05$). CRP levels of the group with 25-hydroxyvitamin D3 values between 0-20 ug / L were significantly higher than the other groups ($p < 0.05$); There was no statistically significant difference in terms of CRP levels between the control group and the obese patients with 25-hydroxyvitamin D3 values greater than 20 ug / L ($p > 0.05$). There was no significant correlation between 25-hydroxyvitamin D3 and CRP levels in obese adolescents ($p > 0.05$).*

***Conclusion:** In obese adolescents with insulin resistance, we found 25-hydroxyvitamin D3 levels similar to healthy controls. We found high CRP levels in obese adolescents with insulin-resistant and decreased 25-hydroxyvitamin D3 levels. Routine administration of vitamin D3 prophylaxis may reduce inflammation and prevent potential complications in these patients.*

Keywords: *Insulin resistance, obesity, adolescent, 25-hydroxyvitamin D3, CRP*

INTRODUCTION

Vitamin D3 acts on the bone, intestine, kidney and parathyroid glands and regulates the metabolism of calcium and phosphorus (1). In addition to healthy bone development, in the prevention of many cancers, autoimmunity, cardiovascular diseases and infection vitamin D3 has been shown to benefit in previous studies (2). If 25-hydroxyvitamin D3 level is lower than 20 ug / L, vitamin D3 deficiency is mentioned (3). In vitamin D3 deficiency, the mineral content of bone decreases due to the decrease in calcium absorption, leading to rickets in children (2). Decreased levels of vitamin D3 can lead to inflammation (4). This reduction has also been associated with many non-skeletal diseases including insulin resistance and diabetes (5). In obese patients, vitamin D3 is stored in adipose tissue and it is reported that vitamin D3 levels are lower in obese patients than in normal weight as it cannot be used systemically (6).

Obesity is an important public health problem with an increasing frequency worldwide and affecting about 25-30% of children (7). It was observed that 50% of obese adolescents were also obese in their adulthood (8). There is a low-grade inflammation due to an increase in proinflammatory cytokine levels in obesity characterized by excessive accumulation of lipids and adipose tissue that form ectopic fat accumulation in different tissues (9, 10).

C-reactive protein (CRP) is an acute phase reactive protein that elevates in inflammatory conditions (11). CRP is the most widely studied biomarker of low-grade systemic inflammation because it has a well-known relationship with the disease and has a stable half-life and has well-known cut-off values (12). An inverse relationship between vitamin D3 and CRP levels is mentioned, and vitamin D3 supplementation has been reported to reduce CRP concentrations (13, 14). The aim of this study was to investigate the levels of 25-hydroxy vitamin D3 in obese adolescents with insulin resistance and to evaluate its effects on CRP levels.

MATERIAL AND METHODS

In this study, the hospital records of 70 patients, aged between 10 and 16 years, who were admitted to the pediatric outpatient clinic between July and December 2018, 38 of whom were obese and having insulin-resistance and 32 were normal-weighted healthy controls, were retrospectively reviewed. The body mass index (BMI) was obtained by division of weight of the patient in kg to the square of the height in meters. Adolescents having BMI on 95% percentile and over according to their age and sex were defined as obese (15). For insulin resistance, Homeostatic model of assessment mg (HOMA-IR) was calculated with the formula (insulin IU / L x glucose mg / dL) / 40 (16). The obese adolescents with HOMA-IR value over 2.5 are defined as obese adolescents with insulin resistance. The normal weight adolescents without insulin resistance and obesity were included in the healthy control group. Then, obese adolescents with insulin resistance were divided into two groups according to their 25-hydroxyvitamin D3 levels as 0-20 ug / L and> 20 ug / L sub-groups. Between groups, laboratory tests [HbA1c, glucose, urea, creatinine, aspartate amino transferase (AST), alanine amino transferase (ALT), total cholesterol, triglyceride, calcium, 25-hydroxy vitamin D3, insulin, HOMA-IR, red blood cell (RBC), white blood cell (WBC), platelet (PLT) levels], sex, age and BMI were compared. Correlations between 25-hydroxy vitamin D3 and other laboratory parameters were investigated in the obese adolescent group.

Adolescents without insulin resistance were not included in obese group and adolescents with insulin resistance were not included in the healthy group. Patients with a history of smoking and/or drinking alcohol, patients with chronic diseases, infections, metabolic and endocrinological diseases, those who received drug treatments such as corticosteroids, and those with malignancy were not included in the study.

HbA1c was studied in auto analyser (Biorad, Variant II turbo, Japan) with High performance liquid chromatography method; glucose, urea, creatinine, AST, ALT, total cholesterol, triglyceride and calcium tests were studied in autoanalyser (Beckman Coulter Brand, AU 5800 model, USA) by colorimetric method, 25-hydroxyvitamin D3 and insulin levels were measured in autoanalyser (Beckman Coulter Brand, DXI 800 model, USA) by immune comiluminescence method. RBC, WBC and PLT levels were studied in the hemogram autoanalyser (Mindray brand, BC6800 model, China).

Ethical Committee Approval

The study was approved by the ethics committee of University of Health Sciences, Istanbul Okmeydani Training and Research Hospital.

Statistical Analysis

IBM SPSS Statistics 22 (IBM SPSS, Turkey) program was performed. The conformity of the parameters to the normal distribution was evaluated by Shapiro Wilks test. Together with the descriptive statistical methods (mean, standard deviation, frequency), in the comparison of the quantitative data, Oneway Anova test was used to compare the normally distributed parameters between groups and the Tukey HDS test and Tamhane's T2 test were used for the determination of the group that caused the difference. The Kruskal Wallis test was used for the comparison of the parameters that did not show normal distribution and Mann Whitney U test was performed for the determination of groups causing difference. Student t-test was used to compare normal distributing parameters and Mann-Whitney U test was used to compare the parameters that did

not show normal distribution between two groups. Chi square test and Continuity (Yates) Correction were used to compare qualitative data. Pearson correlation analysis was used to examine the relationships between parameters which are compatible with normal distribution. Spearman's rho correlation analysis was performed to examine the relationships between parameters which are not compatible with normal distribution. Significance was set at p <0.05.

RESULTS

The mean age of the adolescents in our study was 13.01 ± 1.96 years. BMI values ranged from 16.84 to 42.09 kg/m^2. There were 38 adolescents in the obese group with insulin resistance. Of the obese group, 21 patients had 25-hydroxyvitamin D3 values between 0 and 20 ug / L and 17 had 25-hydroxyvitamin D3 values over 20 ug / L.

Table1. *Demographic and laboratory data of the study participants*

	Obeseadolescent group (n:38)	**Healthy control adolescent group (n:32)**	**P**
	Mean ±SD	**Mean ±SD**	
Age(years)	13.16±1. 99	12,83±1,93	[1]0,502
Gender$_{n\ (\%)}$			
female	16 (%42,1)	16 (%50)	[2]0,686
male	22 (%57,9)	16 (%50)	
BMI (kg/m^2)	**31,94±4,52**	**23,54±2,98**	**[1]<0,001***
HbA1c (%)	**5,42±0,32**	**5,23±0,33**	**[1]0,019***
Glucose (mg/dL)	90±8,85	86,43±7,43	[1]0,081
Urea (mg/dL)	26,39±7,6	23,97±6,17	[1]0,161
Creatinine (mg/dL)	0,56±0,12	0,53±0,15	[1]0,287
AST (U/L) *(median)*	25,34±10,88 (22)	21,6±4,9 (20,5)	[3]0,152
ALT (U/L) *(median)*	**26,39±15,79 (21,5)**	**15,7±6,35 (14)**	**[3]<0,001***
CRP (mg/dL) *(median)*	**4,3±3,58 (4,1)**	**2,87±3,33 (1,7)**	**[3]0,039***
Cholesterol (mg/dL)	163,95±33,8	152,23±34,74	[1]0,166
Triglyceride (mg/dL) *(median)*	**109,32±44,94 (101,5)**	**85,97±45,04 (72)**	**[3]0,009***
Calcium (mg/dL)	10,07±0,33	10,01±0,35	[1]0,457
25-hydroxyvitamin D3 (ug/L)	20,01±6,6	17,35±7,26	[1]0,120
Insulin (IU/L) *(median)*	**18,95±7,28 (17,7)**	**7,2±2,76 (7,6)**	**[3]<0,001***
HOMA-IR *(median)*	**4,17±1,6 (3,8)**	**1,54±0,61 (1,6)**	**[3]<0,001***
WBC (x10^3/µL) *(median)*	7,91±1,46 (8,1)	8±2,35 (7,3)	[3]0,553
RBC(x10^6/µL)*(median)*	4,93±0,39 (4,8)	5±0,55 (4,9)	[3]0,921
PLT (x10^3/µL)	313,05±65,98	292,7±68,49	[1]0,219

[1]Student t test *[2]Continuity (yates) correction* *[3]Mann whitney U test* **p<0.05*

There was no statistically significant difference between obese and control groups in terms of age, gender, glucose, urea, creatinine, AST, cholesterol, calcium, 25-hydroxyvitamin D3, WBC, RBC and PLT levels (p> 0.05).BMI, HbA1c, ALT, CRP, triglyceride, insulin and HOMA-IR levels of the obese group were found to be significantly higher than the control group (p <0.05).

Table2. *Data of obese adolescent sub-groups according to 25-hydroxyvitamin D3 levels and control groups*

	Obese adolescent group with 25-hydroxyvitamin D3 levels between 0-20 ug/L (n:21)	**Obese adolescent group with 25-hydroxyvitamin D3 levels between >20 ug/L (n:17)**	**Healthy control adolescent group (n:32)**	**P**
	Mean ±SD	**Mean ±SD**	**Mean ±SD**	
Age (years)	13,1±2	13,24±2,05	12,83±1,93	[1]0,781
Gender$_{n\ (\%)}$				
female	11 (%52,4)	5 (%29,4)	16 (%50)	[2]0,298
male	10 (%47,6)	12 (%70,6)	16 (%50)	
BMI (kg/m^2)	**32,57±4,3**	**31,17±4,79**	**23,54±2,98**	**[1]<0,001***
HbA1c (%)	5,4±0,33	5,45±0,32	5,23±0,33	[1]0,057
Glucose (mg/dL)	89,67±9,58	90,41±8,13	86,43±7,43	[1]0,214

Urea (mg/dL)	25,62±8,16	27,35±6,95	23,97±6,17	[1]0,283
Creatinine (mg/dL)	0,56±0,14	0,56±0,08	0,53±0,15	[1]0,560
AST (U/L) *(median)*	25,43±12,22 (21)	25,24±9,32 (24)	21,6±4,9 (20,5)	[3]0,245
ALT (U/L) *(median)*	**25,48±13,58 (21)**	**27,53±18,53 (22)**	**15,7±6,35 (14)**	**[3]<0,001***
CRP (mg/dL) *(median)*	**5,39±4,11 (4,7)**	**2,96±2,23 (1,4)**	**2,87±3,33 (1,7)**	**[3]0,021***
Cholesterol (mg/dL)	160,33±32	168,41±36,37	152,23±34,74	[1]0,297
Triglyceride (mg/dL) *(median)*	**120,14±47,37 (112)**	**95,94±39 (89)**	**85,97±45,04 (72)**	**[3]0,008***
Calcium (mg/dL)	10±0,33	10,16±0,31	10,01±0,35	[1]0,235
25-hydroxyvitamin D_3 (ug/L)	**15,32±3,3**	**25,8±4,74**	**17,35±7,26**	**[1]<0,001***
Insulin (IU/L) *(median)*	**18,66±7,63 (17,6)**	**19,32±7,04 (18,3)**	**7,2±2,76 (7,6)**	**[3]<0,001***
HOMA-IR *(median)*	**4,11±1,77 (3,7)**	**4,25±1,4 (4,1)**	**1,54±0,61 (1,6)**	**[3]<0,001***
WBC (x10^3/µL) *(median)*	7,8±1,42 (7,5)	8,04±1,55 (8,3)	8±2,35 (7,3)	**[3]0,560**
RBC(x10^6/µL)*(median)*	4,87±0,39 (4,8)	5±0,38 (4,9)	5±0,55 (4,9)	**[3]0,614**
PLT (x10^3/µL)	312,9±68,54	313,24±64,77	292,7±68,49	**[1]0,472**

*[1]Oneway anova test [2]Chi-square test [3]Kruskal wallis test *p<0.05*

There was no statistically significant difference between the groups in terms of age, gender, HbA1c, glucose, urea, creatinine, AST, cholesterol, calcium, WBC, RBC and PLT levels (p> 0.05).BMI and ALT levels of the control group were significantly lower than both obese groups with 25-hydroxyvitamin D3 levels between 0-20 ug / L and >20 ug / L(p <0.05).

Triglyceride levels of the group with 25-hydroxyvitamin D3 values between 0-20 ug/L were found to be significantly higher than the control group (p: 0.003; p <0.05). There was no statistically significant difference between the other groups in terms of triglyceride levels (p> 0.05). 25-hydroxyvitamin D3 levels of the group with 25-hydroxyvitamin D3 levels >20 u/ L were found to be significantly higher than the control groups (p: < 0.05).There was no statistically significant difference regarding the 25-hydroxyvitamin D3 values between the control group and the group with 25-hydroxyvitamin D3 levels between 0-20 ug/L (p> 0.05).

The levels of insulin, and HOMA-IR of the control group were found to be significantly lower than obese adults with 25-hydroxyvitamin D3 between 0-20 ug/ L and >20 ug / L (p <0.05). There was no statistically significant difference between the obese groups with 25-hydroxyvitamin D3 values between 0-20 ug/ L and >20 ug / L (p> 0.05).

The CRP levels of the obese group with 25-hydroxyvitamin D3 values between 0-20 ug / L were significantly higher than the control group and the obese group with 25-hydroxyvitamin D3 value of greater than 20 ug / L (p1: 0.037; p2: 0.011; p <0.05).There was no statistically significant difference in terms of CRP levels between the control group and obese group with 25-hydroxyvitamin D3 values greater than 20 ug / L (p> 0.05).

Table3. *Correlations between 25-hydroxyvitamin D3 levels and other parameters in the obese group*

		BMI	HbA1c	Glucose	Urea	Creatinine	AST	ALT	CRP	Cholesterol	Triglyceride	Calcium	Insulin	HOMA-IR	WBC	RBC	PLT
25-hydroxyvitamin D3	**r**	-0,181	0,091	0,099	0,311	-0,129	-0,016	-0,047	-0,163	0,131	-0,209	**0,337**	-0,092	-0,020	0,100	0,149	0,066
	p	0,276	0,587	0,553	0,057	0,441	0,923	0,779	0,328	0,434	0,208	**0,039***	0,584	0,904	0,548	0,371	0,694

*Pearson correlation analysis [+]Spearman Rho correlation analysis *p<0.05*

In the obese group; there was a statistically significant relationship between 25-hydroxyvitamin D3 and calcium levels at a level of 33.7% (p <0.05). There was no significant relationship between 25-hydroxyvitamin D3 levels and other parameters (p> 0.05).

DISCUSSION

It has been reported that vitamin D may have direct effects on insulin resistance and pancreatic beta cell dysfunction via its receptor and indirect effects by effecting calcium homeostasis (17).It has been shown that the stimulation of pancreatic islet cells with 1.25-dihydroxyvitamin D3 increases the level of cytosolic calcium and increases the level of intracellular calcium levels and insulin secretion (18).As a result of deficiency in dietary intake of vitamin D, the disorder in extracellular and intracellular calcium balance may lead to an alteration in insulin secretion, leading to insulin resistance. In addition, vitamin D3

supplementation has been shown to reduce insulin resistance (19, 20).In our study, there was no statistically significant difference regarding insulin and HOMA-IR levels in obese adolescent sub-groups produced regarding 25-hydroxyvitamin D3 levels. In addition, no correlation was found between 25-hydroxyvitamin D3 and insulin and HOMA-IR levels in this study.

The body's vitamin D3 requirement is met by sunlight and nutrients. Factors such as geographic location, seasons, weather, direct exposure to the sun or behind the glass, the density of melanin in the skin, the protective creams used and the way of dressing affect the power of ultraviolet-B rays of the sun to synthesize vitamin D3 in the skin (21-23).It has also been reported that inadequate dietary intake of vitamin D3 or a variety of drugs may cause vitamin deficiency (22). In our country, it was shown that serum vitamin D3 levels were low in general and the most common cause was insufficient synthesis and inadequate intake with nutrients (24).

In our study, 25-hydroxyvitamin D3 levels were not statistically significantly different in obese adolescents with insulin resistance compared to healthy control adolescents. In our study, we got 20 ug / L as cut-off for vitamin D3 deficiency. However, the values between 21- 29 ug/ L are considered to be insufficient and 25-hydroxyvitamin D3 levels above 30 ug / L are considered as sufficient (25).Therefore, we observed that 25-hydroxyvitamin D3 levels were not sufficient in both control and obese adolescents. Pilar et al. (26) reported that 25-hydroxyvitamin D3 levels were significantly lower in obese children aged 9-14 years compared to controls. In a study on morbidly obese children, low 25-hydroxyvitamin D3 levels were associated with obesity. In that study, it was reported that 25-hydroxyvitamin D3 was associated with visceral fat amount and development of comorbidites (27). In a study on obese children, an increase of 5 ug / L in serum 25-hydroxyvitamin D3 levels was shown to be associated with a reduction in BMI of 1 kg / m2 (28). Although our findings were not consistent with some previous studies in the literature, a significant percentage of obese adolescents with insulin resistance in our study, 55.2% (n: 21) had 25-hydroxyvitamin D3 levels at deficiency stage, 36.8% (n: 14) had at the level of insufficiency. Only 4 obese adolescents had sufficient 25-hydroxyvitamin D3 levels.In our country, there is a deficiency of vitamin D3 in general which is usually observed due to inadequate synthesis and nutrition intake (24). This condition makes it difficult to establish a clear relationship between obesity and insulin resistance and vitamin D3.

In our study, we found increased CRP levels in obese adolescents with insulin resistance and having 25-hydroxyvitamin D3 levels between 0-20 ug / L compared to other groups. There was no significant difference regarding CRP levels between healthy control group and the obese group with 25-hydroxyvitamin D3 levels > 20 ug / L. This finding suggests that vitamin D3 may have some effects on CRP levels. However, we could not detect any correlation between these two variables.Pilar et al. (26) did not report a difference in CRP levels between obese adolescents having 25-hydroxyvitamin D3 levels0- 20 ug / L or > 20 ug / L. This data seems to be incompatible with our work. However, the study group consisted of obese adolescents with only insulin resistance in this study which may have caused a difference between the two studies. Since the number of studies performed on the obese adolescents in the literature is low, we have examined similar studies in the literature.

Targher et al. (29) reported that CRP levels of diabetic patients with vitamin D3 deficiency were high. In a study (30), elevated CRP levels were noted in non-diabetic obese patients with decreased levels of 25-hydroxyvitamin D3 levels and lower CRP levels were shown in those with adequate levels of 25-hydroxyvitamin D3 levels (30).Alrefai et al reported increased CRP and decreased 25-hydroxyvitamin D3 levels with disease activity in Crohn's disease (31). Mathur et al reported the reduction of CRP levels with vitamin D3 supplementation in patients with ulcerative colitis (32). Based on this information, the literature supports our results. Since increased CRP levels are associated with decreased 25-hydroxyvitamin D3 in our obese adolescent patients with insulin resistance, vitamin D3 supplementation may be useful in preventing inflammation in these patients.

One of the most important complications related to obesity is cardiovascular diseases caused by atherosclerosis (33). Decreased 25-hydroxyvitamin D3 levels were associated with increased risk of obesity (6, 26). Elevated CRP levels are also associated with an increased risk

of cardiovascular disease, and increased levels of 25-hydroxyvitamin D3 can reduce this risk (34). Therefore, increased levels of CRP in our adolescents with insulin resistance may be associated with a particular complication of cardiovascular disease in these patients. For that reason, maintaining adequate levels of 25-hydroxyvitamin D3 levels may be a preventive medicine approach in terms of cardiovascular complications in the adolescent group.

In conclusion, we found similar levels of 25-hydroxyvitamin D3 in obese adolescents with insulin resistance compared to healthy controls. We determined high CRP levels in obese adolescents with insulin-resistance having low 25-hydroxyvitamin D3 levels. We believe that routine administration of vitamin D3 prophylaxis in the adolescent age group may lessen inflammation and prevent possible complications in these patients.

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