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The Relationship Between Vitamin D Level and Ambulatory Blood Pressure Parameters and Cardiovascular Risk Factors

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Abstract

Objective: It has been reported that the level of vitamin D in obese children is lower and that the low level of vitamin D creates a predisposition to hypertension. In this study, it was aimed to evaluate the relationship between vitamin D level, ambulatory blood pressure parameters, and cardiovascular risk factors in obese children.

Methods: Age, gender, and anthropometric measurements, fasting serum glucose, insulin, transaminase levels, lipid profile, 25(OH) vitamin D levels, 24-hour ambulatory blood pressure monitoring data, electrocardiography and echocardiography data of the patients were retrospectively obtained from hospital records.

Results: A total of 57 patients between the ages of 8-17 years, 26 females and 31 males, were included in the study. Patients were divided into two groups based on their vitamin D levels below and above 20 ng/mL. A total of 40 patients (70%) were hypertensive, and no correlation was found between blood pressure values and serum vitamin D levels in obese children in the correlation analysis. In the group with a vitamin D level lower than 20 ng/mL, the insulin level and homeostatic model assessment for insulin resistance (HOMA-IR) score were found to be significantly higher than in the other group ($p=0.01$, $p=0.016$, respectively). Furthermore, there was a positive correlation between the HOMA-IR score and systolic blood pressure load ($r=0.280$, $p=0.03$).

Conclusion: Increased insulin resistance in obese children is associated with high blood pressure values. However, no direct relationship could be found between vitamin D levels and blood pressure profile.

Keywords: Obesity, cardiovascular risk factor, hypertension, vitamin D

INTRODUCTION

Obesity is an increasing public health problem in children. The prevalence and mortality rate of hypertension secondary to obesity, hyperinsulinemia, increased insulin resistance, type 2 diabetes mellitus, hyperlipidemia, atherosclerosis, and as a result, cardiovascular diseases also increase especially in developed and developing countries (1,2).

Many studies have demonstrated that obese children have lower vitamin D levels than the lean ones (3-9). In addition to the classical physiological function of vitamin D in the regulation of calcium and bone metabolism, it is also known that it has other functions, such as modulating the immune system, enabling anti-inflammatory activity, suppressing the renin-angiotensin system and decreasing insulin resistance (10-13). Vitamin D deficiency has been proved to contribute to increased blood pressure due to the activation of the renin angiotensin-aldosterone system, the production of reactive oxygen species, and endothelial dysfunction caused by impaired nitric oxide secretion (14). As per the data obtained from the NHANES 2001-2006 study, low serum 25(OH) vitamin D level was associated with increased waist circumference, systolic blood pressure, homeostatic model

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assessment for insulin resistance (HOMA-IR) index and low HDL-cholesterol (15).

A twenty-four-hour ambulatory blood pressure monitoring provides an earlier detection of abnormal blood pressure. It supplies an evaluation of the circadian variability of blood pressure. It provides to separate hypertension from white coat hypertension and in revealing masked hypertension observed particularly in young people (16,17). In a few studies evaluating the correlation between vitamin D level and hypertension in children, a closer correlation was found particularly between the blood pressure load at night and vitamin D level (18-20). In many studies carried out in obese children, different results have been reported with regard to the correlation between serum cholesterol levels, insulin resistance, fasting blood glucose, insulin levels and vitamin D (5,7,21-23). Similarly, different results were obtained in the studies evaluating the changes in these parameters through a vitamin D replacement therapy. However, the role of vitamin D treatment in preventing the development of cardiovascular diseases is controversial (6,24-26).

There are very few studies have evaluating the relationship between hypertension and vitamin D in children with ambulatory blood pressure parameters. In these studies, there are non-homogeneous patient groups such as obese and non-obese patients and patients receiving antihypertensive treatment. At the same time, the number of patients was limited and the results were different. Therefore, our aim in this study is to evaluate patients who do not use drugs in homogeneous patient group together with cardiovascular risk factors using ambulatory blood pressure parameters, dyslipidemia, and insulin resistance.

METHODS

This is a retrospective review of 618 patients who underwent ambulatory blood pressure monitoring between January 2016 and January 2020 at the pediatric cardiology clinic of the Eskişehir Osmangazi University Hospital. The inclusion criteria were being obese, being aged between 8 and 17 years, and the measurement of vitamin D levels. Ninety-six patients with a body mass index above the 95th percentile (obese) was identified. The patient whose vitamin D level and ambulatory blood pressure monitoring were performed at the same visit were included in the study. Thirty-nine patients were excluded from the study due to the existence of accompanying renal, cardiovascular, and endocrinological diseases, and the remaining 57 patients were included. The present study was approved by the Non-Interventional Research Ethics Committee of Eskisehir Osmangazi University (12 May 2020-25403353-050.99-E.52038). This study was conducted per the principles of the Declaration of Helsinki.

The age, gender, and anthropometric measurements [height, body weight, body mass index (BMI)], lipid profile [low-density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglycerides], fasting serum glucose, calcium, phosphor, creatinine, alanine aminotransferase (ALT), insulin, 25(OH) vitamin D levels and 24-hour ambulatory blood pressure monitoring data (systolic/diastolic load during 25 hour, systolic/diastolic dipping, daytime/night-time mean systolic/diastolic pressure) of the patients were collected from the hospital records retrospectively. Blood pressure indices were calculated by dividing them to the 95th percentile of blood pressure. Examinations for hypertension etiology of hypertensive patients, as well as the data on transthoracic echocardiography and fundus examination evaluated in terms of target organ damage were obtained from hospital records for all patients. The patients were weighed on an electronic scale (SECA digital scale, sensitive to 0.1 kg measurement) in thin clothes and without shoes. Using a Harpenden stadiometer, height measurements were made in a standing upright position with bare feet and feet brought together in a parallel position, and with the shoulder and gluteal region touching the wall (sensitive to 0.1 cm measurement). Body mass indexes (BMI) [weight (kg)/height^2 (m^2)] of patients were calculated using height and weight measurements. Those having a BMI over the 95th percentile was considered obese. Percentile curves determined by the World Health Organization were used.

A 24-hour ambulatory blood pressure measurement was done using a Medset scanlight 2 recorder (Medset Scanlight II ABPM recorder, Germany). Systolic, diastolic, and mean arterial blood pressures were measured for 24 hours. Hypertension was defined as a case, in which measurements over the 95th percentile made based on age, gender and height yielded a rate over 25%. The blood pressure index was calculated by dividing the measured blood pressure value by the 95th percentile value as per gender and height (22). Patients who had a decrease in blood pressure by 10% or more in the night-time blood pressure data compared to daytime were considered dipper, and those who did not were considered non-dipper.

Glucose, insulin, HDL-cholesterol, LDL-cholesterol, triglyceride, 25(OH) vitamin D level, creatinine, and ALT were studied from the venous blood samples taken after 12 hours of fasting. Insulin resistance was calculated through the HOMA-IR formula [fasting glucose (mg/dL) x fasting insulin (uIU/mL)/405].

The cut-off value of 25(OH) vitamin D was accepted as 20 ng/mL in children and adolescents (27,28). Cases were divided into two groups as per their 25(OH) vitamin D levels based on 25(OH) vitamin D concentrations below or above 20 ng/mL.

Statistical Analyis

The data were analyzed through the SPSS package program. The values of qualitative variables were shown as frequency and percentage, and quantitative variables as mean ± standard deviation. The suitability of quantitative variables for normal distribution as per the groups was evaluated with the Shapiro-Wilk test. The comparison of the two groups was carried out through the t-test for normally distributed variables, and through the Mann-Whitney U for those not distributed normally. The correlation between the qualitative variables was examined through the chi-square analysis. Cases with an analysis result of $p<0.05$ were considered significant.

RESULTS

A total of 57 patients between the ages of 8 and 17 years, consisting of 26 females (45.6%) and 31 males (54.4%), were included in the study. There were 43 cases (75.4%) with a 25(OH) vitamin D level of <20 ng/mL, and 14 cases with a 25(OH) vitamin D level of ≥20 ng/mL. Demographic data of the patients and the comparison of the groups are given in Table 1. Age, body weight, BMI and gender distribution were similar between the two groups. In the group with vitamin D level below 20 ng/mL, the insulin levels and HOMA-IR score were significantly higher than the other group (p=0.012, p=0.016, respectively).

The comparison of ambulatory blood pressure monitoring data between the groups is given in Table 2. There was no statistically significant difference between the systolic and diastolic hypertension load (p=0.107, p=0.059, respectively). The night-time and daytime mean systolic blood pressure values were found to be significantly higher in the group having 25(OH) vitamin D level of <20 ng/mL (p=0.046, p=0.025, respectively).

Office blood pressure measurements of all patients were over the 95^{th} percentile as per the age and height percentiles (29). In 70% (40/57) of the patients with high office measurements, systolic blood pressure load as per the ambulatory blood pressure monitoring was >25%, and that was compatible with hypertension. Vitamin D levels of 32 (80%) patients diagnosed with hypertension were below 20 ng/mL, and those of 8 (20%)

Table 1. Comparison of demographic and biochemical parameters between groups according to vitamin D level (mean ± SD)

	D vit <20 ng/mL	D vit ≥20 ng/mL	p
	n=43	n=14	
Age (year)	13.86±2.14	13.16±2.16	0.294
Gender (girls/boys)	22/21	4/10	0.244
Height (cm)	162.37±12.21	157.57±10.63	0.136
Weight (kg)	84.97±19.18	75.97±16.45	0.191
BMI (kg/m^2)	32.00±5.68	30.17±3.94	0.267
Systolic blood pressure (mmHg)	145.30±15.49	137.38±13.5	0.106
Diastolic blood pressure (mmHg)	88.02±14.44	85.07±16.98	0.577
Fasting blood glucose	86.18±8.23	89.07±11.41	0.307
Insulin (uIU/mL)	22.48±12.99	13.32±5.43	**0.012**
HOMA-IR	4.86±3.01	2.82±1.59	**0.016**
LDL-cholesterol (mg/dL)	116.30±34.59	108.80±21.92	0.559
HDL-cholesterol (mg/dL)	45.28±10.54	44.61±9.47	0.968
Triglycerides (mg/dL)	108±36.04	97.36±37.7	0.347
Creatinin (mg/dL)	0.57±0.13	0.56±0.11	0.955
ALT (IU/L)	26.21±21.32	23.92±14.08	0.902
Calcium (mg/dL)	9.77±0.34	9.94±0.33	0.238
Phosphor (mg/dL)	4.27±0.68	4.90±0.69	0.73
25(OH) vitamin D (ng/mL)	12.76±3.16	25.61±7.01	<0.001
Hypertension (yes/no)	32/11	8/6	0.314

BMI: Body mass index, HOMA-IR: Homeostasis model assessment of fasting insulin resistance, ALT: Alanine aminotransferase, LDL: Low density lipoprotein, HDL: High-density lipoprotein patients were above 20 ng/mL. There were no significant differences with regard to the prevalence of hypertension. Six out of seven patients diagnosed with grade 1-3 hepatosteatosis were in the group with 25(OH) vitamin D levels below 20 ng/mL. In both groups, there was a case with grade 2 retinopathy; while the group with vitamin D deficiency had 4 patients with grade 1 retinopathy, there was one patient with grade 1 retinopathy in the group with a vitamin D level of >20 ng/mL. As per the electrocardiography and echocardiography findings, there were not any cases with left ventricular hypertrophy. As a result of the correlation analysis, a positive correlation was found between the HOMA-IR score and office diastolic blood pressure and systolic blood pressure load (r=0.372, p=0.007) (r=0.280, p=0.037). Correlation analyses of the HOMA-IR score and blood pressure parameters are given in Table 3.

DISCUSSION

According to our results of our study, insulin resistance increased in obese children with low vitamin D levels, and it was found to be associated particularly with high night-time systolic blood pressure levels.

In this study, 80% of these cases who had hypertension the vitamin D level was below the cut-off value. In a meta-analysis evaluating the correlation between vitamin D and cardiometabolic risk factors in children, it was reported that there was a negative correlation between the vitamin D level and systolic blood pressure in 11 studies, in addition to the diastolic blood pressure in 5 studies, while no correlation was found in a randomized controlled study (19). Similarly, in three different studies, no correlation could be found between vitamin D levels and hypertension and hypertensive organ damage, although a correlation was found between the fat tissue rate and insulin resistance (8,18,30). Similar to our study, Gul et al. (8) found a higher rate of vitamin D deficiency in the hypertensive group. In another comprehensive study involving 2.908 children, which investigated the correlation between hypertension and vitamin D, the prevalence of prehypertension and hypertension was 1.7% in patients with a vitamin D level of <10 ng/mL, while it was reported as 0.6% in those with a vitamin D level of >30 ng/mL as per the office measurements. In the same study, it was also emphasized that the effect of vitamin D level on systolic blood pressure was not independent of BMI and that the determining effect of vitamin D on systolic blood pressure did not continue when BMI was taken as a covariant (31). In our study, in which all our cases had BMI >95 p, we found that vitamin D level was not a determining factor for hypertension. In addition, in a comprehensive study involving adolescent children, it was stated that low vitamin D level was strongly correlated with excess weight, abdominal obesity, and an inverse correlation was found with high systolic blood pressure and increased fasting glucose (32). In our study, the higher systolic blood pressures and HOMA-

Table 2. Comparison of ambulatory blood pressure monitoring data between groups (mean ± SD)

	D vit <20 ng/mL	D vit >20 ng/mL	p
	n=43	n=14	
Systolic load during 24 h (%)	38.22±25.92	25.47±19.44	0.107
Diastolic load during 24 h (%)	21.20±21.20	9.31±8.74	0.059
Systolic blood pressure dipping	26.8	21.5	0.736
Diastolic blood pressure dipping	35	29	0,508
Daytime mean systolic blood pressure (mmHg)	125.38±10.48	118.92±6.88	0.39
Daytime systolic index	0.981±0.077	0.955±0.073	0.290
Daytime mean diastolic blood pressure (mmHg)	71.75±7.19	68.07±5.18	0.088
Daytime diastolic index	0.885±0.082	0.856±0.070	0.244
Night-time mean systolic blood pressure (mmHg)	115.03±9.33	109.14±8.01	0.046
Night-time systolic index	0.901±0.074	0.875±0.066	0.416
Night-time mean diastolic blood pressure (mmHg)	60.75±5.73	69.21±5.79	0.409
Night-time diastolic index	0.752±0.065	0.744±0.080	0.717
Systolic blood pressure during 24 h (mmHg)	122.95±10.02	116.42±5.57	0.025
Systolic index during 24 h	0.966±0.072	0.931±0.062	0.329
Diastolic blood pressure during 24 h (mmHg)	69.52±7.18	66.02±5.49	0.106
Diastolic index during 24 h	0.863±0.084	0.830±0.078	0.196

SD: Standard deviation

IR values that we detected in obese children with low vitamin D levels support the results of Reis et al. (32).

In our study, no significant difference was found in office systolic and diastolic blood pressures, ambulatory blood pressure load and blood pressure indexes between the two groups in the comparison of office and ambulatory blood pressure data. Although the number of studies on office blood pressure measurements in children is relatively high, there are few studies in the literature where the correlation between ambulatory blood pressure data and vitamin D deficiency is evaluated. Different results were reported in the aforementioned studies (4,14,22). The study, in which patients with primary hypertension were included, yielded no correlation between vitamin D level and ambulatory and office blood pressure measurements. Although the results in this study are similar, 30% of the patients are obese and 28% are overweight, unlike our study. Moreover, half of the patients receive antihypertensive treatment (14). In our study, all patients were either obese, with no antihypertensive treatment. Banzato et al. (22), investigated the correlation between vitamin D levels and ambulatory blood pressure data of 32 obese children and found negative correlations particularly with regard to night-time blood pressure load and blood pressure index. They also found a negative correlation between the daily blood pressure index, triglyceride level and HOMA-IR and vitamin D levels in this study. In this study, unlike our study, patients were divided into 3 groups as <10 ng/mL, 10-20 ng/mL, >20 ng/mL based on vitamin D level. The group with <10 ng/mL was determined to be the group with a significant difference, while the study was made with a total of 32 patients, which was quite a low number. In our study, it was thought that grouping in this manner would not be appropriate since the number of patients below <10 ng/mL was Colak et al. (4), the data of obese and normal-weight children were compared, and when another comparison was made among obese children based on the level of vitamin D, no significant difference could be found in terms of ambulatory blood pressure load. However, negative correlation was found between vitamin D level and age, BMI, fat rate, night-time blood pressure load and carotids intima media thickness. Similarly, in our study, daytime and night-time systolic blood pressures were found to be higher in the group with vitamin D deficiency, but no significant difference could be found in the comparison of blood pressure load and index.

In our study, insulin level and HOMA-IR scores were found to be significantly higher in the group with vitamin D deficiency. There are studies in the literature showing that an increased fasting blood glucose and insulin resistance are inversely correlated with vitamin D level (5,22,23). Distinctively, there are also studies that do not find a correlation between HOMA-IR and vitamin D level (7,21). In most of these studies, the

Table 3. Office, ambulatory blood pressure parameters and HOMA-IR correlation analysis

	r	p
Office systolic blood pressure (mmHg)	0.256	0.067
Office diastolic blood pressure (mmHg)	0.372	0.007[s]
Systolic load (%)	0.280	0.037
Diastolic load (%)	0.086	0.526
Systolic dipping (>10%)	-0.05	0.716
Diastolic dipping (>10%)	0.032	0.815
Daytime mean systolic blood pressure (mmHg)	0.122	0.405
Daytime systolic index	0.096	0.512
Daytime mean diastolic blood pressure (mmHg)	0.189	0.194
Daytime diastolic index	0.180	0.215
Night-time mean systolic blood pressure (mmHg)	0.246	0.103
Night-time systolic index	0.242	0.109
Night-time mean diastolic blood pressure (mmHg)	0.222	0.143
Night-time diastolic index	0.200	0.188
Mean systolic blood pressure during 24 h (mmHg)	0.139	0.313
Systolik index during 24 h	0.140	0.310
Mean diastolic blood pressure during 24 h (mmHg)	0.136	0.324
Diastolic index during 24 h	0.132	0.336

[s]Spearman's, HOMA-IR: Homeostatic model assessment for insulin resistance

correlation between low vitamin D level and BMI, adipose tissue rate and metabolic syndrome were emphasized. In a study carried out in Korea on 1.504 children, where this correlation could not be demonstrated, an inverse correlation was found between vitamin D level and diastolic blood pressure, waist circumference and BMI, yet no significant correlation could be found between hypertension, insulin resistance, hyperglycaemia, hypertriglyceridemia, and low HDL-cholesterol. However, the presence of a significant correlation between low vitamin D level and BMI was found to be of significance with regard to metabolic syndrome and cardiovascular diseases (33). In our study, triglyceride, LDL and HDL-cholesterol levels were similar between the two groups. Many studies have shown that increased triglyceride, total and LDL-cholesterol levels, and decreased HDL-cholesterol levels are associated with low vitamin D levels (7,21,23). In some studies, it was not possible to show any significant differences that are to our study (6,32,33). It is considered that the difference in the manner the results are reported is related to the differences in study group characteristics and vitamin D levels. In our study, although there was no significant correlation between vitamin D level and blood pressure load and indexes, a strong correlation was determinated between HOMA-IR and vitamin D level. In the correlation analysis, there was positive correlation between HOMA-IR score and office diastolic blood pressure value and systolic blood pressure load ($r=0.280$, $p=0.03$). Although vitamin D deficiency is not directly effective in blood pressure, it has been indirectly associated with hypertension due to its contribution to insulin resistance and obesity.

In a study evaluating insulin resistance and hepatosteatosis in obese children, insulin resistance and hepatosteatosis were found to be significantly high in patients with low vitamin D levels (5). Similarly, in our study, 6 (85%) out of 7 patients with hepatosteatosis were in the group with vitamin D deficiency. Five (71%) of the patients with hypertensive retinopathy were in the group with vitamin D deficiency. Although it is not possible to show a direct correlation between blood pressure parameters and vitamin D level, hypertensive organ damage was found to be higher.

Study Limitations

No evaluations were made regarding the post-vitamin D treatment process in our study, which is one of its limitations. At the same time, its retrospective design, the fact that a relatively small number of patients were included, accompanied by a quite limited number of patients with vitamin D levels below <10 ng/mL and above >30 ng/mL, and the absence of a comparison made with patients having a level of >30 ng/mL, which is considered an optimal level, as well as a lack of seasonal evaluations are the limitations of our study.

CONCLUSION

As a result, night-time systolic blood pressure and HOMA-IR score were found to be higher in obese children with low vitamin D levels. In addition, obese children with high insulin resistance have higher blood pressure values. Therefore, it can be said that an increased insulin resistance contributed by vitamin D deficiency in obese children is associated with high blood pressure values. In order to explain the correlation between vitamin D level and blood pressure in obese children, there is a need for prospective, randomized controlled studies involving more patients.

Ethics

Ethics Committee Approval: The present study was approved by the Non-Interventional Research Ethics Committee of Eskisehir Osmangazi University (12 May 2020- 25403353-050.99-E.52038). This study was conducted per the principles of the Declaration of Helsinki.

Informed Consent: Retrospective study.

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Authorship Contributions

Surgical and Medical Practices: A.S., E.A., P.K., H.K., B.U., Concept: A.S., P.K., B.U., Design: A.S., P.K., B.U., Data Collection or Processing: A.S., E.A., H.K., Analysis or Interpretation: A.S., P.K., H.K., Literature Search: A.S., E.A., H.K., Writing: A.S., E.A., P.K., B.U.

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