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Mean Platelet Volume and Vitamin D Deficiency

Ortalama Trombosit Hacmi ve D Vitamini Eksikliği

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ABSTRACT

Aim: To evaluate whether vitamin D deficiency has an effect on mean platelet volume (MPV).

Materials and Methods: This was a retrospective study. The children followed-up at the pediatrics endocrinology polyclinic and diagnosed as nutritional rickets were included in this study. The patient group was created, and by screening the files of 478 case files, those compatible with the patient group for age and gender, were taken as the control group.

Results: A total of 684 children and adolescents cases between the ages 0.1-18 years were included in the study. The cases were divided into 3 groups according to the vitamin D levels. Those with vitamin D levels of less than 15 ng/mL were classified as the vitamin D deficiency group, those between 15-20 ng/mL were classified as the insufficiency group, and those between 20-100 ng/mL were classified as the normal Vitamin D level group. There was no statistically significant difference between the groups in terms of age and gender. There was no significant difference observed between the groups in terms of the MPV levels. There was no statistically significant correlation determined in the correlation analysis between the vitamin D level and the MPV (p>0.05). In the multiple regression analysis, it was observed that vitamin D had no statistically significant effect on MPV. In the performed partial correlation analysis, when hemoglobin, hematocrit, calcium, phosphorus and parathyroid hormone were selected as controlling factors, again, there was no statistically significant correlation observed between the MPV and the vitamin D (r=-0.19, p>0.05).

Conclusion: In the pathophysiology of the cardiac dysfunctions appearing as a result of vitamin D deficiency, we wished to emphasize that the hypothesis of the probable effect of vitamin D on MPV should be questioned in more detail.

Keywords: Vitamin D, mean platelet volume, cardiac disfunctions

ÖZ

Amaç: D vitamini eksikliğinin ortalama trombosit hacmi (MPV) üzerindeki etkilerini göstermek.

Gereç ve Yöntemler: Bu retrospektif bir çalışmadır. Bu çalışmaya çocuk endokrinoloji polikliniğinde takip edilen ve nutrisyonel rikets tanısı konan çocuklar alındı. Hasta grubu ile yaş ve cinsiyet uyumlu 478 olgu dosya taramalarında bulunarak kontrol grubu olarak alındı.

Bulgular: Çalışmaya yaşları 0,1-18 arasında değişen toplam 684 çocuk ve adölesan olgu alındı. Olgular D vitamini düzeyine göre 3 gruba bölündü. Vitamin D düzeyi 15 ng/mL'nin altında olanlar D vitamini eksikliği olan grupta, 15-20 ng/mL arasında olanlar yetersizlik, 20-100 ng/mL arasında olanlar ise vitamin D düzeyi normal olan grup olarak sınıflandırıldı. Gruplar arasında yaş ve cinsiyet açısından istatistiksel olarak anlamlı fark yoktu. Gruplar arasında MPV düzeyleri açısından anlamlı fark görülmedi. Korelasyon analizinde de vitamin D düzeyi ile MPV arasında istatistiksel olarak anlamlı korelasyon bulunamadı (p>0,05). Yapılan multiple regresyon analizlerinde MPV üzerine vitamin D'nin istatistiksel olarak anlamlı bir etkisinin olmadığı görüldü. Yapılan parsiyel korelasyon analizinde hemoglobin, hematokrit, kalsiyum, fosfor ve parathormon kontrol edici faktörler olarak seçildiğinde MPV ile vitamin D arasında yine istatistiksel olarak anlamlı bir korelasyon olmadığı görüldü (r=-0,19; p>0,05).

Sonuç: Vitamin D eksikliği sonucu ortaya çıkan kardiyak disfonksiyonların patofizyolojisinde vitamin D'nin MPV üzerindeki etkisi ile ilişkili olabileceğine dair hipotezlerin daha ayrıntılı bir şekilde sorgulanması gerektiğini vurgulamak istiyoruz.

Anahtar Kelimeler: Vitamin D, ortalama trombosit hacmi, kardiyak disfonksiyonlar

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Introduction

Endothelial cells, cardiomyocytes and vascular smooth muscle cells belonging to the cardiovascular system expressing vitamin D receptor interact with vitamin D. In a pilot study, in which the cardiomyocytes incubated with active vitamin D, cellular proliferation was inhibited, cardiomyocytes formation increased and there was an anti-apoptotic effect as well as a decrease in the expression of the genes playing a role in cell cycles were reported (1). In another recent comprehensive study, vitamin D deficiency is reported to be associated with hypertension, high blood glucose, cardiovascular diseases and metabolic syndrome (2). Again, in a study by Wang et al. (3) it has been reported that in the cases in which the serum 25-hydroxy vitamin D (25-OHD) level was lower than 15 ng/mL, the risk for initial onset of cardiovascular system problem was found to be higher (at least two-fold) than the control group (serum 25-OHD >15 ng/mL). As a result of these studies, it can be suggested that vitamin D deficiency is associated with a risk for cardiovascular disease (CAD).

Platelets play a crucial role in the pathophysiology of thrombogenesis and atherogenesis (4). Many recent studies have linked platelet activity with the development and progression of atherosclerosis (5). Platelet functions have been found to be associated with the risk for adverse events in various types of CAD patients (6). There are available tests for measuring platelet function, but most are expensive and are only available for research purposes rather than routine clinical practice (7). Mean platelet volume (MPV) is a simple marker of platelet size and it may reflect the platelet activity and be associated with plaque burden, plaque morphology, progression and vulnerability in the vessel. Larger platelets are younger, contain more alpha granules, have more expression of adhesion receptors, are more metabolically and enzymatically active, and hence, possess increased thrombogenic properties (8). Recently a meta-analysis in adults strongly suggested an association between MPV and CAD (9).

It has been revealed that vitamin D deficiency is related to cardiovascular diseases and literature suggests vitamin D supplementation eliminates this risk. According to our knowledge, this study is the first in the literature that investigates the relationship between MPV and vitamin D in childhood.

Materials and Methods

This was a retrospective study. Children followed-up at the Yüzüncü Yıl University (YYU) Faculty of Medicine Pediatric Endocrinology outpatient service and diagnosed as nutritional rickets were included in the study. Of these patients, those who had malabsorption, chronic disease, abnormal renal and liver function tests, those who used any medications, those with a history of chronic medication use, those using anti-convulsants, those who had infection during admission, those who had a history of multivitamin and vitamin D supplementation history were excluded from the study. A total of 216 cases were included in the study. These cases were accepted as the study group and divided into two separate groups according to vitamin D levels. Those with vitamin D level <15 ng/mL, were accepted as deficiency while those with vitamin D level of 15-20 ng/mL were accepted as insufficiency. Again, 1.516 cases with similar age and gender who had presented to the YYU Faculty of Medicine Pediatric Endocrinology and General Pediatrics outpatient services without any complaint for routine control and had available vitamin D levels (above 20 ng/mL) and no chronic disease or history of medication use were accepted as the control group and they were screened through files.

The laboratory parameters of the study and control groups were obtained from the electronic medical records.

Measurements of the biochemical parameters, serum electrolyte levels, renal and hepatic functions, and calcium, phosphorous and alkaline phosphatase levels were performed in the biochemistry laboratory of the hospital using the Hitachi modular PP analyzer, Roche Diagnostics-Germany (Roche Diagnostics GmbH, Mannheim, Germany). Intact parathormone (PTH) levels were analyzed using the Architect i4000sr (Abbott Diagnostics, Abbott Park, IL, USA) and the chemiluminescent method. Serum calcitriol levels were analyzed using Agilent 1200 series HPLC system (Agilent Technologies, Santa Clara, CA, USA). Hematological tests that measured the hemoglobin (Hgb), platelets, white blood cells (WBC) and MPV were performed using the Cell-Dyn Ruby analyzer (Abbott Diagnostics).

The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Local Ethics Committee of YYU, Faculty of Medicine, Van, Turkey.

After the information had been recorded, statistical analysis was performed using the SPSS version 13.0. The mean and the standard deviation values with minimum and maximum levels were used for the statistical expression of the groups. While the comparison of the continuous variables between the groups was performed using the one-way ANOVA for normally distributed variables, comparison of the abnormally variable and non-parametric parameters was performed using the Kruskall-Wallis H test and the chi square tests. A p value of <0.05 was considered as statistically significant. While the correlation analyses were performed with the Spearman correlation test or partial correlation tests, the effects of the variables on MPV were questioned using the multiple linear regression analysis.

Results

A total of 684 children and adolescents cases aged 0.1-18 years were included to the study. The cases were divided into 3 groups according to vitamin D levels. Those with vitamin D levels of less than 15 ng/mL were classified as vitamin D deficiency group, those with vitamin D levels of between 15-20 ng/mL are defined as insufficiency group

and those between 20-100 ng/mL were classified as the normal vitamin D level group. There were 156 cases in the deficiency group, 50 cases in the insufficiency group and 478 cases in the normal group. There was no statistically significant difference between the groups in terms of age and gender (Table I). There was a statistically significant difference between the groups in terms of Hgb, hematocrit (Htc), calcium, phosphorous, PTH and vitamin D levels. As expected, while the calcium was lowest in the vitamin D deficiency and insufficiency groups, PTH was highest in this group (Table II). When the correlation analysis was performed, while positive correlations were found between vitamin D and WBC, red cell distribution width (erythrocyte distribution volume), platelet, calcium and phosphorous, negative correlations were found with Hgb, Hct, mean corpuscular volume, red blood cell and PTH (Table III). There was no statistically significant correlation between vitamin D level and MPV in the correlation analysis ($p>0.05$). In the multiple regression analyses, again, no significant difference found when the effect of vitamin D on MPV was examined. However, in the linear regression analyses, it was seen that especially age, Hgb and phosphorus levels were effective on MPV (Table IV). In the partial correlation analysis, when Hgb, Htc, calcium, phosphorus and PTH were selected as the controlling factors, again, there was no significant difference observed between MPV and vitamin D ($r=-0.19$, $p>0.05$).

Discussion

Vitamin D deficiency is very common throughout the world, especially in Turkey and in Van, which is a town in the East Anatolia Region (10). There are various opinions regarding the vitamin D level that leads especially to cardiovascular diseases. In a study performed by Cigolini et al. (11) while this level was accepted as 20 ng/mL, in the study of Zittermann (12), this level was reported as 10 ng/mL. While the deficiency limit was accepted as 15 ng/mL in the 2008 guideline of the Lawson Wilkins Pediatric Endocrine Association, we evaluated the patient groups by dividing them into 3 different groups: Those in whom the vitamin

Table I. Distributions of the groups according to age and gender

		Deficiency (n=156)	Insufficiency (n=50)	Normal (n=478)	p
		Mean ± SDS (min-max)	Mean ± SDS (min-max)	Mean ± SDS (min-max)	
Age (years)		6.61±5.46 (0.1-18)	6.67±5.00 (0.1-16)	9.86±4.98 (0.1-17)	>0.05
Gender					
	Boy n (%)	77 (49.4)	27 (54)	265 (55.4)	>0.05
	Girl n (%)	79 (50.6)	23 (46)	213 (44.6)	

SDS: Sodium dodecyl sulfate, min: Minimum, max: Maximum

Table II. Comparison of the groups according to laboratory parameters

	Deficiency	Insufficiency	Normal	
	Mean ± SDS (min-max)	Mean ± SDS (min-max)	Mean ± SDS (min-max)	p
Leucocyte (mm^{-3})	9.07±2.65 (4.10-15.60)	8.49±3.02 (3.90-15.80)	9.34±2.99 (3.60-15.90)	>0.05
RBC (mm^{-3})	4.77±0.46 (3.30-5.90)	4.80±0.40 (3.60-5.38)	4.69±0.51 (3.10-5.83)	>0.05
Hemoglobin (g/dL)	12.17±1.50 (7.00-15.80)	12.14±1.18 (9.50-14.80)	11.79±1.38 (4.80-15.80)	<0.05
Hematocrit (%)	36.51±4.51 (21.00-47.40)	36.41±3.54 (28.50-44.40)	35.36±4.13 (14.40-47.40)	<0.05
MCV (fL)	80.94±7.98 (60.00-103.00)	79.90±7.19 (54.00-93.00)	79.45±7.76 (12.90-104.00)	>0.05
Erythrocyte distribution volume (RDW) (%)	14.41±2.23 (11.60-24.30)	14.93±2.69 (11.90-25.70)	18.12±68.04 (10.90-1501.00)	>0.05
Platelet (mm^{-3})	338403.8±116608.56 (119000-961000)	352760±114459.25 (208000-735000)	354799.2±114043.23 (131000-865000)	>0.05
MPV (fL)	7.93±0.96 (5.80-11.00)	8.02±0.88 (6.50-9.90)	7.93±1.13 (4.10-17.20)	>0.05
Calcium (mg/dL)	9.90±0.60 (8.40-11.60)	9.82±0.59 (8.03-11.09)	10.1±0.57 (9-11.80)	<0.05
Phosphor (mg/dL)	4.98±0.86 (2.10-7.97)	5.06±0.92 (2.40-7.09)	5.13±0.89 (1.40-7.50)	<0.05
Alkaline Phosphatase (U/L)	739.62±491.21 (128-3857)	700.00±369.47 (3.8-2326)	735.58±548 (139-6129)	>0.05
Parathormone (pg/mL)	80.72±119.88 (8.00-1039.00)	57.02±34.51 (11.00-190.00)	62.38±102.45 (1.00-1095.00)	<0.01
Vitamin D (ng/mL)	12.3±1.75 (0.00-14.09)	16.2±1.09 (15.02-19.9)	36.16±21.18 (21-99.84)	<0.001

SDS: Sodium dodecyl sulfate, min: Minimum, max: Maximum, RBC: Red blood cell, MCV: Mean corpuscular volume, MPV: Mean platelet volume, RDW: Red cell distribution width

Table III. Correlation analysis between vitamin D level and laboratory parameters

		Vitamin D
Leucocyte	r	0.107
	p	0.005
Erythrocyte	r	-0.131
	p	<0.001
Hemoglobin	r	-0.170
	p	<0.001
Hematocrit	r	-0.170
	p	<0.001
Mean erythrocyte volume	r	-0.134
	p	<0.001
Erythrocyte distribution volume	r	0.160
	p	<0.001
Platelet	r	0.132
	p	<0.001
Mean platelet volume	r	-0.026
	p	>0.05
Calcium	r	0.115
	p	0.002
Phosphorous	r	0.141
	p	<0.001
Alkaline phosphatase	r	0.045
	p	>0.05
Parathormone	r	-0.200
	p	<0.001

Table IV. Factors affecting mean platelet volume (Multiple regression analysis)

	B	Standard error	T	p
Vitamin D	-0.001	0.002	-0.258	0.796
Hct	0.004	0.012	0.318	0.751
Calcium	0.078	0.080	0.980	0.327
Phosphorus	0.123	0.053	2.346	0.019
Age	0.040	0.011	3.725	0.000
PTH	-0.001	0.000	-1.786	0.075
Hemoglobin	0.090	0.020	3.370	0.001

Hct: Hematocrit, PTH: Parathormone

D level was below 15 ng/mL, were accepted as deficiency; those between 15-20 ng/mL were accepted as insufficiency; and those above 20 ng/mL were accepted as normal (13).

In the National Health and Nutrition Examination Survey study conducted on 3.577 adolescents, after excluding age, gender, race and socio-economic status and physical activity, the cases with serum 25-OH level of below 15 ng/mL were reported to have a 2.3-fold higher high blood pressure, 2.5-fold higher blood glucose levels and 3.9-fold higher metabolic syndrome rate than those above 26 ng/mL (14). Several small observational studies have suggested that vitamin D deficiency is associated with insulin resistance or impaired insulin secretion, while insulin resistance and hyperglycemia are associated with hypertension and coronary heart disease (15). A previous study also showed that vitamin D supplementation given to patients with heart failure decreases symptoms that may be related to decreased levels of inflammatory cytokines (16).

In previous investigations on the potential adverse effects of vitamin D deficiency on the heart, MPV (known to cause cardiac events such as myocardial infarction and acute coronary syndrome) has not been considered in the analyses. We found only one study which was conducted on adults that investigated the relationship vitamin D and MPV values. In that study, they found that low levels of vitamin D (β=-0.109, p=0.019) were independently associated with increased MPV (17). Finally, the authors suggested a strong association between a low vitamin D level and a high MPV, and stated that vitamin D deficiency may be associated with increased MPV. In our study we did not find any relationship between vitamin D and the MPV values. Furthermore, we also found no significant correlation between vitamin D and the MPV values, and in the multiple linear regression analysis, again, we did not find any statistically significant relationship between vitamin D and the MPV values.

In previous studies, it was reported that the cytokine balance changes in vitamin D deficiency, TNF-α and IL-6 levels increase and these cytokines, which are related with oxidative stress, decrease after vitamin D treatment (18,19). In our study, the lack of a relationship between vitamin D levels and MPV can be either due to these undefined additional factors.

Study Limitations

Our study has some limitations; firstly, the patient population was not large enough, and the secondly the cardiovascular risk factors were not examined in this group.

Conclusions

Consequently, under the scope of the results of our study, more comprehensive studies are needed in order to illuminate the pathophysiology of cardiac dysfunctions as a result of vitamin D deficiency and we wanted to emphasize that the hypothesis of the probable effect of vitamin D on MPV should be questioned in more detail.

Ethics

Ethics Committee Approval: The study conformed to the principles outlined in the Declaration of Helsinki and was approved by the Local Ethics Committee of Yüzüncü Yıl University, Faculty of Medicine, Van, Turkey.

Peer-review: External and Internal peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Keziban Aslı Bala, Concept:

Murat Doğan, Design: Sultan Kaba, Mesut Garipardiç, Data Collection or Processing: Oktay Aslan, Şekibe Zehra Doğan, Analysis or Interpretation: Murat Doğan, Lokman Üstyol, Literature Search: Selami Kocaman, Writing: Keziban Aslı Bala.

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