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Effect of vitamin D deficiency on uric acid/HDL cholesterol ratio

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ABSTRACT

Aims: It has been suggested that vitamin D deficiency is involved in the etiology of cardiovascular diseases. High uric acid and low HDL cholesterol levels are critical risk factors for cardiovascular diseases. High uric acid levels, high total cholesterol and triglyceride levels, and low HDL-C levels are often encountered in cases with vitamin D deficiency. Our study aimed to investigate the relationship between vitamin D levels and uric acid /HDL-C (UHR) and plasma atherogenic index (PAI, triglyceride /HDL-C) in patients with vitamin D deficiency.

Methods: This retrospective study included patients whose vitamin D levels were checked in our clinic. The subjects were divided into two groups according to their vitamin D levels and the relationship between laboratory variables, such as uric acid, HDL cholesterol, UHR, and plasma atherogenic index, was examined.

Results: A total of 675 patients, 167 (24.7%) males and 508 (75.3%) females, were included in the study. The mean age of the patients was 53.6±15.2 years. It was found that patients with vitamin D deficiency had high UHR and PAI levels and low HDL-C levels (p=0.001, p=0.025; p=0.032, p=0.016).

Conclusion Our results suggest that vitamin D deficiency has a positive correlation with HDL cholesterol levels and an impact on the risk of cardiovascular diseases by increasing the uric acid/HDL ratio and plasma atherogenic index..

Keywords: Vitamin D deficiency on uric acid/HDL cholesterol ratio

INTRODUCTION

Vitamin D is taken with food in the form of ergocalciferol and cholecalciferol. It is actually formed through a process where 7-dehydrocholesterol in the skin absorbs solar ultraviolet-B ray photons and it is converted into previtamin D3 or cholecalciferol.[1] The active form of vitamin D is 1.25-dihydroxy vitamin D (1.25 (OH) 2D), which is produced by the 1α-hydroxylase enzyme in the renal proximal tubules, and its well-known impact is to ensure bone mineralization by increasing the absorption of calcium from the intestines.[2] The mechanism of 1.25 (OH) 2D works by binding to vitamin D receptors (VDR) found in many cells of the body, including cardiomyocytes, endothelium, and vascular smooth muscles. In addition, there are studies in the literature showing that VDR is present in many tissues and that vitamin D deficiency and insufficiency have an impact on common cancers, immune system diseases, metabolic syndrome, dermatological diseases, cardiovascular diseases, and lipid metabolism.[3-5] There is available data that 1.25(OH) 2D regulates the renin-angiotensin-aldosterone system. It has been experimentally observed that 1α-hydroxylase deficiency leads to the development of high-renin hypertension. In light of these studies, it is thought that vitamin D has a protective effect against cardiovascular diseases.[6]

It has been observed that high uric acid is associated with diabetes, hypertension, metabolic syndrome, insulin resistance, stroke, and cardiovascular events.[7,8] In addition to unclear data in the literature, there are many studies supporting the association of hyperuricemia and vitamin D deficiency.[9,10] In a meta-analysis of 32 studies by Isnuwardana et al.,[11,12] the likelihood of hyperuricemia due to vitamin D deficiency was determined to be approximately 1.5 times the normal level of vitamin D. It has been suggested that serum uric acid may reduce the conversion of 25-hydroxyvitamin D (25-OHD) to the active VIT D form of 1.25-di hydroxyl vitamin D (1,25-(OH)2D) by suppressing the 1-alpha-hydroxylase enzyme. It is considered that vitamin D deficiency may result in hyperuricemia by causing secondary hyperparathyroidism.

When the literature is reviewed, it can be seen that there is an inverse correlation between serum levels of 25(OH)D

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and serum lipid levels. In a study involving 8,592 patients, individuals with low 25(OH)D levels had higher levels of total cholesterol (TC), triglycerides (TGs), and low-density lipoprotein cholesterol (LDL-C) but lower levels of high-density lipoprotein cholesterol (HDL-C).[13] In another study, it was suggested that serum 25(OH)D levels had a negative correlation with total cholesterol, triglyceride, and LDL-cholesterol and a positive correlation with HDL cholesterol.[14] Lipid/lipoprotein abnormalities, which mean high uric acid, TC, TG, LDL-C, triglyceride/HDL cholesterol, uric acid/HDL cholesterol levels, and decreased HDL-C levels, are critical risk factors for atherosclerosis and CVDs. The TG/HDL cholesterol ratio (plasma atherogenic index-PIA), which best shows us small and dense LDL (sdLDL), which accumulates more easily in the artery wall than LDL cholesterol, has also become a guiding marker for atherosclerosis and coronary artery disease.[15]

In our study, we aimed to examine the relationship of 25(OH) vitamin D deficiency with the uric acid/HDL ratio, a marker for cardiovascular diseases, and TG/HDL cholesterol ratio (plasma atherogenic index).

METHODS

This investigation received authorization from the Hitit University Clinical Research Ethics Committee (April 30, 2024, approval 2024-11) and all protocols undertaken in investigations involving human subjects were conducted in strict compliance with the ethical guidelines outlined by the institutional and/or national research governing body, the 1964 Declaration of Helsinki, and its subsequent revisions or analogous ethical criteria. The present study is a retrospective multicenter study. Patients who applied to the internal medicine clinic between January 1, 2020 and January 30, 2023 were, a total of 675 patients, 167 men and 508 women, were included in the study. The patients who were <18 years old; who had Type 1 or Type 2 Diabetes mellitus, prediabetes or those who were on metformin therapy; who were pregnant; who had chronic diseases such as hypertension, chronic renal disease, liver diseases. The patients who were <18 years old; who had Type 1 or Type 2 Diabetes mellitus, prediabetes or those who were on metformin therapy; who were pregnant; who had chronic diseases such as hypertension, chronic renal disease, liver diseases, hypertension, cardiac insufficiency; who had active infection; who had hematological or immunological diseases or malignancies; who had primary hyperparathyroidism; and who were on medications for calcium and lipid metabolism and those using antihypertensive medications were excluded from the study. The demographics and anthropometric data of the patients were recorded. Vitamin D levels (ng/ml), triglyceride (mg/dl), total cholesterol (mg/dl), high-density lipoprotein cholesterol (HDL-C) (mg/dl), low-density lipoprotein cholesterol (LDL-C) (mg/dl) and uric acid levels (mg/dl) of all patients who met the inclusion criteria for the study were recorded from the hospital automation system. Patients with vitamin D levels <10 (ng/ml) were classified as group-1, patients with vitamin D levels between 10-20 (ng/ml) were classified as group-2, patients with 20-30 (ng/ml) were classified as group-3, and patients with >30 (ng/ml) were classified as group-4. The correlation between uric acid/HDL-C, tgl/HDL-C levels according to the patients' vitamin D levels was evaluated.

Statistical Analysis

The data were analyzed on the IBM SPSS Statistics Standard Concurrent User V 29 software (IBM Corp., Armonk, New York, USA). Summary statistics were given as numbers (n) and percentages (%) for categorical variables and arithmetic mean, standard deviation, standard error, median, and interquartile range values according to the distribution of the data for numerical variables. The normality of the data of numerical variables was evaluated with the Shapiro-Wilk normality test. The Levene test was employed to analyze the homogeneity of the variance of the groups. Comparisons between two groups of numerical variables were made with independent samples t-test for normally distributed data and with the Mann-Whitney U test for non-normally distributed data. One-way analysis of covariance was employed to compare age-adjusted uric acid/HDL ratios according to vitamin D groups. The bonferroni test was used as a multiple comparison test. Pearson chi-square test was utilized to compare groups with categorical variables. A value of $p<0.05$ was considered statistically significant.

RESULTS

A total of 675 patients, 167 (24.7%) males and 508 (75.3%) females, were included in the study. The age range of the patients was 18 to 85 years, with the mean age being 53.6±15.2 years.

As seen in Table 1, vitamin D deficiency was observed in 63.5% of male patients and 68.5% of female patients. There was no statistically significant difference between the vitamin D distributions of male and female patients. Age, creatinine, HDL, and aspartat transaminaz (AST) values of patients with vitamin D deficiency were statistically low. Total cholesterol, LDL, uric acid, uric acid/HDL ratio, glucose, alanin aminotransferaz (ALT), triglyceride values, and TGL/HDL ratio were not statistically different by vitamin D groups.

According to the comparisons in Table 1, since the ages of the patients were statistically different in the vitamin D groups, considering that the age variable could be a confounding factor, the uric acid/HDL and TGL/HDL ratios were adjusted for age and compared again. As seen in Table 2, uric acid/HDL and TGL/HDL ratios in patients with vitamin D deficiency were statistically higher than in patients without deficiency.

As seen in Table 3, uric acid/HDL ratios showed statistical differences in vitamin D groups. Patients with vitamin D<10 (ng/ml) had statistically higher uric acid/HDL ratios than those with vitamin D>30(ng/ml). Differences between other groups were not statistically significant. TGL/HDL ratios showed statistical differences in vitamin D groups. Patients with vitamin D>30(ng/ml) had statistically lower TGL/HDL ratios than other groups. TGL/HDL ratios of other vitamin D groups were not statistically different.

Table 1. Comparison of demographic and laboratory values of patients with vitamin D levels below and above 20 ng/mL

	Vitamin D		Test Statistics	
	<20 (ng/ml) n=454	≥20(ng/ml) n=221	Test value	p value
Gender. n (%)				
Male	106 (63.5)	61 (36.5)	1.445	0.229‡
Female	348 (68.5)	160 (31.5)		
Age. (year)	52.4±15.3	55.6±14.8	2.550	0.010†
Creatinine	0.70±0.18	0.74±0.20	2.360	0.019†
Total cholesterol	188.71±37.44	192.83±39.00	1.325	0.186†
LDL	104.67±30.35	106.78±31.27	0.840	0.401†
HDL	54.68±10.73	57.96±12.91	3.270	0.001†
Uric acid	4.64±1.24	4.79±1.30	1.422	0.155†
Uric acid/ HDL ratio	9.00±3.13	8.78±3.49	0.823	0.411†
Glucose	93.00 (19.00)	95.00 (21.00)	1.504	0.133&
AST	19.00 (6.00)	20.00 (5.50)	2.057	0.040&
ALT	17.00 (9.00)	18.00 (10.50)	1.606	0.108&
TGL	130.50 (96.25)	120.00 (88.00)	0.955	0.340&
TGL/HDL	2.84±1.73	2.61±1.63	1.685	0.093†

n: Number of patients, %: Row percentage, Data were presented as mean±standard deviation or median (interquartile range) values. ‡: Pearson chi-square test, †: Independent samples t test, &: Mann-Whitney U test ,AST: aspartat transaminaz ,ALT: alanin aminotransferaz

Table 2: Comparison of uric acid/HDL and TGL/HDL ratios in vitamin D groups for adjusted age

	Vitamin D		Test Statistics	
	<20(ng/ml) n=454	≥20(ng/ml) n=221	test value	p value
Uric acid/HDL	9.03±0.16	8.82±0.22	5.073	0.025¥
TGL/HDL	2.86±0.07	2.56±0.11	4.606	0.032¥

Data were summarized as mean±standard error estimate. ¥: One-way covariance analysis, TGL: Trigliserid

Table 3: Comparison of uric acid/HDL ratios in four vitamin D groups for adjusted age

	Vitamin D				Test Statistics	
	<10 (ng/ml) n=165	10-20 (ng/ml) n=289	20-30 (ng/ml) n=146	>30 (ng/ml) n=75	Test value	p value
Uric acid/ HDL	9.12±0.27a	8.98±0.19ab	9.08±0.27ab	9.08±0.27ab	3.788	0.010¥
TGL/ HDL	2.79±0.13a	2.89±0.10a	2.75±0.13a	2.75±0.13a	3.463	0.016¥

Data were summarized as mean±standard error estimates. ¥: One-way analysis of covariance; Superscripts a and b indicate the difference between groups. There was no statistically significant difference between groups containing the same superscript

DISCUSSION

Uric acid/HDL cholesterol and triglyceride/HDL cholesterol levels were high in patients with 25(OH)D below 20 (ng/ml). Our study is the first in the investigation of uric acid/HDL cholesterol and plasma atherogenic index simultaneously in patients with vitamin D deficiency.

Some studies have shown that vitamin D deficiency is a new risk factor for cardiovascular diseases.[4] It has been found that vitamin D levels are lower in conditions that increase the risk of cardiovascular disease, such as metabolic syndrome, diabetes mellitus, and hypertension.[16] Patients with low vitamin D face more cardiovascular mortality than individuals with normal vitamin D levels.[17]

There are some studies in the literature suggesting that high uric acid levels and low levels of HDL cholesterol may have synergistic negative effects on the cardiovascular system through insulin resistance and oxidative damage to endothelial cells.[18,19] Hu et al.[20] showed that high serum UA levels had an effect on carotid atherosclerosis of HDL-C. In a meta-analysis conducted by Yang et al.[21] in 480 patients with acute myocardial infarction, high uric acid and low HDL cholesterol levels were found as risk factors for AMI.

In a study conducted by Lupton et al.[22] on 20,360 individuals, it was observed that HDL cholesterol was low and LDL-cholesterol, total cholesterol, and triglyceride levels were significantly higher in individuals with low vitamin D. In a study conducted by Mashahit et al.,[23] it was observed that serum 25(OH)D was inversely associated with high TG and low HDL cholesterol levels in both diabetic and control groups.Ray Chaudhuri et al.[24] reported that 25-hydroxy vitamin D deficiency was significantly associated with dyslipidemia (P=0.0001) in the Indian population. There are some studies in the literature supporting that vitamin D deficiency is associated with dyslipidemia, as well as meta-analyses showing no association.[25,26] Data supporting literature findings were obtained in our study. It was observed in our study that HDL cholesterol levels were significantly lower in individuals with low vitamin D. However, supporting the studies in the literature, no significant relationship was detected in terms of total cholesterol, triglyceride, LDL-Cholesterol levels, and vitamin D deficiency.

In a study that included 18,596 patients, Hang Y. et al.[27] found a negative relationship between vitamin D and hyperuricemia. A study conducted in 2013 showed that vitamin D deficiency was significantly associated with high uric acid among postmenopausal Chinese women but not in premenopausal women.[28] It was observed that the uric acid levels of the patients with prediabetes and vitamin D deficiency, whose uric acid level was above 6 mg/dl, decreased after vitamin D supplementation.[29] On the other hand, there are some other studies that have not detected any relationship between vitamin D deficiency and hyperuricemia.[30] In our study, no significant relationship was found between uric acid and vitamin D deficiency.

There are studies in the literature indicating that high uric acid/HDL cholesterol levels may have synergistic harmful effects on the cardiovascular system by increasing endothelial oxidative damage and insulin resistance.[31-33] In our study, we found that vitamin D deficiency had a significant relationship with high uric acid/HDL cholesterol levels ($p>0.025$, $p<0.010$). In light of this study, we think that vitamin D deficiency may be a risk factor for cardiovascular diseases by increasing the uric acid/HDL cholesterol level. Plasma atherogenic index (PAI-TG/HDL cholesterol) is an important noninvasive biomarker used in the diagnosis of atherosclerotic coronary heart disease in recent years. In the KERCADR study conducted by Mahmodii et al.,[34] it was determined that there was an inverse relationship between PAI and vitamin D levels in healthy men. In the same study, it was stated that an improvement in vitamin D levels would cause a significant decrease in PAI to reduce the risk of

cardiovascular disease in individuals with a normal body mass index. In a case-control study in the literature, it was observed that vitamin D level and PAI were inversely proportional in patients with metabolic syndrome.[35] In our study, PAI was found to be statistically higher in patients with vitamin D deficiency than in patients without deficiency (p=0.032, p=0.016). As a result of our study, we think that the uric acid/HDL cholesterol ratio and PAI can help predict the risk of cardiovascular disease in individuals with vitamin D deficiency and that we can also reduce cardiovascular risk with vitamin D supplementation.

CONCLUSION

This is the first study in the literature simultaneously showing the relationship between UHR and PAI, which are used as biomarkers for cardiovascular risk, and vitamin D. We think that vitamin D deficiency and UHR and PAI increased by the deficiency may be a risk factor for cardiovascular events.

ETHICAL DECLARATIONS

Ethics Committee Approval

Ethics committee approval was obtained from Hitit University Clinical Researchs Ethics Committee (Date: 30.04.2024, Decision No: 11).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version.

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