ORIGINAL ARTICLE

The relationship between a combination of vitamin D deficiency and hyperuricemia and the severity of coronary artery disease in myocardial infarction patients

Miyokart enfarktüslü hastalarda D vitamini eksikliği ve hiperürisemi birlikteliğinin koroner arter hastalığı ciddiyeti ile ilişkisi

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ABSTRACT

Objective: Vitamin D deficiency has been shown to be associated with coronary artery disease (CAD). In addition, there are studies suggesting that hyperuricemia is an independent risk factor for atherosclerosis, whereas the relationship between the combination of these 2 parameters and severity of CAD remains unclear. The aim of this study was to investigate the association between the combination of vitamin D deficiency and hyperuricemia and the extent of CAD.

Methods: A total of 502 patients who had experienced myocardial infarction (MI) were included in this cross-sectional study. The 25-hydroxyvitamin D (25OHD) and serum uric acid (SUA) levels were measured in blood samples taken at the time of admission. A 2x2 factorial design was used to create groups according to the presence of hyperuricemia (>7 mg/dL) and vitamin D deficiency (<20 ng/mL). All of the patients underwent coronary angiography and the severity of CAD was determined using the Gensini score, SYNTAX score, and the number of diseased vessels.

Results: Both vitamin D deficiency and hyperuricemia were present in 83 patients (16.5%). Patients with hyperuricemia/vitamin D deficiency had more multivessel disease (24.1% vs 8.5%), and a higher SYNTAX score and Gensini score compared with the control group (13.9±8.0 vs. 9.5±6.3, 54.8±24.0 vs. 40.5±19.9, respectively). Age, male sex, presence of diabetes mellitus, family history of CAD, and levels of SUA and 25OHD were independent predictors of the severity of CAD. Moreover, the hyperuricemia/vitamin D deficiency group had 4 times greater odds of severe CAD than the control group.

Conclusion: The combination of hyperuricemia and vitamin D deficiency appears to be an independent predictor of severe CAD in MI patients.

ÖZET

Amaç: Vitamin D eksikliğinin koroner arter hastalığıyla ilişkisi gösterilmiştir. Ayrıca, hiperüriseminin de aterosklerozun bağımsız prediktörü olduğuna dair çalışmalar mevcuttur. Bununla birlikte, bu iki parametrenin birlikteliğinin koroner arter hastalığının ciddiyeti ile ilişkisi net değildir. Çalışmamızda, Vitamin D eksikliği ve hiperürisemi varlığının koroner arter hastalığının ciddiyeti ile ilişkisi olup olmadığını araştırmayı amaçladık.

Yöntemler: Bu kesitsel çalışmaya miyokart enfarktüs tanılı 502 hasta alındı. 25-hidroksivitamin D (25OHD) ve serum ürik asit (SUA) seviyesi hastane başvurusu sırasında alınan kandan ölçüldü. Hiperürisemi (>7 mg/dL) ve vitamin D eksikliği (<20 ng/mL) varlığına göre 2x2 faktöryel dizayn kullanılarak gruplar oluşturuldu. Tüm hastalara koroner anjiografi uygulandı ve koroner arter hastalığı ciddiyeti; Gensini skoru, SYNTAX skoru ve lezyonlu damar sayısına göre belirlendi.

Bulgular: Vitamin D eksikliği ve hiperürisemi birlikteliği 83 hastada mevcuttu (%16.5). Hem Vitamin D eksikliği hem de hiperürisemisi olan hastalarda daha fazla çoklu-damar hastalığı, daha yüksek SYNTAX skoru ve Gensini skoru mevcuttu (sırasıyla, %24.1 ve %8.5, 13.9±8.0 ve 9.5±6.3, 54.8±24.0 ve 40.5±19.9). Yaş, erkek cinsiyet, diyabet mellitus, aile öyküsü, SUA ve 25OHD koroner arter hastalığının ciddiyetinin bağımsız prediktörleriydi. Ayrıca, hiperürisemi/vitamin D eksikliği grubu kontrol grubuna göre dört kat daha fazla ciddi koroner arter hastalığına sahiptir.

Sonuç: Hiperürisemi ve vitamin D eksikliği birlikteliği, miyokart enfarktüs hastalarında koroner arter hastalığının ciddiyetinin bağımsız prediktörlerinden biridir.

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The 25-hydroxyvitamin D (25OHD) molecule has an important role in regulating the absorption of vitamin D and its presence and activity have complex effects in different parts of the body. It has a notable influence on the cardiovascular system, since it causes changes in cardiomyocytes through its receptors in the renin-angiotensin system.[1] Cardiovascular-adverse outcomes may be observed in the presence of vitamin D deficiency in tissues associated with cardiac events, such as arterial surfaces, cardiomyocytes, platelets, and inflammatory cells.[2] It has been determined that there is a relationship between a low serum 25OHD level and the frequency of cardiovascular disease.[3]

Uric acid is another molecule that has been studied for its relationship with cardiovascular disease. Serum uric acid (SUA) has been detected to be a mediator of endothelial dysfunction and inflammation; thus, hyperuricemia may initiate coronary artery plaque formation directly via this pathophysiological way.[4,5] Hyperuricemia may also affect cardiovascular risk factors, such as hypertension and metabolic syndrome, creating another avenue of potential CAD.[6,7] Studies have recognized that an elevated SUA level increases the risk of CAD through both direct and indirect mechanisms.[8,9]

The relationships between hyperuricemia, vitamin D deficiency, and the severity of CAD have been investigated separately;[10–12] however, as far as we know, any association between a combination of these molecules and CAD severity in myocardial infarction (MI) patients has not been described to date. The objective of this study was to investigate the rate of vitamin D deficiency and hyperuricemia in a study population and the additional effects of 25OHD and SUA on the severity of atherosclerosis in MI patients.

METHODS

Study population

A 2x2 factorial design was used in this cross-sectional study to create groups according to the presence of vitamin D deficiency and hyperuricemia. A total of 502 patients who were admitted to a large-volume center between May 2017 and April 2018 with a diagnosis of MI and who underwent coronary angiography were included. Patients who had missing or unavailable data; malignant and infectious disease or other systemic inflammatory conditions; renal dysfunction (glomerular filtration rate <30); a history of parathyroidectomy or use of medications for hypothyroidism or hyperthyroidism and thyroid-stimulating hormone values outside the normal range; treatment with phenytoin, carbamazepine, antituberculosis or anti-HIV/AIDS medications, which can affect vitamin D levels; use of xanthine oxidase inhibitors, diuretics, or cyclosporine, which can change uric acid levels; or a history of a 25OHD or SUA metabolism disorder were excluded. ST-elevated myocardial infarction (STEMI) patients were defined as patients with typical chest discomfort or other ischemic symptoms who developed new ST-segment elevations in 2 or more contiguous leads or new bundle branch blocks with ischemic repolarization patterns on a standard 12-lead electrocardiogram (ECG). Patients with high troponin levels but without STEMI ECG criteria were defined as non-ST elevated myocardial infarction (NSTEMI). Informed consent was obtained from all of the patients, and approval for the study was granted by the local ethical committee (2019/03). The guidelines of the Helsinki Declaration were observed throughout the study.

Abbreviations:

25OHD	*25-hydroxyvitamin D*
AUC	*Area under the curve*
CAD	*Coronary artery disease*
CI	*Confidence interval*
ECG	*Electrocardiogram*
MI	*Myocardial infarction*
NSTEMI	*Non-ST-elevated myocardial infarction*
OR	*Odds ratio*
ROC	*Receiver operating characteristic*
STEMI	*ST-elevated myocardial infarction*
SUA	*Serum uric acid*

Analysis of coronary angiogram

Patient angiographic data were collected from the catheter laboratory records. A coronary angiogram was performed on each patient using a radial or femoral route according to the operator's experience and patient suitability. A minimum of 4 projections were used for imaging of the left main coronary artery, left anterior descending artery, and circumflex artery, and a minimum of 2 projections were used for the right coronary artery. After the procedure, an interventional cardiologist blinded to the study evaluated the angiograms. CAD severity was determined according to the Gensini score, SYNTAX score, and the number of diseased vessels. The percentage of stenosis was obtained according to the ratio of the diameter of the narrowest portion of the vessel to the diameter of the nearest normal proximal segment. Luminal stenosis of more than 50% in the all

the major epicardial vessels or main lateral branches of these vessels was considered significant. The patients were classified as having 1-, 2-, or 3-vessel disease according to the lesions of the major epicardial arteries. If there were multiple lesions in the same vessel with a normal segment of >20 mm between the lesions, it was accepted as 2-vessel disease. In order to calculate the Gensini score, the severity of the stenosis was evaluated. According to the localization of the lesion, these values were multiplied by the predetermined coefficients. The total score of all coronary arteries was expressed as the Gensini score.[13] The Gensini score was used to determine independent predictors of the severity of CAD and in receiver operating characteristic (ROC) analysis, was was the most frequently used angiographic scoring method in the literature.[14] The SYNTAX score, another coronary angiographic scoring system, was also used in the present study. The total SYNTAX score is calculated according to the characteristics of the lesion (tortuosity, calcification, thrombus, etc.) in individuals with luminal stenosis of more than 50% in all vessels of more than 1.5 mm in diameter. Previous studies have demonstrated that the SYNTAX score, which indicates the degree of complexity of coronary atherosclerosis, could predict major cardiovascular events in patients with acute coronary syndrome and stable angina.[15]

Laboratory measurement

A 5-mL venous blood sample was taken in the morning after overnight fasting. When an urgent angiography was needed, the patient blood test was performed after 12 hours of fasting following the procedure. The SUA level was tested using the Roche UA version II kit (Roche Diagnostics GmbH, Risch-Rotkreuz, Switzerland) with a Cobas C501 analyzer (Roche Diagnostics GmbH, Risch-Rotkreuz, Switzerland). The measurement range was 0.2–25 mg/dL, and the coefficient of variation was 2.1%. A SUA measurement of >7 mg/dL was accepted as hyperuricemia, as used in most studies in the literature. The vitamin D total II kit (Roche Diagnostics GmbH, Risch-Rotkreuz, Switzerland) and a Cobas e601 analyzer (Roche Diagnostics GmbH, Risch-Rotkreuz, Switzerland) was used for total vitamin D measurement. The measurement range was 3–100 ng/mL, and the coefficient of variation was 7.2%. In previous studies, a minimum of 20 ng/mL of vitamin D has been required to indicate proper functioning of bone metabolism; therefore, a level of <20 ng/mL was considered a deficiency of vitamin D.[16]

Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 21.0 (IBM Corp., Armonk, NY, USA). Visual and analytical methods were applied to determine normal distribution. Descriptive analyses were presented as mean and SD for variables with normal distribution, and as median and interquartile range for variables without normal distribution. Categorical variables were expressed as numbers and percentages. The study groups were compared using one-way analysis of variance for continuous variables that demonstrated normal distribution and the Kruskal-Wallis test for continuous variables that did not present a normal distribution. The Bonferroni correction was employed to adjust for multiple comparisons. Categorical data were compared with a chi-square test. ROC curves were drawn to distinguish the severity of CAD. Youden's index was used to derive the best cut-offs for the plasma concentration of 25OHD and SUA. Multivariate logistic regression with backward stepwise selection of $p<0.1$ variables determined in univariate analysis was carried out to identify independent predictors of the severity of CAD. The Gensini score was used to perform regression analysis instead of the SYNTAX score since the Gensini score is more widely represented in the literature and has demonstrated no inferiority.[17] Using the criteria of previous studies, a Gensini score of ≥40 was determined to indicate severe CAD.[18] Two dichotomized variables, namely the presence of vitamin D deficiency and hyperuricemia, were used to identify the effect of interaction between 25 OHD and SUA levels. Nagelkerke R-squared values were recorded for logistic regression. A p value <0.05 was considered statistically significant.

RESULTS

After excluding inappropriate cases, a total of 502 patients were included in this study. The prevalence of isolated vitamin D deficiency was 44.0%, 11.3% for isolated hyperuricemia, and 16.5% for both vitamin D deficiency and hyperuricemia. The 25OHD and SUA levels and baseline characteristics of the 4 groups did not reveal a significant difference (Table 1).

Table 1. Baseline characteristics of the study population, mean±SD or n (%)

Variables	Control (n=141)	HU (n=57)	Vit D def. (n=221)	Vit D. def + HU (n=83)	*p*
Age, years	58.5±11.5	61.9±11.2	60.0±12.2	61.9±10.1	0.111
Male, n (%)	107 (75.9)	40 (70.2)	171 (77.4)	56 (67.5)	0.281
HL, n (%)	27 (19.1)	14 (24.6)	37 (16.8)	21 (25.3)	0.364
DM, n (%)	38 (27.0)	18 (31.6)	71 (32.1)	32 (38.6)	0.349
HT, n (%)	51 (36.2)	27 (47.4)	96 (43.4)	44 (53.2)	0.094
Smoking, n (%)	60 (42.6)	20 (35.1)	98 (44.3)	26 (31.3)	0.159
Family history, n (%)	14 (9.9)	8 (14.0)	18 (8.1)	12 (14.5)	0.317
BMI, kg/m^2	26.2±2.3	26.7±2.8	26.0±2.0	26.7±2.5	0.106
Creatinine, mg/dL	0.99±0.68	1.00±0.26	0.93±0.49	1.06±0.49	0.240
SBP, mmHg	127.4±25.0	131.3±28.0	130.2±24.2	132.2±27.8	0.324
DBP, mmHg	72.3±11.4	72.9±14.7	72.9±13.3	73.0±12.7	0.934
HR, bpm	76.6±14.1	76.3±14.4	79.6±14.3	80.4±12.1	0.077
Ca, mg/dL	8.79±0.48	8,77±0.47	8.72±0.53	8.73±0.45	0.597
LDH, U/L	377.7±234.7	351.6±182.6	351.8±169.3	377.4±293.5	0.572
HDL-cholesterol, mg/dL	40.6±8.7	42.0±7.9	39.9±8.7	41.7±12.8	0.319
Triglyceride, mg/dL	159.6±115.3	196.4±115.0	165.3±108.6	182.3±103.5	0.132
Uric acid, mg/dL	5.3±0.7	8.0±1.2	5.4±0.8	8.0±1.2	<0.001
25OHD, ng/mL	25.7±6.2	23.8±5.2	13.5±3.4	11.6±3.3	<0.001

25OHD: 25-hydroxyvitamin D; BMI: Body mass index; Ca: Calcium; DBP: Diastolic blood pressure; Def: Deficiency; DM: Diabetes mellitus; HDL: High-density lipoprotein; HL: Hyperlipedemia; HT: Hypertension; HR: Heart rate; HU: Hyperuricemia; LDH: Lactic acid dehydrogenase; SBP: Systolic blood pressure; Vit: Vitamin.

A comparison of the study groups according to the parameters of infarct-related artery, MI type, and form of treatment revealed no significant differences (Table 2). A statistically significant difference was detected among the 4 groups in single-vessel and 3-vessel disease (p=0.004, p=0.015, respectively). In binary comparisons, there was no significant difference found between the patients with isolated vitamin D deficiency or isolated hyperuricemia in terms of single-vessel disease compared with the control group (p=0.086, p=0.184 respectively); however, the patients with both hyperuricemia and vitamin D deficiency had less single-vessel disease than the control group (Odds ratio [OR]: 0.34, 95% confidence interval [CI]: 0.19–0.61; p<0.001). In contrast, patients with isolated hyperuricemia and with isolated vitamin D deficiency had more 3-vessel disease than the control group (OR: 2.54, 95% CI: 1.05–6.13, p=0.033; OR: 2.33, 95% CI: 1.16–4.65, p=0.014, respectively). Furthermore, the presence of 3-vessel disease was found to be statistically more significant in patients with both hyperuricemia and vitamin D deficiency compared with the control group (OR:3.59, 95% CI: 1.65–7.81; p=0.001).

Another parameter used to determine the severity of CAD in our study was coronary angiographic scoring systems (Table 2). There were statistically significant differences between the 4 groups in the Gensini and SYNTAX scores. According to comparisons in binary groups, patients with a vitamin D deficiency had a higher Gensini score than the control group, but the same difference was not observed in hyperuricemic patients (p=0.019, p=0.552 respectively). Individuals with both hyperuricemia and vitamin D deficiency had a higher Gensini score than those with isolated vitamin D deficiency, those with isolated hyperuricemia, and the control group (54.8±24.0 *vs.* 45.5±22.7, p=0.023; 54.8±24.0 *vs.* 45.4±18.5, p=0.019; 54.8±24.0 *vs.* 40.5±19.9, p<0.001, respectively). Assessment of the SYNTAX score revealed no statistically significant difference in the separate presence of vitamin D deficiency or hyperuricemia

Table 2. Angiographic and procedural charecteristics of the study population, mean±SD or n (%)

Variables	Control (n=141)	HU (n=57)	Vit D def. (n=221)	Vit D. def + HU (n=83)	*p*
MI type n (%)					0.697
STEMI	83 (58.9)	35 (61.4)	140 (63.3)	47 (57.6)	
NSTEMI	58 (41.1)	22 (38.6)	81 (36.7)	36 (43.4)	
IRA, n (%)					0.631
LAD	54 (38.3)	28 (49.1)	94 (42.5)	39 (47.0)	
CX	40 (28.4)	11 (19.3)	46 (20.8)	19 (22.9)	
RCA	42 (29.8)	14 (24.6)	71 (32.1)	23 (27.7)	
Other	5 (3.5)	4 (7.0)	10 (4.5)	2 (2.4)	
Number of diseased vessels , n (%)					
1	107 (75.9)	37 (64.9)	151 (68.3)	43 (51.8)	0.004
2	22 (15.6)	9 (15.8)	33 (14.9)	20 (24.1)	0.271
3	12 (8.5)	11 (19.3)	36 (16.3)	20 (24.1)	0.015
Gensini score	40.5±19.9	45.4±18.5	45.5±22.7	54.8±24.0	<0.001
SYNTAX score	9.5±6.3	10.8±5.4	10.4±6.5	13.9±8.0	<0.001
Treatment, n (%)					0.172
PCI	101 (71.6)	41 (71.9)	175 (79.2)	54 (65.1)	
Medical	11 (7.8)	4 (7.0)	14 (6.3)	5 (6.0)	
CABG	29 (20.6)	12 (21.1)	32 (14.5)	24 (28.9)	

CABG: Coronary artery bypass grafting; CX: Circumflex; Def: Deficiency; DM: Diabetes mellitus; HDL: High-density lipoprotein; HL: Hyperlipedemia; HT: Hypertension; HR: Heart rate; HU: Hyperuricemia; IRA: Infarct related artery; LAD, left anterior descending; LDH: Lactic acid dehydrogenase; NSTEMI: Non-ST elevated myocardial infarction; PCI: Percutaneous coronory intervention; RCA: Right coronary artery; SBP: Systolic blood pressure; STEMI: ST-elevated myocardial infarction; Vit: Vitamin.

(p=0.310, p=0.717); however, the co-existence of these pathologies was found to be significantly related to a higher SYNTAX score (13.9±8.0 *vs*. 10.4±6.5, p=0.049; 13.9±8.0 *vs*. 10.8±5.4, p=0.024; 13.9±8.0 *vs*. 9.5±6.3, p<0.001, respectively) (Fig. 1).

In logistic regression analysis, age, male sex, diabetes mellitus (DM), family history, SUA and 25OHD levels were identified as independent predictors of the severity of CAD. The isolated hyperuricemia group had a 1.8 times greater likelihood of severe CAD, the isolated vitamin D deficiency group had a 1.7 times greater probability, and patients with both hyperuricemia and vitamin D deficiency had 4.0 times greater odds of severe CAD compared with the control group, independent of other risk factors (Table 3). An SUA cut-off of 6.8 mg/dL had an area under the curve (AUC) of 0.619 with 36.7% sensitivity and 83.2% specificity for distinguishing the severity of CAD. A

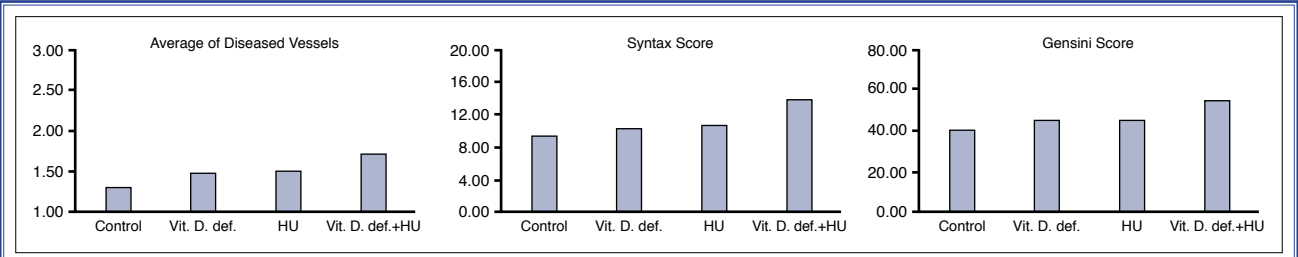

Figure 1. Bar graph showing the average number of diseased vessels, SYNTAX score, and Gensini score in the groups according to the presence of vitamin D deficiency and hyperuricemia. Def: Deficiency; HU: Hyperuricemia; Vit: Vitamin.

Table 3. Multivariate logistic regression analysis for the severity of coronary artery disease*

	Univariate analysis		Multivariate analysis¶	
	OR (CI 95%)	*p*	OR (CI 95%)	*p*
Age, years	1.031 (1.015–1.048)	<0.001	1.035 (1.018–1.053)	<0.001
Male gender	1.451 (0.969–2.173)	0.071	2.196 (1.383–3.486)	0.001
BMI, kg/m^2	1.030 (0.961–1.103)	0.406		
HL	1.739 (1.101–2.746)	0.018	1.643 (0.986–2.737)	0.057
DM	1.835 (1.247–2.700)	0.002	1.729 (1.113–2.686)	0.015
Smoking	1.072 (0.750–1.532)	0.703		
HT	1.295 (0.909–1.845)	0.153		
Family history	2.339 (1.248–4.381)	0.008	2.974 (1.494–5.920)	0.002
Creatinine, mg/dL	0.890 (0.639–1.240)	0.492		
HDL, mg/dL	1.016 (0.997–1.036)	0.107		
Seum uric acid, mg/dL	1.336 (1.175–1.519)	<0.001	1.313 (1.150–1.500)	<0.001
25OHD ng/mL	0.955 (0.931–0.979)	<0.001	0.958 (0.933–0.984)	0.002
Control group‡	Ref.	Ref.	Ref.	Ref.
Only hyperuricemia‡	1.973 (1.075–3.621)	0.028	1.871 (1.001–3.502)	0.049
Only vitamin D deficiency‡	1.807 (1.180–2.767)	0.007	1.759 (1.126–2.749)	0.013
Both hyperuricemia and vitamin D deficiency‡	3.935 (2.198–7.046)	<0.001	4.004 (2.151–7.451)	<0.001

*Gensini score ≥40 was considered severe coronary artery disease. ‡These groups were included in a second model instead of 25OHD and serum uric acid. ¶Nagelkerke R–square for the first model was 26.9% and 26.1% for the second model.
25OHD: 25– hydroxyvitamin D; BMI: Body mass index; CI: Confidence interval; DM: Diabetes mellitus; HDL: High–density lipoprotein; HL: Hyperlipidemia; HT: Hypertension; OR: Odds ratio.

25OHD cut-off of 17.4 ng/mL had an AUC of 0.595 with 64.2% sensitivity and 52.5% specificity (Fig. 2). The p value for differences between the model examining 25OHD and SUA levels was 0.473.

DISCUSSION

We can summarize the findings of our study as follows: (a) among MI patients, 44.0% had isolated vitamin D deficiency, 11.3% had isolated hyperuricemia, and 16.5% had both hyperuricemia and vitamin D deficiency; (b) patients with higher levels of SUA and low levels of 25OHD had significantly severe CAD quantified by the number of diseased vessels, Gensini score, and SYNTAX score; (c) after adjustment for potential confounders, the presence of hyperuricemia or vitamin D deficiency was an independent predictor of severe CAD (OR: 1.871, 95% CI: 1.001–3.502, p=0.049; OR: 1.759, 95% CI: 1.126–2.749, p=0.013, respectively). In addition, we found an additive effect of the existence of both vitamin D deficiency and hyperuricemia on severity of coronary artery disease in MI patients (OR: 4.004, 95% CI: 2.151–7.451, p<0.001). Age, DM,*f* family history, and male sex were other independent predictors of severity.

Many mechanisms have been proposed to explain the relationship between vitamin D and atherosclerosis. The reduction of matrix metalloproteinase activity due to vitamin D deficiency leads to a deterioration of extracellular matrix components and the destruction of the fibrous cap.[19] Vitamin D also has a protective effect by inhibiting vascular endothelial growth factor, thereby reducing neo-vascularization in atherosclerotic plaques, stabilizing plaques, and consequently, preventing acute coronary syndromes.[20] It also contributes to the anticoagulant and antiplatelet pathway by suppressing procoagulant tissue factors, reducing adhesion molecules expression and activating thrombomodulin.[21]

The effects of these mechanisms on clinical outcome have been investigated many times. It was reported in a large prospective study that vitamin D deficiency was related to the risk of MI.[22] In the Fram-

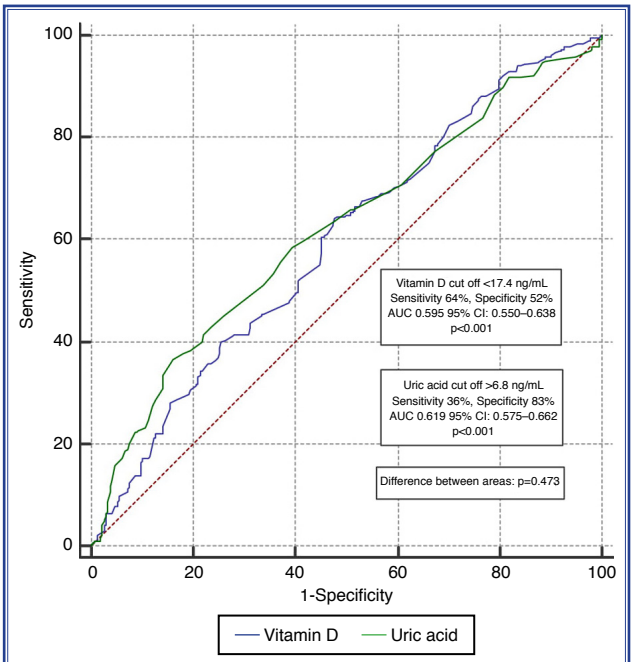

Figure 2. Receiver operating characteristic (ROC) curve showing the distinguishing ability of the 25-hydroxyvitamin D and serum uric acid levels for the severity of coronary artery disease. AUC: Area under the ROC curve; CI: Confidence interval.

ingham Heart Study, low-level 25 OHD levels were shown to partially enhance cardiovascular events.[23] The value of <20 ng/mL predicted severe coronary lesions in another study, but no correlation was found between the number of affected vessels and the level of vitamin D.[24] Moreover, among patients with acute coronary syndrome who had a 25OHD level of 12 to 31 ng/mL included in another study, the group with the highest quartile vitamin D level had a better survival at 7 years of follow-up.[25] The median 25OHD value in the Atherosclerosis Risk in Communities study was 23.9 ng/mL and patients with an 25OHD concentration of 17.2 ng/mL had a greater risk for stroke and CAD.[26] Similarly, values below the 17.4 ng/mL cut off were related to the severity of CAD in our study.

Uric acid may contribute to tissue damage and thus to CAD by activating an inflammatory response as a result of its conversion to monosodium urate crystals.[27] Hyperuricemia may also cause CAD through mechanisms such as vasoconstriction, oxidative stress, and impairment of endothelial function.[28] In a randomized clinical study of patients with heart failure, endothelial dysfunction regressed with the inhibition of xanthine oxidase provided by allopurinol treatment.[29]

There are many studies evaluating the relationship between SUA and CAD severity in the literature and a significant correlation has been found in most of them.[30,31] These studies used the Gensini score to assess the severity of CAD. In a study conducted in a Chinese population, SUA was also determined to be an independent predictor of CAD severity using the SYNTAX score.[32] Formont et al.[33] found that individuals with coronary atherosclerosis had a higher SUA level than healthy individuals. The SUA level in patients with acute coronary syndrome was higher than that of patients with stable angina in the same study.

There are also studies that found no connection between vitamin D deficiency and CAD.[34] Alsancak et al.[16] did not establish a relationship between the Gensini score and 25OHD level. According to the results of various meta-analyses, it is not possible to say that uric acid is a cardiovascular risk factor.[35,36] Since the use of drugs that may affect the uric acid value was not controlled for in the study populations in these meta-analysis, and there were no data on the use of xanthine oxidase inhibitors, we maintain that the relationship between 25OHD, SUA, and cardiovascular events remains a matter of debate.

The primary advantage of our study was that we used multiple parameters to determine the extent of CAD and different results were obtained according to the definition of the severity of CAD. Although 3-vessel disease was more common in patients with vitamin D deficiency and hyperuricemia, there was no significant difference in terms of the SYNTAX score. When the severity of CAD was evaluated according to the Gensini score, a statistically high score was found in patients with a vitamin D deficiency while the same was not valid for hyperuricemic patients. In other words, it is not surprising that the results of studies investigating the association between low 25OHD or high SUA level and CAD have generated conflicting opinions. Although contradictory results have been obtained regarding the effect of vitamin D deficiency and hyperuricemia on the degree of CAD according to the selected angiographic scoring system, our results indicated that the combination of vitamin D deficiency and hyperuricemia predicted the severity of CAD with statistical significance in all definitions.

Following the determination of a relationship between vitamin D deficiency and CAD, the question of whether vitamin D supplementation is beneficial or not for atherosclerosis and cardiovascular outcome has emerged. Although there are a few, small studies on this issue, the effect of vitamin D supplementation on cardiovascular outcome remains controversial. In one of these studies, vitamin D supplementation in chronic kidney patients was shown to reduce myocardial hypertrophy and had cardioprotective effects.[37] In a meta-analysis of randomized clinical trials, it was found that vitamin D supplementation was associated with a decrease in all deaths in individuals with vitamin D deficiency.[22] However, vitamin D supplementation did not reduce calcified plaques in coronary arteries.[38] In our study, clinical response to treatment for vitamin D deficiency and hyperuricemia was not evaluated. The data from our study indicate that a low level of 25OHD and a high level of SUA were associated with the severity of CAD, which was determined using different angiographic scoring systems and the number of diseased vessels in MI patients. Considering this finding, it could be speculated that vitamin D supplementation and treatment of hyperuricemia by changing eating habits (low purine diet and low alcohol intake) or drug use may reduce the severity of CAD, especially in the presence of the combination of these 2 pathologies. In addition, a treatment for vitamin D deficiency and hyperuricemia may be more effective in individuals with risk factors such as older age, male gender, hyperlipidemia, DM, a family history of CAD, which were seen to be associated with the severity of CAD in our study.

There are some limitations to our research. This was a single-center study, which may result in selection bias. It is difficult to compare our results with other studies on this subject due to the differences in pre-analytical medical therapy, storage techniques, and assay kits. Repeated measurements of 25OHD and SUA were not calculated, so changes that could have affected the result could not be assessed. The cross-sectional design suggests an association, but does not establish a cause and effect relationship. The fact that the patients came from different geographic regions, participated in the study in different seasons, differed in eating and clothing habits may have affected the results related to vitamin D.[39] The data collection process covered 12 months, which meant that patients were included in the study during all seasons. However, the effects of seasonal changes in vitamin D on CAD could not be clearly determined. Since this was an observational study, no medication was administered for vitamin D deficiency or hyperuricemia. Therefore, we do not have any data about whether an intervention for these risk factors affects the progression of CAD. In addition, pathophysiological mechanisms of how vitamin D deficiency or hyperuricemia cause CAD were not investigated.

Conclusion

In summary, we found a synergistic effect in hyperuricemia and vitamin D deficiency on the severity of CAD that was quantified using different angiographic scoring systems and the number of diseased vessels. Patients with older age, male sex, DM, and a family history constituted the risk group for severity of disease. As MI patients with more CAD have lower successful procedure rates, and consequently have more frequent adverse events in-hospital and in long-term follow-up, clinicians need to focus on 25OHD and SUA levels, and especially the combination, in all MI patients. These patients may also have a severe plaque burden before acute coronary syndrome occurs. For this reason, clinicians in outpatient clinics should be more careful about cardiovascular disease in the presence of the coexistence of hyperuricemia and vitamin D deficiency and consider more intensive control of traditional risk factors and treatment of these pathologies. Further studies are needed to understand the additional effect of 25OHD and SUA levels on the pathogenesis of atherosclerosis and to identify the utility of vitamin D deficiency and hyperuricemia treatment on cardiovascular outcome.

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