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Patients with Vitamin D Deficiency Are at Higher Risk of Developing Calcified and Mixed Plaques

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Abstract

Objectives: Vitamin D plays a role in the cardiovascular system through its pleomorphic effects. In some studies, it has been reported that the relationship between vitamin D deficiency and coronary artery calcification is inconsistent. In this study, it was aimed to evaluate the relationship between the vitamin D level and coronary artery calcium score (CACS), plaque presence, and plaque type.

Materials and Methods: Included in this retrospective cohort study were 719 patients who had no previously known coronary artery disease (CVD), and for whom coronary computed tomography angiography (CCTA) was performed between 2015 and 2019. Patients were classified as normal, inadequate, or deficient according to their levels of vitamin D deficiency. They were evaluated according to the presence of plaque on their CCTA or CACS >0 atherosclerosis. Moreover, patients were separated into four groups, comprising zero-plaque (those that were not plaque according to the plaque type), mere fatty plaque (CACS=0), mere calcified plaque, and mixed plaque. Age, sex, smoking status, diabetes mellitus, hypertension, and hyperlipidemia were evaluated as traditional risk factors.

Results: In 18.4% of the patients, the vitamin D levels were normal, whereas they were inadequate in 65% and deficient in 16.7%. The median CACS of the patients was 0 (range: 0-3759), and mere fatty plaque was found in 13.5% of patients,

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whereas 13.4% had mere calcified plaque, and 27.5% had mixed plaque. A negative correlation was detected between the vitamin D levels and CACSs (r=0.345; p<0.001). The median CACS in those with vitamin D deficiency was higher when compared to those with inadequate and normal levels (normal: 0 vs inadequate: 0 vs deficient: 7; p<0.001). Regardless of the traditional risk factors, vitamin D deficiency was found to be an independent predictor of atherosclerosis [odds ratio (OR): 6.9; 95% confidence interval (CI): 3.53-13.52; p<0.001], fatty plaque (OR: 3.04; 95% CI: 1.34-6.87; p=0.008), mere calcified plaque (OR: 13.11; 95% CI: 3.53-13.52; p<0.001), and mixed plaque (OR: 14.27; 95% CI: 5.58-36.50; p<0.001). Moreover, regardless of the traditional risk factors, the vitamin D deficiency increased the risk of fatty plaque development by 2.37 times in patients with CACS: 0 (OR: 2.37; 95% CI: 1.01-5.62; p=0.045).

Conclusion: A decrease in vitamin D level is associated with an increase in the CACS, and the development of calcified and mixed plaque is more likely when there is vitamin D deficiency. Depending on the incidence of CVDs and vitamin D deficiency in asymptomatic patients, vitamin D supplements can be beneficial.

Keywords: Vitamin D, coronary artery calcium score, atherosclerosis, coronary artery disease

Introduction

Vitamin D deficiency, which is a major public health problem worldwide, has been shown to be an important risk factor in cardiovascular diseases[1,2]. In cardiovascular diseases, coronary artery disease (CAD) is one of the leading causes of morbidity and mortality. Growing evidence has suggested that many factors, including vitamin D, play a role in coronary plaque formation[2-4]. Vitamin D deficiency affects a large number of cells involved in atherogenesis (such as immune cells, endothelial cells, smooth muscle cells, and cardiomyocytes)[5-8].

Coronary artery calcification (CAC) is the pathognomonic finding of atherosclerosis, as well as a good marker of atherosclerotic plaque load[9,10]. Moreover, coronary calcium measurements have been associated with histological measurements of atheromatous plaque[11,12]. The growing evidence supports the role that vitamin D plays in the development of cardiovascular impacts and CAC; however, there have also been studies that have shown no relationship between them[13-18]. Different geography and patient groups form the basis of this contrast. However, no studies that have assessed the relationship between the vitamin D level and the coronary artery calcium score (CACS), presence of plaque, and plaque-type in a wide cohort could be found.

In this study, it was aimed to examine the role of vitamin D deficiency by evaluating the relationship between vitamin D levels and the CACS, presence of plaque, and plaque type.

Materials and Methods

Study Population

This retrospective cohort study was designed and undertaken at the Cardiology and Thoracic Surgery Clinics of the İstanbul Yedikule Training and Research Hospital. All aspects of the research were carefully designed to comply with the 2013 Declaration of Helsinki, as well as the principles of good clinical practices. The relevant ethics committee granted approval of the study [İstanbul Training and Research Hospital, University of Health Sciences, Clinical Research Ethics Committee (decision date/no: 24.07.2020/2481)]. Furthermore, the consent of all participants was also obtained in both verbal and written form before the study began.

Included in the study were 719 patients who had no previously known CAD, and for whom coronary computed tomography angiography (CCTA) was performed between 2015 and 2019. The exclusion criteria of the study included the presence of cardiac failure, congenital heart

disease, history of asthma, and history of CVD, history of pulmonary embolism, chronic obstructive lung disease, and history of kidney disease.

The demographic data (gender, age, hypertension, diabetes mellitus (DM), hyperlipidemia, and smoking status), the laboratory data, and the CCTA data of all participants were obtained from their patient files using the electronic information system of the hospital.

Laboratory Testing

Results of the blood sample tests were obtained from the patient files as described above. Platelets were measured using the impedance method, and other hemogram parameters were measured using a Sysmex XE 2100 hematology analyzer (Roche Diagnostic, Corp. IN, USA), and hemoglobin was measured photometrically. C-reactive protein was measured using the immunoturbidimetric method, albumin was measured using the bromine cresol green method, triglycerides and total cholesterol were measured using the enzymatic colorimetric method, and high-density lipoprotein (HDL) cholesterol was measured using the homogeneous enzymatic colorimetric method in a Beckman Coulter DX1800 Analyzer (Indianapolis, USA). Low-density lipoprotein (LDL) cholesterol was calculated according to the Friedewald formula.

Vitamin D levels were measured using the 25 (OH) 2D3 radioimmunoassay method (Beckman Coulter, Indianapolis, USA) in an auto analyzer. Vitamin D was classified as normal (vitamin D >30 ng/mL), insufficient (10-30 ng/mL), or deficient (<10 ng/mL)[19].

Coronary Artery Calcification Assessment

All imaging was performed with a 64 multi-slice computed tomography (Toshiba Aquillon, Japan). During the examination, the heart was scanned in the craniocaudal direction, from the carina to the apex. During the process, imaging was performed using the parameters 120 Kvp, 300 mA, 75 mAs, and 3-mm section thickness. Next, all of the images were transferred to the workstation for calcium scoring and evaluated using a Toshiba Aqua 4.1 device (Otawara, Japan). The CACS was calculated considering a threshold of 130 HU, as described by Agatston et al.[20]. A CACS: 0 was evaluated as the absence of CAC. The CACS was categorized into the following five classes: 0, 1-99, 100-399, 400-999 and ≥1000. In all of the coronary segments, the coronary plaque was defined as 1) zero-plaque, 2) calcified (a more intense computed tomography (CT) density than the coronary lumen filled by contrast), 3) non-calcified (less density than the coronary lumen filled by contrast, but more CT density than the connective tissue around it), or 4) mixed (plaque containing both calcified and non-calcified components). One coronary plaque was assigned per coronary segment.

Statistical Analysis

IBM SPSS Statistics for Windows 20.0 (IBM Corp., Armonk, NY, USA) was used for all of the statistical analyses. To determine whether or not the data were normally distributed, the Kolmogorov-Smirnov test was applied. While the numerical variables were given as the mean ± standard deviation or median (minimum-maximum), the categorical values were given as numbers and percentages. The chi-square test and Fisher exact test were applied to compare the categorical data. The student t-test or Mann-Whitney U test was used in the comparison of numerical variables in two groups according to the normality of the distribution. The ANOVA test (post hoc: Bonferroni test) or Kruskal-Wallis H test (post hoc: Dunn test) was used to compare the numerical variables between the plaque types according to the normality of the distribution. The Spearman correlation analysis was used for the relationship between the CACS and the vitamin D level. Age, gender, smoking status, DM, hypertension, and hyperlipidemia were considered as traditional risk factors. The association of vitamin D deficiency and the presence of plaque was used in the logistic regression analysis and adjusted traditional risk factors. $P<0.05$ was considered as statistically significant.

Results

The mean age of patients was 51.9±6.9 (range: 35-65) years, 63.3% were male, and the median vitamin D level was 17.2 (range: 2.2-57.6). The ratio of patients who had normal vitamin D levels was 18.4% (n=132), whereas it was 65% for those who had inadequate levels, (n=467), and it was 16.7% for those who had vitamin D deficiency (n=120). The median CACS score of the patients was 0 (range: 0-3759), and 59.1% had normal calcium scores, whereas 11.3% had minimal, 16.7% had mild, 9.5% had moderate, and 3.5% had severe calcium scores (Table 1). Demographic and laboratory findings of the patients are shown in detail in Table 1.

Table 1. Demographic and laboratory findings

Variables	All population (n=719)	Vitamin D			
		Normal (n=132)	Insufficient (n=467)	Deficient (n=120)	p-value
Age, years	51.9±6.9	52.4±6.4	51.7±7.1	51.7±7.0	0.558
Gender, n (%)					
Female	264 (36.7)	29 (22.0)	193 (41.3)	42 (35.0)	**<0.001***
Male	455 (63.3)	103 (78.0)	274 (58.7)	78 (65.0)	
Diabetes mellitus, n (%)	211 (29.3)	33 (25.0)	142 (30.4)	36 (30.0)	0.477
Hypertension, n (%)	323 (44.9)	57 (43.2)	206 (44.1)	60 (50.0)	0.464
Hyperlipidemia, n (%)	263 (36.6)	34 (25.8)	173 (37.0)	56 (46.7)	**0.003***
Cigarette smoking, n (%)	301 (41.9)	53 (40.2)	196 (42.0)	52 (43.3)	0.880
CACS	0 (0-3759)	0 (0-587)	0 (0-3759)	7 (0-1100)	**<0.001***
Normal, n (%)	425 (59.1)	115 (87.1)	263 (56.3)	47 (39.2)	**<0.001***
Minimal, n (%)	81 (11.3)	2 (1.5)	60 (12.8)	19 (15.8)	
Mild, n (%)	120 (16.7)	9 (6.8)	80 (17.1)	31 (25.8)	
Moderate, n (%)	68 (9.5)	4 (3.0)	50 (10.7)	14 (11.7)	
Severe, n (%)	25 (3.5)	2 (1.5)	14 (3.0)	9 (7.5)	
Plaque, n (%)					
No plaque	328 (45.6)	99 (75.0)	197 (42.2)	32 (26.7)	**<0.001***
Yes	391 (54.4)	33 (25.0)	270 (57.8)	88 (73.3)	
Only fatty plaque	97 (13.5)	16 (12.1)	66 (14.1)	15 (12.5)	**<0.001***
Only calcific plaque	96 (13.4)	6 (4.5)	67 (14.3)	23 (19.2)	
Mixt plaque	198 (27.5)	11 (8.3)	137 (29.3)	50 (41.7)	
Hemoglobin, g/dL	13.6±1.5	13.6±1.2	13.6±1.6	**13.3±1.5**	**0.008***
Platelet, x10^3 µL	256.9±61.3	251.8±58.5	257.1±60.1	261.5±68.5	0.455
HDL, mg/dL	50.2±12.8	**55.7±13.6**	49.5±11.7	47.1±14.2	**<0.001***
LDL, mg/dL	136 (35-410)	144 (37-275)	136 (35-410)	127.5 (48-353)	0.068
Triglyceride, mg/dL	132 (36-992)	**118 (36-491)**	133 (40-992)	145 (57-857)	**0.033***
Albumin, g/dL	4.4±0.3	4.4±0.3	4.4±0.3	**4.2±0.3**	**<0.001***
Creatinine, mg/dL	0.7±0.2	0.7±0.2	0.7±0.2	0.7±0.2	0.505
hs-CRP, mg/L	0.5 (0-5.5)	**0.2 (0-1.5)**	0.6 (0-5.5)	0.5 (0-3.9)	**<0.001***
Vitamin D, ng/mL	17.2 (2.2-57.6)	31.9 (9.3-57.6)	17.2 (10-29.9)	7.5 (2.2-9.8)	**<0.001***

Numerical variables were shown as mean ± standard deviation or median (min-max).
Categorical variables were shown as number (%).
**p<0.05 shows statistical significance.*
Bold characters differ between groups (posthoc: Bonferroni or Dunn's test)
Vitamin D was classified as normal (vitamin D >30 ng/mL), insufficient (10-30 ng/mL), or deficient (<10 ng/mL)[19].
CACS: Coronary artery calcium score, HDL: High density lipoprotein, LDL: Low density lipoprotein, hs-CRP: High sensitivity C-reactive protein, n: Number

A negative correlation was detected between the vitamin D levels and CACS scores (r=-0.345; p<0.001) (Figure 1a). The median CACS in those with vitamin D deficiency was higher when compared to those with inadequate and normal levels (normal: 0 vs inadequate: 0 vs deficient 7; p<0.001). In terms of the plaque distribution, the ratio of those who had calcified plaque among those with vitamin D deficiency (normal: 4.5% vs inadequate: 14.3% vs deficient 19.2%; p<0.001) and the ratio of those who had mixed plaque (normal: 8.3% vs inadequate: 29.3% vs deficient 41.7%; p<0.001) were detected higher (Figure 1b) (Table 1). In the CACS: 0 patients, it was determined that the ratio of those with a mere fatty plaque was higher in those who had vitamin D deficiency when compared to those who had inadequate or normal samples. In those who had inadequate vitamin D, the ratio of those with

Table 2. Demographic and laboratory findings according to plaque types

Variables	No plaque (n=328)	Plaque type			p-value
		Only fatty plaque (n=97)	Only calcific plaque (n=96)	Mixed plaque (n=198)	
Age, years	51.2±6.2	50.5±7.1	51.0±7.9	54.0±6.9	**<0.001***
Gender, n (%)					
Female	82 (25.0)	44 (45.4)	38 (39.6)	100 (50.5)	**<0.001***
Male	246 (75.0)	53 (54.6)	58 (60.4)	98 (49.5)	
Diabetes mellitus, n (%)	73 (22.3)	30 (30.9)	34 (35.4)	74 (37.4)	**<0.001***
Hypertension, n (%)	125 (38.1)	45 (46.4)	38 (39.6)	115 (58.1)	**<0.001***
Hyperlipidemia, n (%)	52 (15.9)	38 (39.2)	57 (59.4)	116 (58.6)	**<0.001***
Cigarette smoking, n (%)	125 (38.1)	44 (45.4)	47 (49.0)	85 (42.9)	0.215
CACS	0 (0-0)	0 (0-0)	**11 (1-992)**	**60.5 (1-3759)**	**<0.001***
Normal, n (%)	328 (100.0)	97 (100.0)	-	-	**<0.001***
Minimal, n (%)	-	-	47 (49.0)	34 (17.2)	
Mild, n (%)	-	-	41 (42.7)	79 (39.9)	
Moderate, n (%)	-	-	5 (5.2)	63 (31.8)	
Severe, n (%)	-	-	3 (3.1)	22 (11.1)	
Hemoglobin, g/dL	13.5±1.4	13.8±1.6	13.5±1.5	13.8±1.6	0.069
Platelet, x10³ µL	257.7±60.3	254.5±61	250.6±57.5	259.7±65	0.653
HDL, mg/dL	**54.0±12.7**	47.3±10.5	49.0±14.9	46.0±10.9	**<0.001***
LDL, mg/dL	**143 (37-410)**	131 (49-250)	128.5 (35-299)	131.5 (48-257)	**0.001***
Triglyceride, mg/dL	**124.5 (36-992)**	140 (47-673)	138.5 (46-691)	142.5 (54-857)	**0.002***
Albumin, g/dL	**4.4±0.3**	**4.3±0.3**	4.2±0.3	4.2±0.3	**<0.001***
Creatinine, mg/dL	0.7±0.1	0.7±0.2	0.7±0.2	**0.8±0.2**	**<0.001***
hs-CRP, mg/L	**0.3 (0-1.5)**	0.5 (0-2.6)	0.5 (0-3.9)	**0.7 (0.1-5.5)**	**<0.001***
Vitamin D, ng/mL	20.3 (4-43.6)	20.4 (5.1-39)	14.2 (4-57.6)	14.2 (2.2-44.2)	**<0.001***
Normal, n (%)	99 (30.2)	16 (16.5)	6 (6.3)	11 (5.6)	**<0.001***
Insufficient, n (%)	197 (60.1)	66 (68.0)	67 (69.8)	137 (69.2)	
Deficient, n (%)	32 (9.8)	15 (15.5)	23 (24.0)	50 (25.3)	

Numerical variables were shown as mean ± standard deviation or median (min-max).
Categorical variables were shown as number (%).
**p<0.05 shows statistical significance.*
Bold characters differ between groups (posthoc: Bonferroni or Dun's tests)
CACS: Coronary artery calcium score, HDL: High density lipoprotein, LDL: Low density lipoprotein, hs-CRP: High sensitivity C-reactive protein, n: Number

fatty plaque was found to be higher when compared to the normal ones (normal: 13.9% vs inadequate: 25.1% vs deficient: 31.9%; p=0.013) (Figure 1c).

The median vitamin D level was similar in those with mixed plaque and mere calcified plaque, and the vitamin D levels were lower when compared to those with mere fatty plaque and those with zero-plaque. The median vitamin D levels did not differ significantly in those with and without fatty plaque (Figure 1d and Table 2).

Compared to those with no atherosclerosis, the median CACS level and vitamin D efficiency of those with atherosclerosis (0 vs. 15; p<0.001) were higher (9.8% vs 22.5%; p<0.001). The findings associated with atherosclerosis are detailed in Table 3.

Regardless of the traditional risk factors, vitamin D deficiency was found as an independent predictor for atherosclerosis (OR: 6.9; 95% CI: 3.53-13.52; p<0.001), fatty plaque (OR: 3.04; 95% CI: 1.34-6.87; p=0.008), mere calcified plaque (OR: 13.11; 95% CI: 3.53-13.52; p<0.001), and mixed plaque (OR: 14.27; 95% CI: 5.58-36.50; p<0.001 (Table 4). Moreover, regardless of the traditional risk factors, vitamin D deficiency increased the risk of fatty plaque development by 2.37 times in patients with CAC: 0 (OR: 2.37; 95% CI: 1.01-5.62; p=0.045).

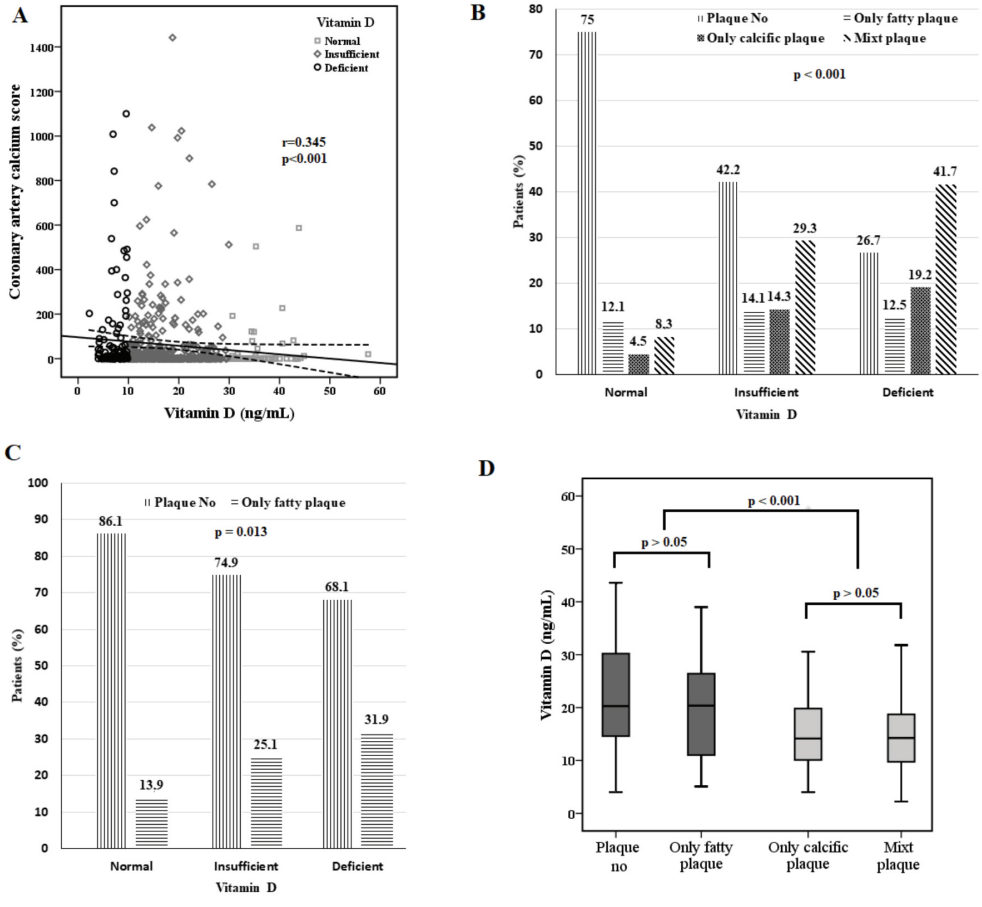

Figure 1. Vitamin D distributions: **a)** Relationship between coronary artery calcium score and vitamin D, **b)** Plaque distributions according to vitamin D sufficiency, **c)** vitamin D levels according to plaque distributions, **d)** Presence of plaque according to vitamin D adequacy in patients with coronary artery calcium score 0

Table 3. Factors associated with atherosclerosis

Variables	Atherosclerosis		p-value
	No (n=328)	Yes (n=391)	
Age, years	51.2±6.2	52.4±7.5	0.022*
Gender, n (%)			
Female	82 (25.0)	182 (46.5)	<0.001*
Male	246 (75.0)	209 (53.5)	
Diabetes mellitus, n (%)	73 (22.3)	138 (35.3)	<0.001*
Hypertension, n (%)	125 (38.1)	198 (50.6)	0.001*
Hyperlipidemia, n (%)	52 (15.9)	211 (54.0)	<0.001*
Cigarette smoking, n (%)	125 (38.1)	176 (45.0)	0.062
CACS	0 (0-0)	15 (0-3759)	<0.001*
Hemoglobin, g/dL	13.5±1.4	13.7±1.5	0.037*
Platelet, x103 µL	257.7±60.3	256.2±62.2	0.732
HDL, mg/dL	54.0±12.7	47.1±12.0	<0.001*
LDL, mg/dL	143 (37-410)	131 (35-299)	<0.001*
Triglyceride, mg/dL	124.5 (36-992)	140 (46-857)	0.001*
Albumin, g/dL	4.4±0.3	4.2±0.3	<0.001*
Creatinine, mg/dL	0.7±0.1	0.8±0.2	<0.001*
hs-CRP, mg/L	0.3 (0-1.5)	0.6 (0-5.5)	<0.001*
Vitamin D, ng/mL	20.3 (4.0-43.6)	15.2 (2.2-57.6)	<0.001*
Normal, n (%)	99 (30.2)	33 (8.4)	<0.001*
Insufficient, n (%)	197 (60.1)	270 (69.1)	
Deficient, n (%)	32 (9.8)	88 (22.5)	

Numerical variables were shown as mean ± standard deviation or median (min-max).
Categorical variables were shown as number (%).
**p<0.05 shows statistical significance.*
CACS: Coronary artery calcium score, HDL: High density lipoprotein, LDL: Low density lipoprotein, hs-CRP: High sensitivity C-reactive protein, n: Number

Discussion

In this study, a negative relationship was found between the CACSs and vitamin D levels, which are indicators of subclinical atherosclerosis in patients without previously known CAD. While a higher percentage of calcified and mixed plaque was detected in patients with vitamin D deficiency, vitamin D inadequacy and deficiency were identified as independent predictors of atherosclerosis. In patients with CACS: 0, the ratio of those with a fatty plaque in vitamin D deficiency was higher and was found as the predictor of fatty plaque, regardless of traditional risk factors. These findings suggested that there may be a higher risk of CAD in asymptomatic patients with inadequate or insufficient vitamin D levels.

CAC, which is found in coronary before the development of clinically significant narrowness, is an important predictor of subclinical atherosclerosis[21]. However, vitamin D deficiency is also considered to be a potential risk factor for CAD due to its contributions to atherosclerosis[22,23]. Although vitamin D plays a role in the cardiovascular system through its pleomorphic impacts, the pathophysiology of its relationship with CAC is not fully understood; however, a number of mechanisms have been put forward. Vitamin D deficiency causes impaired calcium

Table 4. Association of vitamin D deficiency and presence of plaque

Dependent variables	Vitamin D		Nagelkerke R^2
	Insufficient	Deficient	
Atherosclerosis (ref: No plaque or CACS=0)			
OR	3.24	6.9	0.385
95% CI	1.94-5.42	3.53-13.52	
p	**<0.001***	**<0.001***	**<0.001***
Only fatty plaque (ref: No plaque)			
OR	2.08	3.04	0.235
95% CI	1.14-3.80	1.34--6.87	
p	**0.017***	**0.008***	0.001
Only calcific plaque (ref: No plaque)			
OR	5.81	13.11	0.415
95% CI	2.11-16.08	4.04-42.50	
p	**0.001***	**<0.001***	**<0.001***
Mixed plaque (ref: No plaque)			
OR	5.43	14.27	0.494
95% CI	2.46-11.98	5.58-36.50	
p	**<0.001***	**<0.001***	**<0.001***
Only calcific plaque (ref: Only fatty plaque)			
OR	4.61	8.62	0.272
95% CI	1.48-14.31	2.29-32.45	
p	**0.008***	**0.001***	**<0.001***
Mixed plaque (ref: Only fatty plaque)			
OR	4.91	6.72	0.258
95% CI	1.92-12.54	2.27-19.89	
p	**0.001***	**0.001***	**<0.001***
Mixed plaque (ref: Only calcific plaque)			
OR	1.12	1.18	0.064
95% CI	0.40-3.15	0.39-3.60	
p	0.837	0.764	**0.002***

Age, gender, smoking, diabetes mellitus, hypertension and hyperlipidemia were adjusted in all analysis.
Those with normal vitamin D levels were considered as reference.
**p<0.05 shows statistical significance.*
Vitamin D was classified as normal (vitamin D >30 ng/mL), insufficient (10-30 ng/mL), or deficient (<10 ng/mL)[19].
OR: odds ratio, CI: confidence interval, ref: Reference

balance and secondary hyperparathyroidism. Differences in calcium and parathyroid hormone homeostasis are a predisposing factor for vascular calcification[24]. A study on pigs found that vitamin D deficiency increased the karyopherin α4 expression and NF-λB activation[25]. As a result, it was suggested that increased chronic inflammation of epicardial adipose tissue accelerates the progression of CAD[26]. It was suggested that vitamin D plays a role in

the coronary calcification process by acting on antigen-presenting cells, such as dendritic cells and macrophages, by suppressing cholesterol intake[27]. However, vitamin D has an impact on all stages of atherosclerotic plaque formation, destabilization, and rupture[28].

In the current study, a negative correlation between vitamin D and CACS was detected, but lower Vitamin D levels were determined only in patients with the calcified plaque and mixed plaque. Conflicting results have been reported in studies that researched the relationship between vitamin D and CAC in the literature[15-18]. This may have depended on research being conducted in different geographical regions. Moreover, this may have been associated with the fact that the impacts of traditional cardiovascular risk factors (age, sex, smoking status, DM, hypertension, hyperlipidemia) were not eliminated[29]. These risk factors may affect the relationship between vitamin D and CAC. In the current study, it was observed that a significant relationship continued, even in the regression model, in which the effects of these risk factors were eliminated. Furthermore, in the case of vitamin D deficiency or inadequacy, it was found that the probability of the presence of calcified and mixed plaque increased when compared to the patients with fatty plaque.

Mere non-calcified plaque was observed in 4-38% of the asymptomatic patients[30-32]. A meta-analysis showed that only 1% of patients with CACS: 0 were diagnosed with acute coronary syndrome after presenting with acute chest pain, normal troponin level, and suspected electrocardiography[33]. Moreover, it was determined in this study that CACS >0 had a 99% sensitivity value, 57% specificity value, 24% positive predictive value, and 99% negative predictive value for acute coronary syndrome[33]. In this research, it was observed that while the fatty plaque ratio in the whole population was 13.5%, this rate increased to 25.1% in vitamin D inadequacy and 31.9% in vitamin D deficiency in patients with CACS: 0. Furthermore, it was found that vitamin D deficiency, independent of traditional risk factors, increased the likelihood of fatty plaque by about 2.4 times in this patient group. This can speed up the atherosclerotic process due to the increased presence of calcium from simple fatty plaque to mixed plaque, which is the very early stage of CAD[11,12].

Vitamin D supplement reportedly does not change coronary artery plaque load in patients with calcified plaque[12], but it has been associated with improvement in cardiac results[23,34]. As far as observed in the current research, no studies that have assessed the effect of vitamin D supplements in patients with a fatty plaque in their coronary could be found. Therefore, the atherosclerotic process can be slowed down or prevented with vitamin D supplements, especially in patients with vitamin D deficiency or inadequacy. To this end, randomized controlled studies are needed.

The strengths of this study were the wide number of samples and the consideration of mixing factors. However, there were some significant restrictions. Due to fact that the study was a retrospective research, the $1.25(OH)_2D$ levels of the patients could not be measured. Circulating vitamin D levels are transmitted by the VDR signal. Therefore, the measured vitamin D levels did not reflect the circulating active form of the $1.25(OH)_2D$ levels. Given the complex nature of its metabolism and signal, referring to systemic levels of vitamin D alone may be insufficient to fully understand its physiological effect, especially in disease conditions. Moreover, CAC can develop over time, and the development of current calcium lesions in patients was not investigated.

Conclusion

It was found that there was a negative relationship between the vitamin D levels and the CACS, and there is a higher risk of atherosclerosis and developing calcified and mixed plaque in vitamin D deficiency. Moreover, considering the increase in the rates of fatty plaque in vitamin D deficiency in patients with a CACS of 0, it is thought that the atherosclerotic process begins and CAD may speed up. Depending on the incidence of CVDs and vitamin D deficiency in asymptomatic patients, vitamin D supplements can be beneficial.

Ethics

Ethics Committee Approval: İstanbul Training and Research Hospital, Clinical Research Ethics Committee (decision date/no: 24.07.2020/2481).

Informed Consent: All of the participants' consents were obtained in both verbal and written form before the study began.

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Authorship Contributions

Surgical and Medical Practices: F.E., Y.Y., M.S.A., O.Y., A.K., Concept: F.E., M.S.A., Design: F.E., Y.Y., O.Y., A.K., Data Collection or Processing: F.E., Y.Y., M.S.A., O.Y., A.K., Analysis or Interpretation: F.E., Y.Y., M.S.A., O.Y., A.K., Literature Search: F.E., Y.Y., M.S.A., O.Y., A.K., Writing: F.E., Y.Y., M.S.A., O.Y., A.K.

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