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Original Article

Comparing Serum Level of Vitamin D3 in Patients With Isolated Coronary Artery Ectasia and Normal Coronary Artery Individuals

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Abstract

Background: Coronary artery ectasia (CAE) is identified as dilation of one or more segments of coronary arteries that reaches 1.5 times or more, compared with near segments that are normal. Several etiologies like atherosclerosis, autoimmune diseases and congenital anomalies have been proposed for this condition. Vitamin D deficiency activates the renin-angiotensin-aldosterone system, which affects the cardiovascular system. For these reasons, we investigated the serum level of vitamin D in patients with CAE compared with individuals with normal coronary arteries.

Methods: The study group included 30 patients (20 males and 10 females, mean age: 57 ± 9 years) with isolated CAE without any stenotic lesions, and the control group consisted of 60 age/gender matched subjects who had normal coronary angiograms (CAG) (40 males and 20 females, mean age: 57 ± 8 years). All participants underwent CAG at Tehran Heart Center between December 2015 and March 2016. Along with routine lab tests, vitamin D, serum albumin, calcium, phosphorus and alkaline phosphatase levels were analyzed and the unadjusted and adjusted effects of vitamin D on CAE were evaluated using logistic regression model.

Results: The median vitamin D level of the patients with CAE was lower than that of the control group (6.5 [3.0, 18.8] ng/mL vs. 17.7 [8.9, 27.1] ng/mL; $P = 0.002$). The logistic regression model showed that vitamin D deficiency was a predictor for the presence of CEA ($P = 0.013$). After adjustment for confounding variables, this association remained significant ($P = 0.025$).

Conclusion: An association between CAE and vitamin D deficiency was found in our study.

Keywords: Coronary artery angiography, Coronary artery ectasia, Vitamin D

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Introduction

Coronary artery ectasia (CAE) is a segmental dilatation (more than 1.5 times than the normal adjacent vessel diameter, but less than 2 times) of the coronary arteries.[1] Prevalence of CAE is estimated to be around 1.5%-8% and it is more frequent in men.[2-5]

Most CAEs are caused by coronary atherosclerosis (50%), and the rest are caused by congenital anomalies and inflammatory conditions.[6] Various systems such as nitric oxide system, renin-angiotensin-aldosterone system (RAAS), matrix metalloproteinases and inflammation system are involved in CAE pathophysiology.[6-0]

Vitamin D is in close association with cardiovascular health.[11] Vitamin D deficiency has been related to coronary artery disease (CAD), hypertension (HTN), diabetes mellitus, obesity, metabolic syndrome, congestive heart failure and importantly, atherosclerosis.[12,13] However, the association of CAE and vitamin D has not been well discussed yet.[14]

Calcitriol (1, 25-dihydroxyvitamin D3) is known to be one of the negative endocrine regulators of RAAS.[15] There is increasing evidence supporting the role of the RAAS in aneurysm development. The RAAS has been invoked in the development of both abdominal and thoracic aortic aneurysms.[16] For these reasons, in the present study, we investigated the serum level of vitamin D in patients with CAE compared with individuals with normal coronary arteries. To date, only one study has investigated the association between vitamin D deficiency and CAE.[14]

Methods

In this case-control study, the study group included 30 patients (20 males and 10 females, mean age: 57 ±

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9 years) with isolated CAE, who had ectatic coronaries without any significant stenotic lesions under visual assessment (<50% stenosis). The control group consisted of 60 age (± 5 years), gender matched subjects (40 males and 20 females, mean age: 57 ± 8 years) who had near normal (< 25% stenosis) coronary angiograms (CAG). We doubled the number of controls in order to increase the power of the study. We enrolled consecutive candidates for coronary angiography at Tehran Heart Center between December 2015 and March 2016. The inclusion criteria were: 1) age >18 years; 2) individuals with near normal coronary arteries (<25% stenosis) for the control group, and individuals with isolated CAE without significant stenotic vessels (<50%) for the case group. The exclusion criteria were as follows: (1) history of cardiac surgery; (2) history of cardiovascular disease (i.e. myocardial infarction, valvular heart disease, congestive heart failure and arrhythmias); (3) use of over-the-counter or prescribed vitamin complements; (4) history of parathyroid or musculoskeletal disease and (5) hospital admission in summer months (i.e. between June and September). Written informed consents were obtained from the patients at the time of admission, declaring that their data would be used anonymously for research purposes.

Demographic (age and gender), physiologic (height, weight, blood pressure and pulse rate) and clinical (medical and drug history) data of the study population were recorded at the time of admission. Definition of the clinical conditions and the cardiovascular risk factors has been described elsewhere.[17] Body mass index (BMI) was calculated as weight/square height (kg/m^2).

The patients with a blood pressure ≥140/90 mm Hg and those taking antihypertensive drugs were accepted as hypertensive.[18] Diabetes was defined as a fasting blood glucose level >126 mg/dL or current use of medication(s) to lower blood glucose.[19] Hyperlipidemia was defined as cholesterol >200 or triglyceride >150 or current use of antihyperlipidemic drugs.[20]

All selective coronary angiographies were performed on the discern of the cardiologist according to clinical indications such as high clinical suspicion to significant CAD or positive stress tests. The coronary angiography was performed with a femoral approach using the Judkins technique in the catheterization laboratory of our center by manual contrast injection and using Siemens Axium artis or Philips Allura clarity angiographic unit. Iodixanol or iopamidol were used as contrast media for all coronary angiographies.

The results of the angiographies were reviewed by two expert cardiologists who were blinded to the study protocol. A vessel was considered ectatic if its luminal diameter was >1.5 times than the normal proximal neighboring coronary segment. When there was no identifiable adjacent normal segment, the mean diameter of the corresponding coronary segment in the control group served as the normal value.[21]

Coronary blood flow was estimated by the method described previously by Gibson et al.[22] The average TIMI frame count (TFC) values obtained from each coronary artery (corrected left anterior descending [LAD], left circumflex [LCX] and right coronary artery [RCA]) were reported as means of total frame count. In our catheterization laboratory, digital coronary images were obtained at 15 frames per second. So, recorded frame counts were multiplied by 2 to adjust for Gibson et al method.

Isolated CAE was determined according to the Markis classification:[23] Type I - diffuse ectasia of two or three vessels; Type II - diffuse ectasia in one vessel and localized disease (i.e., aneurysm) in another; Type III- diffuse ectasia in only one vessel; and Type IV- only localized or segmental involvement (aneurism).

The venous blood sample for routine biochemistry, complete blood cell count and lipid profile was obtained in the morning of the angiography day. Venous sampling for vitamin D (25-hydroxy vitamin D_3), calcium, phosphor, albumin and alkaline phosphatase was done at the same time. Levels of 25- hydroxyl vitamin D_3 were measured using the commercially available kit (Roche diagnostics, Indianapolis, Indiana, USA) in accordance with the manufacturer's instructions. 25-OH vit D_3 serum level of less than 20 ng/mL was considered as vitamin D deficiency, serum level between 20-30 ng/mL was considered insufficient, and serum level higher than 30 ng/mL was considered desirable.[24]

Finally, the study variables particularly the laboratory measurements were compared between two groups of subjects with and without CAE.

Statistical Analysis

The continuous variables were expressed as mean ± standard deviation (SD) or median with interquartile range (IQR), and were compared using student's t test or Mann-Whitney U test between CAE and normal coronary groups. Categorical variables were described through frequency and percentage, and were compared among above-mentioned groups using chi-square or Fisher's exact test where appropriate. The unadjusted and adjusted effects of vitamin D on CAE were evaluated using logistic regression model and the effects were reported as odds ratio (OR) with 95% confidence interval (CI). *P* value ≤0.05 was considered statistically significant. Confounding variables were defined as variables with a *P* value <0.05 in the univariable regression model. The statistical analyses were performed by using IBM

SPSS statistics for Windows, version 21.0 (IBM Corp., Armonk, NY).

Results

We compared 30 CAE patients with 60 individuals with normal coronary arteries as controls. In the CAE group, LAD in 22 patients (73%), LCX in 6 patients (20%) and RCA in 11 patients (36.6%) were involved. In 5 (16.6%) patients, 2 coronary arteries were ectatic. Also LAD and LCX in 2 (6.6%) patients, LAD and RCA in 2 patients (6.6%) and LCX and RAC in 1 patient (3.3%) were involved. There were 2 patients (6.6%) with three ectatic coronary arteries. Twenty-seven patients (90%) had type 4 CAE (Markis classification), 2 patients (6.6%) had type 3, 1 patient (3.3%) had type 2 and no one had type 1.

The patients with CAE had higher TIMI frame count for LAD, LCX and RCA compared with control groups ($P < 0.001$) (Table 1).

There was no significant difference between the groups regarding demographic, physiologic and clinical characteristics as described in Table 1. However, the frequency of aspirin use was significantly higher in the CAE group ($P = 0.024$), typical chest pain was more common in patients with CAE ($P = 0.001$) and atypical chest pain was more common in patients without CAE ($P = 0.050$). In laboratory measurements, levels of high density lipoprotein were significantly lower in CAE group ($P = 0.016$) (Table 2). In ectasia group, vitamin D deficiency was more common and 80% had vit-D deficiency, but in normal coronary group, 56.7% had vitaD deficiency ($P = 0.029$). Median level of vitamin D was significantly lower in CAE group ($P = 0.002$) (Figure 1). Logistic regression model showed that vitamin D level was inversely associated with presence of CAE (OR = 0.949, 95% CI: 0.910–0.988); $P = 0.013$). After adjustment for the affected vessel, HDL level, calcium level and serum albumin level, vitamin D level remained significantly associated with ectasia (OR = 0.944, 95% CI: 0.897–0.993; $P = 0.025$).

Correlation analysis in the ectatic group showed that there was no correlation between vitamin D and TFC (Table 3).

Table 1. Comparison of the Demographic, Physiologic and Clinical Characteristics Between the study Groups

Characteristic[a]	Normal Coronary (n = 60)	Coronary Ectasia (n = 30)	*P* Value[b]
Age, year	57.10 ± 8.87	57.33±9.61	0.909
Male gender, No. (%)	40 (66.7)	20 (66.7)	0.999
BMI, kg/m^2	27.71 ± 3.88	28.68 ± 5.88	0.418
Diabetes mellitus, No. (%)	14 (23.3)	7 (23.3)	0.999
Hypertension, No. (%)	20 (33.3)	10 (33.3)	0.999
Dyslipidemia, No. (%)	16 (26.7)	9 (30.0)	0.739
Smoking, No. (%)	14 (23.3)	8 (26.7)	0.729
Opium, No. (%)	6 (10.0)	4 (13.3)	0.726
Family history of CAD, No. (%)	4 (6.7)	2 (6.7)	0.999
Systolic blood pressure, mm Hg	125.1 ± 12.1	126.0±17.3	0.792
Diastolic blood pressure, mm Hg	75.6 ± 6.7	76.6±9.5	0.567
Heart rate, No. (%)	72.3 ± 8.1	71.8±8.4	0.772
No symptom, No. (%)	2(3.3%)	0	0.550
Atypical chest pain, No. (%)	35(58.3%)	11 (36.7)	0.053
Typical chest pain, No. (%)	12(20%)	16 (53.3%)	0.010
Palpitation, No. (%)	4 (6.7)	1 (3.3)	0.661
Syncope, No. (%)	3 (5.0)	2 (6.7)	0.999
LAD corrected TFC	23 [20–25]	33 [22–42]	<0.001
LCX TFC	20 [18–22]	29 [21–38]	<0.001
RCA TFC	20 [16–23]	27 [22–40]	<0.001
Aspirin, No. (%)	21 (35.0)	18 (60.0)	0.024
Beta blocker, No. (%)	7 (11.7)	7 (23.3)	0.216
Calcium channel blocker, No. (%)	4 (6.7)	3 (10.0)	0.682
ACE inhibitor/ARB, No. (%)	16 (26.7)	8 (26.7)	0.999
Statin, No. (%)	13 (21.7)	10 (33.3)	0.232
Oral antiglycemic agent, No. (%)	12 (20.0)	7 (23.3)	0.715
Insulin, No. (%)	1 (1.7)	0 (0)	0.999

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; CAD, coronary artery disease; IQR: interquartile range; TFC, TIMI Frame Count;

[a] Variables are shown as mean ± standard deviation, median [interquartile range] or frequency (percentage) where appropriate;

[b] *P* value < 0.05 was considered as statistically significant.

Table 2. Comparison of the Laboratory Measurements Between the Study Groups.

Characteristic*	Normal Coronary (n = 60)	Coronary Ectasia (n = 30)	*P* Value†
FBS, mg/dL	99.0 [93.2, 109.0]	106.0 [94.5, 126.2]	0.249
Triglyceride, mg/dL	115.5 [87.5, 167.7]	115.0 [80.2, 177.2]	0.898
Cholesterol, mg/dL	158.2 ± 39.8	161.7 ± 37.5	0.695
HDL, mg/dL	46.4 ± 13.9	39.5 ± 9.3	0.016
LDL, mg/dL	94.0 [69.2, 118.5]	92.5 [73.0, 116.5]	0.881
Urea, mg/dL	30.9 ± 8.1	28.1 ± 9.3	0.144
Creatinine, mg/dL	0.80 [0.70, 1.00]	0.75 [0.60, 0.90]	0.273
Hemoglobin, g/d	14.8 ± 1.8	14.8 ± 1.6	0.986
WBC (n)	7306 ± 1393	7580 ± 1895	0.487
Platelet (n)	240 ± 55	238 ± 71	0.903
Vitamin D, ng/mL	17.7 [8.9, 27.1]	6.5 [3.0, 18.8]	0.002
Calcium, mg/dL	8.9 ± 0.7	8.5 ± 0.8	0.037
Corrected Ca, mg/dL	8.9 ± 0.7	8.5 ± 0.8	0.038
Phosphorus, mg/dL	3.2 ± 0.7	3.1 ± 0.7	0.260
Alkaline phosphatase, mg/dL	66.5 ± 16.3	67.0 ± 15.2	0.880
Serum albumin, g/dL	4.2 ± 0.5	4.0 ± 0.4	0.024
Hypoalbuminemia, No. (%)	19 (31.7)	15 (50.0)	0.091

Abbreviations: FBS, fasting blood sugar; HDL, high density lipoprotein; LDL, low density lipoprotein; MCV, mean corpuscular volume; MPV, mean platelet volume; PDW, platelet distribution wide; RDW, red cell distribution wide.
[a] Variables are shown as median [interquartile range], mean ± standard deviation or frequency (percentage) where appropriate.
[b] *P* value < 0.05 was considered as statistically significant.

The serum levels of calcium, corrected calcium[26] and albumin were statistically lower in the CAE group ($P = 0.037$, $P = 0.038$ and $P = 0.024$, respectively). Moreover, the frequency of individuals with low albumin –serum albumin <4 g/dL– was not statistically different between groups ($P = 0.091$).

Discussion

In the present study, we compared the serum levels of vitamin D between patients with isolated CAE and individuals with normal coronary artery. We found that the levels of vitamin D as well as the calcium levels were significantly lower in the CAE group.

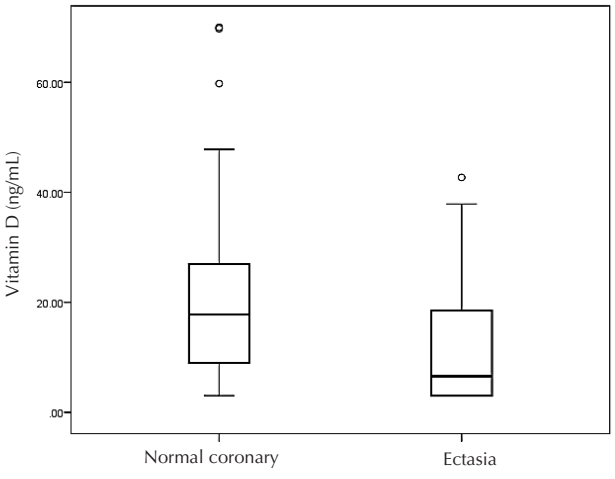

Figure 1. Comparing the Levels of Serum Vitamin D Between the Study Groups.

As the histopathologic characteristics of the CAE is similar to that observed in atherosclerotic vessels, it is probable that they have similar pathophysiology.[6] CAE has been linked to inflammatory processes, connective tissue disorders and angiotensin converting enzyme (ACE) genotype.[6,14,25]

There is a growing body of evidence suggesting that low levels of vitamin D may adversely affect the cardiovascular system. Association of vitamin D and frequency, severity and clinical outcome of CAD has been well defined before.[26-28] Vitamin D deficiency, which is affected by multiple factors, appears to have an association with diverse cardiac diseases such as CAD and heart failure, as well as some risk factors such as diabetes and HTN.[29]

A recent study showed that vitamin D levels could be independently related to the risk of cardiovascular disease.[30] Calcitriol is known to be one of the negative endocrine regulators of RAAS.[15] In several trials, calcitriol supplementation was shown to reduce plasma renin activity, angiotensin II levels, blood pressure, and myocardial hypertrophy.[15,31] Experimental data suggest that activation of the renin angiotensin system

Table 3. Correlation between Vitamin-D & TIMI Frame Count

Characteristic	r (Spearman's Correlation)	*P* Value
LAD TFC	0.251	0.181
LCX TFC	0.033	0.862
RCA TFC	0.073	0.702
Mean TFC	0.172	0.364

may lead to an increased inflammatory response in vessel wall, activation of matrix met-alloproteinases, or polymorphism of angiotensin converting enzyme (ACE) which can cause coronary vascular tone and development of aneurysms.[25]

On the other hand, it was show that vitamin D deficiency was associated with endothelial dysfunction and inflammatory responses like activation of pro-inflammatory cytokines such as interleukin (IL)-8 and tumor necrosis factor (TNF)-alpha.[32-34]

One study showed that insufficiency of vitamin D was an independent associated factor for thoracic aortic dilatation.[35] A recent study has also shown the association of vitamin D insufficiency and coronary artery tortuosity. Also vitamin D insufficiency was independently associated with coronary tortuosity.[36] Therefore, we presume that there should be a relationship between low levels of vitamin D and development of CAE. However, this relationship may be genetically modulated, since a study showed the association of genetic variation in vitamin D receptor gene with CAD.[37] Therefore, a similar process can be considered for development of CAE.

On the other hand, vitamin D has a negative regulatory role for rennin, and CAE pathophysiology is influenced by the rennin-angiotensin-aldosterone system.[25,38] Thus, it is possible that low levels of vitamin D can be followed by development of CAE via the changes in the rennin-angiotensin-aldosterone system.

The strength of our study was that the size of the control group was twice as the CAE group. Also we measured serum electrolytes and calcium and compared CBC inflammatory markers such as PLT/Lymphocyte ratio, neutrophil/lymphocyte ratio, MCV, RDW, PDW and MPV. Additionally, low levels of 25 (OH) D are independently associated with CAE. In our study, however, CBC inflammatory markers were not significantly higher in the ectatic group, it can be due to our case selection manner that selected specific group of patients with CAE without significant stenosis and restricted number of the ectatic patients.

Study Limitations

This study had some limitations. First, we did not measure the levels of parathormone. Restricted number of the ectatic patients is another limitation of this study. Moreover, we did not measure inflammatory markers and cytokines. Larger studies are required to find the exact relationship between vitamin D insufficiency and CAE and its pathophysiology.

In conclusion, the present study showed the association of low levels of 25-hydroxy vitamin D and presence of CAE. Future studies should focus on the pathophysiology of this finding.

Authors' Contribution

AH, HA: study concept; MF, AS: Data collection; AS: Drafting; AJ: Statistical analysis; MSA: pathology consult; YN, HP, MS, AA, SEK, MA, AH, EN: case management. All authors approved the final version of the manuscript.

Conflict of Interest Disclosures

The authors have no conflicts of interest.

Ethical Statement

The protocol of the study was approved by the committee of medical ethics at Tehran Heart Center.

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