Clinical research

Is there any association between vitamin D levels and isolated coronary artery ectasia?

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Abstract

Introduction: It has been postulated that low vitamin D levels are associated with coronary artery diseases. Coronary artery ectasia (CAE) is associated with atherosclerosis, congenital cardiac defects, immunological diseases and connective tissue diseases. In this study, we aimed to investigate whether there is an association between vitamin D and parathormone levels and isolated coronary artery ectasia and its extent.

Material and methods: The study included 93 participants: 47 patients (35 male, 12 female) with isolated CAE and 46 subjects (28 male, 18 female) with normal coronary arteries. Demographic characteristics of patients and controls were obtained from medical records, and Markis scores of patients were calculated. Serum vitamin D and parathormone levels were quantitatively measured by the paramagnetic particle chemiluminescence method.

Results: Serum vitamin D levels were found to be significantly lower in patients with isolated CAE than the control group (9.15 ±4.4 ng/ml, 13.35 ±5.9 ng/ml, $p < 0.001$). Parathormone levels were significantly higher in the CAE group than the control group (61.4 ±31.6, 48.7 ±25.5, $p < 0.036$). However, the study revealed no association between serum vitamin D levels and the extent of CAE according to the Markis classification ($p = 0.23$).

Conclusions: This study revealed that lower vitamin D levels and higher parathormone levels were associated with isolated CAE, but there was no association between vitamin D levels and the extent of CAE.

Key words: vitamin D, parathormone, coronary artery ectasia.

Introduction

Coronary artery ectasia (CAE) is not a very rare finding of coronary angiography, which is characterized by abnormal coronary dilatation. Coronary artery ectasia is defined as local or diffuse luminal dilatations of coronary artery segments which are 1.5 times greater than the diameter of the adjacent normal segment [1, 2]. It is a unique form of atherosclerotic coronary artery disease (CAD) [1]. The incidence of CAE is reported to be between 0.3% to 10% in different studies, and it is either congenital or acquired. It has been asserted that 50% of CAE patients have atherosclerosis [3–5]. Other associated diseases are congenital coronary anomalies and other cardiac

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defects (20–30%), inflammatory diseases (10–20%) and connective tissue diseases (10–20%) [5]. Although the underlying pathophysiology of CAE has not been well defined yet, CAE is frequently associated with atherosclerosis and has similar histopathological features [6, 7]. Vitamin D (vit-D) is a hormone with significant cardiovascular effects [8]. Scragg *et al.* first published a report about the association between cardiovascular diseases and vit-D deficiency in 1990 [9]. They reported that there is higher myocardial infarction prevalence in patients with reduced vit-D levels than in patients with normal vit-D levels [9]. Subsequent studies showed that there is an association between vit-D deficiency and CAD, heart failure and stroke, and suggested that vit-D deficiency is a risk factor for diabetes, hypertension, dyslipidemia, endothelial dysfunction, subclinical atherosclerosis and atherosclerosis [10–14]. The receptors of vit-D are located in vascular smooth muscle cells, and the role of vit-D in the inflammatory response, renin-angiotensin-aldosterone system and insulin resistance may help to explain the association between vit-D deficiency and CAD [14, 15]. Recently, Demir *et al.* reported an association between 25(OH)D and CAE [16]. They compared healthy people with normal levels of 25(OH)D to patients with CAE. However, 25(OH)D levels are generally low in our population [17, 18]. Also, they did not study the association between 25(OH)D levels and the extent of CAE.

In this study, we aimed to investigate whether there is an association between serum 25(OH)D and parathormone (PTH) levels and isolated CAE and its extent in our population generally having low levels of 25(OH)D.

Material and methods

Study population

This comparative observational study was conducted in a tertiary hospital. Ninety-three patients were included in the study between 2012 and 2013. Forty-seven patients were diagnosed with isolated CAE (12 female, 35 male) and 46 sex- and age-matched controls consisted of people having a normal coronary angiogram (CAG) (18 female, 28 male). Demographic characteristics were obtained from medical records. Family history of CAD was accepted as positive if any member of their immediate family (parents or siblings) had a fatal or nonfatal myocardial infarction and/or coronary revascularization before 55 years of age. Body mass index (BMI) was calculated according to World Health Organization criteria. Electrocardiogram (ECG) and transthoracic echocardiography (TTE) were performed in all patients before CAG. TTE recordings were performed using a Vivid 7 (GE Medical systems, USA) device with a 1.5–3.3 MHz transducer. Patients with known CAD, estimated glomerular filtration rate (e-GFR) < 60 ml/min, serious valvular heart disease, congenital heart disease, pregnancy, uncontrolled hypertension, heart failure, serious hepatic failure, acute or chronic inflammatory disease, autoimmune or connective tissue disease, rheumatic valvular disease, malignancy, osteoporosis, older than 75 years old and under vit-D treatment were excluded from the study. The study protocol was approved by the local ethics committee and written informed consent was taken from all participants. The study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and International Conference on Harmonization (ICH) guidelines.

Coronary angiography

Coronary angiogram was performed with the standard Seldinger technique using a CAG device (Axiom Artis, Siemens Medical Solutions, UK). All of the angiograms were recorded and evaluated visually later by two experienced interventional cardiologists. Coronary artery ectasia was defined as localized or diffuse coronary artery luminal dilatation at least 1.5-fold higher than the adjacent normal coronary artery diameter. The extent of CAE was scored using the Markis score [2, 6]. Markis *et al.* classified CAE into 4 groups according to the topographic extent of the ectasia in the major epicardial coronary artery [2, 6]. Type 1 – diffuse ectasia in 2–3 vessels; type 2 – diffuse ectasia in one vessel and focal ectasia in another vessel; type 3 – diffuse ectasia in a single vessel, type 4 – focal or segmental ectasia in a single vessel [2, 6].

Vitamin D and parathormone measurements

For vit-D measurement, blood samples were collected from all patients and centrifuged and stored in Eppendorf tubes with protection from light, at –80°C until studied. All of the samples were studied quantitatively by the paramagnetic particle chemiluminescence method using a Beckman Coulter, UniCel DxI800 Immunoassay analyzer (Beckman Coulter Inc, U.S.A.). Results were expressed as ng/ml. For PTH measurement, blood samples were collected from all patients and centrifuged immediately to separate the serum sample. All of the samples were studied quantitatively by the chemiluminescence method with an Immulite 2000 model analyzer using original kits (Siemens Healthcare, Germany). Results were expressed as pg/ml.

Statistical analysis

Statistical analyses were performed using SPSS software version 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Normal distributions of numeric

data were analyzed by visual (histogram) and analytic (Kolmogorov-Smirnov) methods. Determinative analyses were expressed as mean ± standard deviation. The parameters not normally distributed among groups were assessed by the Mann-Whitney U test, and normally distributed parameters among groups were assessed by Student's t-test. The frequencies of categorical variables such as demographic features were analyzed among groups by cross tables. Statistical differences of these frequencies among groups were analyzed by χ^2 or Fisher tests. The Spearman test was used for determining correlation coefficients and statistical significance of variables not normally distributed,

and Pearson's test was used for determining correlation coefficients and statistical significance of normally distributed variables. To determine the independent risk factors for CAE, a forward stepwise logistic regression model was established. One-way ANOVA was used for determining the median PTH and vit-D levels of the 4 sub-groups of patients who had CAE because both of the parameters showed normal distribution. P-values lower than 0.05 were considered as statistically significant.

Results

Baseline characteristics and laboratory results of groups are presented in Table I. There were no

Table I. Baseline characteristics and laboratory results of the CAE and control group

Parameter	CAE group (N = 47)	Control group (N = 46)	P-value
Age, median ± SD	55.3 ±10.5	54.8 ±8.9	0.8*
Gender, n (%):			
Female	12 (26)	18 (39)	0.16**
Male	35 (74)	28 (61)	
Smoking			
Yes, n (%)	16 (34)	12 (26)	0.4**
No, n	31	34	
Diabetes mellitus			
Yes, n (%)	10 (21)	10 (22)	0.95**
No, n	37	36	
Hypertension			
Yes, n (%)	29 (62)	21 (46)	0.12**
No, n	18	25	
Hyperlipidemia			
Yes, n (%)	10 (21)	9 (20)	0.8**
No, n	37	37	
Family history			
Yes, n (%)	10 (21)	14 (30)	0.31**
No, n	37	32	
BMI, median ± SD:	29.2 ±4.2	29 ±3.7	0.8*
< 25 kg/m², n	6	3	0.48***
≥ 25 kg/m², n (%)	41 (87)	43 (93)	
Ca [mg/dl]	9.3 ±0.4	9.4 ±0.4	0.47*
P [mg/dl]	3.15 ±0.48	3.1 ±0.56	0.65*
ALP [U/l]	84 ±21	85.3 ±26.3	0.79*
Total cholesterol [mg/dl]	198 ±37	192.5 ±46.3	0.52*
Triglyceride [mg/dl]	169.6 ±83	147 ±83.2	0.19*
HDL [mg/dl]	41.9 ±8.5	46 ±12.7	0.17****
LDL [mg/dl]	122.2 ±32.4	117 ±35.9	0.46*
Vitamin D [ng/ml]	9.15 ±4.4	13.35 ±5.9	< 0.001*
PTH [pg/ml]	61.4 ±31.6	48.7 ±25.5	0.036*

*CAE – coronary artery ectasia, BMI – body mass index, Ca – calcium, P – phosphorus, ALP – alkaline phosphatise, HDL – high-density lipoprotein, LDL – low-density lipoprotein, PTH – parathormone. *Student's t test; **χ^2 test; ***Fisher's test; ****Mann-Whitney U test.*

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significant differences among groups. The distributions and frequencies of CAE among vessels are given in Table II. The left anterior descending artery (LAD) was the most frequently involved vessel in CAE (35.37%), followed by the right coronary artery (RCA) (31%), circumflex (Cx) artery (27%) and left main coronary artery (LMCA) (5%). Mean 25(OH)D levels were significantly lower in the CAE group than the control group (9.15 ±4.4 ng/ml vs. 13.35 ±5.9 ng/ml, $p < 0.001$), and PTH levels were significantly higher in the CAE group than the control group ($p = 0.036$) (Table I). It was found that PTH ($p < 0.001$) and 25(OH)D ($p < 0.001$) levels were independent predictors of CAE as a result of the forward stepwise logistic regression analysis. Comparisons of vitamin D levels among groups are presented in Table III. The Markis classification of the CAE group is given in Table IV. Twenty patients had type 1, 10 patients had type 2, 10 patients had type 3 and 7 patients had type 4 CAE. The comparisons of vit-D and PTH levels and the extent of CAE are given in Table IV. The lowest vit-D and PTH levels were detected in the Markis type 4 group (6.14 ±2.12 ng/ml and 68.5 ±32.8 ng/ml., respectively) and the highest vit-D levels were detected in the Markis type 1 group (10.14 ±5.17 ng/ml and 46.6 ±20 ng/ml, respectively). The ANOVA variance test revealed no significant difference among groups in terms of mean vitamin D and PTH levels ($p = 0.23$, $p = 0.41$, respectively) (Table IV).

Discussion

The present study showed that there were significantly lower vit-D and higher PTH levels in patients with CAE than in patients with normal coronary arteries. However, there was no association between vitamin D levels and the extent of CAE classified by the Markis score. Coronary artery ectasia is an example of exaggerated over-expansive remodeling [2]. Decreased synthesis or increased degradation of collagen may cause development of ectasia [19]. Although the specific pathophysiological mechanism of CAE still remains unclear, some autopsy series showed progressive atherosclerotic changes in segments with ectasia [20]. On the other hand, some other studies also investigated other possible factors that might be responsible for CAE [20]. Yolcu *et al.* reported higher plasma von Willebrand factor levels and plasminogen activator inhibitor-1 levels in patients with isolated CAE [21]. Yetkin *et al.* demonstrated thinner carotid intima media thickness in CAE patients with stenotic CAD than in patients with CAD only [22]. Coronary artery ectasia is now recognized as a component of inflammatory-related systemic arteriopathy disease [23]. Vitamin D is essential for optimal functioning of many organ and tissue systems including the cardiovascular system [8]. Recently published studies have demonstrated an association between vit-D deficiency and atherosclerosis [9, 11]. Although

Table II. Distribution and frequency of CAE

Vessels with CAE	LMCA (n)	LAD (n)	CX (n)	RCA (n)	1-vessel (n)	2-vessel (n)	3-vessel (n)	4-vessel (n)
Number	5	35	25	29	17	16	11	3
Percentage	5	37	27	31	36	34	24	6

LMCA – left main coronary artery, LAD – left anterior descending artery, Cx – circumflex artery, RCA – right coronary artery.

Table III. Comparisons of vitamin D levels among groups

Vitamin D [ng/ml]	Patients	Controls	*P*-value
< 10, n (%)	29 (62)	11 (24)	< 0.001**
≥ 10, n	18	35	

**χ² test.

Table IV. Comparison of vitamin D and PTH levels and extent of CAE

Type	Patients, n (%)	Vitamin D, median ± SD	*P*-value*	PTH, median ± SD	*P*-value*
1	20 (42)	10.14 ±5.17		68.5 ±32.8	
2	10 (21.3)	9.33 ±3.59	0.23	55.4 ±37.1	0.41
3	10 (21.3)	9.08 ±4.21		63.6 ±29.6	
4	7 (14.9)	6.14 ±2.12		46.6 ±20	

PTH – parathormone, *one-way ANOVA.

the underlying pathophysiology is not fully understood yet, the role of vit-D in the inflammatory response, the renin-angiotensin-aldosterone system, and insulin resistance may help to reveal the pathogenesis [14]. Vitamin D deficiency has been associated with CAD, heart failure and stroke and identified as a risk factor for diabetes, hypertension, dyslipidemia and endothelial dysfunction [10]. The NHANES III (National Health and Nutrition Examination Surveys) study demonstrated an inverse relation between 25-hydroxyvitamin D_3 (25(OH)D_3) levels and hypertriglyceridemia, diabetes, hypertension and obesity [24]. The Framingham Offspring study revealed 53–80% higher major cardiovascular event incidence in patients with low 25(OH)D_3 levels who do not have a history of cardiovascular disease after 5.4 years of follow-up [25]. Hao *et al.* studied the association between vit-D deficiency and subclinical atherosclerosis by measuring carotid-intima-media thickness (CIMT) [11]. They included 1001 middle-aged male patients and emphasized vit-D deficiency as an independent factor influencing to CIMT [11]. Carrelli *et al.* also observed an inverse association between CIMT and vit-D levels in 203 community-dwelling adults [26]. Joergensen *et al.* reported a higher coronary artery calcification score (CACS) in patients with low vit-D levels than the control group in a study that included 200 diabetic patients without known CAD [27]. Similarly, Young *et al.* determined vit-D deficiency as a predictor of coronary artery plaque burden in patients with type 1 diabetes [12]. In another study, it was found that low levels of 25(OH)D were associated with coronary atherosclerosis and plaque burden, but there was no significant correlation between 25(OH)D and plaque morphology [28]. Demir *et al.* reported an association between 25(OH)D and coronary artery ectasia, and our results are partly consistent with their results in terms of the lower level of 25(OH)D in patients with CAE [16]. In our study, we found that 25(OH)D levels were low in both groups, which is consistent with other studies in our population [17, 18].

This study does have some limitations. The main limitation of our study was its small patient population size. We diagnosed CAE visually, so we did not support the diagnosis by using an invasive diagnostic method, such as intravascular ultrasound, which provides information about the vessel wall. On the other hand, such invasive diagnostic methods are not used for the proof of CAE and/or atherosclerosis routinely in daily clinical practice because of the high cost. We did not evaluate vit-D deficiency effects on atherosclerosis histopathologically, since it is outside the scope of the present study. However, we used the knowledge from previously published data indicating the association between vit-D deficiency and atherosclerosis [9–11, 25]. Because of inadequate data, we were not able to investigate the associations between CAE and other factors such as microalbuminuria, hyperhomocysteinemia, plasma uric acid, von Willebrand factor, plasminogen activator inhibitor-1, insulin resistance, diabetes and metabolic syndrome. Despite all the limitations, the strength of the present study derives from the fact that it is the first study investigating the associations between vit-D levels and the extent of CAE.

In conclusion, this study revealed that lower vitamin D levels and higher parathormone levels were associated with isolated CAE, but there was no association between vitamin D levels and the extent of CAE.

Conflict of interest

The authors declare no conflict of interest.

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