Original paper

The relationship between vitamin D deficiency and coronary artery ectasia

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Abstract

Introduction: The pathophysiology of coronary artery ectasia (CAE) has not been clearly identified although multiple abnormalities including arteritis, endothelial dysfunction, and atherothrombosis have been reported. The role of vitamin D deficiency suggests cardiovascular diseases such as coronary artery disease, heart failure, and hypertension. Vitamin D deficiency activates the renin-angiotensin-aldosterone system, which affects the cardiovascular system. For this reason, it could be suggested that there is a relationship between vitamin D deficiency and CAE.

Aim: We aimed to compare the 25-OH vitamin D levels of CAE patients with those of controls.

Material and methods: This study included 50 CAE patients (20 male, mean age: 60.26 ±10.6 years) and 30 controls (10 males, mean age: 57.86 ±11.6 years). Along with routine tests, 25 OH vitamin D and parathormone (PTH) levels were analysed. Twenty-five OH vitamin D and PTH levels were compared.

Results: No statistically significant difference was found between the two groups in terms of basic characteristics. The average PTH level of the group of patients with CAE was higher than the average PTH level of the controls (97.8 ±46.3 pg/ml vs. 59.1 ±23.7 pg/ml; $p < 0.001$). The average 25 OH vitamin D level of the group of the patients with CAE was lower than the average 25 OH vitamin D level of the control group (18.9 ±8.5 ng/ml vs. 31.3 ±11.2 ng/ml; $p < 0.001$).

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

Key words: coronary artery ectasia, renin-angiotensin-aldosterone system, inflammation, endothelial dysfunction, vitamin D.

Introduction

Coronary artery ectasia (CAE) has been characterised as a localised or diffuse non-obstructive lesion of the epicardial coronary arteries with a luminal dilation exceeding 1.5-fold the normal adjacent segment or vessel diameter [1]. The prevalence of CAE varies from 1.2% to 4.7% among patients undergoing coronary angiography [2–5].

The etiopathogenesis of this coronary enlargement is completely unknown. Although the exact mechanisms leading to CAE are not clear as yet, atherothrombosis and endothelial dysfunction have been suggested as possible responsible factors. The CAE has also been reported in association with various conditions such as congenital coronary anomalies, connective tissue diseases, and vasculitis [6, 7].

The role of vitamin D deficiency suggests cardiovascular diseases such as coronary artery disease, heart failure, and hypertension. Vitamin D deficiency actives the renin-angiotensin aldosterone system (RAAS), which affects the cardiovascular system [8].

There is increasing evidence supporting a role of the RAAS in aneurysm development. The RAAS has been invoked in the development of both abdominal and thoracic aortic aneurysms [9, 10]. Experimentally, this has been demonstrated by the chronic subcutaneous infusion of angiotensin II, which consistently leads to the development of abdominal aortic aneurysms in mice [11].

For this reason, it could be suggested that there is a relationship between vitamin D deficiency and CAE. To our knowledge, there has been no study performed about the association of vitamin D deficiency with CAE.

Aim

In our study, we compared 25 OH vit. D levels, between CAE patients and control groups with normal coronary arteries.

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Material and methods

The study group included 50 patients (20 male, mean age: 53.9 ±11 years) with isolated CAE, who had irregularities with ectatic coronaries without any stenotic lesions under visual assessment. The control group consisted of 30 age- and gender-matched subjects (10 males, mean age: 49.16 ±9.2 years) who had normal coronary angiograms. The indication for coronary angiography was either the presence of typical angina or positive or equivocal results of noninvasive screening tests for myocardial ischaemia in both of the groups.

Since the level of vitamin D (25OHD) differs due to seasonal changes (an effect of sunlight), the study was started in the winter season and continued up to the end of March.

Physical examination, medical history of patients, blood biochemistry, and transthoracic echocardiographic examination were evaluated in both groups to exclude systemic diseases. Patients with obstructive coronary artery disease (who had coronary stenotic lesions of > 20%), chronic renal failure, chronic liver disorders, chronic lung disease, moderate or severe valvular disease, hypertension, diabetes mellitus, congenital heart disease, left ventricular systolic dysfunction on echocardiography (EF < 50%), anaemia, pregnancy, obstructive sleep apnoea, haematological disorders, known malignancy, thyroid dysfunction, hypercholesterolaemia, electrolyte imbalance, previous gastrectomy, intestinal malabsorption syndromes, and drug history including anti-gout agent, anti-inflammatory agent, calcium, vitamin D, and anti-depressive agents, were excluded from the study.

The patients with a systolic blood pressure ≥ 140 mm Hg and/or a diastolic blood pressure ≥ 90 mm Hg and those taking antihypertensive drugs, were accepted as hypertensive. Diabetes was defined as a fasting blood glucose level > 126 mg/dl or current use of a diet or medication to lower blood glucose. Current cigarette smoking was defined as use of > 10 cigarettes/day at the time of diagnosis.

Coronary angiography

Coronary angiograms were performed with a femoral approach using the Judkins technique without the use of nitroglycerin, adenosine, or a calcium channel blocker. All patients in the study population underwent elective coronary artery angiography using Siemens Axiom Artis DFC (Siemens Medical Solutions, Erlangen, Germany) following the appropriate patient preparation. Coronary angiograms were judged with regard to smooth appearance, luminal wall irregularities, epicardial local or diffuse calibre reduction, and stenosis. Coronary artery ectasia was defined as dilation of the coronary artery > 1.5-fold the diameter of the adjacent normal coronary vessels, according to Falsetti and Carroll [12].

Laboratory tests

Biochemical parameters were analysed spectrophotometrically on an Architect C16000 (Abbott. USA) autoanalyser using enzymatic-colorimetric assay. For whole blood the blood samples were collected in tubes with EDTA and analysed on a CELL-DYN 3700 (Abbott. USA) device using impedance and optic scatter methods. Serum parathormon (PTH) measurements were done using electrochemiluminescence method on an E 170 Modular Analytic System (Roche, USA) device. 25-hydroxy vitamin D levels were measured using BioSource 25OH-Vit D_3-Ria-CT Kit (Biosource Europe S.A. Rue de L'Industrie, 8, B-1400 Nivelles, Belgium).

Statistical analysis

SPSS 16.0 statistical program (SPSS Inc., Chicago, IL, USA) was used for statistical study. All values are given as mean ± standard deviation. Mean values of continuous variables were compared between groups using the Student *t* test or Mann-Whitney *U* test, according to whether they were normally distributed or not, as determined by the Kolmogorov-Smirnov test. To determine the independent risk factors for the CAE, a forward stepwise logistic regression model was established. A p value of less than 0.05 was considered significant.

Results

Evaluating basic clinical and demographic characteristics, there was no statistically significant difference between two groups in terms of age, gender distribution, body mass index, and smoking status (Table I).

The average PTH level of the group of the patients with CAE was higher than the average PTH level of the controls (97.8 ±46.3 pg/ml vs. 59.1 ±23.7 pg/ml; $p < 0.001$). The average 25 OH vitamin D level of the group of the patients with CAE was lower than the average 25 OH vitamin D level of the control group (18.9 ±8.5 ng/ml vs. 31.3 ±11.2 ng/ml; $p < 0.001$) (Table I).

As a result of the forward stepwise logistic regression analysis, it was found that PTH and 25 OH vitamin D level were independent predictors of CAE (Table II).

Discussion

In our study we found significant differences in vitamin D and PTH levels between CAE patients and the control group.

The pathophysiology of CAE has not been clearly identified yet, although multiple abnormalities including inflammation, endothelial dysfunction, vasculitis, and atherothrombosis have been reported [5]. The CAE in association with connective tissue disorders such as scleroderma, in Ehlers-Danlos syndrome, also in syphilitic aortitis and in Kawasaki disease [13].

Table I. Comparison of basic clinical and biochemical features of patients and controls

Parameter	Patients (n = 50)	Controls (n = 30)	Value of p
Age, mean ± SD [years]	60.26 ±10.6	57.86 ±11.6	NS
Gender, males, *n* (%)	20 (40)	10 (33)	NS
Body mass index, mean ± SD [kg/m^2]	29.8 ±5.4	28.5 ±4.6	NS
Smoking, *n* (%)	9 (18)	6 (20)	NS
Glucose, mean ± SD [mg/dl]	95.7 ±9	97.6 ±8.5	NS
Creatinine, mean ± SD [mg/dl]	0.75 ±0.1	0.72 ±0.2	NS
Total cholesterol, mean ± SD [mg/dl]	211 ±45	181 ±36	NS
Triglyceride, mean ± SD [mg/dl]	162.5 ±65	151.9 ±41	NS
TSH, mean ± SD [µIU/ml]	1.7 ±0.6	1.6 ±0.4	NS
Leukocyte, mean ± SD [10^3/µl]	9.13 ±2.6	8.4 ±2.1	NS
Haemoglobin, mean ± SD [g/dl]	13.8 ±1.95	13.5 ±1.15	NS
Platelet, mean ± SD [10^3/µl]	232.36 ±77	234.4 ±60	NS
PTH, mean ± SD [pg/ml]	97.8 ±46.3	59.1 ±23.7	< 0.001
25 OH vitamin D, mean ± SD [ng/ml]	18.9 ±8.5	31.3 ±11.2	< 0.001

TSH – thyroid-stimulating hormone, PTH – parathormone, NS – nonsignificant

Table II. Logistic regression analyses

Parameter	HR (95% CI)	Value of p
25 OH vitamin D [ng/ml]	0.84 (0.76–0.92)	< 0.001
Parathormone [pg/ml]	1.36 (1.18–1.54)	< 0.001

Recent studies have revealed functions of vitamin D other than those in bone metabolism. It was reported that it involved in autoimmune disorders such as rheumatoid arthritis, multiple sclerosis, psoriasis, diabetes, certain cancer types, hypertension, heart failure, atherosclerosis, peripheral artery disease, aortic dilatation, an several infectious diseases [14–16]. Since the discovery of the presence of vitamin D receptors (VDR) within many cells, e.g. cardiomyocytes, vascular smooth muscle cells, and endothelium, several mechanisms have been proposed to explain the association between vitamin D and cardiovascular disease development [8].

Vitamin D has direct and indirect cardioprotective effects. Vitamin D directly leads to VDR and CYP27B1 expression in the vascular smooth muscle cells and in endothelial cells, it enhances the proliferation of vascular smooth muscle cells and expression of vascular endothelial growth factor within these cells, and inhibits the proliferation of cardiomyocytes [17]. The indirect cardioprotective effects of vitamin D are explained by certain mechanisms. Vitamin D ensures blood pressure regulation and prevents cardiac hypertrophy by inhibiting activation of renin; it hinders the formation of vascular calcification by reducing the productions of matrix metalloproteinase (MMP) 2 and 9; it provides glycaemic control; it leads to pro-inflammatory cytokine suppression and an increase in IL-10 levels; and it has a cardioprotective effect through hindering secondary hyperparathyroidism [17–19].

The studies showed that the levels of renin and angiotensin II could be diminished with vitamin D and its analogues [20]. Although the underlying mechanisms are not fully understood, CAE is considered to be an original form of vascular remodelling in response to atherosclerosis.

Experimental data suggest that activation of the renin angiotensin system may lead to an increased inflammatory response in the vessel wall or to the activation of MMPs. In addition, an insertion/deletion (ID) polymorphism of angiotensin converting enzyme (ACE) has been associated with coronary vascular tone and the development of ectasia [21]. Recently, Uyarel *et al.* found a relationship between ACE DD genotype and CAE and speculated that ACE may be a potential factor influencing the genesis of CAE [22].

Considering the importance of RAAS in the pathophysiology of CAE and the negative regulatory role of vitamin D for renin, we thought that vitamin D deficiency could be related to CAE. As far as we know, there is no study available in the literature about the association between CAE and vitamin D deficiency. Our study is of importance for this reason and we ascertained if there is an association between vitamin D deficiency and CAE.

There is currently scant information on the potential benefit of RAAS inhibition on ascending aortic arch aneurysms. Specific genetic associations of Marfan's

syndrome have been associated with enhanced expression of ACE [23]. Two recent studies have demonstrated that ACE inhibitors reduced both aortic stiffness and aortic root diameter in patients with Marfan's syndrome. Indeed, the angiotensin II type 1 (AT_1) receptor blocker losartan was effective in lowering aortic root growth in mice and patients with Marfan's syndrome [24, 25].

When two groups were compared in our study, the 25 OH vitamin D levels of the patients having CAE were significantly lower than the 25 OH vitamin D levels of the control group, and the PTH levels of CAE patients were significantly higher than the PTH levels of the controls. Our present data show that vitamin D deficiency may be related to CAE in the Turkish population. This result suggests that hyperparathyroidism secondary to vitamin D deficiency may play a role in CAE.

As far as we know, there is no study available in the literature about the association between CAE and vitamin D. In our study we found significant differences in PTH and vitamin D levels between CAE patients and the control group.

The most important restriction of our study is the limited number of patients. Another limitation is that angiographic diagnosis of normal coronary arteries was based on axial contrast angiograms of the vessel lumen, which underestimates the presence of atherosclerotic plaques. Further studies are required to determine the relation between low vitamin D status and CAE.

Conclusions

Our results may contribute to etiopathogenesis of CAE and pathophysiological mechanisms of increased prevalence of cardiovascular morbidity and mortality risk in these patients.

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