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ORIGINAL ARTICLE

Lower vitamin D level is associated with poor coronary collateral circulation

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Abstract

Objectives. Vitamin D regulates calcium and bone homeostasis, and parathyroid hormone (PTH) secretion. Cross-sectional associations between lower vitamin D levels and cardiovascular diseases have been reported, but the relationship between vitamin D levels and collateral arteries in stable coronary artery disease (CAD) has not been reported before. *Design.* Two hundred and fourteen patients with above 95% stenosis in at least one epicardial coronary artery were consecutively recruited after coronary angiography (CAG) during the winter season. The coronary collateral circulation (CCC) was graded using Rentrop classification. Poor CCC group included patients with Rentrop Grade 0–1 CCC and control group included patients with Rentrop Grade 2–3 CCC. Vitamin D and PTH levels were measured on the day of CAG. *Results.* In the poor CCC group, vitamin D levels were lower (34 ± 25 pmol/L vs. 49 ± 33 pmol/L; $p = 0.01$) and the prevalence of vitamin D deficiency (< 37 pmol/L) was higher (67% vs. 43%; $p = 0.01$) compared to the controls. PTH levels, calcium, and phosphate levels were not significantly different between the groups. Female gender, lower HDL cholesterol, and lower vitamin D levels were independently correlated with poor CCC in the study population. *Conclusion*. Lower vitamin D levels may be associated with poor collateral development in patients with stable CAD.

Key words: *coronary artery disease, collateral, parathyroid hormone, vitamin D*

Introduction

Vitamin D is known for its primary role in calcium and bone homeostasis and regulation of parathyroid hormone (PTH) secretion. There is increasing evidence for health benefits accomplished by activated vitamin D through interaction with the vitamin D receptor (VDR) that go beyond these classical functions. The VDR is expressed by many tissues such as arteries, heart, immune, and endocrine system (1). Clinical studies have reported cross-sectional associations between lower vitamin D levels and atherosclerosis risk factors (2), plasma renin activity (3), blood pressure (4), coronary artery calcification (5), and cardiovascular diseases (6).

Coronary collateral arteries serve as alternative conduits for blood flow in arteries with critical stenosis. Well-developed coronary collateral circulation (CCC) may limit infarct size, preserve myocardial viability, and decrease the incidence of adverse events in patients with acute myocardial infarction and in patients with stable coronary artery disease (CAD) (7,8).

In this study, we investigated the correlation of vitamin D levels with the degree of CCC development in patients with stable CAD. Our hypothesis was that lower levels of vitamin D may be associated with poor CCC, which may affect the prognosis in stable CAD.

Methods

Patient population

We recruited consecutive patients referred for coronary angiography (CAG) between November

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2012–April 2013 and November 2013–Februrary 2014, in total 214 patients who had a coronary artery stenosis of above 95% in at least one epicardial coronary artery were included. Indications for CAG were presence of symptoms suggestive of CAD and/or positive results on noninvasive tests compatible with myocardial ischemia. Patients with elevated levels of cardiac biomarkers, prior coronary artery bypass operation, myocardial infarction or percutaneous coronary intervention within the 3 months, active cancer, renal/hepatic dysfunction or vitamin D supplementation therapy, have been excluded from the study.

Definitions

Stable angina pectoris was defined as typical chest pain or angina equivalent symptoms, triggered either by exercise or stressful conditions. Clinical and demographic properties of subjects including prior coronary interventions, body mass index, and severity of angina pectoris according to Canadian Cardiovascular Society (CCS) and medications used were recorded. Hypertension was defined as a systolic pressure above 140 mmHg and/or a diastolic pressure above 90 mmHg or if the individual was taking antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level above 7 mmol/L and/or if the patient was taking anti-diabetic medication. Hypercholesterolemia was defined by elevated total serum cholesterol level above 6.21 mmol/L. Individuals who reported smoking of at least one cigarette per day during the year before examination were classified as smokers. Body mass index was calculated as weight (kg) divided by height (m^2). The left ventricular ejection fraction was measured using a modified Simpson's rule. Written informed consent was obtained from each participant and the study protocol was approved by the local ethics committee.

Laboratory analyis

From each patient fasting blood samples were drawn by antecubital vein puncture on the day of CAG according to the hospital protocol. Routine laboratory parameters including complete blood counts, glucose, urea, creatinine, total protein, albumin, aspartat transferase, alanine transferase, calcium, phosphate levels were immediately determined. The blood samples were snap frozen for vitamin D and PTH measurements and stored at − 80°C until analysis. Serum concentrations of 25(OH) vitamin D were measured using a radioimmunoassay (DiaSorin Antony, France; Stillwater, USA) with an intra and inter-assay coefficient of variation of 8.6% and 9.2%, respectively. Serum vitamin D levels lower than 37 pmol/L were classified as vitamin D deficiency. Intact PTH was determined in serum using ElectroChemiLuminescence Immunoassay (ECLIA) on an Elecsys 2010 (Roche Diagnostics, Mannheim, Germany), with a normal range of 15–65 ng/L and an inter-assay coefficient of variation of 5.7–6.3%.

CAG and grading of CCC

Coronary angiographies were performed using Philips Multidiagnosis C2 (Philips, Eindhoven, the Netherlands) with the technique of Judkins. All angiograms were evaluated by two cardiologists who were blinded to the clinical and laboratory parameters of the patients. The CCC was defined according to the Rentrop classification (9). Coronary collaterals were graded as Grade 0 = no opacification; Grade 1 = filling of side branches of the artery perfused by way of collateral vessels without visualization of the epicardial segment; Grade 2 = partial filling of the epicardial segment by way of collateral vessels; Grade 3 = complete filling of the epicardial segment by way of collateral vessels. Poor CCC was defined as presence of Rentrop grade 0–1 collateral development and patients with Rentrop grade 2–3 collaterals served as the control group. The severity of CAD was also evaluated by calculation of the Gensini score for each patient (10).

Statistical analysis

All analyses were carried out using SPSS 18.0 for Windows (SPSS Inc., Chicago, Illinois, USA). Continuous variables were defined as mean ± SD or median [interquantile range]; categorical variables were defined as percentages. Continuous variables were checked for the normal distribution assumption using Kolmogorov–Smirnov statistics. Differences between patients and control subjects were evaluated using the Student's *t* test or the Kolmogorov–Smirnov test when appropriate. Categorical variables were tested by Pearson's χ^2 test and Fisher's Exact Test. The relation between numerical variables was identified using Pearson or Spearman's rho test. In addition, forward stepwise multivariate logistic regression models were created to identify the independent correlates of poor CCC. The results of the model were reported as an odd ratio (OR), 95% Confidence Interval and p values. A two-tailed p value less than 0.05 was considered significant.

Results

A total of 214 patients (mean age 63.3 ± 11.4 years, 67.4% men) were included. Poor CCC group (Rentrop

0–1 CCC present) comprised 144 patients and 70 patients had well-developed CCC (Rentrop 2–3) and served as the control group. Comparison of baseline demographic, angiographic properties and laboratory parameters are summarized in Tables I and II. The frequency of female gender was higher in the poor CCC group, whereas the distribution of other cardiovascular risk factors and the medications used were similar between the two groups. Angina pectoris was the chief complaint in most of the subjects and the frequency of subjects with angina pectoris with CCS class above 1 severity was similar between the poor CCC and control groups (13.9% vs. 18.6, respectively; $p = 0.37$). The total number of arteries with critical stenosis (> 70%) were 1.75 ± 0.79 in the study group and 1.81 ± 0.75 in the control group ($p = 0.82$). Likewise, the Gensini scores were not higher in the poor CCC group (median 74 IQR [64.5] vs. median 89 IQR [68.5]; $p = 0.14$). The distribution of arteries with a stenosis of above 95% was not statistically different between the two groups. In poor CCC group, 69 subjects (48%) and in the control group 37 subjects (52%) had a totally occluded artery ($p = 0.49$).

Hematological and biochemical parameters including fasting glucose, urea, creatinine, aspartat transaminase, alanine transaminase, albumin, total cholesterol, LDL cholesterol, and triglyceride levels were comparable between the two groups (Table II). HDL cholesterol levels were significantly lower in the poor CCC group ($p = 0.02$). Patients with poorly developed CCC had significantly lower vitamin D levels compared to the controls (34.1 ± 24.7 pmol/L vs. 48.6 ± 32.7 pmol/L; $p = 0.01$) and the frequency of subjects with vitamin D deficiency (vitamin D < 37 pmol/L) was significantly higher in the poor CCC group (67.4% vs. 42.9%; $p = 0.01$). PTH levels (median 62.8 IQR [63.3] ng/L vs. median 51.3 IQR [42.9] ng/L; $p = 0.53$) and calcium and phosphate levels were not significantly different between the groups ($p = 0.18$ and $p = 0.73$, respectively).

In subgroup analysis, female subjects had significantly lower levels of vitamin D (29.7 ± 21.7 pmol/L vs. 42.0 ± 29.2 pmol/L; $p = 0.01$) and higher levels of PTH (median 65.7 IQR [65.9] ng/L vs. median 52.9 IQR [42.2] ng/L; $p = 0.01$) compared to the male subjects. Serum calcium levels were comparable between females and males ($p = 0.56$). In addition, females with poor CCC had significantly lower vitamin D levels compared to females with good CCC (26.2 ± 18.7 pmol/L vs 43.7 ± 27.7 pmol/L; $p = 0.01$). Likewise, male subjects with poor CCC had lower vitamin D levels compared to males with good CCC (37.9 ± 26.2 pmol/L vs 49.6 ± 33.9 pmol/L). Serum phosphate levels were significantly higher in the

Table I. Clinical and demographic properties of the patients with poor coronary collateral circulation (CCC) and the controls.

	Poor CCC ($n = 144$)	Control ($n = 70$)	*P*
Age, years	63.6 ± 11.4	62.7 ± 11.3	0.59
Male gender, *n* (%)	97 (67)	58 (82)	0.02
Hypertension, *n* (%)	101 (70)	46 (65)	0.51
Diabetes mellitus, *n* (%)	60 (41)	31 (44)	0.71
Hyperlipidemi, *n* (%)	73 (50)	31 (44)	0.38
Current smoker, *n*(%)	52 (36)	31 (44)	0.25
Left ventricular EF, %	49 ± 10	48 ± 11	0.60
Prior myocardial infarction, *n* (%)	55 (38)	25 (35)	0.76
Angina pectoris, *n* (%)	125 (86)	61 (87)	0.94
Angina pectoris with CCS class > 1, *n* (%)	20 (13)	13 (18)	0.37
Angiographic findings			
Number of vessels > 70% stenosis, *n* (%)	1.75 ± 0.79	1.81 ± 0.75	0.82
Occluded artery present, *n* (%)	69 (48)	37 (52)	0.49
Gensini scores	74 [64.5]	89 [68.5]	0.14
Rentrop 0 CCC, (%)	73 (50)	–	–
Distribution of arteries with > 95% stenosis			
LAD, *n* (%)	51 (35)	25 (35)	0.96
Cx, *n* (%)	47 (32)	21 (30)	0.69
RCA, *n* (%)	53 (36)	26 (37)	0.94
Medications			
Acetylsalicylic acid, *n* (%)	120 (83)	61 (87)	0.47
Beta blocker, *n* (%)	78 (54)	39 (55)	0.66
Calcium channel blocker, *n* (%)	16 (11)	5 (7)	0.36
Nitrates, *n* (%)	47 (32)	23 (32)	0.97
Statins,*n* (%)	59 (41)	28 (40)	0.89

CCC, coronary collateral circulation; CCS, Canadian Cardiovascular Society; EF, ejection fraction; PCI, percutaneous coronary intervention.

Table II. Comparison of vitamin D levels and other laboratory parameters in the study groups.

	Poor CCC ($n=144$)	Control ($n=70$)	P
Hemoglobin, g/L	128 ± 19	132 ± 18	0.13
Platelet, 10^9/L	266 ± 69	251 ± 63	0.36
Creatinine, μmol/L	93.7 ± 24.7	93.7 ± 24.7	0.98
Urea, mmol/L	15.6 ± 5.4	17.7 ± 5.8	0.06
Fasting glucose, mmol/L	6.6 [4.0]	6.3 [2.9]	0.49
Aspartate transaminase, U/L	25 [18]	23 [33]	0.95
Alanine transaminase, U/L	21 [15]	26 [22]	0.55
Vitamin D, pmol/L	34.1 ± 24.7	48.6 ± 32.7	0.01
Vitamin D < 37 pmol/L, n(%)	97 (67.4)	30 (42.9)	0.01
PTH, ng/L	62.8 [63.3]	51.3 [42.9]	0.53
Calcium, mmol/L	2.2 ± 0.40	2.3 ± 0.35	0.18
Phosphate, mmol/L	1.13[0.25]	1.13 [0.32]	0.73
Albumin, g/L	41.3 ± 4.6	41.5 ± 5.3	0.80
Total protein, g/L	71.6 ± 7.1	70.7 ± 9.7	0.62
Total cholesterol, mmol/L	4.81 ± 1.21	5.02 ± 1.24	0.44
LDL cholesterol, mmol/L	2.79[1.28]	3.15 [1.68]	0.48
HDL cholesterol, mmol/L	1.05 ± 0.30	1.16 ± 0.27	0.02
Triglycerides, mmol/L	1.63 [1.0]	1.38 [1.0]	0.95

CCC, coronary collateral circulation; PTH, parathyroid hormone
Parametric variables without normal distribution were reported as median [interquantile range].

female subjects (median 1.19 IQR [0.24] mmol/L vs. median 1.09 IQR [0.28] mmol/L; $p=0.01$). Regarding angiographic findings, total number of vessels with above 70% stenosis and Gensini scores were not significantly different between female and male patients ($p=0.92$ and $p=0.24$, respectively).

In univariate correlation analysis, vitamin D levels correlated with PTH levels ($r=0.26, p=0.01$), Rentrop class of CCC ($r=0.28$; $p=0.01$), but not with age ($r=0.08$; $p=0.29$), and Gensini scores ($r=-0.06$; $p=0.38$). PTH level correlated with age ($r=0.18$; $p=0.01$) and Gensini scores ($r=0.16$; $p=0.02$) but not correlated with Rentrop class of CCC ($r=-0.05$; $p=0.45$). Gensini scores were not, however, different between the two groups, but positively correlated with Rentrop class of CCC ($r=0.17$; $p=0.02$).

In univariate binary logistic regression analysis, female gender, lower vitamin D and HDL cholesterol levels correlated with presence of poor CCC in the study population (Table III). In multivariate regression analysis using model adjusted for these variables, lower levels of vitamin D (OR: 1.04, 95% CI 1.01–1.07, $p=0.01$), lower levels of HDL cholesterol (OR: 1.04, 95% CI 1.01–1.07, $p=0.01$) and female gender (OR: 2.65, 95% CI 1.13–6.25, $p=0.04$) remained as the independent correlates of poor CCC in the study population.

Discussion

In the present study, we found a strong association between lower levels of vitamin D and poor development of CCC in patients with stable CAD. The other independent correlates were lower HDL cholesterol levels and female gender.

Collateral circulation offers an important alternative source of blood supply when the original vessel fails to provide sufficient oxygenation of the myocardium. The severity of coronary artery stenoses (11) and the duration of myocardial ischemia are the major triggers for CCC development (12). The process of angiogenesis is complex and includes many chemokines, adhesion molecules, and growth factors such as vascular endothelial growth factor, beta fibroblast growth factor and nitric oxide. Inflammatory status estimated by increased levels of hs-CRP and red cell distribution width have been shown to be correlated with poor CCC (13). In addition, metabolic disorders such as diabetes mellitus may result in inadequate formation of CCC (14). In our study, neither presence of DM nor fasting glucose levels were correlated with CCC grades.

Vitamin D in the form of 1,25(OH)2 D3 is produced primarily in the kidney and exerts various effects in addition to calcium and bone homeostasis (15). Although vitamin D deficiency is associated with cardiovascular disease, a causal mechanism has not been established (16). In patients with lower vitamin D levels 1) endothelial functions are abnormal estimated via decreased flow mediated dilation; 2) pulse wave velocity is increased indicating arterial stiffening (17); 3) platelet aggregation may be increased (18); 4) inflammatory markers such as interleukin-6, C-reactive protein, and adhesion molecules are increased (19); and 5) renin and angiotensin levels are increased (20).

Table III. Univariate and multivariate regression analysis of possible predictors of impaired coronary collateral circulation in the study population.

Variables	Unadjusted OR (95% CI)	*p*	Adjusted OR (95% CI)*	*P*
Age, 1-SD increase	1.01 (0.98–1.03)	0.59	–	–
Female gender	2.29 (1.12–4.68)	0.02	2.65 (1.13–6.25)	0.04
Hypertension	1.34 (0.72–2.48)	0.35	–	–
Hyperlipidemia	1.85 (0.87–3.95)	0.12	–	–
Smoking	0.75 (0.42–1.35)	0.34	–	–
Diabetes mellitus	0.88 (0.51–1.56)	0.65	–	–
Fasting glucose, 1-SD increase	1.01 (0.99–1.11)	0.16	–	–
Creatinine, 1-SD increase	1.01 (0.36–2.83)	0.98	–	–
Total cholesterol, 1-SD increase	0.99 (0.98–1.01)	0.44	–	–
LDL cholesterol, 1-SD increase	0.99 (0.98–1.01)	0.41		
HDL cholesterol, 1-SD decrease	1.03 (1.01–1.06)	0.02	1.04 (1.01–1.07)	0.01
Triglycerides, 1-SD increase	1.0 (0.99–1.01)	0.85	–	–
Hemoglobin, 1-SD decrease	1.13 (0.97–1.31)	0.13	–	–
Albumin, 1-SD decrease	1.09 (0.59–2.02)	0.79	–	–
Vitamin D, 1-SD decrease	1.05 (1.02–1.08)	0.01	1.04 (1.01–1.07)	0.01

*Adjusted for gender, HDL cholesterol and vitamin D levels.

Directly or indirectly, 1,25(OH)2 D3 regulates over 200 genes, including those involved in growth and proliferation of both vascular smooth muscle cells (VSMC) and cardiomyocytes (21). Experimental studies have shown that 1,25(OH)2 D3 promotes leukocyte adhesion, increases vascular endothelial growth factor A (VGFE A) expression, VSMC proliferation and migration which are important reactions in collateral development (22–24). Theoretically, vitamin D deficiency may cause abnormalities in these reactions and as a consequence may result in impaired collateral development.

Patients with lower vitamin D levels have higher Gensini and SYNTAX scores detected by CAG and higher calcium scores detected by computed tomography (25–27). We found a positive correlation between higher Gensini scores and better CCC. These angiographic parameters are strongly correlated with future cardiovascular events. In this study, we show for the first time in literature, that CCC is worse in patients with stable CAD and lower vitamin D levels. Accordingly we may postulate that inadequate angiogenesis may be one of the pathophysiological mechanisms causing higher cardiovascular risk in patients with vitamin D deficiency. Lower levels of HDL cholesterol and female gender were the other independent risk markers for poor CCC development in multivariate regression analysis.

In our study, the frequency of female gender was significantly higher in the poor CCC group (33%) compared to that of the good CCC group (18%) and females had lower levels of vitamin D compared to males. Seasonal variation in vitamin D levels may affect the results of studies investigating the correlation between vitamin D levels and cardiovascular diseases. In addition, individual factors such as sunlight exposure and clothing habits may cause differences between the study participants. We recruited patients during November–April which is accepted as the optimal interval in order to minimize the interindividual variability of sunlight exposure.

Previously, Hekimsoy et al. reported the level of 25(OH) vitamin D during winter in 209 randomly selected healthy subjects from Turkey. Vitamin D levels were significantly lower in females (mean 37.9 pmol/L) compared to males (51.6 pmol/L) (28). These reference values are comparable to the vitamin D levels in patients with good CCC in our study. Thus, we can assume that in our study population, patients with good CCC had vitamin D levels which can be accepted as normal for a Turkish population.

However, our findings do not implicate that vitamin D supplementation may facilitate development of CCC and decrease the incidence of adverse cardiovascular events in patients with stable CAD. Further studies are warranted to investigate the clinical use of vitamin D supplementation in CAD, especially in female patients with stable CAD.

Limitations

First, we have measured 25(OH) vitamin D which may not reflect circulating 1,25(OH) D_3 levels which is the active form of vitamin D. Second, in order to limit the effect of sunlight exposure on the vitamin D levels, we have investigated subjects who had undergone CAD only during the winter period. Thus, we needed to recruit two sets of patients between November 2012 and Februrary 2014.

Conclusion

In our study, we found that vitamin D levels are lower in patients with poor CCC compared to those of

patients with well-developed CCC. As our findings do not clarify the pathophysiological mechanisms of this correlation, more clinical and experimental studies are warranted.

Declaration of interest: The authors report no declarations of interest. The authors alone are responsible for the content and writing of the paper.

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