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Relationship between coronary atherosclerosis in coronary computed tomography angiography and serum vitamin D level

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ABSTRACT

Objectives: Vitamin D deficiency has been shown to influence the development of some cardiovascular disease. In this study, the association between the existence of coronary artery plaque and vitamin D was examined among participants who were not previously diagnosed with coronary artery disease.

Methods: A total of 339 participants (246 men and 93 women) who visited a health examination center for check-up including blood test for serum vitamin D level and coronary computed tomography angiography (CCTA) were selected for this study.

Results: Among the total 339 participants, 106 displayed coronary artery plaques. The serum 25-hydroxy vitamin D (25(OH)D) level of the group with plaque was lower than that of the group without (17.7 ± 7.72 ng/mL vs. 19.6 ± 7.12 ng/mL, P = 0.0316). The group with plaque had higher incidence rates of diabetes mellitus, hypertension, and dyslipidemia than that without (P = 0.0078, P = 0.0065, and P = 0.0174, respectively). The former displayed higher serum glucose and glycated hemoglobin levels than the latter (P = 0.0055 and P = 0.0137, respectively). The group with plaque showed higher systolic and diastolic blood pressure than that without (P < 0.0001 and P = 0.0012, respectively). Stepwise multivariate logistic regression analysis revealed that 25(OH)D (coefficient, −0.06; odd ratio, 0.9433; 95% confidence interval, 0.8967–0.9924), age, and sex were independently related with presence of coronary artery plaque.

Conclusions: Relatively low vitamin D level was observed among participants with plaque, which was determined through CCTA during a health examination. Plaque formation and serum 25(OH)D level showed inverse relationship.

1. Introduction

For a long time, serum 25-hydroxy vitamin D (25(OH)D) was only known as a factor that has important role in calcium metabolism and bone health. Recently, many studies revealed that 25(OH)D influences the development of several diseases, such as hypertension, peripheral vessel disease, diabetes mellitus, obesity, coronary artery infarction, and heart failure [1–3]. One study showed that 25(OH)D has an important role in the progression of cardiovascular disease [4]. Another study reported that 25(OH)D deficiency promoted coronary calcification [5]. Moreover, a study also revealed that 25(OH)D deficiency resulted in the development of atherosclerosis and sufficient 25(OH)D can protect the artery against this condition [6]. Nowadays, increasing interest has been shown on the new effects of vitamin D on health, and many papers have been published on this topic.

Coronary computed tomography angiography (CCTA) resulted in improved diagnostic accuracy with computed tomography (CT) technology development, therefore it is used a lot for diagnosis of coronary artery disease (CAD) [7,8]. In a previous study, serum 25(OH)D level was shown to have an inverse relationship with CAD severity based on the results CCTA [9]. To our knowledge, no study has been conducted to date on the relationship between coronary atherosclerosis identified through CCTA during health check-up and serum 25(OH)D level. Therefore, we aimed to analyze the association between coronary atherosclerosis detected via CCTA during health check-up and several factors, including serum vitamin D level.

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2. Methods

2.1. Study population

This retrospective, single-center, cross-sectional study was performed in a medical checkup center. A total of 339 participants who underwent CCTA along with blood test for serum 25(OH)D level during a routine medical check-up from January 2013 to December 2015 were included in this study. They also answered questions related to social history of alcohol consumption and smoking habits and medical history of diabetes mellitus, hypertension, and dyslipidemia. Those who were previously diagnosed with CAD were excluded in this study. In addition to CCTA and blood test, the blood pressure, height and weight of the participants were also measured The body mass index (BMI) was calculated by dividing the weight in kilograms with the square of height in meters.

This study was approved by the Institutional Review Board (IRB) of Konyang University Hospital (approval number: 2017-09-007). Informed consent was waived by the IRB.

2.2. Coronary computed tomography angiography

Coronary angiography was performed using a 128-channel dual-source coronary CT scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany) in accordance with the following standard protocol: 128 × 0.6-mm slice collimation, 0.28-s rotation time, 120-kVp tube voltage, and 320-mA tube current. A nonionic contrast agent (Iomeron 400, 400 mg/Ml; Braccon, Milan, Italy) was injected using a dual injector (Medrad, Pittsburgh, PA, USA), and images were obtained. The segment thickness and interval were set to 0.75 mm and segment interval was set to 0.5 mm for image reformatting. After the reconstruction of the images using a 3-dimensional workstation, a radiologist checked for the presence of plaques in the main coronary arteries. Plaques were defined as structures that were clearly identified protrusion to the vessel lumen with focal wall thickening. In cases where plaques were detected in CCTA, participants were diagnosed with atherosclerotic plaques in the coronary arteries. Plaques with >50% calcification were classified as calcified lesions. Those with <50% calcification were categorized as mixed calcified lesions. The absence of calcification in the plaques was categorized as noncalcified lesion [10].

2.3. Laboratory measurements

Blood sample was collected in the morning after an all-night fasting. Serum 25(OH)D, glucose, glycated hemoglobin (HbA_{1c}), total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, uric acid, and sensitive C-reactive protein (S-CRP) concentrations were measured using an automatic chemical analyzer (AU-5400, Olympus Optical Co, Tokyo, Japan) and subsequently recorded.

2.4. Statistical analysis

All statistical analyses were performed using MedCalc ver. 17.2 (MedCalc, Ostend, Belgium). All data were presented as mean ± standard deviation unless otherwise stated. Depending on the characteristics of the variables, comparison of parametric values between the 2 groups was performed using independent samples t-test or Mann-Whitney U test or chi-square test. In contrast, comparison of parametric values among the 3 groups was conducted using analysis of variance test.

Stepwise multivariate regression analysis was performed to determine the independent risk factors for presence of plaque. The variables included in the analysis were age, sex, alcohol consumption habit, smoking habits, BMI, systolic and diastolic blood pressure, history of diabetes mellitus, hypertension and dyslipidemia, and 25(OH)D, HbA_{1c}, glucose, HDL, LDL, S-CRP, total cholesterol, triglyceride, and uric acid level.

All the statistical analyses were 2-sided. If P-value was below 0.05, it was regarded as statistically significant.

3. Results

Table 1 shows the general demographic and clinical characteristics of the participants. Among the 339 participants, 106 showed plaques in the CCTA, whereas the remaining 233 did not (Table 1). The group with plaque had higher male to female ratio than that without. Additionally, the participants of the former group were older than those of the latter group. The group with plaque showed significantly lower serum 25(OH)D level than that without (17.7 ± 7.7 ng/mL vs. 19.6 ± 7.1 ng/mL, P = 0.0316) (Table 1). The group with plaque demonstrated higher average systolic and diastolic blood pressure, serum glucose, HbA_{1c} and incidence of diabetes mellitus, hypertension, and dyslipidemia than without. There were more participants with alcohol drinking habits in the plaque absence group. The total cholesterol, LDL, triglyceride, uric acid, and S-CRP levels, and the BMI, and smoking habits were not significantly different between the 2 groups (Table 1).

The group with plaque was further divided into 3 groups with noncalcified, mixed-calcified and calcified plaques, and Table 2 shows the statistical characteristics of these groups. There was no significant difference in serum 25(OH)D levels among the groups (Table 2).

A stepwise multivariate logistic regression analysis was performed to determine which variables were independently related to the presence of coronary artery plaque. The independent variables were age, sex, alcohol habit, smoking habit, BMI, systolic and diastolic blood pressure, history of dyslipidemia, hypertension, and diabetes mellitus, HbA_{1c}, glucose, HDL, LDL, total cholesterol, triglyceride, S-CRP, and uric acid levels. As a result, 25(OH)D (coefficient, −0.06; odds ratio, 0.9433; 95% confidence interval, 0.8967–0.9924), age, and sex were independently correlated with the presence of coronary artery plaque (Table 3).

Table 1
Clinical characteristics of plaque absence group and plaque existence group.

Characteristic	Plaque positive (n = 106)	Plaque negative (n = 233)	P-value
Male sex	91 (85.8)	155 (66.5)	0.0002
Age, yr	56 ± 11	45 ± 9	<0.001
BMI, kg/m^2	24.8 ± 3.6	24.3 ± 3.2	0.1932
Glucose, mg/dL	110 ± 24	102 ± 23	0.0055
HbA_{1C}, %	5.9 ± 0.8	5.6 ± 0.7	0.0137
Total cholesterol, mg/dL	199 ± 46	207 ± 43	0.1182
LDL, mg/dL	136 ± 37	140 ± 32	0.368
HDL, mg/dL	52 ± 14	55 ± 13	0.041
Triglyceride, mg/dL	157 ± 91	159 ± 165	0.624
Uric acid, mg/dL	5.83 ± 1.33	5.72 ± 1.47	0.52
S-CRP, mg/dL	0.21 ± 0.45	0.16 ± 0.30	0.1661
25-hydroxy vitamin D, ng/mL	17.7 ± 7.7	19.6 ± 7.1	0.0316
Systolic BP, mmHg	119 ± 14	112 ± 13	<0.0001
Diastolic BP, mmHg	79 ± 9	75 ± 10	0.0012
Diabetes	15 (14.2)	13 (5.6)	0.0078
Hypertension	25 (23.6)	28 (12.0)	0.0065
Dyslipidemia	9 (8.5)	6 (2.6)	0.0174
Current smoker	64 (60.4)	127 (54.5)	0.27
Alcohol	69 (65.7)	182 (78.1)	0.0158

Values are presented as number (%) or mean ± standard deviation.
P-value is calculated by t-test or Mann-Whitney U-test or chi square test.
BMI, body mass index; HbA_{1C}, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; S-CRP, sensitive C-reactive protein; BP, blood pressure.

Table 2
Comparisons of groups with coronary artery plaque according to plaque characteristics.

Characteristic	Noncalcified (n = 29)	Mixed-calcified (n = 26)	Calcified (n = 51)	P-value
Male sex	25 (86.2)	24 (92.3)	42 (82.4)	0.502
Age, yr	50 ± 8	53 ± 10	60 ± 10	<0.001
BMI, kg/m^2	25.2 ± 8.5	26.1 ± 4.0	24.0 ± 3.5	0.039
Uric acid, mg/dL	6.27 ± 1.29	6.44 ± 1.20	5.26 ± 1.19	<0.001
S-CRP, mg/dL	0.25 ± 0.54	0.11 ± 0.08	0.24 ± 0.52	0.502
Glucose, mg/dL	107 ± 19	112 ± 27	111 ± 25	0.75
HbA_{1C}, %	5.7 ± 0.6	5.9 ± 0.7	6.0 ± 0.9	0.381
Total cholesterol, mg/dL	208 ± 42	216 ± 50	186 ± 43	0.01
LDL, mg/dL	145 ± 35	147 ± 37	126 ± 36	0.017
HDL, mg/dL	52 ± 12	52 ± 14	52 ± 15	0.963
Triglyceride, mg/dL	168 ± 89	186 ± 113	137 ± 75	0.068
25-hydroxy-vitamin D, ng/mL	18.9 ± 8.5	18.2 ± 6.4	16.8 ± 7.9	0.476
Diabetes	3 (10.3)	3 (11.5)	9 (17.6)	0.612
Hypertension	7 (24.1)	5 (19.2)	13 (25.5)	0.831
Dyslipidemia	1 (3.4)	2 (7.7)	6 (11.8)	0.441
Smoking	19 (65.5)	15 (57.7)	30 (58.8)	0.828
Alcohol	21 (72.4)	19 (73.1)	29 (56.9)	0.289
Systolic BP, mmHg	120 ± 11	125 ± 17	117 ± 14	0.062
Diastolic BP, mmHg	78 ± 9	84 ± 9	76 ± 9	0.004

Values are presented as number (%) or mean ± standard deviation.
Differences between groups were assessed using the analysis of variance test.
BMI, body mass index; S-CRP, sensitive C-reactive protein; HbA_{1C}, glycated hemoglobin; LDL, low-density lipoprotein; HDL, high-density lipoprotein; BP, blood pressure.

Table 3
Stepwise logistic regression analysis to determine independent risk factors for presence of coronary artery plaque.

Variable	Coefficient	P-value	Odd ratio	95% Confidence interval
25-hydroxy-vitamin D	−0.06	0.024	0.9433	0.8967–0.9924
Age	0.12	<0.001	1.1374	1.0923–1.1842
Sex	−2.11	<0.001	0.1207	0.0452–0.3226

4. Discussion

Our study demonstrated vitamin D levels of participants with coronary atherosclerosis was significantly lower than those without plaques. And also, serum vitamin D levels, age, and sex were independently associated with coronary artery plaque in this study.

In a previous study on an elderly cohort, no specific correlation between vitamin D level and carotid intima-media wall thickness was found, however, an inverse relationship between these 2 variables was observed only in the participants with history of hypertension [11]. In a recent study, no statistically meaningful association between vitamin D level and the presence of carotid atherosclerosis based on the carotid intima-media thickness was found [12]. Another study investigated the association between vitamin D level and severity of CAD, not the carotid artery, and the result revealed that an inverse relation between vitamin D level and coronary artery stenosis [4].

We could not found significant difference between vitamin D level and composition of coronary plaque, which was consistent with the results of the previous studies [9].

In a community-based cohort study in Korea that involved elderly participants aged >65 years, lower vitamin D levels have been associated with stenosis [13]. In our study, the vitamin D level to atherosclerosis odds ratio was 0.9433, which was less than 1, the same as that of the previous studies (Table 3). Moreover, the participants of our study not only include those who were >65 years of age, but also younger adults during the routine check-up. In the logistic regression analysis, the known independent risk factors for atherosclerosis, such as lipoprotein, history of diabetes mellitus, and others, were not included. Instead, vitamin D was included as an independent risk factor, so this could cause confusion in the result. The coefficient of vitamin D was −0.06 which was rather small. We think that this confusing result could be attributed to the small number of participants.

There are several possible mechanisms to explain the association between vitamin D and atherosclerosis. Vitamin D has been shown to protect against endothelial dysfunction, vascular smooth muscle cell proliferation and migration, and modulation of the immune system. In addition, vitamin D also may have anti-inflammatory effect and systemic effects on insulin resistance [14].

The results of our logistic regression analysis showed that sex was an independent risk factor for atherosclerosis (Table 3). Sex is a known risk factor and a study revealed that females had lower possibility of developing coronary heart disease than males [15]. This finding is also consistent with our result with the female to male odds ratio being 0.1207, therefore indicating that females had lower possibility of developing atherosclerosis than males.

Despite the high calorie intake of individuals in France, the prevalence of coronary heart disease was lower in this country than in others, which led to the coinage of the term of French paradox. In a study on French paradox, coronary heart disease and alcohol consumption were inversely related [16]. A subsequent study had shown that moderate alcohol consumption lowered the risk of coronary heart disease [17]. In our study, the group with atherosclerosis displayed higher incidence of alcohol habit than that without (P = 0.0158) (Table 1). The result of our study was consistent with those of previous studies, in that the group with atherosclerosis had higher incidence of alcohol habit than that without.

Age has long been well known as a risk factor for the development of CAD [15,18]. In our study, when the participants were further divided into 3 groups based on plaque calcification, those in the group with calcified plaque had higher average age than those in the other groups (P < 0.001) (Table 2). Therefore, our result was compatible with that of the previous study.

Lipid profile is known to play an important role in the progression of coronary atherosclerosis. In particular, LDL is known to accumulate in the coronary artery intima, leading to oxidation and inflammation [19]. In our study, the lipid profiles were studied, but no differences in these lipid profiles between the groups with and without atherosclerosis were observed except for HDL (Table 1). The prevalence of dyslipidemia was high in the group with atherosclerosis (P = 0.0174). With this finding, the result on the absence of differences in the lipid profiles between the two groups except for HDL was highly possible because the patients were already treated with dyslipidemia medication. Additionally, the small number of participants may affect this result. Moreover, despite the small number of participants, the group with atherosclerosis displayed statistically significantly lower HDL level than without which enabled us to partially identify the effect of the lipid profile.

The limitations of this study are the small sample size and the study design, which is impossible to generalize and evaluate the causality. Also, another limitation of this study is not considering the seasonal variation of vitamin D and the effect of vitamin supplement. Therefore, further prospective studies with large number of participants and the consideration of seasonal variation of vitamin D and vitamin supplements are necessary.

5. Conclusions

In conclusion, the results of the CCTA, which was conducted for

the purpose of screening, showed that the 25(OH)D concentration tended to be low in the presence of plaques and the lower vitamin D level might indicate higher probability of plaque formation.

Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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