Relationship between serum 25-hydroxyvitamin D levels and the SYNTAX score in patients with acute coronary syndrome

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Abstract

Objective: The extent of severity and complexity of coronary artery disease (CAD) in patients presenting with ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI) and possible correlations between serum 25-hydroxyvitamin D (25(OH)D) have not yet been adequately studied. We evaluated the relationship between 25(OH)D levels and the burden of CAD as assessed by the SYNTAX score (SXscore) in patients with acute coronary syndrome (ACS) including STEMI and NSTEMI.

Methods: After exclusion, a total of 113 patients who were admitted to our hospital due to ACS and who were referred for undergoing coronary angiography were prospectively included. Their mean age was 63.3±18.5 years, and 80.5% of them were men. In total, 44.2% of the patients had NSTEMI and the remaining had STEMI. Blood samples were drawn at admission to evaluate serum 25(OH)D levels. CAD severity was assessed using the SXscore. Patients were classified as having low (SXscore ≤22) or high (SXscore >22) SXscores. Pearson's and Spearman's correlation coefficients were used to examine the relationship between serum 25(OH)D levels and the SXscore.

Results: 25(OH)D levels were significantly lower in the group with a high SXscore than in the group with a low SXscore (21.0±8.0 vs. 16.7±6.8, p=0.005). Correlation analysis showed a significant correlation between 25(OH)D levels and the SXscore. Multiple linear regression (MLR) analysis was used to determine the significance of the relationship between the SXscore and 25(OH)D, parathyroid hormone, and C-reactive protein levels and eGFR. MLR analysis revealed that only 25(OH)D levels (coefficient beta, –0.217, p=0.029) was significantly associated with the severity of CAD.

Conclusion: The present study showed that serum 25(OH)D levels were significantly lower in patients with STEMI/NSTEMI and that low serum 25(OH)D levels were significantly correlated with CAD severity and extent. *(Anatol J Cardiol 2017; 17: 293-7)*

Keywords: 25-Hydroxyvitamin D, SYNTAX Score, acute coronary syndrome

Introduction

Cardiovascular disease (CVD) is the leading cause of death in the developed world. Atherosclerosis is the principal cause of myocardial infarction and accounts for majority of these deaths. Evidence is increasingly showing that a deficiency of 25-hydroxyvitamin D [25(OH)D] causes a higher risk of several cardiovascular conditions including hypertension heart failure, coronary calcification, myocardial infarction, subclinical atherosclerosis, diabetes mellitus (DM), obesity, and peripheral vascular disease (1–8).

More severe and diffuse coronary lesions have a worse prognosis in patients with coronary artery disease (CAD). Although several studies have shown a relationship between the serum levels of 25(OH)D and the presence of CAD, peripheral arterial disease, myocardial infarction, and cardiovascular mortality, the role of serum 25(OH)D levels in the severity of CAD has not yet been adequately investigated. We evaluated the relationship between the levels of 25(OH)D and the burden of CAD as assessed by the SYNTAX score (SXscore) in patients with acute coronary syndrome (ACS) including ST-segment elevation myocardial infarction (STEMI) and non-STEMI (NSTEMI).

Methods

After exclusion, a total of 113 consecutive patients who were aged >18 years, who were admitted to our hospital due to ACS, and who were referred for undergoing coronary angiography were prospectively included. Eighteen patients were excluded according to the exclusion criteria. The study was conducted in the summer when sun exposure was the highest.

The abstract of this study was presented as a poster at the 30th Turkish Society of Cardiology National Congress 2014.

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Accepted Date: 23.11.2016 **Available Online Date:** 01.02.2017

DOI:10.14744/AnatolJCardiol.2016.6977

Patients with any predominant non-cardiac chronic disease (infection, acute or chronic inflammatory disease, renal or hepatic insufficiency, or a known malignant disease) and those on vitamin D or calcium supplements or with hyperparathyroidism or hypercalcemia were excluded. All patients with an eGFR higher than 60 mL/min per 1.73 m^2 were eligible to exclude the effect of chronic kidney disease on vitamin D. Hypertension was defined as a blood pressure of 140/90 mm Hg or higher or if patients had a history of antihypertensive drug use. DM was defined as taking hypoglycemic agents or previously having been diagnosed as having a fasting plasma glucose level at or above 126 mg/dL, a 2-h value in an oral glucose tolerance test at or above 200 mg/dL, or a random plasma glucose concentration of ≥200 mg/dL in the presence of symptoms. Active smoking was defined as the current use of cigarettes.

Serum triglyceride, total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and parathyroid hormone (PTH) levels were measured in fasting blood samples after admission using standard enzymatic methods within 24 h. Blood glucose and creatinine concentrations at admission were expressed in mg/dL. The estimated glomerular filtration rate (eGFR) was determined by the Cockcroft–Gault equation. Body weight and height were measured during admission. A normal serum 25(OH)D level was defined as ≥30 ng/mL. Vitamin D deficiency was defined as ≤20 ng/mL. Blood samples were drawn on admission to evaluate serum 25(OH)D levels. Serum 25(OH)D levels were measured by a high-performance liquid chromatography device using the chromatographic method. (Shimadzu LC 20AD/T, Kyoto, Japan) The intra-assay coefficient of variation 4.12%, and the interassay coefficient of variation was 6.8%.

Coronary angiography was performed using the standard Judkins technique. Angiographic characteristics, which included lesion location and stenosis percentage, of all coronary lesions in the index coronary angiogram were obtained from reviewing the angiogram. Two experienced cardiologists who were blinded to the study protocol performed the angiographic analysis. CAD severity was assessed using the SXscore. Patients were classified according to their SXscore into two groups: low (SXscore ≤22) and high (SXscore >22) SXscore. An SXscore cut-off of ≤22 was defined according to the difference in treatment strategy in patients with an SXscore of ≤22, and various studies investigated the SXscore and several parameters (9–11). A coronary lesion resulting in a ≥50% luminal obstruction in vessels of ≥1.5 mm was separately scored and added to provide the SXscore and then summed to provide the overall patient SXscore. The SXscore was calculated using a dedicated software that includes the number of lesions and the specific morphologic features of each lesion, as previously reported (12). We changed following sentences "The local hospital education committee approved the study protocol" as "The Kayseri Education and Research Hospital education committee approved the study protocol".

All analyses were performed using International Business Machines Statistical Package for the Social Sciences 21 software package (This program is licensed from under Kayseri Training and Research Hospital network). Continuous variables were defined as mean±standard deviation (SD), and categorical variables were defined as percentages. The Kolmogorov–Smirnov test was used to determine whether data conformed to normal distribution. Continuous variables between the two groups were compared with the independent samples t-test. Non-parametric data were compared with the Mann–Whitney U test, and categorical data was compared with the chi-square test. The relationship between serum 25(OH)D levels and the SXscore was evaluated using Pearson's correlation analysis. A $p<0.05$ was considered to be statistically significant. Multiple linear regression analysis was performed to determine the significance of the relationship between the SXscore and 25(OH)D, PTH, and high-sensitive C-reactive protein (hs-CRP) levels and age.

Results

In total, 113 patients were included (mean age, 63.3±18.5 years, 80.5% men), 44.2% of who were admitted with non-ST-segment elevation ACS and the remaining with STEMI. There were no significant differences in the baseline characteristic of patients between the groups with low and high SXscores (Table 1). The Vitamin D concentration had a normal distribution, with a mean of 19.4±7.8 ng/mL.

The 25(OH)D level was found to be significantly lower in the group with a high SXscore than in the group with a low SX score (21.0±8.0 vs. 16.7±6.8, p=0.005) Other parameters were not significantly different between the two groups (Table 2).

The classification of 25(OH)D levels into two ranges (vitamin D deficiency of ≤20 ng/mL or non-deficiency of >20 ng/mL) showed 68

Table 1. Baseline characteristic of the study population

	Group with a low SYNTAX score (SXscore ≤22) n=73	Group with a high SYNTAX score (SXscore >22) n=40	*P*
Age, years	62.4±12.7	64.9±12.4	0.299
Sex, male	61 (84%)	30 (75%)	0.272
Hypertension, %	34 (47%)	21 (53%)	0.463
Diabetes mellitus, %	20 (27%)	12 (30%)	0.707
Current smoker, %	42 (58%)	23 (58%)	0.883
SBP, mm Hg	120±22	119±19	0.786
DBP, mm Hg	73±13	74±12	0.485
BMI, kg/m^2	27±3	26±3	0.950
LVEF on admission, %	46±9	44±10	0.532
STEMI, n (%)	41 (56%)	22 (55%)	0.903
Non-STEMI, n (%)	32 (44%)	18 (45%)	

Data are expressed as mean±SD or median for normally distributed data and as percentage (%) for categorical variables. BMI - body mass index; DBP - diastolic blood pressure; LVEF - left ventricular ejection fraction; SBP - systolic blood pressure; STEMI-ST - segment elevation myocardial infarction

Table 2. Laboratory findings of the study population

	Group with a low SYNTAX score (SXscore ≤22) n=73	Group with a high SYNTAX score (SXscore >22) n=40	*P*
25(OH)D level, ng/mL	**21±8**	**16.7±6.8**	**0.005**
PTH, pg/dL	49±33.5	51±29.6	0.760
hs-CRP, mg/dL	10.5±7.5	11.4±8	0.710
Calcium, mg/dL	9.2±0.6	9.2±0.6	0.890
Phosphor, mg/dL	3.3±0.9	3.3±0.9	0.990
Glucose, mg/dL	154±99	150±89	0.840
eGFR, mg/dL	100.3±29.5	96.4±24.7	0.127
Total cholesterol, mg/mL	185±48	186±37	0.890
LDL, mg/dL	118±32	114±31	0.570
Triglyceride, mg/dL	175±123	177±101	0.940
HDL, mg/dL	39±8	40±10	0.830

Data are expressed as mean±SD or median for normally distributed variable. eGFR - estimated glomerular filtration rate; HDL - high-density lipoprotein; hs-CRP - high-sensitive C-reactive protein; LDL - low-density lipoprotein; PTH - parathyroid hormone

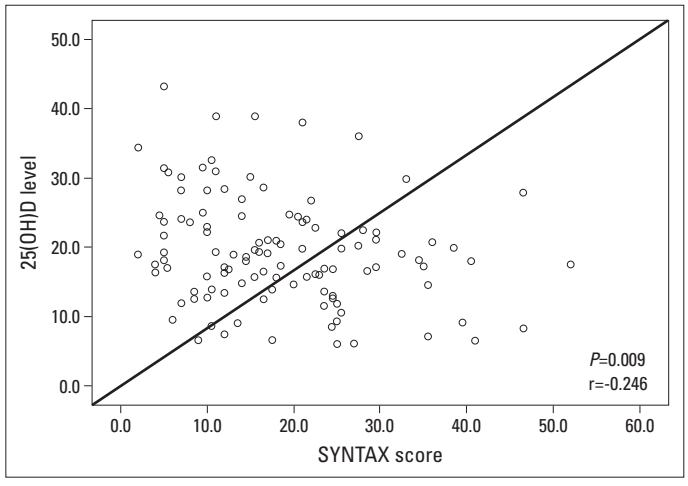

Figure 1. Correlation between vitamin D levels and the SYNTAX score

patients (60.2%) to be deficient and 45 (39.8%) to be non-deficient. Only 13(11.5%) patents had normal 25(OH)D levels of >30 ng/mL.

Correlation analysis showed a significant correlation between vitamin D levels and the SXscore (Fig. 1). Multiple linear regression analysis was used to determine the relationship between the SXscore and 25(OH)D, PTH, and hs-CRP levels and eGFR. This analysis revealed that 25(OH)D levels (coefficient beta, –0.217, p=0.029) were significantly associated with severity of the SXscore (Table 3).

Discussion

The present study showed how low serum 25(OH)D levels in patients with ACS are correlated with the extent, severity, and complexity of CAD. This study also showed that 25(OH)D levels are significantly associated with the severity of CAD.

Table 3. Effects of various variables on the SYNTAX score in multiple linear regression analyses

Variables*	Coefficients β	*P*
25(OH)D	**–0.217**	**0.029**
PTH	–0.014	0.885
hs-CRP	0.041	0.671
eGFR	–0.051	0.595

eGFR - estimated glomerular filtration rate; hs-CRP - high-sensitive C-reactive protein; PTH - parathyroid hormone

The SXscore is an angiographic scoring system used in grading the complexity of CAD based on a coronary angiogram. This score predicts the outcome after PCI in patients with CAD who are undergoing revascularization (13). In addition, an increased SXscore has been shown to be an independent predictor of major adverse cardiac events in patients with ACS (14). Various biochemical markers including the mean platelet volume, serum bilirubin level, and neutrophil-to-lymphocyte ratio have been shown to be associated with the SXscore in patients with ACS (9–11). The SXscore has the capability to effectively predict severity in patients with CAD (15). The relationship between vitamin D deficiency and various clinical and subclinical conditions such as increased arterial stiffness, endothelial dysfunction, increased intima–media thickness, maximal carotid plaque thickness, and endothelial dysfunction in patients with chronic kidney disease and improving endothelial function with vitamin D supplementation in both patients with diabetes and healthy vitamin D insufficient adults has been described in previous reports (16–21).

Vitamin D is essential for the proper mineralization of bones by increasing the intestinal absorption of calcium (22). However, 1,25-dihydroxyvitamin D, the active form, binds to the vitamin D receptor, which is present on cardiomyocytes, vascular smooth muscles, and the endothelium (23–25). Recent evidence has demonstrated the protective effect of vitamin D on the heart, and vitamin D-deficient individuals are prone to have CVD or are at a risk of developing adverse cardiovascular events. Vitamin D deficiency remains common in healthy adults, and its prevalence in patients with CAD is high (26, 27). Goleniewska et al. (28) reported that only 2% of patients with STEMI had proper 25(OH) D levels. Although the present study was conducted in the summer time when sun exposure was highest, 11.5% of patients had levels within normal range. A traditional clothing style leading to lower sun exposure to the skin in our region may additionally clarify the high deficiency and insufficiency (29).

The Framingham Heart Study demonstrated a 60% higher risk of heart disease in those with low vitamin D concentrations than in those with higher concentrations (30). In addition, Giovannucci et al. (5) found that subjects with low vitamin D concentrations are associated with a higher risk of myocardial infarction. The mechanism of the protective effect has not been fully elucidated. Proposed mechanisms are negatively regulating renin to lower

the blood pressure, improving vascular compliance, decreasing PTH levels, improving glycemic control, and suppressing inflammation or the direct effect on cardiomyocytes and the endothelium (31, 32). Inflammation has a leading role in the pathogenesis of atherosclerosis and ACS (33). 25(OH)D has anti-inflammatory and immunosuppressive effects that modulate cytokines and molecules. Although increased PTH levels are associated with cardiovascular events, the present study showed similar PTH levels within the normal range between two groups, and multiple linear regression analysis also indicated there was no relationship between PTH levels and CAD severity (34).

The relationship between vitamin D levels and CAD severity has been previously investigated in various patient subsets. Akın et al. (35) found that low serum 25(OH)D levels are associated with CAD severity as evaluated using the Gensini score in patients with stable angina pectoris who were referred for undergoing coronary angiography. However, the Gensini score is a semi-quantitative angiographic tool to determine the extent and severity of CAD (36). In another study, Syal et al. (37) found that patients with lower 25(OH)D levels had a higher prevalence of double- or triple-vessel CAD and diffuse CAD. The limitation of the study was that the investigators did not use a quantitative and clinically proven scoring tool to assess the severity of CAD.

The relationship between 25(OH)D deficiency and the SX-score was first described in a recent report by Chen et al. (38). 25(OH)D levels were lower in patients with CAD, and the 25(OH)D level showed a negative correlation with the SXscore. However, in this report, only 15% of the patients had ACS. The present study demonstrated that patients with ACS also had a negative correlation with the SXscore.

Study limitations

This study has several limitations. 25(OH)D levels were measured only once on admission. This single measurement may not reflect the vitamin D status for a lifetime. The small study population limits the power of statistical analyses.

Conclusion

The present study showed that serum 25(OH)D levels were significantly lower in patients with STEMI/NSTEMI and that low serum 25(OH)D levels were significantly correlated with CAD severity and extent.

Conflict of interest: None declared.

Peer-review: Externally peer-reviewed.

Authorship contributions: Concept – A.O.B., Y.D.; Design – A.O.B., Ö.S.; Supervision – A.O.B., M.A., H.A.; Fundings – E.O., E.D., Ö.S.; Materials – E.O., Y.D.; Data collection &/or processing – E.O., Y.D., A.O.B.; Analysis &/or interpretation – M.A., Ö.S., A.O.B.; Literature search – B.Ş., A.O.B., H.A.; Writing – A.O.B., Y.D., Ö.S.; Critical review – Ö.S., A.O.B., H.S.

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