# Assessment of 25-OH vitamin D levels and abnormal blood pressure response in female patients with cardiac syndrome X

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## Abstract

**Objective:** Vitamin D deficiency is associated with coronary artery disease, hypertension, heart failure, endothelial dysfunction, and metabolic syndrome. The pathophysiology of cardiac syndrome X (CSX) involves many pathways that are influenced by vitamin D levels. This study aimed to investigate the relationship between vitamin D deficiency and abnormal blood pressure response to exercise in patients with CSX.

**Methods:** This was a cross-sectional and observational study. Fifty females with normal epicardial coronary arteries who presented with typical symptoms of rest or effort angina and 41 healthy age-matched female controls, were included. Patients with cardiomyopathy, severe valvular disease, congenital heart disease, and left ventricular hypertrophy were excluded. All patients underwent stress electrocardiography examination and 25-hydroxy (OH) vitamin D level measurements.

**Results:** Levels of 25-OH vitamin D were significantly lower in CSX patients (9.8±7.3 ng/mL vs. 18.1±7.9 ng/mL; p<0.001). Systolic blood pressure (SBP) (188±15 mm Hg vs. 179±17 mm Hg; p=0.013) and diastolic blood pressure (DBP) (98±9 mm Hg vs. 88±9 mm Hg; p<0.001) during peak exercise were higher in CSX patients. Levels of 25-OH vitamin D were negatively correlated with peak SBP (r=–0.310, p=0.004) and peak DBP (r=–0.535, p<0.001) during exercise. To discard the multicollinearity problem, two different models were used for multivariate analyses. In the first model, metabolic equivalents (METs) (p=0.003) and 25-OH vitamin D levels (p=0.001) were independent predictors. METs (p=0.007), 25-OH vitamin D levels (p=0.008), and peak DBP were determined as independent predictors in the second multivariate model.

**Conclusion:** In patients with CSX, 25-OH vitamin D levels were lower than those in controls; moreover, 25-OH vitamin D deficiency was also associated with higher levels of peak DBP during exercise. *(Anatol J Cardiol 2016; 16: 000-00)*

**Keywords:** 25-OH vitamin D, cardiac syndrome X, abnormal blood pressure response

## Introduction

The causes and consequences of vitamin D deficiency are widespread public health concerns that are still being investigated. Vitamin D deficiency is associated with coronary artery disease, hypertension, heart failure, endothelial dysfunction, and metabolic syndrome (1). The receptors for vitamin D are expressed on smooth muscle cells, endothelium, and myocytes (2). The mechanisms underlying the potential cardioprotective effects of vitamin D have been investigated previously, where the most impressive finding was that the plasma vitamin D levels were inversely associated with renin and angiotensin II levels (3, 4). Although vitamin D replacement therapy can reportedly result in suppressed systemic inflammation, decreased blood pressure levels, and enhanced endothelial function, the mechanisms underlying its clinical effects are not clear (5).

Cardiac syndrome X (CSX), also named as microvascular angina, is defined as effort angina with detectable ischemia on noninvasive tests; however, no evidence of stenosis or vasospasm of epicardial coronary arteries is present (6). Impaired coronary microcirculation, inflammation, and insulin resistance resulting in endothelial dysfunction are accepted as the etiology for CSX; in addition, a decrease in coronary flow reserve and autonomic dysfunctions are believed to be associated with the onset of symptoms (7–9). This phenomenon has been detected in about 10%–20% of coronary angiographies (9).

Further, hypertensive response to exercise is associated with future hypertension, cardiovascular diseases, and end organ damage (10). However, to the best of our knowledge, its significance in patients with CSX and relationship with plasma

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vitamin D levels has not yet been studied.

In this study, to define the pathophysiological significance of vitamin D deficiency in patients with CSX, we aimed to evaluate the following: 1) 25-hydroxy (OH) vitamin D (vitamin D) levels in patients with CSX compared with those in healthy controls, 2) the relationship between abnormal blood pressure response to exercise and vitamin D levels in patients with CSX, and 3) plasma vitamin D levels and exercise electrocardiography (ECG) data in combination.

## Methods

### Study design

The study was designed as a cross-sectional and observational study. For this purpose, we included 50 females diagnosed with CSX at our clinic and 41 healthy age-matched females as the control group.

Female patients with normal epicardial coronary arteries who presented with symptoms of typical rest or effort angina and were referred to coronary angiography because of exercise ECG test positivity constituted the patient group. The control group was composed of females with similar demographic properties, atypical angina, and negative exercise ECG test. We enrolled female patients who were in their perimenopausal period because prevalence of CSX has been reported to increase in this population in previous studies that included patients with CSX (6, 7, 9). None of the subjects in the patient or control group were involved in any type of professional sports. Patients with cardiomyopathy, severe valvular disease, congenital heart disease, left ventricular hypertrophy, right ventricular failure, and pulmonary arterial hypertension on echocardiographic examination and those with a history of peripheral arterial disease, chronic hepatitis, renal failure, endocrinal disorders, and osteoarthritis or inflammatory polyarthritis were excluded. During the visual evaluation of the angiographic views, if any atheromatous plaques, slow flow, ectasia, myocardial bridge, or vasospasm were detected, then that patient was not included in the study. This study was approved by our institutional ethical committee; oral and written informed consents were obtained from all study participants.

### Exercise electrocardiography

All patients underwent exercise ECG test (GE T2100, USA) with Bruce protocol as a stress test to identify inducible ischemia. Heart rate and blood pressure were monitored. Patients receiving antihypertensive therapy underwent exercise ECG stress test without drug discontinuation. Twelve-lead ECG was recorded at rest, with 1 min intervals during exercise, at peak exercise, and at the recovery phase. Test results were categorized as positive (≥1.0 mm horizontal or down-sloping ST depression, ≥1.5 mm up-sloping ST depression, or ≥1.0 mm up-sloping ST depression if associated with anginal symptoms) or negative exercise ECG test. Test results with submaximal heart rate during exercise or new onset ventricular or supraventricular arrhythmias were excluded. The test time, metabolic equivalent (MET), and exercise blood pressure were recorded using standard display methods. After the first measurement at rest, systolic blood pressure (SBP) and diastolic blood pressure (DBP) measurements were recorded at the end of each 3-min steps and during peak exercise. Any abnormal response to exercise was described as follows: (i) SBP at peak exercise ≥230 mm Hg, (ii) DBP at peak exercise ≥120 mm Hg, or (iii) increase in DBP ≥12 mm Hg, provided that DBP was >100 mm Hg.

### Coronary angiography

Coronary angiography was performed using the femoral or radial access, whenever it was available, with standard Judkins catheters and iohexol (Omnipaque) contrast material. Coronary arteries were visualized in multiple projections in 15 frames per second. Each coronary artery was evaluated for irregularities on its luminal surface and local or diffuse stenosis, and no evidence of luminal irregularities by visual inspection was regarded as a normal coronary artery.

### Blood samples

Blood samples were collected to evaluate hemoglobin, platelet, urea, creatinine, alkaline phosphatase (ALP), calcium, and low-density lipoprotein cholesterol (LDL-C) levels. Additionally, vitamin D levels were measured using electrochemiluminescence protein binding assay. Normal values of vitamin D were accepted as >20 ng/mL using Cobas® kit.

### Statistical analysis

Continuous variables are expressed as mean±standard deviation and median (maximum–minimum). Categorical data are shown as frequencies and percentages. Continuous variables were tested using the Kolmogorov–Smirnov test and histograms. The correlation coefficients were presented using Pearson's correlation analysis. Unpaired t-test was employed to determine differences in continuous variables that had normal distribution between the patient and control groups. Mann–Whitney U test was used to test non-normally distributed continuous variants. Fisher's exact test was used to compare categorical variables. Because variables such as, peak SBP, peak DBP, test duration, MET, and vitamin D levels were correlated with each other, we tried to ignore multicollinearity. Therefore, we considered two different multiple logistic regression models, which used significant independent variables at 10% level from univariate analyses. The results of the models were reported as odds ratio (OR) with 95% confidence interval, β-, and p-values. A p value of <0.05 was considered significant for all tests. Statistical Package for the Social Sciences (SPSS version 11.0, SPSS Inc., Chicago, IL, USA) was used.

## Results

The demographic characteristics of 50 female with CSX and 41 control patients (age, body mass index, hypertension, hyperlipidemia, diabetes mellitus, and smoking) were matched. The frequencies of antihypertensive (all of them were receiving ACE

inhibitors), statin, and oral antidiabetic drug use were similar for both the groups. Echocardiographic parameters such as ejection fraction and left atrial diameter did not differ significantly between the two groups. ALP, calcium, creatinine, and hemoglobin levels were similar between the patient and control groups, whereas vitamin D levels were less than normal in both the groups. In addition, these levels were also significantly lower in CSX patients (9.8±7.3 ng/mL vs. 18.1±7.9 ng/mL; p<0.001).

Abnormal response to exercise test was not different when the two groups were compared [16 (32%) vs. 6 (14.6%); p=0.084]; however, when the components of abnormal response were analyzed, SBP (188±15 mm Hg vs. 179±17 mm Hg, p=0.013) and DBP during peak exercise (98±9 mm Hg vs. 88±9 mm Hg, p<0.001) were detected to be significantly higher in CSX patients. Increase in the DBP was also similar between the two groups (10±3 mm Hg vs. 9±1.8 mm Hg; p=0.124). Increase in the DBP was not significant between the two groups (10±3 mm Hg vs. 9±1.8 mm Hg; p=0.124). Moreover, exercise duration was shorter (7.6±1.5 min vs. 8.7±1.5 min; p=0.002) and METs were lower (8.7±1.5 vs. 9.9±1.3, p<0.001) in patients with CSX. Clinical characteristics of both the groups are displayed in Table 1 in a comparative manner. The correlation coefficients calculated using Pearson's correlation analysis are presented in Table 2. Vitamin D levels negatively correlated with peak SBP (r=–0.310, p=0.004) and peak DBP (r=–0.535, p<0.001) during exercise. To remove the multicollinearity problem between the variables with correlation coefficients as shown in Table 3, two different models were used for the multivariate analysis.

First, the logistic regression model used the significant variables (p<0.10) such as METs, vitamin D levels, and abnormal blood pressure response to exercise from univariate analyses. In the second multiple model, we have used METs, vitamin D levels, and peak DBP during exercise as covariates. The results of these models are presented in Table 3. First model revealed that METs [β=–0.652, p=0.003, OR=0.521, 95% CI (0.340–0.797)] and vitamin D levels [β=–0.129, p=0.001, OR=0.879, 95% CI (0.813–0.949)] were independent predictors of CSX (Hosmer and Lemeshow test: p=0.095, Nagelkerke R Square: 0.433). METs [β=–0.571, p=0.007, OR=0.565, 95% CI (0.372–0.859)], vitamin D levels [β=–0.104, p =0.008, OR=0.901, 95% CI (0.834–0.973)], and peak DBP [β=0.075, p=0.027, OR=1.078, 95% CI (1.009–1.151)] were all determined as independent predictors in the second multiple model (Hosmer and Lemeshow test: p=0.755, Nagelkerke R Square: 0.480).

## Discussion

To the best of our knowledge, this is the first study evaluating the relationship between abnormal blood pressure response to exercise and vitamin D levels in patients with CSX. In this study, we observed that in patients with CSX, vitamin D levels and METs were lower, exercise duration was shorter, and peak SBP and DBP were higher those that in the control group. Additionally, METs, vitamin D levels, and peak DBP during exercise were independent predictors of CSX.

**Table 1. Demographic and clinical characteristics of patients and controls**

| | Patients (n=50) | Control (n=41) | *P* |
|---|---|---|---|
| Age, years | 50±6.4 | 50±6 | 0.869* |
| BMI, kg/m$^2$ | 31±3.42 | 30±3.38 | 0.428* |
| HT, n (%) | 12 (24) | 8 (19.5) | 0.800** |
| HL, n (%) | 7 (14) | 6 (14.6) | 1** |
| DM, n (%) | 6 (12) | 3 (7.3) | 0.506** |
| Smoking, n (%) | 5 (10) | 4 (9.8) | 1** |
| **Drugs** | | | |
| Antihypertensive use, n (%) | 11 (22) | 5 (12.2) | 0.275** |
| Statin use, n (%) | 5 (10) | 6 (14.6) | 0.535** |
| OAD use, n (%) | 4 (8) | 2 (4.9) | 0.687** |
| **Treadmill test** | | | |
| MET | 8.7±1.5 | 9.9±1.3 | **<0.001*** |
| PSBP, mm Hg | 188±15 | 179±17 | **0.013*** |
| PDBP, mm Hg | 98±9 | 88±9 | **<0.001*** |
| IDBP, mm Hg | 10±3 | 9±1.8 | 0.124* |
| ARE, n (%) | 16 (32) | 6 (14.6) | 0.084** |
| Test duration, minutes | 7.6±1.5 | 8.7±1.5 | **0.002*** |
| **Laboratory** | | | |
| ALP, IU/L | 51±19 | 45±20 | 0.278* |
| 25-OH-D vitamin, ng/mL | 9.8±7.3 | 18.1±7.9 | **<0.001*** |
| | 6.7, [39–3] | 18, [35.8–4.64] | **<0.001***** |
| Calcium , mg/dL | 8.7±0.72 | 8.6±0.69 | 0.731* |
| Creatine, mg/dL | 0.75±0.13 | 0.80±0.18 | 0.147* |
| Hg, mg/dL | 12.6±1.1 | 12.6±1 | 0.972* |
| EF (%) | 60 [65–55] | 60 [65–60] | 0.415*** |
| LA diameter, cm | 3.65±0.18 | 3.64±0.14 | 0.834* |

*Unpaired t-test was used; **Fisher's exact test was used; ***Mann-Witney U test was used. ALP - alkaline phosphatase; ARE - abnormal response to exercise; BMI - body mass index; DM - diabetes mellitus; EF - ejection fraction; IDBP - increase in diastolic blood pressure; Hg - hemoglobine; HL - hyperlipidemia; HT - hypertension; LA - left atrium; MET - metabolic equivalent; OAD - oral anti-diabetic; PDBP - peak diastolic blood pressure; PSBP - peak systolic blood pressure; 25-OH-D vitamin - 25-hydroxy vitamin D

Vitamin D receptors are expressed on various tissues and cells, where they participate in gene regulation associated with cell proliferation, differentiation, apoptosis, and angiogenesis (1). Vitamin D deficiency was reported to be associated with endothelial dysfunction resulting in atherosclerosis, cardiovascular morbidity, and mortality (11). Different mechanisms have been introduced to explain the protective effects of vitamin D against atherosclerosis and vascular calcification as described below: (i) vitamin D inhibits the proliferation of vascular smooth muscle cells via vitamin D receptor (12), (ii) vitamin D deficiency results in increased levels of parathyroid hormone, which causes myocardial calcification (13), (iii) vitamin D downregulates inflammatory cytokines that have a role in endothelial dysfunction (14),

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**Table 2. Correlations among significant variants in univariate analyses**

| | Test duration | MET | PSBP | PDBP | 25-OH-D vitamin |
|---|---|---|---|---|---|
| Test duration | 1 | | | | |
| MET | .982(**) | 1 | | | |
| | .000 | | | | |
| PSBP | -.135 | -.139 | 1 | | |
| | .201 | .190 | | | |
| PDBP | -.172 | -.195 | .391(**) | 1 | |
| | .103 | .064 | .000 | | |
| 25-OH-D vitamin | .093 | .103 | -.310(**) | -.535(**) | 1 |
| | .402 | .353 | .004 | .000 | |

** Pearson's correlation test was used. MET - metabolic equivalent; PDBP - peak diastolic blood pressure; PSBP - peak systolic blood pressure; 25-OH-D vitamin - 25-hydroxy vitamin D

**Table 3. Two different multivariate logistic regression analyses for the predictors of cardiac syndrome X**

| First model (Hosmer and Lemeshow Test: *P*:0.095, Nagelkerke *R* Square: 0.433)* | | | | |
|---|---|---|---|---|
| | β | *P* | OR | 95% CI |
| MET | -.652 | 0.003 | 0.521 | 0.340–0.797 |
| ARE | 0.749 | 0.295 | 2.114 | 0.813–0.949 |
| 25-OH-D vitamin | -.129 | 0.001 | 0.879 | 0.813–0.949 |
| **Second model (Hosmer and Lemeshow Test: P:0.755, Nagelkerke R Square: 0.480)*** | | | | |
| MET | -.571 | 0.007 | 0.565 | 0.372–0.859 |
| 25-OH-D vitamin | -.104 | 0.008 | 0.901 | 0.834–0.973 |
| PDBP | 0.075 | 0.027 | 1.078 | 1.009–1.151 |

*Multivariate logistic regression test was used. ARE - abnormal response to exercise; MET - metabolic equivalent; PDBP - peak diastolic blood pressure; 25-OH-D vitamin - 25-hydroxy vitamin D

and (iv) vitamin D has important roles in insulin sensitivity (11). Low levels of vitamin D were reported to be associated with early atherosclerosis, increase in carotid intima-media thickness, and atherosclerotic plaque burden (15). In experimental studies, it was postulated that vitamin D increases nitric oxide production and inhibits macrophages that transform into foam cells (16, 17). Although there are some studies that claim that vitamin D deficiency is not related to cardiovascular diseases, vitamin D deficiency was reported to be associated with coronary artery disease, myocardial infarction, stroke, increased incidence of cardiovascular events, and mortality (18, 19). In a meta-analysis by Wang et al. (20), 19 independent studies with 65994 patients with 6123 cardiovascular events were evaluated. An inverse and linear association was detected between cardiovascular event incidence and vitamin D levels of 20 to 60 nmol/L.

Etiological causes of CSX may include impaired coronary microvascular circulation, insulin resistance, and endothelial dysfunction (21, 22). With the development of endothelial dysfunction, decrease in microvascular vasodilatation, increase in intracoronary pressure, and decrease in subendocardial perfusion occur, and the patient experiences angina pectoris (23). Moreover, decreased endogenous nitric oxide and adiponectin, increased plasma endothelin-1, and lipoprotein (a) were observed in CSX patients, and these are all thought to be indicators of endothelial dysfunction and premature atherosclerosis (24, 25). We believe that the relationship between vitamin D deficiency and endothelial dysfunction is an explanation to our finding that vitamin D is associated with CSX and the abnormal response to exercise in patients with CSX. Additionally, in our study vitamin D levels were found to be an independent predictor of CSX.

It is well known that hypertension is associated with endothelial dysfunction, atherosclerosis, left ventricular hypertrophy, cardiovascular morbidity, and mortality. Furthermore, abnormal blood pressure response to exercise was suggested to be associated with future hypertension and cardiovascular disease (26, 27). In the Framingham Heart Study, 1026 male and 1284 female patients were evaluated for the consequences of exercise-induced hypertension, and DBP was reported to be a predictor of future hypertension in both females and males (28). Gupta et al. (29) investigated the prognostic value of exercise-induced SBP in 6145 patients. Maximal exercise SBP had prognostic value for the prediction of cardiovascular mortality, independent of age, ST segment deviation, and exercise capacity. The patients were followed up for more than six years, and an increase in SBP, i.e., ≥44 mm Hg, was associated with 23% improvement in survival. In some studies on CSX, patient risk factors such as hypertension and diabetes were defined as exclusion criteria and myocardial perfusion scintigraphy was used for noninvasive monitoring of ischemia. Therefore, it was difficult to evaluate the effect of hypertensive response to exercise in the patient group. Because we excluded patients with prominent left ventricular hypertrophy and uncontrolled hypertension, the exact definition of "abnormal hypertensive response to exercise" (SBP >260 mm Hg and DBP >130 mm Hg) was not met in any of our participants (30). However, abnormal blood pressure response to exercise was observed in normotensive patients and in hypertensive patients with normal blood pressure levels who were on antihypertensive drugs. In our study, the initial blood pressure levels of the patients and controls were not different from each other; however, exercise-induced peak SBP and DBP were higher in CSX patients, and peak DBP was an independent predictor of CSX.

Autonomic dysfunction has been thought to be one of the etiologic reasons for the angina and ischemia detected in patients with CSX. The major mechanism underlying abnormal blood pressure response to exercise is the inability to obtain necessary hyperemia because of autonomic dysfunction, endothelial dysfunction, and disordered systemic cytokine balance (31, 32). Furthermore, some studies reported that hypertension was associated with vitamin D deficiency, and some stated that although there is no direct relationship, vitamin D replacement therapy in pre-hypertensive and grade 1 hypertensive patients

resulted in decreased blood pressure levels (33, 34). In our patients, the abnormal blood pressure response to exercise may be related to autonomic dysfunction. Apart from specific pathways such as endothelial dysfunction and autonomic dysregulation, the relationship between CSX, vitamin D, and abnormal blood pressure response to exercise may be multifactorial.

## Study limitations

One of the limitations of our study is the relatively small number of patients involved. Another concern is that we did not use intravascular imaging methods such as optical coherence tomography or intravascular ultrasound to describe normal coronary arteries. Coronary angiography could be performed for better documentation of normal coronary anatomy. Moreover, intracoronary ergonovine was also not applied because we had concerns about severe and persistent vasospasms. Similarly, adenosine-induced coronary flow reserve could be tested using echocardiography. Hyperventilation and cold presser tests, which are used for the same purpose, have lower sensitivity. Additionally, vitamin D levels of the patient group were measured in different seasons, although we tried to correct the seasonal differences in vitamin D levels by collecting blood samples from the control group in a short period of time. The levels of inflammatory markers such as CRP or ESR and their relationship with vitamin D levels could have been tested. The effect of abnormal blood pressure response on future hypertension could not be evaluated in this study because a long-term follow-up of the patients was not issued.

## Conclusion

Patients with CSX had lower levels of vitamin D than healthy controls; in addition, vitamin D deficiency was associated with abnormal response to exercise. Further studies are required to understand the pathophysiological mechanisms and effects of vitamin D supplementation in these patients.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

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