Effect of Plasma Level of Vitamin D on Postoperative Atrial Fibrillation in Patients Undergoing Isolated Coronary Artery Bypass Grafting

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Abstract

Objective: Postoperative atrial fibrillation (PoAF) is a common complication after coronary artery bypass grafting (CABG). The aim of the present study was to evaluate the association between development of PoAF and vitamin D levels in patients undergoing isolated CABG.

Methods: This prospective randomized clinical trial was conducted on the patients with isolated CABG. The study was terminated when 50 patients in both PoAF(+) group and PoAF(-) group were reached. Development of AF until discharge period was assessed. Vitamin D level was measured immediately after AF; it was measured on the discharge day for the patients without PoAF. Predictive values of the independent variables were measured for the development of PoAF.

Results: The groups were separated as PoAF(-) group (66% male, mean age 58.18±10.98 years) and PoAF(+) group (74% male, mean age 61.94±10.88 years). 25(OH) vitamin D level (OR=0.855, 95% CI: 0.780-0.938, P=0.001) and > 65 years (OR=3.525, 95% CI: 1.310-9.483, P=0.013) were identified as an independent predictor of postoperative AF after CABG surgery in multivariate analysis. The cut-off level for 25(OH) vitamin D level in receiver-operating characteristic curve analysis was determined as 7.65 with sensitivity of 60% and specificity of 64% for predicting PoAF (area under the curve: 0.679, P=0.002).

Conclusion: Vitamin D level is considered an independent predictor for development of PoAF. Lower vitamin D levels may be one of the reasons for PoAF.

Keywords: Vitamin D. Postoperative Period. Atrial Fibrillation. Coronary Artery Bypass.

INTRODUCTION

Postoperative atrial fibrillation (PoAF) is a common complication after coronary artery bypass grafting (CABG), affecting about 20% to 35% of all patients in the early postoperative period[1]. PoAF is commonly associated with hemodynamic instability, thromboembolic events, increase in early and late mortality rates, heart failure progression and increased duration of hospitalization[1].

Vitamin D exists in two forms: D2 (ergocalciferol) and D3 (cholecalciferol). Vitamin D is converted into calcidiol and calcitriol, respectively in the liver and kidney; and acts on specific target tissues via vitamin D receptors[2]. Vitamin D receptors were found in other extra-osseous tissues, as well as all major cardiovascular cell types, including cardiomyocytes, vascular smooth muscle cells, endothelial cells, the brain, pancreatic beta-cells, skeletal muscles, breast, prostate, colon, macrophages, and

Abbreviations, acronyms & symbols

25(OH) vitamin D = 25-hydroxy vitamin D
ACE = Angiotensin-converting enzyme
AF = Atrial fibrillation
ARB = Angiotensin receptor blocker
CABG = Coronary artery bypass grafting
CI = Confidence interval
COPD = Chronic obstructive pulmonary disease
CPB = Cardiopulmonary bypass
ECG = Electrocardiography
ICU = Intensive care unit
OR = Odds ratio
PoAF = Postoperative atrial fibrillation
RAAS = Renin-angiotensin-aldosterone system
ROC = Receiver-operating characteristic curve

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skin, exerting several pleiotropic effects, and their expression decreases with age[4].

Deficiency of vitamin D may cause a number of diseases. Some of these diseases include type 2 diabetes mellitus, metabolic syndrome, obesity, hypertension, and some cardiovascular disease[5]. Several pathophysiological mechanisms were suggested for the association between vitamin D deficiency and atrial fibrillation (AF). One of the most important mechanisms is the activation of the renin-angiotensin-aldosterone system (RAAS), as it is responsible for both structural and electrical remodeling of the atrium. Vitamin D negatively affects the RAAS, and it has antioxidant effects that reduce oxygen free radicals in the atria which are associated with inflammation and the production of proarrhythmic materials[5].

Presence of vitamin D receptor in extra-osseous tissues; and the link between vitamin D and the RAAS may be shown relationship between vitamin D and AF risk factors. The aim of this study was to determined the relationship between vitamin D levels and PoAF in patients undergoing isolated CABG.

METHODS

The Patients

This prospective randomized clinical trial was conducted on the patients with isolated CABG diagnosed at of Cardiovascular Surgery Department within Bursa Yuksek Ihtisas Training and Research Hospital, Bursa, Turkey, between November 2016 and May 2017. The study was approved by the local institutional Ethical Committee of the University of Health Sciences. All procedures were performed in accordance with the Declaration of Helsinki.

Inclusion criteria was isolated CABG. The exclusion criteria were having preoperative AF or flutter, previous treatment with amiodarone, presence of valvular heart disease, chronic obstructive pulmonary disease (COPD), prolonged intensive care unit (ICU) stay, patients who underwent more than one cardiac surgery, bleeding revision, chronic renal failure. Patients who underwent isolated CABG were followed until the day of discharge from the hospital. Patients who developed AF during the this period were included in the PoAF(+) group, and patients without AF were enrolled in the PoAF(-) group. The study was terminated when 50 patients were reached in both groups.

The data of PoAF(+) group (74% male, mean age 61.94±10.88 years) and PoAF(-) group (66% male, mean age 58.18±10.98 years) are shown in Table 1.

All data were recorded as age, gender, history of hypertension, diabetes mellitus, preoperative drug use [beta-blockers, statins, angiotensin-converting enzyme (ACE) or angiotensin receptor blocker (ARB) inhibitors], ejection fraction, left atrial diameter, body mass index, body surface area, aortic cross clamp time, cardiopulmonary bypass time. Laboratory parameters were also studied from venous blood sample before the surgery except for 25-OH vitamin D levels. In the PoAF(+) group, the level of vitamin D was measured immediately after development AF. In the group of PoAF (-), the level of vitamin D was measured on the day patients were discharged from the hospital.

The inactive vitamin D precursors are first exposed to 25-hydroxylation in the liver to form 25-hydroxy vitamin D [(25(OH) vitamin D]. This is the actual circulating form of vitamin D and therefore is usually considered as a circulating biomarker for vitamin D status[6].

The 25-OH vitamin D levels were measured through Architect 25-OH vitamin D- Reagent Kit (Abbott, Diagnostic Division Lisnamuck, Longford, Ireland). Reference ranges of the 25-OH vitamin D Kit used were 6.2 to 45.5 ng/mL for winter season and 7 to 53.2 ng/mL for summer season.

Diagnosis of PoAF

The patients were monitored in ICU with continuous heart rhythm and invasive blood pressure monitoring. In addition, a 12-lead electrocardiography (ECG) record was also obtained daily in the ICU. Patients were monitored continuously by five-lead telemetry in the regular ward. When the patients complained about palpitation, dyspnea and angina, 12-lead ECG was taken. AF was confirmed by 12-lead ECG. Postoperative AF was described as irregular, fast oscillations or fibrillatory waves instead of regular P waves at ECG. An AF episode longer than 5 minutes was accepted as PoAF. Standard medical cardioversion treatment was conducted with amiodarone (5 mg/kg) for 30 minutes, followed by 900 mg/day.

Statistical Analysis

Statistical analysis data were analyzed with the Statistical Package for the Social Sciences (IBM SPSS Statistic Inc. version 21.0, Chicago, IL, USA). Continuous and ordinal variables were expressed as mean ± standard deviation and nominal variables were expressed as frequency and percentage. Kolmogorov-Smirnov test and Shapiro-Wilk tests of normality were used to identify distribution of variables. Student’s t test was used to compare two groups for continuous variables with normal distribution. Chi Square test was used to compare two groups for nominal variables. Mann-Whitney U test was used to compare two groups for continuous variables without normal distribution. For all tests, a P value of <0.05 was considered statistically significant. The relationship between the preoperative independent variables and the development of postoperative AF was evaluated by a logistic regression analysis. Receiver-operating characteristic (ROC) curve was applied for the prediction of PoAF development in patients undergoing isolated CABG and the area under the curve was calculated for vitamin D levels.

RESULTS

In the present study, 50 patients were enrolled into each group. The demographic and clinical characteristics of the participants are summarized in Table 1. Being over 65 years of age was evaluated as a different parameter. Patients with PoAF were similar to patients without PoAF in regards to demographic properties, in generally. But, in terms of in patients with age > 65 years was statistically significant difference between two groups (P=0.035) (Table 1).

The comparison of laboratory and operative parameters are shown in Table 2. Significant difference only was observed between two groups in terms of 25(OH) vitamin D levels.
Twenty-five(OH) vitamin D level were significantly lower in the PoAF group ($P=0.002$) (Table 2). However, all other parameters were not significantly different between the groups (Table 2).

Risk factors related to the development of PoAF were included univariate logistic regression analysis. In univariate logistic regression analysis, the PoAF was significantly correlated with 25(OH) vitamin D level ($OR \ [odds\ ratio]=0.867, \ 95\% \ CI \ [Confidence\ interval]: 0.793-0.949, \ P=0.002$) and age > 65 years ($OR=0.402, \ 95\% \ CI: 0.171-0.946, \ P=0.037$), but was not correlated with age ($OR=1.032, \ 95\% \ CI: 0.995-1.071, \ P=0.091$), hypertension ($OR=1.379, \ 95\% \ CI: 0.628-3.029, \ P=0.424$), diabetes mellitus ($OR=1.176, \ 95\% \ CI: 0.534-2.593, \ P=0.687$), ejection fraction ($OR=1.011, \ 95\% \ CI: 0.969-1.055, \ P=0.609$), left atrium diameter ($OR=1.019, \ 95\% \ CI: 0.927-1.120, \ P=0.700$) and cardiopulmonary bypass (CPB) time ($OR=1.003, \ 95\% \ CI: 0.984-1.023, \ P=0.742$) (Table 3). Similar to the results in the univariate analysis, 25(OH) vitamin D level ($OR=0.855, \ 95\% \ CI: 0.780-0.938, \ P=0.001$) and age > 65 years ($OR=3.525, \ 95\% \ CI: 1.310-9.483, \ P=0.013$) were identified as an independent predictor of postoperative AF after CABG surgery in multivariate analysis (Table 3). Additionally, it was determined a cut-off level of 7.65 for 25(OH) vitamin D level for predicting PoAF with a sensitivity of 60% and a specificity of 64%, in ROC curve analysis (area under the curve: 0.679, 95% CI: 0.576-0.783, $P=0.002$) (Figure 1).

**DISCUSSION**

In our study, the effect of the vitamin D levels was assessed on development of PoAF in patients who had isolated CABG.
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The incidence of PoAF following CABG surgery is seen in 25%-40% of cases. However, its frequency reaches to 62% following combined CABG and valve surgery\(^\text{[3]}\). The risk of PoAF in valvular and combined surgery, including coronary and valvular, was reported to be higher than that in coronary surgery alone. Mariscalco et al.\(^\text{[8]}\) identified the PoAF rates as 22.9%, 39.8%, and 45.2% for the isolated CABG, valve surgery, and combined surgery, respectively. Therefore, patients with valvular heart disease were excluded to not affect on the outcome of the study.

Postoperative hypoxemia was shown to be the most common cause of cardiac arrhythmias. COPD is an independent risk factor for arrhythmias, especially for AF and cardiovascular morbidity and mortality. In a large-scale, retrospective, case-control study, the association between lower vitamin D levels and PoAF development was determined. Plasma 25 (OH) vitamin D levels was found significantly lower in patients who developed PoAF than the patients with sinus rhythm. In univariate and multivariate logistic regression analysis, lower plasma 25 (OH) vitamin D levels and age > 65 years were found to be an independent variable predicting the development of PoAF. Also it was determined for cut-off level of 7.65 of vitamin D level for predicting PoAF with a sensitivity of 60% and a specificity of 64% in ROC analysis.

### Table 2. Laboratory and operative variables.

|                     | PoAF group (n=50) | PoAF(-) group (n=50) | P value* |
|---------------------|-------------------|----------------------|----------|
| Hematocrit (%)      | 39.37±5.53        | 41.16±4.69           | 0.244    |
| White blood cell (10\(^3/\mu\text{L}\)) | 9.18±2.14         | 9.55±2.87            | 0.733    |
| Platelet (10\(^3/\mu\text{L}\))        | 268.98±91.2       | 237.56±54.69         | 0.126    |
| Red cell distribution width (%) | 13.76±1.13        | 13.98±1.25           | 0.456    |
| Mean platelet volume (FL) | 8.9±0.98          | 8.66±0.86            | 0.208    |
| BUN (mg/dL)         | 18.04±7.71        | 17.78±7.39           | 0.803    |
| Creatinine (mg/dL)  | 0.88±0.21         | 0.89±0.32            | 0.545    |
| Na (mEq/L)          | 138.3±3.07        | 138.64±2.46          | 0.534    |
| K (mEq/L)           | 4.17±0.42         | 4.14±0.6             | 0.673    |
| Ca (mg/dL)          | 9.09±4.02         | 9.17±0.51            | 0.269    |
| Mg (mg/dL)          | 1.91±0.15         | 1.9±0.22             | 0.816    |
| Free T3 (pg/mL)     | 2.94±0.45         | 2.95±0.44            | 0.959    |
| Free T4 (ng/dL)     | 1.11±0.19         | 1.17±0.21            | 0.166    |
| TSH (IU/mL)         | 1.96±1.19         | 2.92±4.72            | 0.608    |
| C reactive protein (mg/dL) | 14.73±23.40   | 12.7±19.09           | 0.871    |
| Total cholesterol (mg/dL) | 202.5±33.41 | 197.92±39.96         | 0.536    |
| LDL-C (mg/dL)       | 128.11±29.44      | 119.37±33.57         | 0.596    |
| HDL-C (mg/dL)       | 43.38±8.36        | 41.55±8.43           | 0.316    |
| TG (mg/dL)          | 153.38±65.66      | 184.4±111.41         | 0.237    |
| 25(OH) vitamin D (ng/mL) | 7.49±3.81     | 12.1±7.98            | 0.002    |
| Ejection fraction (%) | 51.14±9.09       | 50.20±9.42           | 0.648    |
| Left atrium diameter (mm) | 38.40±4.22   | 38.08±4.15           | 0.928    |
| ACC time (min)      | 58.32±14.99       | 57.0±14.38           | 0.473    |
| CPB time (min)      | 88.04±20.99       | 86.7±19.47           | 0.745    |

*Student's-t test; Mann-Whitney U test
25(OH) vitamin D=25-hydroxy vitamin D; ACC=aortic cross clamp; BUN=Blood urea nitrogen; CPB=cardiopulmonary bypass; HDL-C=high density lipoprotein cholesterol; LDL-C=low density lipoprotein cholesterol; PoAF=postoperative atrial fibrillation; T3=triiodothyronine; T4=thyroxine; TG=triglyceride; TSH=thyroid-stimulating hormone
Table 3. Binary logistic regression analysis to identify predictors of PoAF.

| Variables            | Univariate Analysis | Multivariate analysis |
|----------------------|---------------------|-----------------------|
|                      | P               | Exp(B)   | 95% C.I. Lower | 95% C.I. Upper |
|                      | Odds ratio       |          |               |               |
| Age                  | 0.091            | 1.032    | 0.955-1.071   |               |
| Age ≥ 65 years       | 0.037            | 0.402    | 0.171-0.946   | 0.013         | 3.525 | 1.310-9.483 |
| HT                   | 0.424            | 1.379    | 0.628-3.029   |               |
| DM                   | 0.687            | 1.176    | 0.534-2.593   |               |
| EF                   | 0.609            | 1.011    | 0.969-1.055   |               |
| LAD                  | 0.700            | 1.019    | 0.927-1.120   |               |
| 25(OH) Vitamin D     | 0.002            | 0.867    | 0.793-0.949   | 0.001         | 0.855 | 0.780-0.938 |
| CPB time             | 0.742            | 1.003    | 0.984-1.023   |               |

25(OH) vitamin D = 25-hydroxy vitamin D; CPB = cardiopulmonary bypass; DM = diabetes mellitus; EF = ejection fraction; HT = hypertension; LAD = left atrium diameter; PoAF = postoperative atrial fibrillation
found that 25(OH) vitamin D serum levels of 16 ng/mL covers the requirements of approximately 50% of the population. There are different opinions regarding the cut-off values for insufficient or deficient vitamin D level. In our study, 25(OH) vitamin D levels were 12.13±7.98 ng/mL (range: 2.8-36.8), (percentiles 25; 6.67 ng/mL, percentiles 75; 15.35 ng/mL) in patients without PoAF. In patients with PoAF, 25(OH) vitamin D levels were found as 7.49±3.81 ng/mL (range: 1.5-20.5), (percentiles 25; 4.7 ng/mL, percentiles 75; 9.05 ng/mL). When these levels are taken into consideration, a vast majority of the patients in our study are in the vitamin D deficiency group according to the guidelines. It may be due to study period in the winter months. The average blood vitamin D level of the population studied is not clear. Although the blood vitamin D levels in most patients were insufficient according to the guidelines, the cut-off value that 7.65 ng/dl for vitamin D in this study was found to be statistically significant. Furthermore, it was determined a cut-off level of 7.65 for 25(OH) vitamin D level for predicting PoAF with a sensitivity of 60% and a specificity of 64% (AUC: 0.679, P=0.002).

In our study, the risk factors for arrhythmia were minimized and provided homogeneity between the groups; lower vitamin D levels would not affect the outcome of the study. It was more important for us that statistical differences in terms of vitamin D levels between groups are statistically significant predictors of postoperative AF development. On the other hand, our study had homogeneity. For this reason, the risk factors for development atrial fibrillation as COPD and valvular heart diseases were excluded. Therefore, the results of our study may be more specific in terms of the relationship between lower vitamin D levels and PoAF.

Limitations of the Study

Our study has some limitations. The small sample size may be considered as the first limitation of this study, but the excess of exclusion criteria minimized the risk factors for PoAF. This may allow us to ignore the size of the sample, which appears to be a limitation of study. Secondly, parathyroid hormone levels were not measured. Also our work was only carried out in the winter and spring seasons. Further prospective studies with a larger number of patients are required.

CONCLUSION

Many factors contribute to the development of AF after CABG. Many studies have been done on PoAF development. The lack of vitamin D can cause some of cardiovascular disease. In this study, lower vitamin D level was found to be an independent predictor of the development of PoAF. Low vitamin D level may be one of the reasons for PoAF development.

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