

# Does Deficiency of Vitamin D Increase New Onset Atrial Fibrillation after Coronary Artery Bypass Grafting Surgery?

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## ABSTRACT

**Background:** Deficiency of vitamin D is known to be effective in the development of hypertension, coronary artery disease, myocardial infarction, and stroke. Deficiency of vitamin D was also shown to be associated with new onset atrial fibrillation (AF) by activating the renin-angiotensin system. This study investigated whether or not levels of vitamin D are effective in the development of AF after coronary artery bypass grafting (CABG) surgery.

**Methods:** A total of 283 patients undergoing CABG were included in this study. Clinical information, history of medication use, serum 25 hydroxy(OH) vitamin D, and calcium levels of all patients were evaluated preoperatively.

**Results:** AF developed postoperatively in 72 (25%) of patients. Serum 25(OH) vitamin D levels of patients in whom AF developed after CABG were significantly lower than patients in whom AF did not occur ( $15.6 \pm 7.4$  versus  $19.1 \pm 9.1$ ;  $P = .004$ ). Independent variables which were predictors of AF development in multivariate logistic regression analysis were ejection fraction (odds ratio [OR]: 0.93; 95% confidence interval [CI] 0.89-0.97;  $P = .003$ ), left atrial dimensions (OR: 1.47; 95% CI 1.26-1.71;  $P < .001$ ), and serum 25(OH) vitamin D levels (OR: 0.95; 95% CI 0.91-0.99;  $P = .035$ ).

**Conclusion:** This study has shown that deficiency of vitamin D is associated with new onset AF post-CABG surgery.

## INTRODUCTION

Atrial fibrillation (AF) is the most frequently encountered arrhythmia after coronary artery bypass grafting (CABG) surgery, developing in 15-30% of patients postoperatively [Maisel 2001]. Postoperative AF (POAF) increases length of stay in the intensive care unit and hospital, morbidity and mortality, and also the cost of healthcare [Villareal 2004; Filardo 2009]. Thus, it is very important to understand preoperative risk factors and pathophysiologic processes effective in postoperative AF development and take prophylactic measures.

Many pathophysiologic mechanisms were described in new onset postoperative AF. Among these, activation of the

renin-angiotensin system (RAS) is believed to have an important effect on new onset POAF [Mathew 2004]. RAS causes structural remodeling in the atria and also triggers AF development by increasing oxidative stress [Li 2003]. Vitamin D is known to decrease risk factors such as hypertension (HT), coronary artery disease, myocardial infarction, and stroke, which are effective in the development of AF by inhibiting RAS activation [Al Mheid 2013]. On the other hand, recent studies have shown that vitamin D deficiency is directly associated with AF development [Demir 2014; Chen 2014; Ozcan 2015].

In view of these data, we aimed to investigate if vitamin D level had any effect on new onset POAF.

## METHODS

This study was carried out in patients undergoing on-pump CABG between 2014-2015 during fall and winter seasons. All patients were residents of Afyonkarahisar City, which is in the inner region of Western Anatolia in Turkey. Approval was obtained from the local ethics committee for this study. Written informed consent from all patients was also obtained. The study was conducted in accordance with the Helsinki Declaration.

The patients were divided into two groups according to AF development after CABG surgery. Data on preoperative age, sex, obesity, HT, diabetes mellitus (DM), stroke, peripheral arterial disease (PAD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), obstructive sleep apnea syndrome (OSAS), history of medication use (beta blockers, statins, RAS blockers), ejection fraction (EF), left atrial dimensions (LAD), serum 25 hydroxy(OH) vitamin D levels, and calcium levels were recorded. Patients having serious valvular disease requiring surgical treatment, those requiring redo surgery, and those having off-pump surgery were not included. Also, patients with thyroid disease, malignancies, acute infections, or those on treatment with cholecalciferol or vitamin D were excluded, due to the concerns about their potential effects on vitamin D levels.

## Postoperative AF Definition

Patients' follow-up was conducted with continuous rhythm monitoring during their stay in the hospital after surgery. Additionally, electrocardiographic recordings were done in patients reporting palpitation or similar complaints. AF is described as a rhythm characterized by the absence of consistent P waves for 30 seconds postoperatively; instead there are

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rapid oscillations or f waves that are generally associated with irregular R-R distance, according to 2012 European Cardiology Association Atrial Fibrillation guidelines of diagnosis and treatment [Camm 2012].

Body mass index (BMI) was calculated by dividing body weight in kilograms to the square of height in square meters ( $\text{kg}/\text{m}^2$ ). Obesity was defined as a BMI of  $30 \text{ kg}/\text{m}^2$  and over. Hypertension was defined as consecutive blood pressure measurements of over  $140/90 \text{ mmHg}$  or a history of taking antihypertensive medications. Diabetes mellitus was defined as a fasting glucose level over  $126 \text{ mg}/\text{dL}$ , a HbA1c level over  $6.5 \text{ gr}/\text{dL}$ , or a history of taking antidiabetic medications. Stroke was defined as a neurological deficit which had developed due to damage to the central nervous system caused by cerebral infarct, intracerebral hemorrhage, subarachnoidal bleeding, or as a past stroke. Ankle-arm index measurements were done to all patients before surgery for peripheral artery disease. Ankle-arm index is calculated by dividing systolic blood pressure measured from the ankle to the systolic blood pressure measured from the brachial artery. An ankle-arm index  $<0.9$  was defined as peripheral artery disease. In addition to this, patients in whom atherosclerotic stenosis was detected at the carotid, vertebral, upper extremity, mesenteric, renal, or lower extremity arteries with ultrasonography, computed tomography scan, magnetic resonance angiography, or duplex subtraction angiography before CABG were considered as having PAD. Chronic obstructive pulmonary disease was evaluated with spirometry in patients with cough, sputum, and dyspnea lasting longer than 3 months. A diagnosis of obstructive sleep apnea was reached with polysomnography in patients with complaints of snoring or interrupted breathing in the night, and was defined as a decrease in oro-nasal flow for at least 10 seconds in each episode, and presence of more than 30 episodes in a night sleep duration of 7 hours. Serious valvular disease was detected according to European Heart Association guidelines on diagnosis and treatment of valvular disease [Vahanian 2012]. Chronic renal failure was defined as a glomerular filtration rate lower than  $60 \text{ mL}/\text{min}/1.73 \text{ m}^2$ , according to Modification of Diet in Renal Disease Study Equation classification.

### Echocardiographic Examination

Transthoracic echocardiographic examination was done while the patients were lying in the left lateral decubitus position. Standard 2 dimensional and Doppler echocardiographic examinations were done with iE33 (Philips Medical Systems, Andover, MA, USA) echocardiography device, and Mass S5 probe (2-4 MHz). Measurements of left atrial dimensions were done according to the standards defined by the American Echocardiographic Society [Lang 2005]. Left ventricular ejection fraction was measured according to Simpson's method. All measurements were obtained from the average of images captured after 5 consecutive heartbeats.

### Laboratory Examinations

Blood samples were collected after hospitalization before surgery, after a 20-minute rest following 12 hours of fasting. Due to long half-life, serum 25(OH) vitamin D was preferred

instead of 1,25 dihydroxyvitamin D. As serum 25(OH) vitamin D levels show a seasonal variability, in order to obtain standard measurements, only patients who were operated in fall and winter seasons were examined. Serum 25(OH) vitamin D levels were measured by direct chemiluminescence immunoassay method (Eleclys; Roche Diagnostics, Mannheim, Germany). Intra- and inter-assay coefficients of variation (CVs) were below 4.5% and 7.6%, respectively.

### Statistical Analysis

Statistical analysis was performed using the SPSS (version 15.0, SPSS, Chicago, IL, USA) software package. Continuous variables were expressed as mean  $\pm$  standard deviation (mean  $\pm$  SD), and categorical variables were expressed as percentage (%). The Kolmogorov-Smirnov test was performed to test whether variables were normally distributed. Inter-group differences were evaluated using the Student t test for normally distributed continuous variables and the Mann-Whitney U test for variables that did not show normal distribution. Pearson chi-square test was used for the comparison of categorical variables. In order to identify independent factors in

Table 1. Baseline Demographic, Clinical, and Echocardiographic Characteristics of Participants

	Patients with AF, n = 71 (25%)	Patients without AF, n = 212 (75%)	P
Age, y	70 $\pm$ 8.6	61 $\pm$ 9	<.001
Male, n (%)	51 (72)	160 (76)	.542
Obesity, n (%)	16 (23)	55 (26)	.566
HT, n (%)	55 (78)	117 (55)	.001
DM, n (%)	45 (63)	98 (46)	.012
CVE, n (%)	12 (17)	22 (10)	.143
PAD, n (%)	17 (24)	30 (14)	.055
COPD, n (%)	30 (42)	45 (21)	.001
OSAS, n (%)	6 (9)	25 (12)	.435
EF (%)	46 $\pm$ 7.1	52 $\pm$ 8	<.001
LA diameter (mm)	37 $\pm$ 2.8	34 $\pm$ 2.4	<.001
Statin use, n (%)	49 (69)	112 (53)	.017
Beta blocker use, n (%)	71 (100)	197 (93)	.021
RAS blocker use, n (%)	23 (32)	54 (26)	.257
Creatinine, mg/dL	0.99 $\pm$ 0.16	0.91 $\pm$ 0.24	.011
Calcium, mg/dL	9.4 $\pm$ 0.4	9.3 $\pm$ 0.4	.186
Serum 25(OH) vitamin D level, ng/mL in spring or winter	15.6 $\pm$ 7.4	19.1 $\pm$ 9.1	.004

AF indicates atrial fibrillation; COPD, chronic obstructive pulmonary disease; CVE/TIA, cerebrovascular event; DM, diabetes mellitus; EF, ejection fraction; LA, left atrium; OH, hydroxyl; OSAS, obstructive sleep apnea syndrome; PAD, peripheral artery disease; RAS, renin angiotensin system.

Table 2. Multivariate Logistic Regression Analysis for the Independent Risk Factors for Postoperative Atrial Fibrillation

	OR	95% CI	P
EF	0.93	0.89-0.97	.003
LA diameter	1.47	1.26-1.71	<.001
Serum 25(OH) vitamin D level	0.95	0.91-0.99	.035

EF indicates ejection fraction; LA, left atrium; OH, hydroxyl; OR, odds ratio; CI, confidence interval.

predicting POAF, univariate correlates of new-onset atrial fibrillation with a  $P$  value  $<.1$  were included in the multiple logistic regression analyses odds ratios, and 95% confidence intervals were calculated with standard methods. The accuracy of the plasma 25(OH) vitamin D level for the prediction of POAF and determination of the cut-off point were evaluated with the ROC (receiver operating characteristics) curve. A  $P$  value of  $<.05$  was considered statistically significant.

## RESULTS

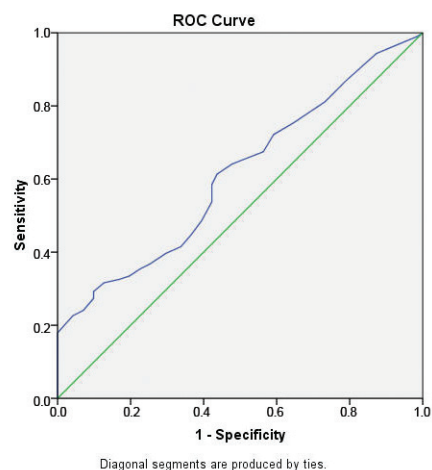
A total of 354 patients were evaluated in this study, and 73 meeting exclusion criteria were excluded. POAF developed in 72 of 283 patients (25%) included in the study. Significant differences were observed between patients in whom POAF have and have not developed in terms of age, HT, DM, COPD, EF, creatinine value, left atrial dimensions, preoperative statin, and beta blocker use ( $P < .05$ ). In addition, serum 25(OH) vitamin D levels of patients in whom POAF has developed were significantly lower than in those patients in whom POAF did not develop ( $15.6 \pm 7.4$  versus  $19.1 \pm 9.1$ ;  $P = .004$ ). Significant differences were not observed between these two groups in terms of other variables ( $P > .05$ ) (Table 1).

EF (0.93; 95% CI 0.89-0.97;  $P = .003$ ), left atrial dimensions (1.47; 95% CI 1.26-1.71;  $P < .001$ ), and serum 25(OH) vitamin D levels (0.95; 95% CI 0.91-0.99;  $P = .035$ ) were found to be independent predictors of POAF developments in multivariate logistic regression analysis (Table 2).

Area under the curve (AUC) value of serum 25(OH) vitamin D levels were 0.611 (95% CI 0.540-0.683;  $P = .005$ ) in ROC analysis (Figure). When a threshold value of 11.5 ng/mL was considered in ROC analysis, serum 25(OH) vitamin D levels predicted POAF development with 72% sensitivity and 41% specificity.

## DISCUSSION

Atrial fibrillation is the most frequently encountered complication after CABG surgery [Amar 2004]. The incidence of AF is still increasing in spite of developments in surgical and cardioplegic arrest techniques. POAF frequently is not tolerated by the patients, and causes hemodynamic instability, thromboembolic events, and dyspnea [Aranki 1996]. On the other hand, length of hospital stay and cost of hospitalization



Receiver operating characteristics curve analysis of serum 25(OH) vitamin D levels for the prediction of new onset atrial fibrillation. Best cut-off value of serum 25(OH) vitamin D for new onset AF is 11.5 ng/mL for patients with CABG, with a sensitivity value of 72% and a specificity value of 41% (area under curve: 0.57; 95% CI: 0.49-0.65;  $P = .04$ )

increase [Almassi 1997]. Thus, detection of preoperative risk factors in patients who will be undergoing CABG and taking prophylactic precautions targeting these risk factors are very important.

Advanced age, male sex, chronic heart failure, preoperative AF episodes, COPD, chronic renal failure, DM, rheumatic heart disease, metabolic syndrome, obesity, and inadequate use of beta blockers or RAS blockers were shown to be independent predictors of new onset POAF in previous studies [Mathew 2004; Mathew 1996; Banach 2006]. In the present study, we detected EF (0.93; 95% CI 0.89-0.97;  $P = .003$ ), left atrial dimensions (1.47; 95% CI 1.26-1.71;  $P < .001$ ), and serum 25(OH) vitamin D levels (0.95; 95% CI 0.91-0.99;  $P = .035$ ) as independent preoperative variables predicting new onset POAF.

Deficiency of vitamin D was shown to be associated with hypertension, coronary artery disease, myocardial infarction, and stroke in previous studies [Harling 2011; Forman 2007; Brøndum-Jacobsen 2012]. Vitamin D was also shown to be associated with new onset AF in recent studies. Demir et al have found that patients with non-valvular AF had lower vitamin D levels in comparison with patients with valvular AF or patients in sinus rhythm [Demir 2014]. Chen et al have found lower vitamin D levels in patients in whom persistent AF have developed in comparison with control patients in sinus rhythm. Low vitamin D levels were associated with high CRP [Chen 2014]. Ozcan et al have shown that vitamin D deficiency is an independent predictor of AF development in hypertensive patients [Ozcan 2015]. This study is the first one evaluating effects of vitamin D on POAF. The data of this study suggests that vitamin D has a negative effect on new onset POAF.

Many pathophysiologic factors play a role in postoperative AF development. Pathophysiologic mechanisms that cause new onset AF after CABG include structural atrial changes

(enlargement of the atrium, hypertrophy, fibrosis), postoperative inflammation [Mostafa 2012], increase in sympathetic nervous system due to stress after surgery [Schauerte 2001], atrial incision, perioperative ischemia, and postoperative oxidative stress [Carnes 2001] and activation of the RAS system. RAS activation increases cardiomyocyte hypertrophy and chronic interstitial fibrosis [Kirchhof 2014]. This process leads to the conduction block resulting in reentry cycle [Khatib 2013]. Vitamin D helps blood pressure regulation by negatively effecting RAAS mechanism, and thus decreases atrial structural remodeling [Li 2003]. In addition, oxidative mechanisms play an important role in new onset POAF. Antioxidant vitamin C and E treatments were shown to decrease AF and arrhythmias developing after cardiac surgery in a metaanalysis [Harling 2011]. Vitamin D exerts an antioxidant effect by decreasing reactive oxygen radicals in the atria, and thus impedes the occurrence of an arrhythmogenic environment. For these reasons, vitamin D is believed to be associated with new onset POAF.

Although low vitamin D levels were found to be independent predictors of POAF development, its sensitivity and specificity (72% sensitivity and 41% specificity) for a threshold value (11.5 ng/mL) are not appropriate enough for it to be applied to clinical practice. On the other hand, it is our hope that this may provide an awareness that vitamin D is probably effective in new onset POAF.

### Study Limitations

Although an association between vitamin D and POAF was observed in this study, it is also necessary to test if treatment of vitamin D deficiency decreases POAF development. While patients undergoing surgery during fall and winter were included in this study, due to seasonal variability of vitamin D levels, vitamin D levels of patients undergoing CABG in spring and summer should also be examined. As our sample size is small, further prospective studies on larger numbers of patients are required.

### Conclusion

Low vitamin D level is a parameter that increases incidence of new onset POAF. Based on these data, measurement of vitamin D levels is suggested before CABG in order to detect patients who are at risk of new onset POAF.

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