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Low-Level Vitamin D Is Associated with Atrial Fibrillation in Patients with Chronic Heart Failure

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A – research concept and design; B – collection and/or assembly of data; C – data analysis and interpretation; D – writing the article; E – critical revision of the article; F – final approval of article

Abstract

Background. Atrial fibrillation (AF) frequently accompanies heart failure (HF), and causes exacerbation of symptoms and treatment failure in such patients. Vitamin D was recently suggested to be an important mediator of cardiovascular disease, including HF.

Objectives. The aim of this study was to evaluate the relationship between vitamin D deficiency and AF in patients with chronic HF.

Material and Methods. The study included 180 chronic HF patients that were divided into 2 groups based on having sinus rhythm [AF (–) group] or chronic AF [AF (+) group]. Vitamin D status was assessed *via* measurement of the serum 25-hydroxyvitamin D (25[OH]D) concentration.

Results. Mean age of the patients was 66 ± 8.7 years and 53.9% were male. There weren't any significant differences in age, gender, body mass index, etiology or chronic HF stage between the 2 groups. The vitamin D level in the AF (+) group was significantly lower than in the AF (–) group (11.05 ng/mL vs. 20 ng/mL, $p < 0.001$) and the parathyroid hormone level was significantly higher in the AF (+) group (76.7 vs. 55 pq mL, $p < 0.001$). The left atrium to body surface area ratio (LA/BSA) was significantly higher in the AF (+) group (45.03 mm²/m² vs. 42.05 mm²/m², $p < 0.01$). Independent predictors (based on multiple regression) of AF were vitamin D level (OR = 0.854, 95% CI: 0.805–0.907, $p < 0.001$) and LA/BSA ratio (OR = 1.077, 95% CI: 1.003–1.156, $p < 0.05$). The optimal vitamin D cut-off value for the prediction of AF was 16.50 ng/mL, with a sensitivity of 76.0% and specificity of 65.5% (AUC = 0.75, 95% CI: 0.67–0.82).

Conclusions. A low plasma vitamin D concentration was strongly associated with AF in patients with chronic HF (Adv Clin Exp Med 2016, 25, 1, 51–57).

Key words: heart failure, atrial fibrillation, vitamin D.

Atrial fibrillation (AF) is the most common sustained clinical arrhythmia [1] and affects 1–2% of the general population [2]. AF is often associated with structural heart disease and the incidence of AF in patients with heart failure (HF) is approximately 24%. AF can result in exacerbation of HF symptoms, reduced exercise capacity, and treatment failure in patients with HF.

Vitamin D plays an important role in bone mineralization and maintenance of the serum calcium level [3]. Vitamin D receptors were identified

in various tissues associated with the cardiovascular system (e.g. cardiomyocytes [4], vascular smooth muscle cells [5], and endothelial cells [6]). Systemically, vitamin D has a negative regulatory effect on the renin-angiotensin system (RAS) [7] and inflammation [8]. Some experimental studies have shown that vitamin D deficiency and elevated plasma renin activity [9] induce ventricular remodeling and an increase in blood pressure [10]. Furthermore, vitamin D locally reduces the level of expression of certain genes that increase myocardial

hypertrophy, and are effective on RAS activity and natriuretic peptides [11]. Vitamin D can prevent cardiomyocyte hypertrophy *via* increasing thrombomodulin and reducing tissue factor [11]. Vitamin D has multiple effects on the development and differentiation of cardiomyocytes [11].

The roles of inflammation [12], the physical structure of the atrium, and RAS [13] in the development of AF are precisely known. Both the local and systemic effects of vitamin D might be associated with factors that cause the development of AF. A review reported that patients with HF had a vitamin D level 34% lower than that in healthy controls [14]. The relationship between the vitamin D level and AF has been analyzed in only a small number of studies, and the findings have been inconsistent [15–16]; however, to the best of our knowledge no study on the relationship between the vitamin D level and AF in patients with HF has been published. As such, the present study aimed to evaluate the relationship between vitamin D deficiency and AF in patients with chronic HF.

Material and Methods

Study Population

The study included 180 patients with chronic HF due to hypertension (HT) or coronary artery disease (CAD) that were admitted to our hospital between May 2013 and January 2014. The patients were staged based on clinical and echocardiographic assessment, as follows: stage A, B, C, and D. The patients were also divided into 2 groups based on having sinus rhythm [AF (-) group] or chronic AF [AF (+) group]. In order to minimize the effect of seasonal variation in the level of vitamin D, the patients were examined at similar seasonal periods. All the patients provided written informed consent in accordance with the Declaration of Helsinki and the local ethics committee approved the study protocol.

Patients with concomitant structural valvular heart disease, hypertrophic cardiomyopathy, restrictive cardiomyopathy, congenital heart disease, constrictive pericarditis, and cardiac tumors were excluded from the study, as these conditions might affect the prevalence of AF. In addition, patients with a history of pericarditis, myocarditis, pulmonary embolism and/or pulmonale, chronic obstructive pulmonary disease, sleep apnea syndrome, and other chronic lung diseases were excluded from the study. Alcohol use disorders, a recent history of surgery, hyperthyroidism, pheochromocytoma, and chronic metabolic

diseases such as diabetes mellitus were also considered exclusion criteria. Patients that were using exogenous vitamin D, those with a history of gastrectomy, intestinal malabsorption, impaired liver function, and extremely elevated liver enzymes, those using antiepileptic medications, those with liver or kidney failure, or any disease relevant to bone metabolism, patients with primary and secondary hyperparathyroidism, those using medications that affect calcium metabolism, and patients with cancer or acute HF were excluded from the study.

The estimated glomerular filtration rate (eGFR) was calculated using the Chronic Kidney Disease Epidemiology Collaboration equation. Patients with an eGFR < 60 mL/min/1.73 m² were excluded from the study. Medical history was considered positive for hypertension if systolic blood pressure was \geq 140 mm Hg and diastolic blood pressure was > 90 mm Hg, and if patients were using antihypertensive medications; medical history was considered positive for CAD in those with documented CAD, or a history of myocardial infarction. Left ventricular systolic function was considered normal if the left ventricular ejection fraction (LVEF) was > 50%. HF stage was determined based on patient medical history and physical examination. Staging of HF was based on the ACC/AHA classification [17], as follows:

Stage A: the presence of risk factors for HF, but left ventricular ejection fraction (LVEF) is normal (i.e. HT and CAD); Stage B: low LVEF, but asymptomatic; Stage C: low LVEF, recent onset or short-term symptoms, and initiation of medical treatment; Stage D: low LVEF and symptomatic (at rest), despite medical treatment.

Laboratory Evaluation

Blood samples were collected after \geq 12 h of fasting, and then routine biochemical analysis was performed. The brain natriuretic peptide (BNP) level was measured *via* the immunochemiluminescence method (Beckman Coulter D I800). C-reactive protein (CRP) was measured using the nephelometric method (Beckman Coulter IMMAGE 800). The serum vitamin D level was determined by measuring 25-hydroxyvitamin D (25[OH]D) *via* high-performance liquid chromatography (HPLC) using a Zivak ONH 100 A device; < 20 ng/mL (< 50 nmol L) was considered very low, 21–29 ng/mL (51–74 nmol L) was considered low, and > 30 ng/mL (> 75 nmol L) was considered normal [18]. The serum parathormone (PTH) level was measured *via* the radioimmunoassay method; 10–65 pg/mL was considered normal. All the patients underwent 12-lead electrocardiography.

Echocardiographic Evaluation

All patients underwent transthoracic echocardiography using a VIVID 3 device (GE Medical Systems, USA). Left ventricular diameter and LVEF (using a modified Simpson's method) were measured using a 1.5–3.3-MHz probe, according to updated ACC/AHA guidelines, while patients were in the recumbent position.

Statistical Analysis

The normality of the distribution of data was analyzed using the Kolmogorov-Smirnov test. Continuous variables are expressed as mean \pm SD and median (interquartile range [IQR]), as appropriate, and categorical variables are expressed as percentage (%). Categorical variables were compared *via* the χ^2 test. The Student's *t*-test and the Mann-Whitney *U* test were used to compare continuous variables. Multivariate logistic regression analysis was performed to identify the independent predictors of AF. Receiver operating characteristic (ROC) curve analysis was performed to determine the optimum vitamin D cut-off value for predicting AF, and the area under curve (AUC) was calculated to determine the accuracy of vitamin D as a biomarker of AF. All analyses were performed using SPSS v. 17.0 for Windows (SPSS, Inc., Chicago, Illinois). A 2-sided *p*-value < 0.05 was considered statistically significant within a 95% confidence interval (CI).

Results

In total, there were 180 chronic HF patients, of which 96 were AF (+) and 84 were AF (-). Mean age of the 97 (53.9%) male and 83 (46.1%) female patients was 66.16 ± 8.7 years. The characteristics of the patients according to AF status are presented in Table 1. There weren't any significant differences in age, gender, BMI, etiology, or chronic HF stage between the AF (+) and AF (-) groups (Table 1). The vitamin D level was significantly lower (11.05 vs. 20 ng mL⁻¹) and the PTH level was significantly higher (76.7 vs. 55 pq mL⁻¹) in the AF (+) group than in the AF (-) group ($p < 0.001$ for both). LA/BSA was significantly higher in the AF (+) group (45.03 vs. 42.05 mm m⁻², $p < 0.01$). LVEF, LVEDD, LVESD, glucose, creatinine, Ca, BNP, and CRP were similar in both groups (Table 1).

Multivariate regression analysis showed that vitamin D (OR = 0.854, 95% CI: 0.805–0.907, $p < 0.001$) and LA/BSA (OR = 1.077, 95% CI: 1.003–1.156, $p < 0.05$) were independent predictors

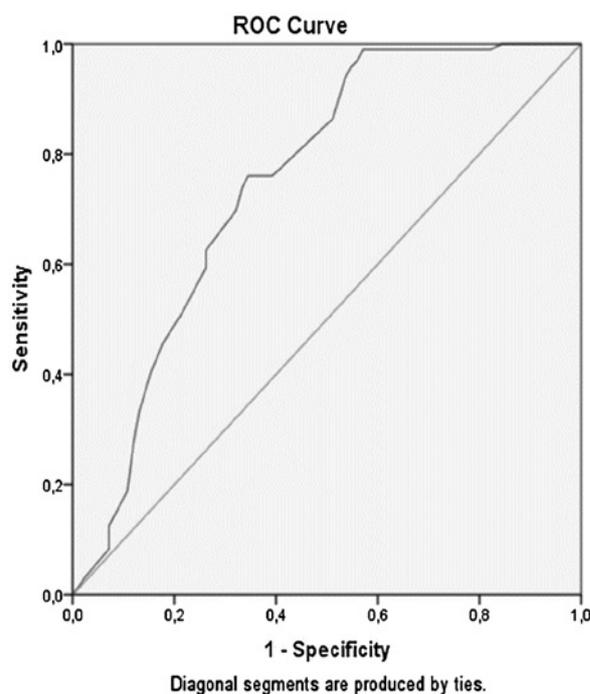


Fig. 1. ROC curve for vitamin D for AF prediction

of AF in the chronic HF patients (Table 2). ROC curve analysis showed that the optimal vitamin D cut-off value for predicting AF was 16.50 nmol L⁻¹, with a sensitivity of 76.0% and specificity of 65.5% (AUC = 0.75; 95%CI: 0.67–0.82) (Fig. 1).

Discussion

The present study shows for the first time that a low plasma vitamin D level is strongly associated with AF in patients with HF. Additionally, the PTH level and LA/BSA were significantly higher in the AF (+) group than in the AF (-) group. The relationship between AF, and BMI and HF clinical stage is well known. The present study found a relationship between the vitamin D level and AF in patients with HF is independent of BMI and HF stage, which indicates that vitamin D might have a direct effect on cardiomyocytes. These findings are similar to those of Hanafy et al., who reported that vitamin D protects against AF or helps reverse AF *via* a direct effect on atrial myocardium [19]. The relationship between the vitamin D level and hypertension is well known; however, there wasn't a difference in the levels of vitamin D among the causes of HF (CAD or HT). This result indicates that vitamin D might contribute to the development of AF, regardless of etiology, by affecting the neurohormonal system and the inflammation cascade, which are activated following formation of the anatomical substrate.

Table 1. Characteristics of patients according to the presence of AF

	AF + (n = 96)	AF - (n = 84)	p
Age (years)	66.40 ± 8.51	65.88 ± 9.09	0.695
Male (n, %)	46 (47.9)	51 (60.7)	0.086
BMI (kg/m ²)	25.13 ± 1.85	24.97 ± 1.56	0.537
ACEI/ARB (n, %)	81 (84.4)	63 (75.0)	0.117
Beta blocker (n, %)	79 (82.3)	65 (77.4)	0.411
Etiology			0.984
HT (n, %)	55 (53.4)	48 (46.6)	
CAD (n, %)	41 (53.2)	36 (46.8)	
CHF stage			0.816
A (n, %)	19 (19.8)	20 (23.8)	
B (n, %)	20 (20.8)	20 (23.8)	
C (n, %)	30 (31.3)	24 (28.6)	
D (n, %)	27 (28.1)	20 (23.8)	
Glucose (mg/dL)	89.66 ± 12.28	92.11 ± 12.77	0.192
eGFR (mL/min/1.73 m ²)	78.55 (25)	77.15 (22)	0.211
Creatinine (mg/dL)	0.96 ± 0.20	0.94 ± 0.24	0.355
Vit D (ng/mL)	11.05(9.08)	20 (16.5)	< 0.001
PTH (pq/mL)	76.7 (31.5)	55 (28.25)	< 0.001
Ca (mg/dL)	8.74 ± 0.73	8.80 ± 0.59	0.554
BNP (pg/mL)	76(116)	90 (246)	0.948
CRP (mg/L)	6.1(5.7)	5.1 (14.1)	0.152
LVEF (%)	39.52 ± 12.72	41.49 ± 14.26	0.329
LVEDD (mm)	56.98 ± 7.85	57.92 ± 8.39	0.441
LVESD (mm)	42.22 ± 10.82	42.71 ± 11.62	0.769
LA/BSA (mm/m ²)	45.03 ± 6.26	42.05 ± 6.15	0.002

Data is presented as mean (± standard deviation), median (interquartile range) and percentages (%).

ACEI – angiotensin converting enzyme inhibitor; ARB – angiotensin receptor blocker; BMI – body mass index; BNP – B-type natriuretic peptide; BSA – body surface area; Ca – calcium; CAD – coronary artery disease; CHF – chronic heart failure; CRP – C-reactive protein; HT – hypertension; LA – left atrium; LVEDD – left ventricular end diastolic diameter; LVEF – left ventricular ejection fraction; LVESD – left ventricular end systolic diameter; PTH – parathyroid hormone; Vit D – vitamin D.

Table 2. Logistic regression analysis for determinants of AF in CHF

Variables	OR (95% CI)	p-value
LA/BSA	1.077 (1.003–1.156)	0.041
Vit D	0.854 (0.805–0.907)	< 0.001
PTH	1.003 (0.992–1.015)	0.564

CI – confidence interval; OR – odds ratio; BSA – body surface area; LA – left atrium; Vit D – vitamin D; PTH – parathyroid hormone.

These findings might have been due to several mechanisms. HF is a progressive state which includes activation of such regulatory systems as the sympathetic nervous system and RAS. Initially, activation of these systems is adaptive, but over time activation becomes permanent, contributing to pathological cardiac remodeling and progression of HF. Persistent activation of regulatory systems leads to myocyte hypertrophy, apoptosis, fibroblast proliferation, and interstitial collagen accumulation. Finally, a potentially arrhythmogenic substrate develops as a result of these pathological changes. The effect of vitamin D in the development of AF may be through these compensatory mechanisms which are activated in heart failure.

Forman et al. [20] reported that patients with the lowest vitamin D levels had the highest levels of angiotensin II (Ang II), and that RAS was produced in excess in the absence of vitamin D. Some small-scale clinical studies have reported that administration of vitamin D resulted in lower plasma renin activity, Ang II levels, and the incidence of myocardial hypertrophy [21]. In addition to the systemic effects of vitamin D that might be associated with AF, it is known to have direct effects on vascular smooth muscle cells and endothelial cell cardiomyocytes [4–6]. The possibility of vitamin D deficiency in patients with HF is high because of inadequate UVB exposure, inadequate dietary vitamin D intake, or an increase in 25(OH) D catabolism. A small number of studies have examined the relationship between vitamin D and AF in the general population, of which one was a follow-up study that included 2930 participants of the Framingham Heart Study. During a mean follow-up of 9.9 years, 425 of the participants developed AF. Based on the Cox proportional hazards model, vitamin D was not observed to be associated with the development of AF [22]. Another study that included patients with non-valvular persistent AF, but no other cardiovascular disease, reported that a low vitamin D level was associated with AF [16]. Another previous study that included 102 patients with non-valvular chronic AF without any other cardiovascular disease has found an association between non-valvular AF and vitamin D deficiency [23]. In contrast, Faiza Qayyum et al. reported that there wasn't an association between vitamin D deficiency and the type of AF or complications of AF [15]. Of note, none of these earlier studies included patients with HF. The relationship between AF and the vitamin D level in patients with HF, as observed in the present study for the first time, might have been due to the additive effect of vitamin D on already elevated RAS activity. Rahman et al. reported that a low vitamin D level is likely associated with the progression of cardiac pathology, rather than with the onset of the pathology in mice with the vitamin D receptor knocked out [24]. Consequently, vitamin D deficiency in HF patients may result in the development of AF more often than in the normal population due to existing neurohormonal activation and anatomical substrates in HF patients.

Angiotensin-converting enzyme inhibitors and angiotensin II receptor blocker, which are RAS blockers, are protective from new-onset AF by a rate of 18%; that rate is as high as 43% among patients with HF. Considering the effect of vitamin D on RAS, it might be necessary to study the relationship between the incidence of AF and vitamin D supplementation in HF patients.

Besides neurohormonal activation and formation of an anatomical substrate, inflammation can also be responsible for the development of AF in vitamin D deficiency. Vitamin D increases interleukin (IL-10) production, and decreases IL-6, IL-12, interferon- γ , and tumor necrosis factor- α (TNF- α) production, leading to a cytokine profile that favors less inflammation [25]. Furthermore, *in vitro* treatment with calcitriol is associated with suppression of the proinflammatory cytokine IL-6 and TNF- α , and upregulation of the anti-inflammatory cytokine IL-10 [26]. Several clinical studies reported a relationship between AF and inflammation, and higher levels of other inflammatory markers (such as IL-6 or TNF) in patients with AF than in those without AF [27]. In 2001 Chung et al. [28] were the first to report higher CRP values (2-fold higher) in AF patients than in controls. In the present study the CRP level did not differ significantly between the AF (+) and AF (-) groups, and there was a negative correlation between vitamin D and the CRP level. Independent of etiology, elevated circulating levels of pro-inflammatory cytokines might play a role in the pathogenesis of HF. Inflammatory markers IL-6, CRP, and TNF- α are well-known risk factors associated with survival in patients with HF [29]. Inflammation in HF patients may become more severe in response to a low vitamin D level and might facilitate the formation of AF in patients with HF.

There is another abnormal hormonal axis implicated in vitamin D deficiency based on the observation that elevated PTH is highly prevalent in HF patients. *In vitro* PTH increases the production and reorganization of collagen, which may play a pathogenic role in the HF process. Additionally, PTH causes the intracellular calcium level to increase, which has a significant impact on the development of AF. Rienstra et al. reported that there is a relationship between PTH and AF in patients with lone AF, and in patients with hypertension and AF [30]. In the present study there was an association between PTH level and AF in patients with HF, which indicated that hyperparathyroidism secondary to vitamin D deficiency might play a role in the development of AF.

Limitations

Measurement of the serum vitamin D level performed at a single time point and the inability to determine the duration of vitamin D deficiency are limitations of the present study. Although the patients included in the study resided in regions with similar climatic conditions, the diversity of ethnic groups in Turkey with variable skin pigmentation might have played a role in the vitamin D levels noted.

The authors concluded that the present findings show that a low serum vitamin D level was strongly associated with an increased risk of AF in patients with HF – independent of all other factors, including HF stage, etiology of HF, and BMI. The risk factors for AF and the results of vitamin D deficiency intersect at multiple points as inflammation and neurohormonal activation. Vitamin D

deficiency may contribute to the development of AF through multiple mechanisms. Novel targets and treatments are urgently needed for AF patients; therefore, additional research on the effects of vitamin D supplementation in specific patient groups, such as heart failure, and to determine whether or not vitamin D supplementation is an effective treatment option, is warranted.

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