Vitamin D deficiency is unrelated to type of atrial fibrillation and its complications

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ABSTRACT

INTRODUCTION: Vitamin D plays an important role in a broad range of organ functions, including the cardiovascular system. Only one study has tested the association between vitamin D deficiency and arrhythmia and it found no association. The aim of the present study was to evaluate the association between vitamin D deficiency and the type of atrial fibrillation (AF) and complications to AF.

MATERIAL AND METHODS: In total, 258 patients were consecutively included from March 2009 to February 2011. All in- and out-patients in the Department of Cardiology at Hvidovre Hospital were invited to participate, provided they had electrocardiographically documented AF. Patients with dementia or terminal illness were excluded. 25 hydroxyvitamin D (25 OHD) was measured with a chemiluminescence assay (Liaison from DiaSorin, Stillwater, Minnesota, USA).

RESULTS: No association between vitamin D level and type of AF was found. Furthermore, no association between vitamin D deficiency and ischaemic heart disease, stroke or acute myocardial infarction was found. Vitamin D deficiency was significantly associated with low age (p = 0.02) and gender with a higher proportion of females having the optimal level of 25 OHD (p = 0.0005).

CONCLUSION: Other studies have found a beneficial effect of vitamin D on cardiovascular diseases, but we found no association between vitamin D deficiency and the type of AF or complications to AF. Further investigation is necessary to determine whether vitamin D supplementation improves cardiovascular outcomes in patients with AF.

FUNDING: The study has received financial support from several private and one public fund.

TRIAL REGISTRATION: The study was approved by the National Ethics Committee (Project-ID: H-C-2009-014).

Atrial fibrillation (AF) is the most common cardiac arrhythmia in clinical practice [1] affecting 1-2% of the population with increasing prevalence in the elderly [2, 3]. In many cases, AF is caused by underlying heart disease: It has been estimated that 33% and 24% of a population of patients with AF suffer from ischaemic heart disease or heart failure, respectively [4]. Although sometimes asymptomatic, AF most often causes symptoms ranging from palpitations to fainting, chest pain or symptoms of congestive heart failure, and patients with AF suffer an increased risk of cardiovascular complications and impaired quality of life [4-6].

Vitamin D plays an important role in maintaining the body's serum calcium level and bone mineralization [7] and it is involved in muscle cell contractility [8]. Regarding the cardiovascular system, investigators have found an association between vitamin D deficiency and chronic heart failure [8]; vitamin D reduces the expression of several genes which are upregulated in myocardial hypertrophy, e.g. by suppressing the cardiac renin-angiotensin system and natriuretic peptides [5]. Vitamin D has been shown to exert antihypertrophic effects on cardiomyocytes by increasing thrombomodulin and decreasing tissue factor [5, 9]. Furthermore, vitamin D exerts various effects on the growth and differentiation of cardiomyocytes, which are largely suggested to improve myocardial structure and function [5]. Parathyroid hormone (PTH) is pro-atherosclerotic [7], and high PTH levels activate the renin-angiotensin system, causing increased blood pressure and cardiac hypertrophy [8]. It is debated whether the beneficial effects of vitamin D on the cardiovascular system are direct or related to the physiological vitamin D-related lowering of PTH levels.

Unfortunately, vitamin D deficiency is common in the northern hemisphere, especially due to the lack of sunshine during the winter season [9]. In Denmark, it is estimated that 30-70% of Danes have vitamin D deficiency, defined as a plasma 25 hydroxyvitamin D (25 OHD) level below 50 nmol/l during some parts of the year [10].

Considering that AF is often to some extent caused by ischaemic heart disease or heart failure and considering the relationship between these cardiac disorders and vitamin D deficiency, it may be hypothesized that vitamin D deficiency is also associated with AF or with the development of complications to AF. The only study that has yet considered the role of vitamin D in AF was a follow-up study which found no association between 25 OHD and AF [11].

The aim of the present study was to evaluate any association between vitamin D deficiency and the type of AF and complications to AF. An association might imply that improving vitamin D status should be a supplementary approach in the prevention and treatment of AF and its complications.

ORIGINAL ARTICLE

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Vitamin D deficiency is implicated in cardiovascular disease, but little is known regarding the relationship between vitamin D and complications to atrial fibrillation.

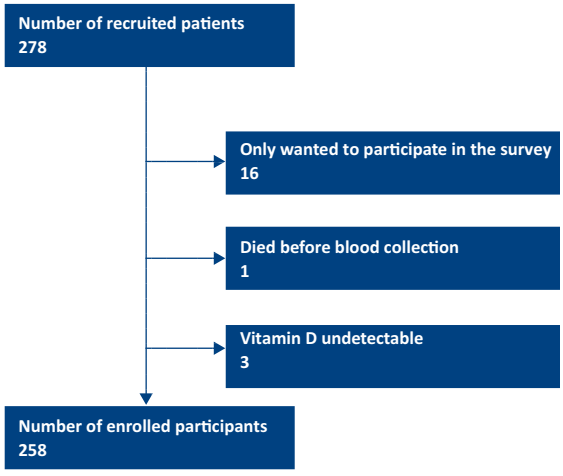
MATERIAL AND METHODS

Study population

The study was a substudy of the Atrial Fibrillation Survey – Copenhagen (ATLAS-CPH) study. As from March 2009, all in- and out-patients at the Department of Cardiology, Hvidovre Hospital, were invited to participate in a prospective atrial fibrillation study if they had electrocardiographically documented paroxysmal, persistent or permanent AF. Patients with dementia or terminal illness were excluded. Patients were asked to complete two questionnaires regarding their own and their family's medical history and their quality of life. Blood tests were taken for analysis as described below. Data regarding concomitant diseases were collected from the questionnaires and verified by checking the patient's file. As of February 1 2011, a total of 676 patients were eligible for enrolment. Of these, 278 were initially recruited, but 16 only agreed to participate in the survey, one died before blood collection, and for unknown reasons, plasma 25 OHD levels were never measured in three patients, leaving 258 patients in the study (**Figure 1**).

FIGURE 1

An overview of the recruited participants, dropout rates and number of included participants.



Ethics

Participation in the study was voluntary and required patients' written consent. The study was in compliance with the Helsinki Declaration and was approved by the National Ethics Committee (Project-ID: H-C-2009-014).

Biochemical analysis

Blood samples were acquired and analysed in the Department of Clinical Biochemistry according to the Department's clinical standards.

Vitamin D analysis was performed on non-anticoagulated plasma samples. We chose to analyse the stable vitamin D precursor 25 OHD rather than the biologically active 1,25 $(OH)_2D$ as this has a half-life of less than one day [12].

25 OHD measurements were performed with a chemilumiscence assay (Liaison from DiaSorin, Stillwater, Minnesota, USA).

In addition, blood was analysed for other biomarkers related to calcium and vitamin D metabolism and kidney function, namely PTH, thyroid stimulating hormone (TSH), alkaline phosphatase and creatinine.

Statistical analysis

Continuous variables were compared using the Kruskal-Wallis test. Categorical data were compared using the χ^2-test and furthermore with Fisher's exact T-test in those cases in which the estimated χ^2-test values were below five.

Univariate and multivariate regression analyses were performed to determine the association between vitamin D level and independent predictors for heart disease such as hypertension, hypercholesterolemia, diabetes mellitus, ischaemic heart disease (IHD), stroke and AF type. All data regarding risk factors were collected from the initial written inquiry.

Patients were stratified according to 25 OHD levels using the classification given by the Institute for Rational Pharmacotherapy [10]: very low (n = 37) < 26 nmol/l, insufficient (n = 73) 26 nmol/l to 50 nmol/l, sufficient (n = 79) 51 nmol/l to 74 nmol/l and optimal (n = 69) ≥ 75 nmol/l.

A p-value < 0.05 was considered statistically significant.

All statistics were calculated using the SAS program, version 9.1.3. (SAS Institute Inc. Cary, NC, USA).

RESULTS

Baseline demographic data are shown in **Table 1**. The average age was 65.1 ± 12.6 years and 66.5% were male.

Vitamin D deficiency, defined as very low or insufficient 25 OHD, was found in 110 patients.

No association between vitamin D level and type of AF could be found in this study (p = 0.53) (**Table 2**).

Further, there was no association between vitamin D deficiency and IHD, stroke or acute myocardial infarction in patients with AF. The lack of association persisted after adjusting for age, sex, smoking status, vitamin D supplementation and season.

Vitamin D deficiency was significantly associated with low age (p = 0.02) (Table 2). Also, a significant association between the vitamin D level and gender was found with a higher proportion of females having an optimal level of 25 OHD (p = 0.0005) (Table 2).

A total of 30 participants (11.6% of the study population) took vitamin D supplements and had a significantly higher vitamin D level than those who did not take any supplement (p = 0.03). Removing these from the calculations raised the proportion of participants with low vitamin D levels from 42% to 44%.

The vitamin D level was significantly lower in the winter-spring and higher in the summer-autumn period (p = 0.0001) (**Figure 2**). The median 25 OHD in winter and spring was 33.5 nmol/l and 52 nmol/l, respectively, while the values in summer and autumn were 66 nmol/l and 63 nmol/l, respectively.

The average 25 OHD levels in patients with AF were similar to those of the general Danish population (p = 0.53).

TABLE 1

Baseline demographic data of all 258 included participants.

Vitamin D, median (IQR), nmol/l	55 (35.5-76)
Age, median (IQR), years	65.11 (57-74.5)
Gender, n (%)	
Male	171 (66.3)
Female	87 (33.7)
Diabetes, n (%)	43 (16.67)
AF type, n (%)	
Paroxysmal	61 (23.6)
Persistent	117 (45.3)
Permanent	39 (15.1)
Unknown	41 (15.9)
Vitamin D supplementation, n (%)	30 (11.6)
Hypertension, n (%)	130 (50.4)
Hypercholesterolaemia, n (%)	34 (13.18)
Pulmonary embolism, n (%)	2 (0.78)
Stroke, n (%)	20 (7.75)
Acute myocardial infarction, n (%)	23 (8.91)
Ischaemic heart disease, n (%)	42 (16.28)
Smoking, n (%)	
Current smoker	43 (16.7)
Ex-smoker	69 (26.7)
Non-smoker	124 (48.1)
Unknown	22 (8.5)
Alcohol consumption ≥ 1 U/week, n (%)	168 (65.12)
Season for blood collection	
Winter	
n (%)	42 (16.3)
Vitamin D, mean, nmol/l	41.3
Spring	
n (%)	70 (27.1)
Vitamin D, mean, nmol/l	52.5
Summer	
n (%)	58 (22.5)
Vitamin D, mean, nmol/l	64.2
Autumn	
n (%)	88 (34.1)
Vitamin D, mean, nmol/l	61.8
Alcaline phosphatase, median (IQR), U/l	74 (61-86.5)
PTH, median (IQR), pmol/l	4.9 (3.4-7.15)

AF = atrial fibrillation; IQR = interquartile range; PTH = parathyroid hormone.

DISCUSSION

Our results confirm earlier findings that women have higher vitamin D levels than men [13]. This may be explained by the fact that women are more aware of their health and are frequently in contact with health care professionals and are more often given vitamin D supplement than men [13]. A similar explanation probably lies behind the association between age and 25 OHD: Older people fall ill and are hospitalized more frequently than younger people [14] and are therefore likely to be started in vitamin D supplementation during their stay in hospital.

Vitamin D level has previously been shown to exhibit a seasonal variation [10], which corresponds to our findings (Figure 2).

Regarding heart failure, patients with heart failure have a far higher frequency of vitamin D insufficiency than control subjects [7]. Such relationship was not found in our study: The proportion of patients with vitamin D deficiency did not differ from that of the general population as studies have shown that 30-70% of Danes have a plasma 25 OHD level below 50 nmol/l at some point during the year [10]. Therefore, nothing in this study suggests that there should be a correlation between a low vitamin D level and AF, which is in accordance with a previous record [11]. The only previous study considering the role of vitamin D in AF was a follow-up study including 2,930 participants of the Framingham Heart Study. During a mean follow-up of 9.9 years, 425 participants developed AF. Using Cox proportional hazards models, 25 OHD was not found to be associated with development of AF [11].

A previous study found an association between a low 25 OHD and an increased risk of myocardial infarction in men [15]. Furthermore, studies have found 1,25 $(OH)_2D$ to have an anticoagulant effect in vitro [9] and Aihara et al found vitamin D receptor knock-out mice to be in a pro-thrombotic state [16]. This effect of vitamin D on the coagulation system is presumably mediated by stimulation of the serum levels of plasminogen

TABLE 2

Baseline characteristics stratified by vitamin D level according to the classification given by the Institute for Rational Pharmacotherapy. The analyses were made for all four groups.

	Vitamin D level				
	very low: < 26 nmol/l	insufficient: 26-50 nmol/l	sufficient: 51-74 nmol/l	optimal: ≥ 75 nmol/l	p-value
Participants, n	37	73	79	69	
Age, median (IQR), years	66 (54.25-7.75)	62.5 (50-71)	67.5(61.75-73)	69 (61.25-76)	0.02[b]
Men, n (%)	34 (91.9)	45 (62.5)	57 (72.2)	37 (53.6)	0.0005[c]
AF type, n					0.53[c]
Paroxysmal	10	19	20	12	
Persistent	15	38	33	31	
Permanent	7	9	11	12	
Unknown	5	6	15	14	
Vitamin D supplementation, n (%)	1 (2.7)	6 (8.2)	9 (11.4)	14 (20.3)	0.03[c]
Diabetes, n (%)	6 (16.2)	12 (16.7)	14 (17.7)	9 (13.0)	0.89[c]
Hypertension, n (%)	18 (48.6)	34 (47.2)	39 (49.4)	36 (52.2)	0.93[c]
Hypercholesterolaemia, n (%)	5 (13.5)	9 (12.5)	16 (20.3)	4 (5.8)	0.079[c]
Chronic obstructive lung disease, n (%)	5 (13.5)	2 (2.8)	4 (5.1)	7 (10.1)	0.11[d]
Pulmonary embolism, n (%)	1 (2.8)	0 (0)	1 (1.3)	0 (0)	0.42[d]
Stroke, n (%)	3 (8.3)	5 (6.8)	3 (3.8)	9 (13.0)	0.22[d]
Acute myocardial infarction, n (%)	3 (8.3)	6 (8.2)	9 (11.4)	5 (7.2)	0.81[d]
Ischaemic heart disease, n (%)	6 (16.7)	11 (15.1)	19 (24.1)	6 (8.7)	0.09[c]
Smoking[a], n (%)	18 (52.9)	32 (44.4)	37 (46.8)	25 (36.2)	0.25[c]
Alcohol consumption ≥ 1 U/week, n (%)	23 (62.2)	46 (63.9)	55 (69.6)	44 (63.8)	0.76[c]
Alcaline phosphatase, median (IQR), U/l	84.5 (66.25-99)	76 (63.75-90)	70 (58.75-82)	73 (59.25-82)	0.06[b]
PTH, median (IQR), pmol/l	6.1 (4.9-9.4)	5.1 (3.7-6.8)	4.75 (3.5-6.9)	3.95 (2.8-6)	0.0003[b]

IQR = interquartile range; PTH = parathyroid hormone.
a) This group included participants who are current smokers. Ex-smokers are excluded as a possible effect of smoking on vitamin D after end smoking is not considered of major importance; b) Kruskal-Wallis test; c) χ^2-test; d) Fisher's exact T-test.

activator inhibitor 1 and tissue plasminogen activator antigen [17]. The net effect is an apparently protective effect of vitamin D against thromboembolic diseases. The clinical relevance of this association was demonstrated in a study concerning Swedish women in which a seasonal variation was established in the incidence of venous thrombotic events, corresponding to the seasonal variation in 25 OHD levels [5]. Our study did not concern the seasonal variation in thromboembolic events, but considering our finding of seasonal variation in 25 OHD, such variation might be expected in our study population.

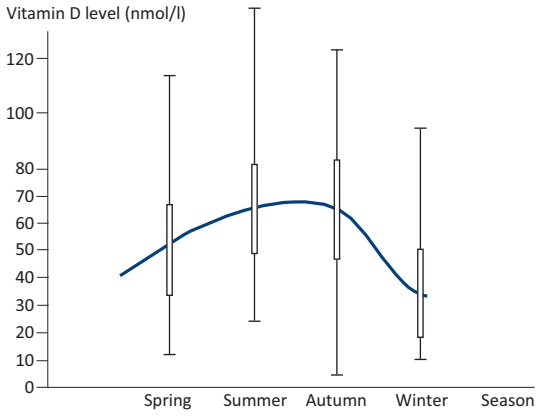
The complexity of the relationship between vitamin D and thromboembolic disease was demonstrated by a study of the kinetics of serum 25 OHD levels after vitamin D supplementation: When measuring lag time, results indicated a pro-thrombotic state in subjects with high serum 25 OHD levels [18]. These contradicting findings may be due to selection of overweight or obese subjects, the use of only one intervention dose of vitamin D, inclusion of subjects who were not vitamin D deficient, and the selected and admittedly crude measures of the haemostatic system in their study [18].

In our study population, there was no relationship between 25 OHD levels and IHD or thromboembolic disease. Apart from the low prevalence of these diseases, one probable explanation for the lacking association is that we measured 25 OHD only at a single point in time, not necessarily reflecting the 25 OHD level at the time of a thromboembolic event. Further, we cannot exclude that the study has been underpowered, failing to detect real, albeit small differences in vitamin D levels despite a relevant sample size of 258 patients.

Taken together, vitamin D deficiency has been al-

FIGURE 2

The distribution of vitamin D according to the season. There is a significant association between vitamin D level and season (p = 0.0001), lowest in winter-spring and highest in summer-autumn.



most consistently demonstrated to be associated with cardiovascular and thromboembolic disease despite lack of complete understanding of the pathophysiological mechanisms. We, however, found no association between vitamin D deficiency and type of AF or complications to AF. Considering the seasonal variations in 25 OHD levels and that the effects of vitamin D deficiency on the cardiovascular system may not be immediate, it would be relevant to perform a follow-up study of vitamin D deficiency and thromboembolic disease in patients with AF to help decide whether vitamin D supplementation should be considered part of the treatment strategy in patients with AF.

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