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Vitamin D Status is Not Related to Development of Atrial Fibrillation in the Community

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Abstract

Background—Atrial fibrillation (AF) is common and is an important cause of cardiovascular morbidity and mortality. Vitamin D is an emerging risk factor in cardiovascular disease, and vitamin D status is modifiable. Thus, we sought to investigate whether vitamin D status predisposed to the development of AF in a community-based sample.

Methods—We evaluated the relation between vitamin D status and development of AF in 2,930 participants of the Framingham Heart Study, Massachusetts, United States, without prevalent AF. The mean age was 65±11 years and 56% were women. Vitamin D status was assessed by measuring 25-hydroxyvitamin D (25[OH]D) concentrations. Multivariable Cox regression models were adjusted for AF risk factors and season.

Results—During a mean follow up of 9.9 years, 425 participants (15%) developed AF. In Cox proportional hazards models, 25(OH)D was not associated with development of AF, with a multivariable-adjusted hazard ratio of 0.99 per SD increment in 25(OH)D levels (95% confidence

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Disclosures

None.

interval [CI], 0.88 to 1.10; $p=0.81$). Also, no relation was found in models including 25(OH)D as a dichotomous variable (above and below the cohort-specific 20th percentile; $p=0.59$).

Conclusion—In our community-based sample, vitamin D status was not related to incident AF. Our data suggest that vitamin D deficiency does not promote the development of AF in the ambulatory setting.

Keywords

Atrial fibrillation; vitamin D; risk factors; biomarker

Introduction

The most common cardiac arrhythmia is atrial fibrillation (AF) and it is an important cause of cardiovascular morbidity and mortality.¹ Although many risk factors for AF have been described, its development remains highly variable and unpredictable. A recently published risk score for the development of AF based on the conventional risk factors accounts for only a part of the AF risk (C-statistic 0.76).² Thus, there is still a substantial proportion of AF risk unexplained.

Vitamin D is an emerging risk factor in cardiovascular disease, with increased risk at low and high concentrations of vitamin D.^{3–6} Vitamin D receptors have been found in cardiomyocytes,⁷ vascular smooth muscle cells,⁸ and endothelial cells.⁹ 1,25-dihydroxyvitamin D (1,25[OH]D) is a potent negative regulator of the renin-angiotensin system^{10–12} and inflammation.¹³ Experimental studies suggest that vitamin D deficiency may increase plasma renin activity,¹⁴ raise blood pressure, and promote adverse ventricular remodeling.¹⁷ Multiple observational studies have shown an association between vitamin D deficiency and the risks of diabetes mellitus,¹⁸ myocardial infarction, heart failure, and sudden cardiac death.²¹

Given the associations of vitamin D status with multiple AF risk factors and the potential link between vitamin D, the renin-angiotensin system, and inflammation, we hypothesized that vitamin D insufficiency is associated with the development of AF. The existence of a link between vitamin D status and AF risk would have potential clinical relevance, because AF is common and vitamin D status is readily modifiable.

Methods

Study sample

The study sample was derived from the Original and Offspring Cohorts of the Framingham Heart Study. The Original cohort was established in 1948, and included 5,209 residents of Framingham, Massachusetts, USA.²² Between 1988 and 1989, 1,130 participants attended the 20th biennial examination, and had measurement of 25(OH)D levels. Since 25-hydroxyvitamin D (25[OH]D) is the precursor of the biologically active form of vitamin D (1,25[OH]D) and integrates endogenous synthesis with intake from diet and supplements, it is the conventional indicator of overall vitamin D status. We excluded 84 participants who had prevalent AF. The Framingham Offspring cohort was initiated in 1971, and included 5,124 offspring (and their spouses) of the original participants.²³ Between 1996 and 2001, 1,972 participants attended the 6th or 7th quadrennial Offspring examinations, and had measurement of 25(OH)D levels. We excluded 88 participants for prevalent AF ($n=78$) or kidney disease (serum creatinine >2.0 mg/dL or missing; $n=10$). Participants were monitored for the first AF event for a maximum of 20 years from the beginning of each follow-up period. The date of last follow-up was August 31, 2009. All participants in both

the Original and Offspring Cohorts were of European ancestry. Study protocols for all examination cycles received ethics approval from the Boston University Medical Center Institutional Review Board, and every participant signed a consent form.

Clinical assessments

A physician-administered medical history, examination, and laboratory assessment was performed at each periodic examination.²⁴ Participants were classified as having heart failure on the basis of major and minor clinical criteria.²⁵ A clinically significant cardiac murmur was diagnosed in the presence of a systolic murmur that exceeded grade 3 of 6 in intensity, or if any diastolic murmur was auscultated by an FHS clinic physician. Participants were classified as having hypertension if the systolic blood pressure was 140 mmHg or greater, or diastolic blood pressure was 90 mmHg or greater, or if participants were receiving antihypertensive treatment. Prevalent heart failure and myocardial infarction were determined by a panel of 3 physicians using previously published criteria.²⁵ A Framingham Heart Study cardiologist reviewed all electrocardiograms (ECGs). Participants were classified by a Framingham cardiologist as having AF if either atrial flutter or fibrillation was present on an ECG. ECGs were obtained at Framingham Heart Study clinic visits, external physician visits, Holter monitoring, or hospital records.

Laboratory assays

Serum samples were obtained after an overnight fast, and frozen at -70°C . At Cohort examination 20, serum 25(OH)D was determined by a competitive protein-binding assay, as previously described. Intra- and interassay coefficients of variation were 7% and 10%, respectively. At Offspring examinations 6 and 7, serum 25(OH)D was determined by radioimmunoassay (DiaSorin, Stillwater, MN), as previously described.³ Intra- and interassay coefficients of variation were 8.5% and 13.2%, respectively, and the lowest limit of detection was 1.5 ng/mL.

Statistical Analyses

The 25(OH)D measures were standardized within each cohort, to mean = 0 and standard deviation (SD) = 1, given the use of different assays in the two cohorts.²⁸ In our primary analysis, we used 25(OH)D as a continuous variable. In secondary analyses, we performed separate analyses for each cohort. In addition, we used a dichotomous variable, based on the 20th percentile of the unstandardized 25(OH)D value of each cohort, identified *a priori*. Also, we analyzed quintiles of the unstandardized 25(OH)D for the total sample and per cohort.

We used multivariable Cox regression models to relate baseline 25(OH)D with incident AF. All analyses were stratified by cohort. We used different models to assess the relation between 25(OH)D and incident AF, since some of the variables (hypertension, heart failure and myocardial infarction) are in the same causal pathway as 25(OH)D. Therefore, in the first model, we adjusted for age and sex; the main model, for characteristics related to AF (age, sex, body mass index, PR-interval, and significant cardiac murmur) but not in the hypothesized causal pathway; and in the final model, for variables in the main model plus hypertension, myocardial infarction, heart failure and winter season (known to influence 25(OH)D levels). All analyses were performed using SAS software, version 9.1.3 (SAS Institute, Cary, NC), and a two-tailed p-value of <0.05 was considered statistically significant.

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

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Results

Characteristics

In total 2,930 participants without prevalent AF, 1,046 from the Original Cohort and 1,884 from the Offspring Cohort, were included in the analysis. The characteristics of the study sample are shown in Table 1. In the Original Cohort, the mean age of participants was 76 ± 6 years and 63% were women. In the Offspring Cohort, the mean age of participants was 60 ± 9 years and 53% were women.

Multivariable analyses

During a mean follow up of 9.9 ± 4.0 years, 425 participants (15%) developed AF. The results of the multivariable Cox regression analyses are shown in Table 2. 25(OH)D levels were not associated with development of AF, when adjusted for age and sex alone ($p=0.49$), conventional risk factors not in the hypothesized causal pathway (main model, $p=0.82$), or conventional AF risk factors and winter season ($p=0.81$). The results did not materially change when we added hypertension, history of MI, history of HF individually or simultaneously.

Secondary analyses

We performed analyses in which 25(OH)D was dichotomized at the cohort specific 20th percentile. The 20th percentile value was 17 ng/mL for the Original Cohort, and 13.4 ng/mL for the Offspring Cohort. 25(OH)D concentrations were not associated with development of AF, in either unadjusted or multivariable-adjusted models. In analyses performed in each cohort separately (Original and Offspring), no significant association of 25(OH)D with AF was observed in either cohort (data not shown). In multivariable regression analyses performed with 25(OH)D categorized by quintiles, there remained no significant association of 25(OH)D with AF (data not shown).

Statistical power

We performed post hoc power analyses to determine whether we had adequate statistical power to detect an association between serum 25(OH)D levels and development of AF in this sample. We calculated that we had 80% power to detect an adjusted hazards ratio of 1.15 per SD increment in 25(OH)D levels, and 90% power to detect an adjusted hazards ratio of 1.17 per SD increment in 25(OH)D levels.

Discussion

In summary, we found no association between vitamin D status and the development of AF in a large, community-based cohort. The validity of our results is supported by the large sample size, the routine ascertainment of both vitamin D status and AF events, the consistency of our findings in the diverse multivariable models, and the analyses adequately-powered to detect a moderate effect size. To our knowledge, this is the first study to examine the relation of vitamin D deficiency with the development of AF.

The potential link between vitamin D status and cardiovascular diseases has attracted great interest. Vitamin D receptors are present in multiple cardiovascular tissues, including cardiomyocytes,⁷ vascular smooth muscle,⁸ and endothelium.⁹ The activated form of vitamin D, 1,25-dihydroxyvitamin D, inhibits renin-angiotensin activation,^{10–12} suppresses cardiac myocyte hypertrophy, and reduces inflammation.¹³ All these factors may contribute

to the increased cardiovascular risk observed in association with vitamin D deficiency. Further, vitamin D deficiency has been related to hypertension, myocardial infarction, heart failure, diabetes mellitus¹⁸ and adiposity,³¹ all conventional risk factors for AF.

Our findings suggest that vitamin D status is not an important contributor to AF in the general population. The recent Institute of Medicine (IOM) report concluded that 25(OH)D concentrations of 16 ng/ml (40 nmol/L) meets the requirements of at least 50% of the adult population, and concentrations of at least 20 ng/ml (50 nmol/L) meet the requirements for at least 97.5%.⁶ These cutoff values are mainly based on the radioimmunoassay, as we used in the Offspring Cohort. Because the majority of the Offspring participants met the estimated average requirement (i.e. 16 ng/mL), it is plausible that we did not have sufficient numbers of vitamin D-deficient participants to find a relation between vitamin D status and AF. We cannot exclude the possibility that poor vitamin D status could raise AF risk in more acute settings, such as after myocardial infarction or in the setting of heart failure. Further, measurement of serum 25(OH)D levels at a single time point might have led us to underestimate the association between vitamin D status and development of AF, although 25(OH)D has a very long half-life and is an extensively-validated surrogate for vitamin D stores. Lastly, our analyses were limited to individuals of European ancestry, and the results may not be generalizable to other racial/ethnic groups.

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Table 1

Sample characteristics (n=2,930)

	Original cohort (n=1,046)	Offspring cohort (n=1,884)
Age, years	76±6	60±9
Women	658 (63%)	997 (53%)
Winter season	361 (35%)	799 (42%)
Smoking	134 (13%)	262 (14%)
Body mass index, kg/m ²	26.7±4.6	28.1±5.2
Systolic blood pressure, mmHg	146±22	128±19
Hypertension	808 (77%)	796 (42%)
Antihypertensive therapy	551 (53%)	571 (30%)
History of heart failure	32 (3%)	13 (0.7%)
History of myocardial infarction	105 (10%)	72 (4%)
Cardiac murmur	273 (26%)	253 (13%)
PR-interval, ms	170±32	162±24
25(OH)D, ng/mL *	29.2±12.6	19.6±7.4
Betablockers	183 (18%)	113 (13%)
Angiotensin converting enzyme inhibitors	79 (8%)	252 (13%)
Cholesterol lowering drugs	44 (4%)	322 (17%)

Values are shown as mean ± SD, or n (%).

* Serum 25(OH)D was determined by a competitive protein-binding assay in the Original Cohort, and a radioimmunoassay in the Offspring Cohort. Due the use of different assays, serum concentrations cannot be directly compared between cohorts; standardized values were used in the regression analyses.

Table 2

Risk of incident atrial fibrillation: results of Cox regression analyses with 25(OH)D as standardized continuous variable and dichotomized at the cohort specific 20th percentile

	Hazards ratio* (95% confidence interval)	p value
25(OH)D as standardized continuous variable		
Age- and sex-adjusted	0.97 (0.88 – 1.07)	0.49
Main model [†]	0.99 (0.89 – 1.10)	0.82
Main model + hypertension, history of MI, history of HF, and winter season	0.99 (0.88 – 1.10)	0.81
25(OH)D < the cohort specific 20th percentile		
Age- and sex-adjusted	1.08 (0.84 – 1.39)	0.54
Main model [†]	1.06 (0.82 – 1.38)	0.65
Main model + hypertension, history of MI, history of HF, and winter season	1.08 (0.82 – 1.41)	0.59

MI, myocardial infarction; HF, heart failure.

* Hazards ratios for incident AF are shown per cohort-specific 1 SD increment in 25(OH)D levels or for presence of a 25(OH)D concentration < the cohort specific 20th percentile.

[†] The main model covariates included: age, sex, body mass index, PR-interval, and cardiac murmur.