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Parathormone, vitamin D and the risk of atrial fibrillation in older adults: A prospective study

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Abstract *Background & aims:* Vitamin D and parathormone (PTH) have been associated with cardiovascular outcomes, but their impact on atrial fibrillation (AF) onset is still unclear. We explored the influence of serum 25-hydroxyvitamin D (25[OH]D) and PTH on AF risk in older adults.
Methods and results: Data come from 2418 participants enrolled in the Progetto Veneto Anziani study. Serum 25(OH)D and intact PTH were measured using radioimmunoassay and two-site immunoassay, respectively. The associations between 25(OH)D, PTH and adjudicated AF cases over 4-years were explored by Cox regression.

Over the follow-up, 134 incident cases of AF were assessed. The incidence rate of the sample was 13.5 (95%CI 11.4–15.9) per 1000 person-years, and was higher among those with high PTH levels (high: 16.4 [95%CI 11.3–24.0] per 1000 person-years), especially when associated to low 25(OH)D (20.3 [95%CI 12.9–32.3] per 1000 person-years). At Cox regression, only high PTH was significantly associated to an increased risk of AF (HR = 1.90, 95%CI 1.27–2.84). A marginal significant interaction (p = 0.06) was found between 25[OH]D and PTH concentrations in influencing AF risk. When exploring the risk of AF for combined categories of 25(OH)D and PTH, we found that those with high PTH and low 25(OH)D levels had an AF risk twice as high as that of people with normal values (HR = 2.09, 95%CI 1.28–3.42).
Conclusion: The risk of AF may be increased by high PTH levels, especially when associated with 25(OH)D deficiency. The identification and treatment of high PTH or vitamin D deficiency may thus contribute to lower the risk of AF.

Introduction

Atrial fibrillation (AF) is the most common chronic arrhythmia in older people and is an important cause of cardiovascular morbidity and mortality [1]. Although many risk factors for AF, such as older age, male sex, hypertension, valvular and ischemic heart disease have been

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studied, its etiology and underlying pathways are still not completely understood and its development remains highly variable and unpredictable [2].

An emerging factor that may influence the onset of cardiovascular diseases is vitamin D [3]. Underlying pathways that could be involved in link between vitamin D and cardiovascular diseases include its effects on inflammation, endothelial cell function, thrombosis and cardiomyocytes' functions [2]. Vitamin D may also negatively influence the renin angiotensin aldosterone system (RAAS). In fact, an inverse association between circulating 25-hydroxivitamin D (25[OH]D) with renin activity and angiotensin II concentrations emerged in previous studies [4], although such effect was not found after vitamin D supplementation in patients with heart failure [5]. All these reported mechanisms may be involved in the pathophysiology of AF. However, the causal relationship between circulating 25[OH]D levels and the risk of AF has still to be fully elucidated, and to date observational and intervention studies on vitamin D supplementation have reported controversial or inconsistent results [5–10]. Moreover, low levels of 25[OH]D seem to be associated with a higher risk of AF among younger but not older individuals [6], and might play a more relevant role in patients with chronic heart failure [11].

Acting via mechanisms similar to vitamin D, parathormone (PTH) may also influence AF development, although its cardiac effects have not yet been fully clarified [12,13]. Indeed, high PTH levels are associated with a pro-inflammatory status and may act on myocardial and endothelial functions that progressively lead to cardiomyocytes hypertrophy, fibrosis of the left ventricle and other vascular smooth muscle dysfunctions [12,14]. On the other hand, low PTH concentrations have also been associated with poor cardiovascular outcomes in end-stage heart failure patients [15], and, in isolated rat hearts, PTH demonstrated an inotropic action by influencing coronary flow and heart rate [13]. Nonetheless, only two prospective studies have so far examined the possible association of PTH with the incidence of cardiovascular diseases, finding contrasting results [16,17]. Furthermore, we are no aware of studies analyzing the possible interaction between vitamin D and PTH, simultaneously, in influencing the risk of AF.

To evaluate the association of vitamin D and PTH with AF onset could have relevant clinical implications especially in older people, due to the high prevalence of AF, vitamin D deficiency and hyperparathyroidism, and the fact that vitamin D and PTH unbalances are modifiable factors. We hypothesized that both vitamin D and PTH may be associated with the onset of AF in the elderly. The aim of our study was therefore to explore the association between 25(OH)D and PTH concentrations with incident AF in community-dwelling older adults during 4 years of follow-up.

Methods

Study population

Our study analyzed data from the *Progetto Veneto Anziani* (Pro.V.A.), an observational cohort study that involved adults ≥65 years living in northern Italy, who were randomly selected between 1995 and 1997 using a multistage stratified method [18]. A total of 3099 participants (1245M, 1854F) underwent a baseline assessment and were followed-up after a mean of four years.

For this study, from the initial 3099 individuals, 374 were excluded because data on serum PTH or 25(OH)D concentrations were not available, 167 because atrial fibrillation was reported at the baseline examination, and 140 were lost at follow-up. The final sample therefore involved 2418 participants (for the comparison between subjects included and excluded from the study see Supplementary data – Appendix S1).

Ethics committees from the University of Padua and Local Health Units no.15 and 18 of the Veneto Region approved the study protocol, and all participants gave their written informed consent. The results of the present study were reported in accordance with the STROBE recommendations.

Participants' data assessment

Trained physicians and nurses evaluated participants at the baseline and follow-up assessments at clinics or at home, when unable to attend a clinic. Data were collected through face-to-face interviews, medical records, standardized questionnaires, and physical examinations. In this study, in particular, we analyzed data on: age, sex, education level, monthly income, smoking habits, drinking habits, body mass index (BMI), waist circumference, and physical performance through the Short Physical Performance Battery (SPPB). Participants' clinical data were collected on the basis of standardized questionnaires, self-reported symptoms, medical and hospital records, blood tests, physical examination, and drugs taken. In this study, we considered the presence at baseline of diabetes, hypertension, chronic obstructive pulmonary disease, osteoporosis, primary hyperparathyroidism, and cardiovascular diseases (CVD). CVD was defined as the presence of at least one among: congestive heart failure, angina requiring a stent, angioplasty or hospitalization, myocardial infarction and stroke (for details see Supplementary data – Appendix S2). The main outcome of our study, AF, was assessed on the basis of participant's medical history; medical and hospital records, using the codes 427.31 in the International Classification of Diseases, Ninth Version for its identification; and from the combination of the use of anti-coagulant drugs with arrhythmic heart rate measured at radial and central pulse by physicians at the physical examination, or with the use of antiarrhythmic drugs.

Biochemical analyses

Venous blood samples were collected at baseline from participants after an overnight fast, centrifuged and stored at −80 °C. For the purpose of our study, we considered data on serum levels of PTH, 25(OH)D, calcium, creatinine and fibrinogen, and the erythrocyte sedimentation rate

(ESR). Routine biochemical analyses were performed at the local hospital, whereas PTH and 25(OH)D tests were performed at the university laboratory of Padova following standard quality-control procedures. Serum 25(OH)D was measured by radioimmunoassay (RIA kit; DiaSorin), with intra-assay and inter-assay coefficients of variation of 8.1% and 10.2%, respectively. Serum intact PTH level was measured using a two-site immunoradiometric assay kit (N-tact PTHSP; DiaSorin), with intra-assay and inter-assay coefficients of variation of 3.0% and 5.5%, respectively. In accordance with the current literature [19] and on the basis of the limits for normal range in our laboratory, we defined vitamin D deficiency as serum 25(OH) D $<$ 75 nmol/l, and high PTH as serum PTH $>$55 ng/l. Serum creatinine was measured by a standard creatinine Jaffe method (Roche Diagnostics, Germany) and used to estimate the glomerular filtration rate (GFR, ml/min) through the Modification of Diet in Renal Disease Study formula. The ESR was measured in sodium citrate–anticoagulated blood samples using the Westergren method.

Statistical analysis

Participants' baseline characteristics are expressed as means $\pm$ SD for quantitative measures, and as frequencies (percentages) for categorical variables. A comparison of participants by 25(OH)D and PTH levels was performed using the Student t-test, for continuous variables, and the Chi-squared test, for categorical variables. A single imputation of missing values of BMI (n = 91), waist circumference (n = 71), blood pressure (n = 110), fibrinogen levels (n = 103) and ESR (n = 49) was performed using the expectation maximization algorithm, considering that the rate of missing values was <5% for each of these variables.

The relationship between serum 25(OH)D and PTH levels was evaluated through simple correlation and linear regression analyses. Age- and sex-standardized incidence rates of AF in participants categorized by 25(OH) and PTH levels were computed by using a direct standardization method that considered the total sample as the standard population. The association between 25(OH)D and PTH concentrations with the development of AF at follow-up was evaluated using Cox regression analyses. This analysis allowed us to take the competing risk of death into account. The proportional hazard assumption was verified considering Schoenfeld's residuals of the covariates. For quantitative variables, the assumption of linearity was evaluated considering the analysis of quartiles. Individuals with normal values of 25(OH)D and/or PTH were taken as the reference category, as appropriate. Time to AF onset (retrieved from medical and hospital records) or to the follow-up assessment or to the death was used in the Cox model. The strength of these associations was estimated through hazard ratios (HR) and 95% confidence intervals (95%CI), first adjusted only by age and sex, then also for other potential confounders.

Since we found a marginal significant interaction between serum 25[OH]D and PTH levels ($p_{interaction} = 0.06$), we performed a Cox regression exploring the association between the combined presence of normal/low serum 25(OH)D and normal/high serum PTH levels with the risk of AF. In this model, individuals with normal 25(OH)D and PTH values were taken as the reference category. As a sensitivity analysis, considering the possible mutual relationship between 25(OH)D, PTH and CVD, we tested the above associations in the sample stratified by presence of baseline CVD.

All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05. The analyses were performed using the SPSS 23.0 for Windows (SPSS Inc., Chicago, Illinois). Standardized incidence rates were computed using the *epitools* package in R (R Foundation for Statistical Computing, Vienna, Austria) [20].

Results

Our study included 2418 individuals (1449 women, 969 men) with a mean age of 76.0 $\pm$ 7.8 years and a mean BMI of 27.6 $\pm$ 4.5 kg/m^2. At the first assessment, 1343 (55.5%) participants exhibited vitamin D deficiency, and 496 (20.5%) had high PTH values. Only 22 individuals (0.9%) showed PTH and serum calcium concentrations suggestive of primary hyperparathyroidism. When exploring the relationship between serum 25(OH)D and PTH levels in the sample as a whole, we found a significant association both at simple correlation ($r = -0.29$, $p < 0.001$) and at linear regression analyses ($\beta = -0.15$, SE = 0.01, $p < 0.001$; for the scatter plot please see Supplementary material, Fig. S1).

Table 1 shows the baseline characteristics in the total sample by serum levels of 25(OH)D and PTH. People with lower 25(OH)D concentrations, as those with higher PTH, were more likely to be older, women, to have lower educational level and poorer physical performance, compared with their counterparts. They also had lower calcium levels, worse renal function, higher inflammatory markers and greater prevalence of hypertension. As regards blood pressure, higher systolic values were observed among people with 25(OH)D deficiency, and higher diastolic values were observed among those with high PTH levels, the latter showing also higher prevalence of cardiovascular diseases. No differences between groups emerged on the use of vitamin D and calcium supplements (data not shown).

At follow-up (mean duration 4.2 $\pm$ 1.2 years), 560 participants were deceased. Among those who completed the follow-up (n = 1858), 134 new cases of AF were reported (90 derived from hospital or medical records, and 44 by evaluating heart rate and the use of antiarrhythmic and anticoagulant drugs). The incidence rate of AF in the sample as a whole was 13.5 (95%CI 11.4–15.9) per 1000 person-years. As shown in Fig. 1, no substantial differences in age- and sex-standardized incidence rate of AF were found comparing participants only on the basis of 25(OH) D concentrations (deficiency: 13.9 [95%CI 10.7–18.0];

Table 1 Baseline characteristics of the 2418 participants of the Pro.V.A. study by serum 25-hydroxyvitamin D and parathormone levels.

Baseline Characteristics	All (n = 2418)	25(OH)D (nmol/l)		PTH (ng/l)	
		Deficient (n = 1343)	Normal (n = 1075)	Normal (n = 1922)	High (n = 496)
Age (y)	76.0 ± 7.8	77.9 ± 8.0	73.6 ± 6.8***	75.2 ± 7.4	79.2 ± 8.2***
Women	1449 (59.9)	985 (73.3)	464 (43.2)***	1107 (57.6)	342 (69.0)***
BMI (kg/m^2)	27.6 ± 4.5	27.8 ± 4.8	27.3 ± 4.2*	27.6 ± 4.5	27.4 ± 4.6
Waist (cm)	96.2 ± 11.3	96.4 ± 11.9	96.0 ± 10.4	96.2 ± 11.2	96.2 ± 11.7
Education (<5 y)	1182 (48.9)	724 (53.9)	458 (42.6)***	908 (47.2)	274 (55.2)**
Smoking habits					
Never	1485 (61.4)	955 (71.1)	530 (49.3)***	1141 (59.4)	344 (69.4)***
Former	718 (29.7)	296 (22.0)	422 (39.3)***	595 (31.0)	123 (24.8)**
Current	215 (8.9)	92 (6.9)	123 (11.4)***	186 (9.7)	29 (5.8)**
Alcohol consumption					
No or occasional	1690 (69.9)	1064 (79.2)	626 (58.2)***	1312 (68.3)	378 (76.2)**
Light to moderate	434 (17.9)	196 (14.6)	238 (22.1)***	349 (18.2)	85 (17.1)
Heavy	294 (12.2)	83 (6.2)	211 (19.6)***	261 (13.6)	33 (6.7)***
SPPB total	7.8 ± 3.7	6.8 ± 3.9	9.2 ± 2.9***	8.3 ± 3.5	6.3 ± 4.0***
SBP (mmHg)	153 ± 21	154 ± 21	152 ± 21*	153 ± 21	154 ± 22
DBP (mmHg)	83 ± 11	82 ± 11	83 ± 11	83 ± 11	84 ± 12*
25(OH)D (nmol/l)	78.8 ± 54.0	43.0 ± 18.6	123.5 ± 50.3***	85.1 ± 55.7	54.4 ± 38.4***
PTH (ng/l)	42.1 ± 27.7	48.0 ± 32.2	34.8 ± 18.5***	32.3 ± 12.5	80.3 ± 36.3***
Calcium (mg/dl)	9.4 ± 0.5	9.4 ± 0.5	9.5 ± 0.5**	9.5 ± 0.5	9.4 ± 0.6**
GFR (ml/min/1.73 m^2)	69.3 ± 18.8	66.5 ± 19.2	72.7 ± 17.7***	70.9 ± 18.2	62.9 ± 19.9***
ESR (mm/h)	21.3 ± 18.9	24.7 ± 20.0	17.0 ± 16.5***	20.3 ± 18.5	24.9 ± 20.1***
Fibrinogen (mg/dl)	345.7 ± 81.1	357.4 ± 83.9	331.2 ± 75.1***	342.8 ± 80.8	356.7 ± 81.5**
Hypertension	1770 (73.2)	1007 (75.0)	763 (71.0)*	1378 (71.7)	392 (79.0)**
Diabetes	401 (16.2)	92 (19.1)	286 (15.7)	317 (16.1)	84 (16.4)
Cardiovascular diseases	361 (14.9)	234 (17.4)	127 (11.8)***	252 (13.1)	109 (22.0)***
COPD	229 (9.5)	130 (9.7)	99 (9.2)	178 (9.3)	51 (10.3)
Use of bisphosphonates	41 (1.7)	28 (2.1)	13 (1.2)	33 (1.7)	8 (1.6)
Use of LLD	86 (3.6)	50 (3.7)	36 (3.3)	73 (3.8)	13 (2.6)

Numbers are mean values (and standard deviations) or frequencies (percentages, %), as appropriate. *Abbreviations:* BMI, Body mass index; SPPB, Short Physical Performance Battery; SPB, systolic blood pressure; DBP, diastolic blood pressure; 25(OH)D, 25-hydroxivitamin D; PTH, parathormone; GFR, glomerular filtration rate; ESR, erythrocyte sedimentation rate; COPD, Chronic Obstructive Pulmonary Disease; LLD, lipid lowering drugs. *p < 0.05; **p < 0.01; ***p < 0.001 for the comparison between participants with different 25(OH)D and PTH levels.

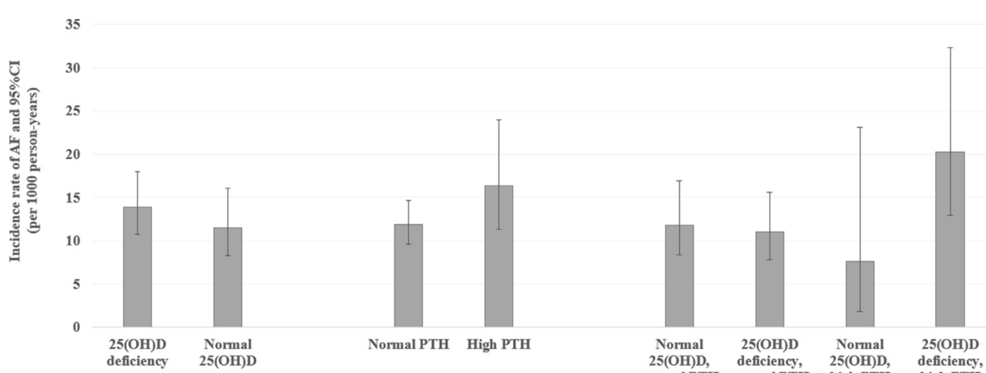

Figure 1 Age- and sex-standardized incidence rate of atrial fibrillation over the 4-year follow-up in participants divided by baseline serum 25-hydroxyvitamin D and parathormone levels. *Notes:* vitamin D deficiency: serum 25-hydroxyvitamin D < 75 nmol/l; normal vitamin D: serum 25-hydroxyvitamin D ≥75 nmol/l; normal PTH: serum parathormone ≤55 ng/l; high PTH: serum parathormone >55 ng/l. Abbreviations: AF, atrial fibrillation; 95%CI, 95% confidence intervals; 25(OH)D, 25-hydroxyvitamin D.

normal: 11.5 [95%CI 8.3–16.1] per 1000 person-years). Instead, AF cases increased among those who had high PTH levels (high: 16.4 [95%CI 11.3–24.0]; normal: 11.9 [95% CI 9.6–14.6] per 1000 person-years), especially when associated to low 25(OH)D (20.3 [95%CI 12.9–32.3] per 1000 person-years).

The association between 25(OH)D, PTH and the development of AF during the 4-year follow-up was explored through Cox regression (Table 2). As reported, after adjusting for potential confounders and taking the normal categories as references, 25(OH)D deficiency was not significantly associated with the onset of AF, while high PTH increased the risk of AF by 90% (95%CI 1.27–2.84). In view of the marginal significant interaction found between serum 25[OH]D and PTH concentrations, we explored the association between combined

Table 2 Cox regression of the associations between 25-hydroxivitamin D and parathormone levels with the risk of atrial fibrillation.

	Hazard ratio of atrial fibrillation and 95% confidence intervals	
	Model 1	Model 2
25(OH)D(nmol/l)		
Normal	[ref]	[ref]
Deficiency	1.16 (0.79–1.69)	1.27 (0.84–1.94)
PTH (ng/l)		
≤55	[ref]	[ref]
>55	1.68 (1.15–2.47)**	1.90 (1.27–2.84)**
Normal 25(OH)D, normal PTH	[ref]	[ref]
25(OH)D deficiency, normal PTH	0.88 (0.57–1.35)	0.96 (0.62–1.50)
Normal 25(OH)D, high PTH	0.68 (0.25–1.89)	0.75 (0.27–2.08)
25(OH)D deficiency, high PTH	1.88 (1.16–3.02)*	2.09 (1.28–3.42)**

Model 1 adjusted for age and sex. Model 2 adjusted also for body mass index, Short Physical Performance Battery total score, glomerular filtration rate, serum calcium levels (all as continuous variables), season, educational level (≥5 vs < 5 years), smoking habits (never vs former vs current), drinking habits (no vs light-to-moderate vs heavy drinkers), hypertension (yes vs no), cardiovascular diseases (yes vs no), use of lipid lowering drugs (yes vs no), serum 25(OH)D levels (only with PTH as exposure variable), PTH levels (only with 25[OH]D as exposure variable). *Abbreviations:* 25(OH)D, 25-hydroxyvitamin D; PTH, parathormone. *$p < 0.05$, **$p < 0.01$.

categories of 25(OH)D and PTH with the risk of AF. We found that the risk of AF of people with combined high PTH and low 25(OH)D levels was twice as high as that of people with normal values (HR = 2.09, 95%CI 1.28–3.42). No significant interactions were found between baseline CVD with PTH, 25(OH)D and their combinations in influencing AF risk ($p > 0.05$ for all), and similar results emerged in the sample stratified by presence of CVD at baseline (Supplementary material, Table S1).

Discussion

Our study suggests that the association between low 25(OH)D and high PTH levels could increase the risk of AF in older adults.

As regards vitamin D, in particular, we observed that 25(OH)D deficiency alone did not significantly increase AF risk, but represented a risk factor for AF only when associated with high PTH levels. Two possible assumptions can be made from these results.

First, individuals with low 25(OH)D and high PTH may had experienced long-lasting vitamin D deficiency such that PTH concentrations increased. This view would support a major role of sustained low vitamin D conditions for the increased risk of AF and strengthens the need of new clinical trials to investigate the effects of an early identification and treatment of vitamin D deficiency on cardiovascular outcomes. In keeping with our findings, previous prospective studies failed to show any substantial association between low 25(OH)D alone and AF [2,6,21], and some RCTs found no significant effects of vitamin D supplementation on CVD risk and outcomes [8–10]. However, the meta-analysis of Zhang et al. found that vitamin D deficiency could moderately influence the development of AF [22]. The heterogeneous mechanisms underlying the influence of vitamin D on the cardiovascular system may involve endothelial and myocardial function, inflammatory status, and the RAAS [23]. Through these effects, low vitamin D could gradually predispose to–or worsen–hypertension and left ventricular hypertrophy (LVH), which are well-known risk factors of AF, particularly in older people [24].

Second, high PTH levels, *per se*, might impact on the risk of developing AF. This hypothesis is partly supported by our results since, even after adjusting for serum 25(OH)D, high PTH were associated with an increased risk of AF. However, people with combined normal 25(OH)D and high PTH levels did not show any significant association with the risk of AF. So far, only Folsom et al. have investigated the relationship between PTH and the onset of AF, and they found no significant results [16]. However, that study included participants younger than those in our cohort and free of any CVD, and these characteristics may justify our different findings. Several mechanisms have been proposed to explain the potential role of PTH on AF onset. One of these concerns the promotion of inflammatory status, which may be induced by the PTH-mediated cytokine release from vascular smooth muscle cells and lymphocytes [25]. Consistently, people in our sample with elevated PTH also showed higher serum inflammatory markers than those with normal PTH levels. The involvement of inflammation in the onset and recurrence of AF has been demonstrated in recent years [26] and seems to influence both electrical and structural remodeling. This effect could be mediated by the PTH-related stimulation of the RAAS [27], and by binding to the cardiomyocytes' receptor that PTH shares with parathyroid hormone-related protein (PTHrP) [12]. Moreover, in vitro studies demonstrated that, through binding to the same receptor, elevated PTH concentrations might have a chronotropic effect on pacemaker cells [13,28] and modulate energy metabolism. Such effects that at first may have a inotropic action, in the long-term could lead to the development of LVH and, finally, of diastolic dysfunction, which is a prevalent condition among patients with AF, especially in advanced age [29]. Finally, the link between high PTH levels and AF may involve valvular and myocardial calcification [12,14], which leads to valve dysfunction and to the development of left atria enlargement and a higher risk of AF [12].

Overall, the stronger association and the interaction between low vitamin D and high PTH in increasing AF risk suggest that such factors could concurrently promote the electrical and structural remodeling that lead to the development of AF, likely exacerbating inflammatory status or hypertrophic processes.

Our work has some limitations. First, the study design with only one follow-up assessment may have led to an underestimation of AF cases, due to the lack of identification of asymptomatic paroxysmal AF, as well as it did not allow us to perform multiple biochemical measurements. The observational nature of our study may further limit the inference from our data, and makes reverse causation a potential bias to be taken into account. However, results were confirmed also in the sensitivity analysis that included only individuals without baseline CVD, and the inverse relationship between 25(OH)D and PTH may suggest that secondary hyperparathyroidism conditions in our sample were more likely due to vitamin D deficiency than to pre-existing diseases. Second, ultrasonography data were not available, and this did not allow us to better explore the association between PTH, vitamin D and AF. Third, we could not evaluate the use of vitamin D or calcium supplements since it was declared by only around 2% of the study participants (without differences between groups by PTH or vitamin D levels) and was more likely to have been under-reported. Instead, the large cohort and the prospective study design are strengths of our work. Moreover, having simultaneously evaluated the impact of 25(OH)D and PTH concentrations, and having adjusted our analyses for a number of potential confounders may support our results.

In conclusion, our study shows that the risk of AF may increase by high PTH levels, especially when associated with low vitamin D concentrations. Since low vitamin D and high PTH are modifiable factors and their cardiovascular effects seem to reverse with the correction of such unbalances, our study suggests the need of RCTs to investigate whether the identification and treatment of high PTH or vitamin D deficiency may contribute towards lowering the risk of AF.

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Conflicts of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.05.064.

References

[1] Kirchhof P, Benussi S, Kotecha D, Ahlsson A, Atar D, Casadei B, et al. 2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS. Europace 2016;18:1609–78. https://doi.org/10.1093/europace/euw295.

[2] Vitezova A, Cartolano NS, Heeringa J, Zillikens MC, Hofman A, Franco OH, et al. Vitamin D and the risk of atrial fibrillation - the Rotterdam study. PLoS One 2015;10:e0125161. https://doi.org/10.1371/journal.pone.0125161.

[3] Zhang R, Li B, Gao X, Tian R, Pan Y, Jiang Y, et al. Serum 25-hydroxyvitamin D and the risk of cardiovascular disease: dose-response meta-analysis of prospective studies. Am J Clin Nutr 2017;105:810–9. https://doi.org/10.3945/ajcn.116.140392.

[4] Forman JP, Williams JS, Fisher NDL. Plasma 25-hydroxyvitamin D and regulation of the renin-angiotensin system in humans. Hypertens (Dallas, Tex 1979) 2010;55:1283–8. https://doi.org/10.1161/HYPERTENSIONAHA.109.148619.

[5] Zittermann A, Ernst JB, Prokop S, Fuchs U, Dreier J, Kuhn J, et al. Effects of vitamin D supplementation on renin and aldosterone concentrations in patients with advanced heart failure: the EVITA trial. Internet J Endocrinol 2018;2018:1–10. https://doi.org/10.1155/2018/5015417.

[6] Alonso A, Misialek JR, Michos ED, Eckfeldt J, Selvin E, Soliman EZ, et al. Serum 25-hydroxyvitamin D and the incidence of atrial fibrillation: the Atherosclerosis Risk in Communities (ARIC) study. Europace 2016;18:1143–9. https://doi.org/10.1093/europace/euv395.

[7] Chen WR, Liu ZY, Shi Y, Yin DW, Wang H, Sha Y, et al. Relation of low vitamin D to nonvalvular persistent atrial fibrillation in Chinese patients. Ann Noninvasive Electrocardiol 2014;19:166–73. https://doi.org/10.1111/anec.12105.

[8] Jenkins DJA, Spence JD, Giovannucci EL, Kim Y, Josse R, Vieth R, et al. Supplemental vitamins and minerals for CVD prevention and treatment. J Am Coll Cardiol 2018;71:2570–84. https://doi.org/10.1016/j.jacc.2018.04.020.

[9] Scragg R, Stewart AW, Waayer D, Lawes CMM, Toop L, Sluyter J, et al. Effect of monthly high-dose vitamin D supplementation on cardiovascular disease in the vitamin D assessment study. JAMA Cardiol 2017;2:608. https://doi.org/10.1001/jamacardio.2017.0175.

[10] Manson JE, Cook NR, Lee I-M, Christen W, Bassuk SS, Mora S, et al. Vitamin D supplements and prevention of cancer and cardiovascular disease. N Engl J Med 2019;380:33–44. https://doi.org/10.1056/NEJMoa1809944.

[11] Belen E, Aykan AC, Kalaycioglu E, Sungur MA, Sungur A, Cetin M. Low-level vitamin D is associated with atrial fibrillation in patients with chronic heart failure. Adv Clin Exp Med n.d. 2016;25:51–7.

[12] Andersson P, Rydberg E, Willenheimer R. Primary hyperparathyroidism and heart disease: a review. Eur Heart J 2004;25:1776–87. https://doi.org/10.1016/j.ehj.2004.07.010.

[13] Ogino K, Burkhoff D, Bilezikian JP. The hemodynamic basis for the cardiac effects of parathyroid hormone (PTH) and PTH-related protein. Endocrinology 1995;136:3024–30. https://doi.org/10.1210/endo.136.7.7789328.

[14] Stefenelli T, Mayr H, Bergler-Klein J, Globits S, Woloszczuk W, Niederle B. Primary hyperparathyroidism: incidence of cardiac abnormalities and partial reversibility after successful parathyroidectomy. Am J Med 1993;95:197–202.

[15] Zittermann A, Fuchs U, Kuhn J, Dreier J, Schulz U, Gummert JF, et al. Parameters of mineral metabolism predict midterm clinical

outcome in end-stage heart failure patients. Scand Cardiovasc J 2011;45:342–8. https://doi.org/10.3109/14017431.2011.611250.
[16] Folsom AR, Alonso A, Misialek JR, Michos ED, Selvin E, Eckfeldt JH, et al. Parathyroid hormone concentration and risk of cardiovascular diseases: the Atherosclerosis Risk in Communities (ARIC) study. Am Heart J 2014;168:296–302. https://doi.org/10.1016/j.ahj.2014.04.017.
[17] Anderson JL, Vanwoerkom RC, Horne BD, Bair TL, May HT, Lappé DL, et al. Parathyroid hormone, vitamin D, renal dysfunction, and cardiovascular disease: dependent or independent risk factors? Am Heart J 2011;162:331–9. https://doi.org/10.1016/-j.ahj.2011.05.005. e2.
[18] Corti M-C, Guralnik JM, Sartori L, Baggio G, Manzato E, Pezzotti P, et al. The effect of cardiovascular and osteoarticular diseases on disability in older Italian men and women: rationale, design, and sample characteristics of the Progetto Veneto Anziani (PRO.V.A.) study. J Am Geriatr Soc 2002;50:1535–40.
[19] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, et al. Guidelines for preventing and treating vitamin D deficiency and insufficiency revisited. J Clin Endocrinol Metab 2012;97:1153–8. https://doi.org/10.1210/jc.2011-2601.
[20] R Development Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2008, ISBN 3-900051-07-0. http://www.R-project.org.
[21] Rienstra M, Cheng S, Larson MG, McCabe EL, Booth SL, Jacques PF, et al. Vitamin D status is not related to development of atrial fibrillation in the community. Am Heart J 2011;162:538–41. https://doi.org/10.1016/j.ahj.2011.06.013.
[22] Zhang Z, Yang Y, Ng CY, Wang D, Wang J, Li G, et al. Meta-analysis of vitamin D deficiency and risk of atrial fibrillation. Clin Cardiol 2016;39:537–43. https://doi.org/10.1002/clc.22563.
[23] Lee JH, O'Keefe JH, Bell D, Hensrud DD, Holick MF. Vitamin D deficiency. J Am Coll Cardiol 2008;52:1949–56. https://doi.org/10.1016/j.jacc.2008.08.050.
[24] Proietti M, Marra AM, Tassone EJ, De Vuono S, Corrao S, Gobbi P, et al. Frequency of left ventricular hypertrophy in non-valvular atrial fibrillation. Am J Cardiol 2015;116:877–82. https://doi.org/10.1016/j.amjcard.2015.05.060.
[25] Cheng S-P, Liu C-L, Liu T-P, Hsu Y-C, Lee J-J. Association between parathyroid hormone levels and inflammatory markers among US adults. Mediat Inflamm 2014;2014:1–8. https://doi.org/10.1155/2014/709024.
[26] Hu Y-F, Chen Y-J, Lin Y-J, Chen S-A. Inflammation and the pathogenesis of atrial fibrillation. Nat Rev Cardiol 2015;12:230–43. https://doi.org/10.1038/nrcardio.2015.2.
[27] Tsai C-T, Lai L-P, Lin J-L, Chiang F-T, Hwang J-J, Ritchie MD, et al. Renin-angiotensin system gene polymorphisms and atrial fibrillation. Circulation 2004;109:1640–6. https://doi.org/10.1161/01.CIR.0000124487.36586.26.
[28] Shimoyama M, Ogino K, Furuse Y, Uchida K, Kinugasa Y, Tomikura Y, et al. Signaling pathway and chronotropic action of parathyroid hormone in isolated perfused rat heart. J Cardiovasc Pharmacol 2001;38:491–9.
[29] Kim T-H, Shim CY, Park JH, Nam CM, Uhm J-S, Joung B, et al. Left ventricular diastolic dysfunction is associated with atrial remodeling and risk or presence of stroke in patients with paroxysmal atrial fibrillation. J Cardiol 2016;68:104–9. https://doi.org/10.1016/j.jjcc.2015.10.008.