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ARTICLE

Investigating the association of vitamin D with blood pressure and the renin–angiotensin–aldosterone system in hypertensive subjects: a cross-sectional prospective study

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Abstract

The hypothesis that vitamin D (25(OH)D) insufficiency plays a role in occurring of various disease has led to a rise in requests of dosages and to an increase of health-care costs. 25(OH)D insufficiency is associated with increased risk of cardiovascular disease and hypertension in many studies. Animal studies demonstrated that 25(OH)D insufficiency activates renin angiotensin system but corresponding humans data are limited. The aim of the study was to document relationship between 25(OH)D, blood pressure, and renin angiotensin system in hypertensive subjects. In all, 248 hypertensive individuals, 46.8 years (±14), were hospitalized for an etiological assessment of hypertension in this cross-sectional study over two calendar years. 25(OH)D, plasma renin activity, and aldosterone were determined in stringent conditions and blood pressure was measure. Statistical analyses were carried out to analyze the association between 25(OH)D, blood pressure, and renin angiotensin system using linear and logistic regressions with adjustments on relevant variables. In all, 80% of the studied population had a 25(OH)D insufficiency. There were no significant association between 25(OH)D and levels of systolic or diastolic blood pressure, plasma renin activity, and aldosterone whatever the statiscal method used after adjustment. 25(OH)D is not associated with blood pressure and renin angiontensin component in hypertensive subjects. These results corroborate the interventional studies which are for a large majority negatives. A new definition of the 25(OH)D insufficiency in general population is necessary.

Introduction

In recent years, numerous observational and epidemiological studies have shown an association between vitamin D insufficiency and cardiovascular mortality.

In this context, an association has been shown between plasma 25-hydroxyvitamin D(25(OH)D) and the risk of incident hypertension or blood pressure level [1–3]. The most common explanation behind this relation is the activation of the renin angiotensin aldosteron system (RAAS) caused by the insufficiency of 25(OH)D, which results in a rise in blood pressure [4]. This has been demonstrated in mice [5] but studies on the RAAS in humans are few and not fully convincing principally due to limitations linked to the study samples and methods used to measure aldosterone and plasma renin activity [6–8].

On the other hand, interventional studies investigating 25(OH)D supplementation in hypertensive or normotensive patients showed negative results regardless of the evaluation criteria adopted (drop in blood pressure, conversion toward arterial hypertension), which questions the nature of the link between hypertension and 25(OH)D [9–13]. This made us wonder if an association exists between, firstly, blood pressure and 25(OH)D and, secondly, between the RAAS and 25(OH)D in subjects with essential hypertension. Finally, we were also interested in determining the principal factors associated with 25(OH)D levels in this population.

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Materials and methods

General concept

This is prospective cross-sectional single-center study. Over the course of two calendar years our study prospectively included all patients referred consecutively to our hypertension unit for an etiological assessment of hypertension.

Study population

This consists of subjects with hypertension diagnosed either by a series of self-measurements of blood pressure or by ambulatory blood pressure measurement (ABPM). The thresholds retained for the diagnosis of hypertension are systolic blood pressure (SBP) > 135 mm Hg or diastolic blood pressure (DBP) > 85 mm Hg for the self-measurements, and 24-h SBP > 130 mm Hg or 24-h DBP > 80 mmHg for the measurements recorded by the ABPM according the European society of hypertension (ESH) criteria [14].

Subjects proceeded to undergo the etiological assessment only in the case of:

- A resistant hypertension type (uncontrolled blood pressure despite triple antihypertensive therapy including a diuretic), a complicated hypertension type (target organ damage: history of stroke, heart failure, coronary heart disease, echocardiographic diagnosis of left ventricular hypertrophy, a glomerular filter rate (GFR) <60 ml (estimated by the MDRD formula),
- Early onset of hypertension (before the age of 40), or lastly
- Presence of hypokaliemia ($K + < 3.7$ mmol/l).

Thus, the study population consists of subjects at high risk for secondary hypertension.

Blood pressure measurement

The blood pressure (BP) measurement was carried out according to the ESC recommendations [14] by a trained nurse assigned to the hypertension unit or by a cardiologist of the unit. The subject is first made to lie down and rest for at least 5 min prior to the measurement. The inflatable cuff is then positioned around the firmest part of the upper arm, and three consecutive measurements are taken and then averaged to obtain both SBP and DBP. The measuring device used is a mercury sphygmomanometer.

Blood sampling

Blood samples were taken under standard conditions at 8 o'clock in the morning after 30 min of rest in lying position. Subjects included in the study could not be under any treatment that interferes with the RAAS. The administration of aldosterone blockers (spironolactone, eplerenone) was suspended for 4 weeks and treatment with diuretics, RAAS blockers, and beta-blockers was suspended for 2 weeks prior to the hormone measurements. In practice, only the intake of calcium channel blockers and central antihypertensive drugs were permitted at the time of the measurements.

Blood samples were conducted under normokalaemic conditions.

Hormone assays

The hormone assessment consisted in measuring plasma renin activity, serum aldosterone, 25(OH)D, cortisol, TSH, and parathormone concentrations.

25(OH)D and aldosterone were assayed using a Liaison analyzer (DiaSorin, France). Cortisol, TSH, and parathormone were assayed using DXi800 analyzers (Beckman-Coulter, France). All coefficients of variations of automated assays were lower than 10% whatever the level of internal control quality samples (two or three per assay).

25(OH)D insufficiency was defined as a serum 25(OH)D level lower than 25 ng/ml.

The measurement of plasma renin activity was carried out by a manual radioimmunoassay (Cisbio international) as previously described [15]. Coefficients of variation of this assay were lower than 13% for the three internal control quality samples.

Ethics

All eligible subjects gave their written and oral consent prior to participating in the study. In the case of minors, we first had to obtain the informed consent of their legal representative.

Exclusion criteria

Subjects with traces of medications other than ones permitted were not included in the analysis. Subjects who had taken a vitamin D supplementation in the last 3 months were also excluded. Subjects with secondary hypertension were not included in the main analysis.

Statistical analysis

Our study population is described globally and according to the underlying cause of hypertension (essential or secondary). We quantitatively and qualitatively examined the concentration of 25(OH)D in the subjects.

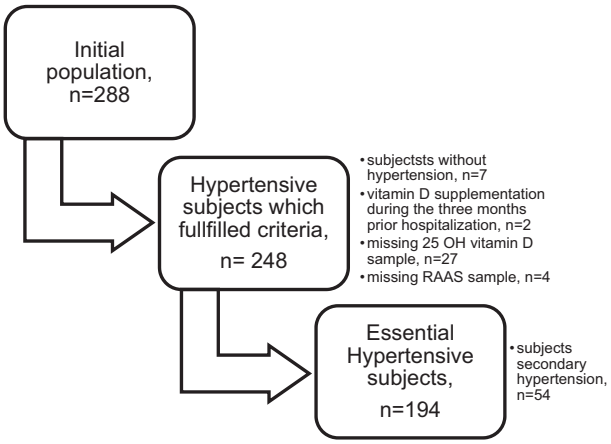

Fig. 1 Flow chart of selection of participants

In our quantitative analysis, we carried out a linear univariate regression analysis for each of the adjustment variables, followed by a multivariate analysis after having verified that the 25(OH)D concentration was normally distributed.

Our variables of interest included office blood pressure measurement, plasma renin activity, and aldosteronemia.

We selected the adjustment variables from those described in the literature associated with 25(OH)D. These include season, parathormone concentration, body mass index, black skin, age, and sex. The model was built through a descending step-by-step process on a constant working sample. The statistical threshold $p < 0.05$ was necessary to retain the variable in the final model with the exception of the variables sex and age, which had to be forced into the model. Interactions were sought between the variables of interest and the adjustment variables.

Using logistic regression analysis we studied the determinants of 25(OH)D insufficiency. The same adjustment variables were used as in the linear regression model. The log-linearity assumption of the quantitative adjustment variables was verified. The model was built using a stepwise procedure on a constant sample size. The statistical threshold $p < 0.05$ was necessary to retain the adjustment variables in the final model.

The statistical analyses were performed using SAS® 9.4 software (California, USA).

Results

From April 2012 to March 2014, 288 hypertensive subjects aged 15–85 years were admitted to our department. Seven patients were hospitalized for an assessment not related to hypertension and were thus excluded from the study (four patients were admitted for an adenoma (Conn syndrome) postoperative assessment, one patient for unrelated malaise, one patient for an assessment of an isolated case of hypokalemia, and one patient for gestational hypertension). Two patients were excluded for having taken 25(OH)D supplementation during the 3 months prior to hospitalization. In the end, 248 patients fulfilled the study eligibility criteria (Fig. 1).

The average age of participants was 46.8 years (±14). Women made up 48% of the subjects and subjects of Black African origin accounted for 11% of the total sample. Serum concentrations of 25-OH vitamin D varied between 4 and 72.2 ng/ml with an average of 18.3 ng/ml. In all, 80% of the total sample was found to have an insufficiency of 25 (OH)D (25-OH vitamin D < 25 ng/ml).

Two population groups were identified according to their etiological diagnosis.

Overall, 194 patients (78%) were found to have essential hypertension and 54 patients (22%) secondary hypertension. The majority of patients with secondary hypertension had primary hyperaldosteronism (23/54). The characteristics of the whole cohort and according to hypertension type are presented in Table 1.

In the univariate linear regression analysis, the level of 25(OH)D is associated with season of the year ($\beta = 2.57$, $p = 0.0002$), serum PTH level ($\beta = -0.16$, $p = <0.0001$), race ($\beta = -4.05$, $p = 0.048$), and BMI ($\beta = -0.43$, $p = 0.0001$). However, SBP, DBP, plasma renin activity, and aldosteronemia were not found to be associated with 25(OH)D plasma levels (Table 2).

The multivariate analysis confirm the previous associations with seasons of the year ($\beta = 2.341$, $p = 0.0002$), serum PHT ($\beta = -0.13$, $p < 0.001$), and BMI ($\beta = -0.34$, $p = 0.0101$). However, the variable race, is no more associated to the level of 25(OH) D even if the statistical test is close to significance ($\beta = -3.87$, $p = 0.059$; Table 3).

The univariate logistic regression analysis shows that 25 (OH)D insufficiency is associated with season (OR = 0.45, p = < 0.0001), serum PTH level (OR = 1.06, p = 0.0001), and BMI (OR = 1.10, p = 0.0274). In the multivariate analysis, only the variables season and PTH are associated with a 25(OH)D insufficiency (Table 4).

Discussion

Despite a rigorous method of patient selection (subjects with confirmed hypertension) and measurements of hormones under standard and stringent conditions in a unit dedicated to hypertension (Hypertension excellence center of the European Society of Hypertension) and with a significantly large patient cohort, we were not able to demonstrate the association between BP and 25(OH)D. Similarly, our results did not suggest any association between the RAAS and level of serum 25(OH)D.

Table 1 Main characteristics of the total population according to type of hypertension, $n = 247$

	Total hypertension		Essential hypertension		Secondary hypertension	
	Population	Mean (SD) or proportion	Population	Mean (SD) or proportion	Population	Mean (SD) or proportion
Age	247	46.8 (14,2)	194	46.3 (14.3)	54	49 (16,4)
Female	247	48.2	194	46.9	54	51.8
BMI	245	27.4 (5.2)	192	27.4 (5.2)	54	27.3 (5.5)
Black skin	247	10.9	192	11.0	54	10.5
SBP	244	151	191	150	53	156
DBP	244	93	191	91	53	103
Heart beat	235	72	183	72	52	73
Dyslipidemia	247	44.5	194	45.9	54	38.9
Diabetes mellitus	247	13.0	194	12.4	54	14.8
Active smoker	246	24.8	193	25.9	54	22.2
Kalemia	247	4.13 (0.41)	NA	NA	NA	NA
PTH	234	50.5 (22.8)	188	47.5 (19.7)	47	61.9 (30.2)
PRA	224	0.99 (1.06)	180	0.88 (0,80)	45	1.41 (1.71)
Aldosteronemia	213	303.7 (124)	170	234.7 (124)	44	565.0 (180)
Winter (Jan–Mar)	47	19	41	21	6	11
Spring (Apr–Jun)	89	36	66	34	23	43
Summer (July–Sept)	72	29	56	29	16	30
Autumn (Oct–Nov)	40	16	31	16	9	17

SD standard deviation, *BMI* body mass index, *SBP* systolic blood pressure in mm Hg, *DBP* diastolic blood pressure in mm Hg, *PTH* parathyroid hormone in pmol/l, *PRA* plasma renin activity in ng/ml/h, aldosteronemia in pmol/l

Table 2 Results from the univariate linear regression analysis of the concentration of 25–OH vitamin D in subjects with essential hypertension ($n = 185$)

	β	p value
Age	0.04	0.2982
Sex	−0.08	0.9446
Race	−4.05	0.0480
BMI	−0.43	0.0001
SBP	−0.03	0.2982
DBP	0.01	0.2740
Season	2.57	0.0002
PTH	−0.16	<0.0001
PRA	0.49	0.4055
Aldosteronemia	−0.01	0.4658

BMI body mass index, *SBP* systolic blood pressure in mm Hg, *DBP* diastolic blood pressure in mm Hg, *PTH* parathyroid hormone in pmol/l, *PRA* plasma renin activity in ng/ml/h, aldosteronemia in pmol/l

Table 3 Results from the multivariate linear regression analysis of vitamin D levels in subjects with essential hypertension ($n = 185$)

	β	CI: 95%	p value
Intercept	23.37	19.61–27.13	<0.0001
Sex	0.72	−0.37–1.81	0.51
Age	0.05	0.01–0.09	0.18
Race	−3.87	−7.89–0.15	0.0590
BMI	−0.34	−0.55–0.07	0.0101
Season	2.41	1.15–3.68	0.0002
PTH	−0.13	−0.20–0.07	<0.0001

BMI body mass index, *SBP* systolic blood pressure in mm Hg, *DBP* diastolic blood pressure in mm Hg; *PTH* parathyroid hormone in pmol/l, *PRA* plasma renin activity in ng/ml/h, aldosteronemia in pmol/l

Table 4 Results from the multivariate logistic regression analysis of the essential hypertension cohort based on vitamin status (Vitamin D deficiency: Vit D < 25 ng/ml), $n = 172$

	Subjects with essential hypertension ($n = 131$)		
	OR	CI	p value
Spring	0.23	0.03–1.98	0.1797
Summer	0.07	0.01–0.56	0.0125
Autumn	0.06	0.01–0.47	0.0080
PTH	1.054	1.02–1.09	0.0004

PTH parathyroid hormone in pmol/l

25(OH)D and BP

Published observational studies show an inverse correlation between 25(OH)D and hypertension in different population groups. In a large-scale meta-analysis (involving 283,537 participants), Kunutsor et al. [3] confirmed a significant

inverse association (RR = 0.88, 95% CI: 0.81–0.97) between 25(OH)D level and risk of incident hypertension in healthy subjects. However, one of the limitations of this study was that participants in four of the 11 selected studies had to self-report their diagnosis of hypertension, which could have resulted in misclassification of hypertension status.

Our results are consistent with those of Snijder et al., who did not find any association between 25(OH)D level and risk of hypertension in a study sample of 1205 normotensive subjects over the age of 65 [16]. Similarly, Jorde et al. did not find any impact of 25(OH)D status on the incidence of hypertension based on data collected from 4125 normotensive adult subjects over the age of 25 [17].In yet another study by Margolis et al., investigating 1863 postmenopausal women over a period of seven years,no significant difference was found in the incidence of hypertension according to 25(OH)D status [18].

As a final point, at present interventional studies on this research topic have all shown negative results, independent of study population (normotensive, hypertensive, elderly, young subjects or subjects with resistant hypertension), applied 25(OH)D doses, and frequency of treatment administration and duration. Consequently, Pilz et al. conducted a randomized single-center study involving 200 hypertensive subjects with 25(OH)D levels below 30ng/ml, receiving either a daily dose of 25(OH)D or a placebo for 8 weeks [19]. In this study, no differences in the SBP levels using 24-h ABPM ($p = 0.712$) were observed between the two treatment groups. Arora et al. [9] carried out a multicenter randomized trial in a sample of 534 pre-hypertensive and stage 1 hypertensive subjects with levels of 25(OH)D less than 25 ng/ml, receiving 25(OH)D supplementation over a 6-month period. Here again, there was no significant difference in 24-h SBP between the two treatment arms ($p = 0.71$) [20]. Similar results were found in 130 subjects with mild hypertension receiving a daily dose of 25(OH)D during 3 months in a study by Larsen et al. [12], in 159 subjects with isolated systolic hypertensionin another study by Witham et al. [13], and in 68 subjects with resistant hypertension [11]. None of these studies showed an improvement in BP in hypertensive subjects despite receiving 25(OH)D supplementation, regardless of stage of hypertension.

A non-causal relationship may explain the associations between 25(OH)D and BP observed in some cross-sectional studies. It appears evident that an unhealthy population with severe comorbidities will have a restricted intake of 25(OH)D, in particular due to reduced sun exposure (principal source of vitamin D) as a result of limited outdoor outings. Furthermore, these restrictions increase with old age.

Moreover, patients with severe cardiovascular comorbidities often have an unbalanced diet, poorer in omega-3 fatty acids (fish fat), which are also the main dietary sources of 25(OH)D. We can therefore deduce that our study sample composed of subjects certainly suffering from severe hypertension, but who are young (average age of 46 years) with a considerable degree of autonomy, not succumbing to outdoor restrictions, is thus not subject to the association under investigation.

This suggests that the association between vitamin D and risk of hypertension can therefore exist in certain population groups, although it appears non-causal.

Vitamin D and the RAAS

To date, studies of the RAAS in humans have been conducted on rather small-size cohorts of hypertensive subjects. The most important of which, in a cohort of 39 hypertensive subjects did not find any association between 25(OH)D and the renin angiotensin system [20]. Some studies also investigated whether 25(OH)D supplementation in hypertensive subjects had an impact on renin and serum aldosterone levels. However, once again, the sample size in these studies is modest (less than 30 subjects) and no association was shown [21–23]. The association between 25(OH)D insufficiency and activation of the RAAS was shown in a model using mice with vitamin D receptor (VDR) knocked out [5]. Hereditary vitamin D-resistant rickets (HVDRR) is the human equivalent of VDR null mice model. The functioning of the renin angiotensin system, BP and cardiac structure was for the first time studied in 2011 by Tiosano et al. in 17 HVDRR subjects aged from 6 to 36 years seeking to better understand the implications of vitamin D on these systems [24].

The study found an increase in PTH but normal levels of the RAAS components in these subjects, without any significant difference compared to the control group. Moreover, none of the patients in the study had been diagnosed with high blood pressure.

Vitamin D and its associated factors

Season

Our results show a distinct seasonal variation in vitamin D levels. We observed significantly lower levels of vitamin D and more subjects with a 25(OH)D insufficiency ($p = 0.012$) in samples collected from individuals in winter compared to those in the summer. Seasonal variation in vitamin D levels is well-known and has been found in several studies [25]. Recently, an American study investigating the vitamin D status of 148,821 patients over a 2-year period clearly demonstrated this seasonal variability [26].

Ethnicity

Lower levels of serum 25(OH)D are found in black individuals than in non-black individuals even though this association is just above the threshold of statistical significance in the multivariate linear regression analysis ($p = 0.059$). This result is consistent with data from the literature [27, 28]. The main source of vitamin D is essentially derived from dermal synthesis under the influence of UVB. This synthesis is determined by skin pigmentation as melanin absorbs UVB rays, which in turn explains the lower levels of vitamin D, found in subjects of sub-Saharan origin despite equal sun exposure.

BMI

Our results show a significant inverse association between BMI and 25(OH)D. Subjects with a high BMI were found to have significantly lower 25(OH)D levels ($p = 0.010$). These results corroborate with those of many other studies which confirm an association between high BMI and low serum 25(OH)D levels [29, 30]. However, the mechanisms are not properly understood, and the association can work in both ways. One explanation could be that obese subjects limit their outdoor activities and therefore their skin tends to be less exposed to the sun than non-obese subjects, inducing a lower synthesis of vitamin D. The hypothesis of a "sequestration" of fat-soluble vitamin D by adipocytes has been supported by studies demonstrating a much lower increase in serum vitamin D concentrations in obese patients compared to non-obese despite receiving oral supplementation of vitamin D or equal skin exposure to UVB radiation [30].

PTH

Our results show a significant correlation between 25(OH)D and PTH: subjects with a 25(OH)D insufficiency have a significantly higher mean PTH level than other subjects ($p < 0.0001$). Numerous studies have reported an inverse association between PTH and 25(OH)D serum concentrations in both older and younger populations [31, 32]. The increase in the serum level of PTH is physiological and reflects an appropriate response to the physiological stress of decreased calcium absorption.

Age and sex

No significant difference was found between the mean 25(OH)D level in males and in females, contrarily to the majority of observational studies which find higher levels of 25(OH)D in male subjects [33, 34].

However, several more recent studies also did not find any difference in vitamin levels between the sexes. One American study compared the prevalence of 25(OH)D insufficiency between the years 2000 and the years 1980–1990. The differences between men and women identified 20 years ago no longer appear true today [33]. A recent study conducted in several European countries finds similar mean 25(OH)D levels between men and women regardless of their generation [35].

It therefore appears gender disparities of serum levels of 25(OH)D have diminished over time and with lifestyle changes. The synthesis of vitamin D, which is less substantial in elderly subjects, is probably also secondary to the reduction of sun exposure and the decrease of outdoor activities. However, this is not observed in our study, most certainly due to our study population comprising young subjects in apparent good health.

Limitations

Our cohort of hypertensive patients are not representative of all hypertensive subjects, as only referred patients with certain hypertension types underwent the etiological assessment. A young population with very low levels of 25(OH)D provides nevertheless good evidence to support the absence of a link between 25(OH)D and BP. The association between 25(OH)D and BP was based on BP office measurements and not on Ambulatory Blood Pressure Monitoring (ABPM) data or home blood pressure measurements, which could have maybe provided yet another level of information. However, ABPM and self-measurements could be performed several months after the hormonal and etiological assessments. Consequently, it seemed difficult to link 25(OH)D levels to a date very different to that of the blood pressure recording. Information on 25(OH)D supplementation was collected in a self-reported manner and it is possible that certain subjects received 25(OH)D supplementation within 3 months prior to the study without recalling it. Nonetheless, the rate of 25(OH)D insufficiency observed remains high and consistent with national data.

Conclusion

Regardless of 25(OH)D status or level of plasma 25(OH)D, we find no association either with BP or with the activation of the RAAS in patients with essential hypertension. These data support and explain the negative results of previous interventional studies. 25(OH)D thresholds that have been defined using the effects of vitamin D on bones should be

reviewed in the hypertensive population and probably in the general population as well.

Summary

What is known about this topic?

- Association between 25(OH)D and blood pressure is controversial
- 25(OH)D supplementation is not associated with a better outcome in terms of cardiovascular events and blood pressure control

What this study adds?

- With 288 subjects, this is the largest cohort of hypertensive patients with measurement of plasma renin activity and aldosteronemia and 25(OH)D.
- It confirms the absence of association between blood pressure and 25(OH)D and between plasma renin activity and aldosteronemia and 25(OH)D.

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