Original Article

Renin–angiotensin system activity in vitamin D deficient, obese individuals with hypertension: An urban Indian study

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ABSTRACT

Background: Elevated renin–angiotensin–aldosterone system (RAAS) activity is an important mechanism in the development of hypertension. Both obesity and 25-hydroxy vitamin D [25(OH)D] deficiency have been associated with hypertension and augmented renin–angiotensin system (RAS) activity. We tried to test the hypothesis that vitamin D deficiency and obesity are associated with increased RAS activity in Indian patients with hypertension. **Materials and Methods:** Fifty newly detected hypertensive patients were screened. Patients with secondary hypertension, chronic kidney disease, or coronary artery disease were excluded. Patients underwent measurement of vitamin D and plasma renin and plasma aldosterone concentrations. They were divided into three groups according to their baseline body mass index (BMI; normal <25 kg/m^2, overweight 25–29.9 kg/m^2 and obese ≥30 kg/m^2) and 25(OH)D levels (deficient <20 ng/ml, insufficient 20–29 ng/ml and optimal ≥30 ng/ml). **Results:** A total of 50 (male:female = 32:18) patients were included, with a mean age of 49.5 ± 7.8 years, mean BMI of 28.3 ± 3.4 kg/m^2 and a mean 25(OH)D concentration of 18.5 ± 6.4 ng/ml. Mean systolic blood pressure (SBP) was 162.4 ± 20.2 mm Hg and mean diastolic blood pressure (DBP) was 100.2 ± 11.2 mm Hg. All the three blood pressure parameters [SBP, DBP and mean arterial pressure (MAP)] were significantly higher among individuals with lower 25(OH)D levels. The *P* values for trends in SBP, DBP and MAP were 0.009, 0.01 and 0.007, respectively. Though all the three blood pressure parameters (SBP, DBP and MAP) were higher among individuals with higher BMIs, they were not achieving statistical significance. Increasing trends in PRA and PAC were noticed with lower 25(OH)D and higher BMI levels. **Conclusion:** Vitamin D deficiency and obesity are associated with stimulation of RAAS activity. Vitamin D supplementation along with weight loss may be studied as a therapeutic strategy to reduce tissue RAS activity in individualswith Vitamin D deficiency and obesity.

Key words: Hypertension, obesity, renin–angiotensin–aldosterone system, vitamin D

Introduction

Obesity is a state of relative vitamin D deficiency[1] and excess tissue renin angiotensin aldosterone system (RAAS) activity.[2] There is a local adipose tissue RAAS that produces all the components of RAAS and is distinctly regulated from the circulating RAAS.[3] Vitamin D is an inhibitor of renin expression in animals via its interaction with vitamin D receptor (VDR).[4]

Li *et al.* showed that VDR knockout mice displayed a phenotype of high plasma renin activity (PRA) and hypertension that was ameliorated with renin–angiotensin system (RAS) antagonism.[5] Inhibiting the production of active 1,25-dihydroxyvitamin D [1,25(OH)2D] by

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inactivating the 1α-hydroxylase enzyme also resulted in high PRA, which was reduced with the administration of 1,25(OH)2D.[6] In contrast, overexpression of the VDR in juxtaglomerular cells of mice suppressed renin expression independently of parathyroid hormone and calcium.[7] These findings have been consolidated by implicating vitamin D as an inhibitor of renin gene expression via its interaction with the VDR.[8]

Cross-sectional human studies have also associated vitamin D deficiency with augmented RAAS activity, particularly in obesity.[9] They have also found that vitamin D metabolites have been inversely associated with circulating renin.[10] Vitamin D deficiency and excess activity of RAAS are associated with cardiovascular disease.[11] In the present study, we tried to evaluate the association between RAAS activity with vitamin D levels and obesity. To ourknowledge, this is the first such study on Indian patients.

Materials and Methods

Subjects who were newly diagnosed to have hypertension defined by a seated blood pressure >140/90 mm Hg at two occasions were screened. All patients underwent a screening history and physical, laboratory examinations. Patients with chronic kidney disease, coronary artery disease, heart failure or known causes of secondary hypertension were excluded.

The study was approved by the hospital ethical committee and all the participants signed informed consent forms after being thoroughly explained about the study.

Measurement of serum 25(OH)D was performed in all patients. All subjects had PRA and plasma aldosterone (PAC) measured from the morning supine blood samples. Subjects were categorized by their vitamin D status on the basis of their 25(OH)D levels as follows: group 1 – optimal (≥30 ng/ml); group 2 – insufficient (20.0–29.9 ng/ml) and group 3 – deficient (<20.0 ng/ml).[12] Similarly, the participants were categorized on the basis of their body mass index (BMI) (normal <25 kg/m^2, overweight: 25–29.9 kg/m^2 and obese ≥30 kg/ m^2).

Statistical analysis

Summary data were expressed as mean ± standard deviation and comparison between groups was done by nonparametric Mann–Whitney U test. Relationship between vitamin D levels and RAAS parameters in the overall study population was analyzed by Pearson correlation analysis. One-way analysis of variance (ANOVA) was used to compare means between BMI categories. *P* values were two-tailed and values <0.05 were considered significant. All the statistical analyses were performed using online GraphPad QuickCalc software.

Results

A total of 50 (male:female = 32:18) patients were included in the study group. The study population's mean age was 49.5 ± 7.8 years (range: 25–68 years). They were overweight with a BMI of 28.3 ± 3.4 kg/m^2 (range: 21.2–36.4) and had a mean 25(OH)D concentration of 18.5 ± 6.4 ng/ml (range: 7.3–33.5 ng/ml). Mean systolic blood pressure (SBP) was 162.4 ± 20.2 mm Hg and mean diastolic blood pressure (DBP) was 100.2 ± 11.2 mm Hg.

Vitamin D and blood pressure and renin angiotensin aldosterone system parameters

Table 1 depicts the blood pressure and RAAS parameters in the participants as per their 25(OH)D levels. The graph in Figure 1 demonstrates the mean blood pressure values as per the vitamin D levels. All the three blood pressure parameters [SBP, DBP and mean arterial pressure (MAP)] were significantly higher among individuals with lower 25(OH)D levels. The *P* values for trends in SBP, DBP and MAP were 0.009, 0.01 and 0.007, respectively. Increasing trends in PRA and PAC were noticed as vitamin D levels were decreasing. Though PRA values were significantly higher in group 2 (insufficient) versus group 3 (optimal) (*P* = 0.004), they did not significantly differ according to the vitamin D status in group 2 (insufficient) versus group 1 (deficient) (*P* = 0.09). However, PAC levels maintained significant trend across the three groups. Patients under group 1 were obese, whereas patients in groups 2 and 3 were overweight. Though BMI was higher among individuals with lower 25(OH)D levels, the difference was statistically not significant.

Body mass index and blood pressure and renin angiotensin aldosterone system parameters

BMI-wise distribution of blood pressure and RAAS

Table 1: Blood pressure and renin angiotensin aldosterone system parameters in subjects as per their vitamin D levels (P* < 0.05)**

	Vitamin D levels (ng/ml)		
	< 20 (n=16, M:F= 10: 6)	20-29 (n=21, M:F= 11: 10)	≥ 30 (n=14, M:F= 12: 2)
Systolic blood pressure (mm hg)	173.7 ± 18.8	156.6 ± 18.5*	149.2 ± 18.1*
Diastolic blood pressure (mm hg)	108.1 ± 11.8	99.1 ± 11.6*	93.3 ± 11.1*
Mean arterial Blood pressure (mm Hg)	195 ± 22.2	175 ± 21.7*	168 ± 20.7*
PRA (ng/ml/hr)	3.7 ± 0.9	3.3 ± 0.6	0.50 ±0.1*
PAC	16.7 ± 2.4	12.4 ± 2.2*	4.1 ± 1.1*
BMI (kg/m^2)	30. 7 ± 4.1	28.5 ± 3.5	25.3 ± 2.8

PRA: Plasma renin activity, PAC: Plasma aldosterone, BMI: Body mass index

parameters is given in Table 2. The graph in Figure 2 demonstrates the mean blood pressure values as per the BMI. Though all the three blood pressure parameters (SBP, DBP and MAP) were higher among individuals with higher BMIs, they did not achieve statistical significance. The *P* values for trends in SBP, DBP and MAP were 0.06, 0.09 and 0.07, respectively. Increasing trends in PRA and PAC were noticed as the BMI was increasing. Though PRA and PAC values were significantly higher in overweight versus lean subjects ($P = 0.001$), they did not significantly differ according to the BMI status in obese versus overweight subjects ($P = 0.1$). Overweight patients had significantly lower levels of 25(OH)D than normal BMI subjects. The 25(OH)D levels did not vary significantly vary between overweight and obese subjects.

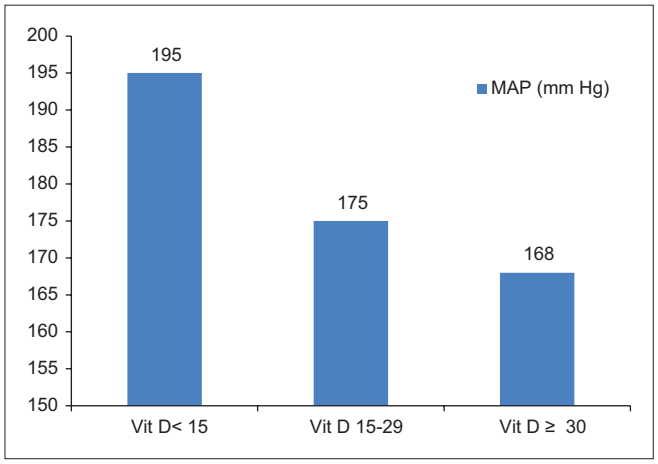

Figure 1: Mean arterial pressure in patients as per their serum vitamin D levels

Table 2: Blood pressure and renin angiotensin aldosterone system parameters in subjects as per their body mass index (P* < 0.05)**

	BMI (Kg/m²)		
	< 25 (n=9, M:F= 5: 4)	**25-29.9 (n=26, M:F= 14: 12)**	**≥ 30 (n=15, M:F= 13: 2)**
Systolic blood pressure (mm hg)	163.4 ± 19.2	155.6 ± 18.8	151.3 ± 18.1
Diastolic blood pressure (mm hg)	103.1 ± 11.7	99.8 ± 11.3	95.6 ± 11.2
Mean arterial Blood pressure (mm Hg)	170 ± 20.8	174 ± 21.2	183 ± 21.9
PRA (ng/ml/hr)	0.6 ± 0.2	2.9 ± 0.7*	3.6 ± 0.9
PAC	5.2 ± 1.6	13.5 ± 2.5*	16.8 ± 2.4
Mean 25 (OH) D (ng/ml)	22.5 ± 9.1	16.1 ± 5.6*	14.5 ± 4.9

PRA: Plasma renin activity, PAC: Plasma aldosterone, BMI: Body mass index

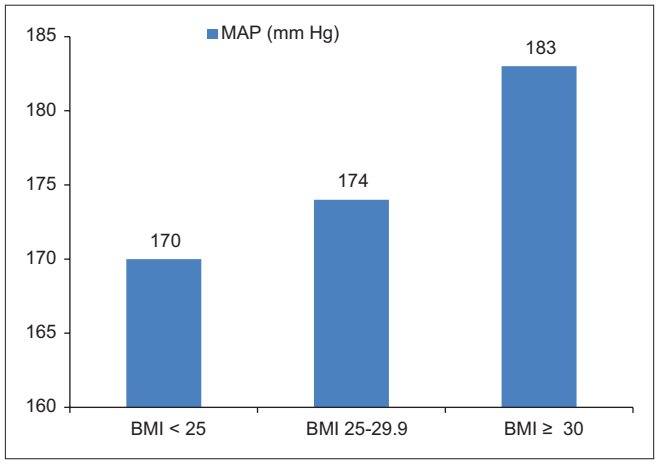

Figure 2: Mean arterial pressure in patients as per their body mass index

Discussion

The relationship between vitamin D, RAAS and obesity is complex and intertwined. Although animal models strongly suggest that vitamin D suppresses the RAAS, there are limited human data supporting this hypothesis. Indian data in this respect are not available s far. We found that lower 25(OH)D levels and higher BMI values were associated with higher plasma renin and aldosterone concentration in Indian subjects with hypertension.

Observational studies strongly support an inverse association between plasma 25(OH)D levels and blood pressure and hypertension.[13-18] In addition to numerous cross-sectional analyses, two prospective studies have demonstrated that lower baseline 25(OH) D levels are associated with an increased risk of incident hypertension.[15,16] In the first study which included 613 men and 1198 women who did not have hypertension at baseline, those with 25(OH)D levels <15 ng/ml (vitamin D deficiency) compared to those with ≥30 ng/ml had a relative risk for incident hypertension of 2.7 after adjusting for multiple demographic and lifestyle factors.[16] The second prospective study also considered levels of parathyroid hormone plus numerous other biomarkers as potential confounders and found that individuals with vitamin D insufficiency [25(OH)D level < 30 ng/ml] had a 1.5-fold higher risk of developing hypertension compared with those with optimal levels.[15]

In contrast, few human studies have examined this relationship. The first human study to investigate the association examined 10 normotensive individuals as well as 51 hypertensive individuals, on ambient diets, divided into low-renin, normal-renin, and high-renin status.[9] The authors reported the highest levels of 1,25(OH)2D in low-renin hypertensives compared with normal- and high-renin hypertensives ($P < 0.01$ for both comparisons) as well as normotensives ($P < 0.01$). Among all 61 individuals, there

was an inverse correlation between PRA and 1,25(OH)2D ($r = -0.65$; $P < 0.001$).[9] The second human study included 10 high-renin hypertensive individuals who were studied initially on a 5-day low-sodium diet (10 mmol/d) and then again after a 5-day high-sodium diet (100 mmol/d).[19] The authors found that changing from a low-sodium to high-sodium diet led to significant increases in urine calcium excretion and 1,25(OH)2D levels, plus a decrease in PRA. The changes in 1,25(OH)2D concentration and PRA were inversely correlated ($r = -0.76$; $P < 0.01$).[19] The authors hypothesized that sodium loading led to an increase in calcium excretion, which in turn led to an increase in 1,25(OH)2D levels, which then suppressed PRA by increasing juxtaglomerular cell calcium concentrations.[19] Levels of 25(OH)D were not measured in either of these studies.

One randomized trial of vitamin D supplementation (with ergocalciferol) documented the effects on markers of the RAS.[20] Sugden *et al*.[20] randomized 34 individuals with type 2 diabetes mellitus and 25(OH)D levels <20 ng/ml to receive either 100,000 IU of vitamin D2 or placebo. Along with a 6-ng/ml increase in 25(OH)D level at 8 weeks of follow-up with supplementation, SBP declined by 14 mm Hg compared with placebo. In addition, Ang II levels decreased by 13.1 pg/ml in the vitamin D group relative to the change in the placebo group; conversely, active renin levels (not PRA) were increased in the vitamin D group relative to the change in the placebo group by 2.6 ng/ml.[20] Neither of these results was statistically significant. Though we did not take into consideration the sodium and calcium intake by our patients, we noticed significantly higher blood pressure among patients with lower serum 25(OH)D levels in our study.

Another study found out that among 184 normotensive individuals in high sodium balance, lower plasma 25(OH)D levels were associated with significantly higher circulating Ang II concentrations, as well as a blunted Renal plasma flow (RPF) response to infused Ang II.[21] In contrast, although PRA was higher among individuals with vitamin D insufficiency and deficiency, the association was not statistically significant. These findings may reflect a renin-independent mechanism for vitamin D suppression of systemic and local Ang II. Indeed, vitamin D signaling may inhibit the expression of angiotensinogen by inhibition of nuclear factor κB transcription factors[22,23] and angiotensinogen may be converted by cathepsins to Ang II in the absence of renin.[24,25] All the patients in our study group were hypertensives; we did not take normotensive subjects into consideration. In our study population, PRA was higher in subjects with vitamin D insufficiency, reflecting a renin-mediated mechanism for hypertension.

We found that lower serum 25(OH)D levels were associated with higher SBP, DBP, MAP and PRA and PAC. Several putative mechanisms have been proposed, including associations between vitamin D deficiency and endothelial dysfunction,[20,26-28] inflammation,[29-31] and insulin resistance.[32,33] However, a major proposed mechanism was documented by Li *et al*.[34] in mice lacking the VDR gene. Absence of vitamin D signaling in these animals led to an increase in renin gene expression and circulating Ang II levels. When placed on a high-salt diet, these knockout mice had slight reductions of renin and Ang II, but maintained the levels substantially higher than those of wild-type mice on a similar diet.[35] Furthermore, renin levels remained elevated despite normalization of plasma calcium concentrations, and injection of 1,25(OH)2D reduced renin expression in wild-type mice.[34,35] Other animal models support these findings, demonstrating that mice lacking the 1α-hydroxylase gene have a similar phenotype[4] and that 1,25(OH)2D analogs help suppress Ang II-mediated kidney injury in diabetic and in 5/6 nephrectomized rats.[36,37] 25(OH)D deficiency could explain the augmented adipose tissue RAAS activity and the resultant changes in adiponectin concentrations in obesity.

Obesity is a state of hypoadiponectinemia and relative vitamin D deficiency. Vaidya *et al*. reported in their study that on comparison of patients with low sodium intake and those with high sodium intake, the latter ones had significantly higher SBP, DBP, MAP, PRA, PAC, and adiponectin levels. Adiponectin was found to be inversely associated with BMI and positively associated with 25(OH)D regardless of dietary sodium intake and circulating RAAS activity,[38] which are known modulators of circulating adiponectin.[39,40] The association between 25(OH)D and adiponectin strengthened with increasing BMI and was only significant among obese individuals where the burden of adipose tissue RAAS activity is expected to be higher. They speculated that adipose tissue RAAS is an important negative paracrine regulator of adiponectin secretion in adipose tissue;[41] the adipose tissue RAAS may in turn be negatively regulated by vitamin D.[9,10] The adipose tissue RAAS is not influenced by the traditional sodium homeostasis and blood pressure feedback mechanisms,[42] and has been shown to modulate adiponectin concentrations in transgenic mice.[41] With this hypothesized mechanism, vitamin D supplementation could raise circulating adiponectin in obesity by downregulating adipose tissue RAAS activity.[43] The findings of insignificantly higher blood parameters in our study population might be reflective of the mixture of high and low sodium intake by the patients. Though PRA and PAC values were significantly higher in overweight versus lean subjects ($P = 0.001$), they did not significantly differ according to BMI status in obese versus overweight

subjects (P = 0.1) in our study. Higher BMI leads to renin-mediated hypertension; the small sample size of our study population might have been a limitation, as the significance of this association was not found in obese subjects. The significantly lower level of 25(OH)D might have led to increased PRA in overweight subjects in our study population.

Our study examined plasma 25(OH)D levels; the aforementioned animal and previous human investigations of vitamin D and the RAS, in contrast, have mostly focused on levels of 1,25(OH)2D. Because plasma 25(OH)D is not under homeostatic control, whereas 1,25(OH)2D levels are homeostatically regulated, individuals with low 25(OH)D levels may have normal levels of 1,25(OH)2D; however, the two hormones are generally well correlated.[44] In addition, and more importantly, the epidemiological data supporting a relation between vitamin D and hypertension, as well as between vitamin D and cardiovascular disease, are essentially limited to the analyses of 25(OH)D and not 1,25(OH)2D. Therefore, to invoke the RAS as a mechanism to explain the epidemiological data, it was critical to analyze the levels of 25(OH)D.

Finally, several lines of evidence suggest that 25(OH)D, like 1,25(OH)2D, may be an "active" hormone. The 1α-hydroxylase gene is widely expressed.[45] So, 25(OH)D may be converted to 1,25(OH)2D locally in various tissues, bypassing the need for conversion in the proximal tubule and thereby having autocrine and paracrine effects. Furthermore, depending on the conformation of the VDR (*cis* or *trans*), it may be located either in the cytoplasm or at the plasma membrane, the latter localization associated with its ability to activate second messengers, such as protein kinase-C, mitogen-activated protein kinase, and phosphatidylinositol 3-kinase.[46] New data suggest that whereas the affinity of cytoplasmic VDR is greatest for 1,25(OH)2D, the binding affinity of 25(OH)D for membrane-associated VDR matches that of 1,25(OH)2D.[47] Considering that 25(OH)D concentrations are 1000-fold higher than those of 1,25(OH)2D, it is increasingly apparent that 25(OH)D may be an important active circulating hormone.

The limitations of our study were the following:

1. This study had a small sample size from a single center with no inclusion of normotensive subjects.
2. We did not measure plasma levels of parathyroid hormone or 1,25(OH)2D, and therefore cannot examine whether these hormones mediate or confound our observed association.
3. We did not gather dietary information on calcium and sodium intake and did not know whether the participants were using vitamin D supplements.
4. We lacked information about sodium and calcium intake.
5. We did not take into account the time of the year and seasonality which are known to influence 25(OH)D levels.[48] We also did not observe the effect of vitamin D supplementation and weight reduction on these parameters.
6. We did not have any information on patients taking nonsteroidal anti-inflammatory drugs (NSAID). Because renal prostaglandins may regulate the 1α-hydroxylase enzyme and thus influence the conversion of 25(OH)D to 1,25(OH)D.[45], NSAIDs by virtue of their inhibitory effect on prostaglandin production might lead to alteration in vitamin D levels.

Nevertheless, given the high prevalence of vitamin D deficiency[49] and ever rising trends in obesity in India, we feel that our study is an important one in supporting the hypothesis of higher incidence of hypertension in vitamin D deficient and obese individuals. Further large-scale, multicenter studies involving larger number of patients with a long follow-up after vitamin D supplementation would serve the purpose of confirming the observations of our preliminary study.

Conclusion

Our findings in newly detected hypertensive individuals show an association between low plasma 25(OH)D levels, high BMI and upregulation of the RAAS. These findings may partly explain the higher risk of developing hypertension observed among individuals with vitamin D insufficiency and deficiency and obesity. Randomized trials should be performed to confirm or refute these observations.

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