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A Study on Plasma 25-Hydroxy Vitamin D Levels in Hypertensive Patients

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Abstract: ***Vitamin D has played a vital role in regulation of our body. It has been identified that vitamin D deficiency is associated with life style disorders like diabetes mellitus, hypertension and metabolic syndrome. In this study we aim to determine the serum 25-hydroxy vitamin D levels in patients with primary hypertension and to demonstrate any co-relation between vitamin D and Hypertension. 50 patients who are primary hypertensives were selected and their vitamin D level was measured and their vitamin D levels were compared to age and sex matched non hypertensive controls.50 hypertensive cases and 50 non hypertensive controls attending to outpatient department and inpatients coming to Yenepoya medical college hospital were investigated for evaluation of vitamin D status. The hypertensive patients had lower levels of vitamin D with vitamin D status of deficiency in 13(26%) of the cases and insufficiency in 20(40%) of the cases and normal levels in 17(34%) of the cases. Non hypertensive controls showed normal vitamin D status in 42(84%) of controls and insufficiency in 7(14%) of the controls and deficiency in 1(2%) of the controls. Age of the cases, duration of hypertension, systolic blood pressure and diastolic blood pressure inversely correlated to vitamin D levels. Body mass index, alcohol consumption and drug compliance did not correlate to vitamin D levels. It was observed from this study that serum vitamin D levels was lower in hypertensive patients when compared to non-hypertensive controls. Vitamin D could be an independent risk factor that is associated with primary or essential hypertension. Further studies with large number of participants are required to confirm the etiology of vitamin D deficiency in Primary Hypertension.***

Keywords: Vitamin D, Hypertension, Blood pressure

1. Introduction

Vitamin D is a steroid molecule and lipid soluble vitamin. The important role of Vitamin D is in the control of bone metabolism and calcium and phosphorus homeostasis. It is mainly produced by the skin and absorbed from the gut in diet that regulates the expression of a large number of genes.[(1)(2)]Vitamin D deficiency has been traditionally associated with poor bone growth and development of rickets in children and osteoporosis in adults.[(2)] New research and data shows that vitamin D could be a risk factor in many chronic diseases like hypertension, dyslipidemia, diabetes mellitus, cardiovascular disease, some cancers, auto immune disease and tuberculosis.[(2)]

There is an inverse relationship between the plasma1,25$(OH)_2$D3 concentration and the blood pressure and/or the plasma renin activity in both normotensive individuals and patients with essential hypertension [(3)].Ultraviolet light exposure, which is required for vitamin D biosynthesis, is inversely related to the rise of blood pressure and the prevalence of hypertension in the general population and was shown to have blood pressure–lowering effects [(3)]. Furthermore, it has been reported that vitamin D3 supplementation reduces blood pressure in patients with essential hypertension[(3)].

There is no definite test to check the vitamin D status in the body. Serum 25(OH) vitamin D is the major circulating metabolite of vitamin D and reflects vitamin D input from cutaneous synthesis and dietary intake[(4)]. Serum 1, 25$(OH)_2$ vitamin D levels maybe normal or even elevated in patients with vitamin D deficiency states. The most beneficial serum concentrations of 25(OH) vitamin D are observed at levels >30ng/ml (>75nmol/L). Most experts agree that vitamin D insufficiency is present with 25(OH) vitamin D levels of 21-29ng/ml. Levels <20ng/ml (<50nmol/L) is indicative of vitamin deficiency[(5)(4)]. A position statement released by international osteoporosis foundation (IOF) in 2010 also gives similar values. The serum level co-relates to the amount of vitamin D stored in fat tissue.[(5)(4)]

Aims and objectives of the study:

- To determine the serum 25-hydroxy vitamin D levels in patients with primary hypertension.
- To demonstrate any co-relation between vitamin D and Hypertension.

2. Methods and Materials

The study was conducted on patients attending the out-patient department (OPD) and in-patients admitted in Yenepoya medical college Hospital. The study was conducted on 50 hypertensive cases and 50 controls. Informed written consent was obtained from cases and controls for participation in the study and for conduction of investigations. The study was conducted between the period of November 2014 and January 2016.

Inclusion criteria

Primary hypertension, Age > 18 years

Exclusion criteria

The patients with following diseases were excluded:

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1) Secondary hypertension
2) Cerebrovascular disease
3) Cardiovascular disease
4) Diabetes mellitus
5) Dyslipidemia
6) Chronic kidney disease
7) Chronic liver disease

Complete clinical history and physical examination of 100 patients were done. All patients underwent the following investigations-Electrocardiogram, Random blood sugar, Serum vitamin D2 level, Blood urea, Serum creatinine, Ultrasound of the abdomen, Lipid Profile

Hypertension was defined as Systolic Blood Pressure > 140 mmHg and Diastolic Blood Pressure > 90 mmHg and on antihypertensive medication irrespective of blood pressure. Resting seated BP was measured three times at a single study visit using a mercury sphygmomanometer, after a 5 min rest using identical equipment. The mean of the last 2 measurements will be used to calculate blood pressure.[12]

Serum 25-hydroxyvitamin D levels were estimated by **CLIA** (fully automated chemi luminescent immuno assay). Values between 30 -100ng/ml were considered as sufficiency, between 21 –29 ng/dl was considered as insufficiency and those <20ng/dl were considered as deficiency.

3. Statistical methods:

Mean and Standard deviation was reported for all continuous variables (Systolic Blood Pressure, Diastolic Blood Pressure, Vitamin D), frequency and percentage for all categorical variables (case/control, gender). Pearson's Co-Relation Coefficient was performed to find out correlation between 2 continuous variables and to check the correlation between 2 categorical variables, Spearman's Rho correlation coefficient with p value was reported. Also to find whether there is any association between 2 categorical variables λ^2 was performed. All the analysis was done using SPSS version 22 software.

4. Results and Analysis

Our study was a cross sectional study on 50 hypertensive cases and 50 nonhypertensive controls conducted to determine the vitamin D status in them. In the study population among the cases, 27 were male and 23 were female while in the control group, 31 were male and 19 were female. The duration of hypertension in majority of the cases were less than 5 years. The compliance to antihypertensive drugs were good (never misses a dose) in 70%, average (misses one dose per week) in 18% and poor (misses more than one dose in a week) in 12% of the cases. In the study population, among the cases, 22% and 78% were vegetarians and non-vegetarians respectively while among the controls, 32% and 68% were vegetarians and non-vegetarians respectively.

In the study population, 19% consumes alcohol while 81% does not consume alcohol. The Pearson Chi-Square relationship between Vitamin D and smoking is 1.468(p value=0.480). In the study population, 31% were smokers and 69% were non-smokers.

Table 1: Correlations between Body Mass Index (BMI) , Systolic Blood Pressure (SBP), Diastolic Blood Pressure(DBP) and Vitamin D (S Vit D)

		BMI	SBP(mm Hg)	DBP(mm Hg)	S VIT D(ng/ml)
BMI	Pearson Correlation	1	.135	.155	-.100
	Sig. (2-tailed)		.181	.123	.320
	N	100	100	100	100
SBP(mm Hg)	Pearson Correlation	.135	1	.880**	-.503**
	Sig. (2-tailed)	.181		.000	.000
	N	100	100	100	100
DBP(mm Hg)	Pearson Correlation	.155	.880**	1	-.465**
	Sig. (2-tailed)	.123	.000		.000
	N	100	100	100	100
S VIT D(ng/ml)	Pearson Correlation	-.100	-.503**	-.465**	1
	Sig. (2-tailed)	.320	.000	.000	
	N	100	100	100	100

**. Correlation is significant at the 0.01 level (2-tailed).
Correlation between BMI and SBP is 0.135(p=0.181), between BMI and DBP is 0.155(p=0.123) and between BMI and S Vitamin D is -0.100(p=0.320)
In the study population, Vitamin D levels were ranging between 8 and 49.4 for the cases & the levels varied between 17.1 and 87 for the cor

All patients had normal cardiovascular examination. All subjects had a normal abdominal ultrasound and normal renal doppler study. All patients had normal range of random blood sugar, blood urea and serum creatinine. The systolic blood pressure most of the patients were between 121 to 130 mm of Hg, there were no patients with SBP more than 180 or less than 110 mm of Hg. The Diastolic blood pressures of most of the patients were between 81 to 90 mm of Hg, there were no patients with DBP more than 102 mm of Hg.

The mean vitamin D in cases was 27.2. The mean Vitamin D in controls was 40. The highest vitamin D level in cases was 49.4 and the lowest vitamin D level in cases was 8. The highest vitamin D level in controls was 87 and the lowest level in controls was 17.1.

Vitamin D deficiency was seen in 13(26%) of the cases and in 1(2%) of controls, Vitamin D insufficiency was seen in 20(40%) of the cases and in 7(14%) of controls and normal levels was seen in 17(34%) of cases and in 42(84%) of controls. There was significant inverse correlation between

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vitamin D and hypertension (p = 0.000). Vitamin D deficiency and insufficiency was seen in most of the hypertensive cases. Among the controls, most of the subjects had normal levels of vitamin D.

Age showed an inverse correlation with Vitamin D (p 0.00), with increasing age there was tendency towards lower levels of vitamin D in both the case and control groups. Systolic blood pressure increased with lower levels of vitamin D (p =0.00). Diastolic blood pressure also increased with lower levels of vitamin D (p= 0.00). Vitamin D levels tended to be lower in hypertensive cases with longer duration of hypertension (p = 0.647). BMI did not show any significant correlation with hypertension (p = 0.320). There was significant correlation between Vitamin D status and ECG showing LVH, family history of hypertension. Other characteristics and parameters like diet, alcohol consumption, smoking, BMI, compliance to therapy, did not have any significant correlation with the levels of vitamin D.

5. Discussion

A large hypertensive populations at risk for cardiovascular morbidity and mortality and essential or primary hypertension is a major and significant risk factor for cardiovascular disease.[5]

Vitamin D is a proximal inhibitor of RAS and inhibition of 1,25(OH)vitamin D synthesis results in an increase in renin expression and increase in 1,25(OH)vitamin D synthesis results in renin suppression[6]. More recently a study[7] showed that both 25(OH)D and 1,25(OH)D were inversely associated with plasma renin and angiotensin II concentrations. Vitamin D plays a role in regulating vascular tone by influencing the concentration of calcium in vascular smooth muscle cells. Intracellular calcium accumulation results in an inhibition of renin secretion in juxtaglomerular cells.[6]

Vitamin D plays a key role in influencing various parameters that regulate high blood pressure via various pathways including, proliferation of vascular smooth muscle cells, endothelial cell function, and regulation of renin-angiotensin pathway and in regulation of blood pressure via increased intracellular calcium leading to decreased renin activity. [8]

In addition to potential effects on the RAS and regulation of vascular smooth muscle contractility, vitamin D has also been hypothesized to have other effects on vascular endothelium and smooth muscle. It is a vascular protective agent; it reduces the deleterious effect of advanced glycation end products on the endothelium, improves activity of the NO system, and reduces inflammatory and atherosclerotic parameters. 1, 25(OH) vitamin D has also been implicated in the growth of vascular myocytes and has been shown to enhance prostacyclin production in vascular smooth muscle cells.[9]

In this study there was a significant correlation between low levels of vitamin D and hypertension. There was also a significant correlation between age, systolic blood pressure and diastolic blood pressure and duration of hypertension.

Initial retrospective observational studies have shown a significant inverse correlation between vitamin D and systolic blood pressure[10,11,12]. Duprez et al[10] in a study conducted on 25 hypertensive patients demonstrated that vitamin D levels inversely correlated with systolic blood pressure. In a study conducted by Kristal-Boneh E et al[11] on normotensive men showed a similar correlation between vitamin D levels and systolic blood pressure.

The third National Health and Nutrition Examination Survey (NHANES 3) study[13] was a large cross-sectional study involving non-institutionalized population aged more 20 years in a total population of 12644 patients and was used to evaluate the relationship between serum 25(OH)vitamin D and hypertension. The mean blood pressure varied inversely with serum 25(OH) vitamin D levels, with the association remaining significant after adjustment for age, gender, race, ethnicity and physical activity.

Epidemiological observations have shown incidence of hypertension increases with higher latitude, and winter months, blood pressure recordings show higher recording of blood pressure and for each 10^0 north or south shift of the equator BP increases by 2.5mm of Hg and prevalence of hypertension increases by 2.5%.

A study involving 613 men from health professionals follow up study [5] and 1198 women from nurse's health study[14] found that lower serum 25(OH)vitamin D levels of 15/ng/mL (<37nmol/L) increased the relative risk for hypertension by 6.13 in men and 2.67 in women when compared to vitamin D sufficient population (>75nmol/L)

In a randomized controlled trial on 148 elderly women demonstrated that a modest amounts of vitamin D (400IU) with calcium given over 8 week period significantly reduced systolic blood pressure (SBP) by 9%[15]. The largest trial to date the women`s health initiative (WHI)[16] done on a population of non-hypertensive at baseline failed to show any significant impact of a small dose of vitamin D (400IU) with calcium 1000mg/day on systolic blood pressure or diastolic blood pressure after a mean follow up of 7 years in post-menopausal women.

Another prospective study in 1448 women demonstrated a 2.21 fold increase in incident hypertension in hypovitaminosis D group versus control groups[17]. A cross-sectional study[18] conducted on 4125 subjects showed a significant association between hypovitaminosis D and hypertension.

These studies demonstrate that vitamin D supplementation may play a key role in controlling high blood pressure however the current evidence is weak and further randomized trials with larger populations may be required.

6. Conclusion

The hypertensive patients had lower levels of vitamin D with vitamin D status of deficiency in 26% of the cases and insufficiency in 40% of the cases and normal levels in 34% of the cases. Non hypertensive controls showed vitamin D status of normal in 84% of controls, insufficiency in 14% of

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the controls and deficiency in 2% of the controls. Age of the cases, duration of hypertension, systolic blood pressure and diastolic blood pressure inversely correlated to vitamin D levels. Body mass index, diet of the patient, alcohol consumption, drug compliance, did not correlate to vitamin D levels. Family history of hypertension, ECG showing LVH and fundus status correlated to vitamin D levels. Vitamin D is an independent risk factor that is associated with primary or essential hypertension.

Vitamin D deficiency may cause hypertension via up-regulation of renin expression, increased renin angiotensin activity, endothelial dysfunction proliferation of vascular smooth muscle and down regulation of vasodilators. Vitamin D supplementation may have a role in reducing the risk of development of hypertension. Vitamin D supplementation may have a role in reduction of blood pressure in hypertensive patients. Further studies with large number of participants are required to confirm the etiology of vitamin D deficiency in Primary Hypertension.

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