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A Study of Plasma Vitamin D Levels as a Risk Factor in Primary Hypertension: A Case Control Study.

Shivaraj Reddy Kandala[1], M S Biradar[2]

[1]Junior Resident, Department of Medicine, BLDE Deemed to be University, Sri B M Patil Medical College Hospital and Research Centre, Vijayapur-586103, Karnataka, India.

[2]Vice chancellor and professor, Department of Medicine, B.L.D.E Deemed to be University, Sri B M Patil Medical College Hospital and Research Centre, Vijayapur-586103, Karnataka, India.

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ABSTRACT

Background: Hypertension is the third leading killer disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide.1 There is strong positive and continuous correlation between BP and the risk of cardiovascular disease (myocardial infarction, heart failure), renal disease, stroke and mortality. The present was aimed to find low plasma vitamin D levels are the risk factors for primary hypertension or not. Aims:. To study the low plasma vitamin D levels are the risk factors for primary hypertension or not. **Methods:** This was a case control study carried out in 100 patients, 50 controls and 50 cases with primary hypertension, aged between 18 to 60 years , admitted in BLDEDU's Shri B.M.Patil hospital. **Results:** The number of patients in both the groups was predominantly female (52%) respectively while male patients constituted 48% of the study population. The mean systolic blood pressure (SBP) value in controls was significantly lower as compared to cases (116.8 ± 6.7 vs. 155.0 ± 8.4 mmHg). The mean diastolic blood pressure (DBP) values in controls was significantly lower as compared to cases (74.5 ± 4.8 vs. 87.6 ± 5.2 mmHg). The mean Vitamin D level in controls was higher as compared to cases (21.2± 11.5 vs. 18.0 ± 6.3ng/ml). However there was no significant difference between the groups as per Student t-test (p>0.05). **Conclusion:** In controls, 8% patients had Vitamin D deficiency while 24% patients had Vitamin D sufficiency. In cases, 10% patients had Vitamin D deficiency while 84% patients had Vitamin D insufficiency. The systolic and diastolic blood pressure values were significantly higher in cases as compared to controls in Vitamin D deficient, insufficient and sufficient patients.

Keywords: Primary Hypertension, Vitamin D.

INTRODUCTION

Hypertension is the third leading killer disease in the world and is responsible for 1 in every 8 deaths. About 1 billion people are affected by hypertension worldwide.[1] Hypertension is a major public health problem in India and other countries as well. There is strong positive and continuous correlation between BP and the risk of cardiovascular disease (myocardial infarction, heart failure), renal disease, stroke and mortality. Hyperuricemia predicts mortality in patients with heart failure or coronary heart disease, cerebrovascular events in individuals with diabetes and cardiac ischemia in hypertension.[2]

Hypertension, defined as a systolic blood pressure ≥140 mmHg and/or a diastolic pressure ≥90 mmHg, is one of the most common chronic diseases. The overall hypertension prevalence among the adult population was estimated at 26.4% in 2000.[3]moreover it has been reported that this prevalence increased from 23.9%, in 1994, to 29.0%, in 2008, in the USA4 from 25.0% in 1993 to 43.2% in 2006, in Mexico;[5] and from 15.3% in 1995, to 24.5%, in 2005, in Canada among other countries.[6] From this prevalence, it is evident that hypertension is a very important public health challenge because its complications, including cardiovascular, cerebrovascular, and renal diseases, are major causes of morbidity and mortality. Reducing blood pressure in individuals with hypertension prevents or attenuates these complications.[7]

Hypertension is due to specific causes in a small fraction of cases, but in the vast majority of individuals (≈90-95%), its etiology cannot be determined; therefore, the essential hypertension term is employed.[8] Essential hypertension is currently understood as a multifactorial disease arising from the combined action of many genetic, environmental, and behavioral factors. Given the multifactorial nature of blood pressure homeostasis, any change in blood pressure as, for example, one

Name & Address of Corresponding Author
Dr. M S Biradar,
Vice chancellor and professor,
Department of Medicine,
B.L.D.E Deemed to be University,
Sri B M Patil Medical College Hospital and Research Centre,
Vijayapur-586103, Karnataka, India.

due to a mutation, is likely to be compensated by feedback, complementary action, or change, in some other control mechanisms, in an effort to return blood pressure to normal. It is only when the balance between the factor(s) that tend to increase the blood pressure and those that try to normalize it is sufficiently disturbed, when the compensatory mechanisms fail to counteract the perturbation, that essential hypertension results.[9] A century of epidemiological, clinical, and physiological research in humans and animals has provided remarkable insights on the relationships existing between dietary salt (Nacl), renal sodium handling, and blood pressure.[10]

Vitamin D is a steroid molecule and lipid soluble vitamin, mainly produced by the skin and absorbed from the gut in diet that regulates the expression of a large number of genes. Its main role is in the control of bone metabolism and calcium and phosphorus homeostasis".

Vitamin D deficiency has been traditionally associated with poor bone growth and development of rickets in children and osteoporosis in adults. During the last two decades new research and data is showing that vitamin D could be a risk factor in many chronic diseases like hypertension, diabetes mellitus, dyslipidemia, CVD, some cancers, auto immune disease and TB.

Vitamin D deficiency, defined as a plasma 25-hydroxyvitamin D3 (25(OH) D) level under 20 ng/mL, is highly prevalent with an incidence of about 30-50% in all over of the world.[11] A low level of vitamin D is linked to the increased risk of cardiovascular diseases (CVD) and mortality.[12]

Adiposity, lack of physical activity and excessive salt intake are some of the best-known environmental factors associated with hypertension. In recent years, yet another cause has been postulated: vitamin D deficiency.[13]

A wealth of observational data has demonstrated relationships between circulating vitamin D metabolite levels and blood pressure (BP). Lower 25-hydroxyvitamin D (25OHD) levels are associated with higher BP levels in cross-sectional studies and with increased rates of incident hypertension.[14]

Vitamin D has been shown to improve endothelial function in some studies,[15] reduce the production of proinflammatory cytokines, "reduce activity of the renin-angiotension-aldosterone system, and reduce parathyroid hormone (PTH) levels.[16] Any or all of these mechanisms therefore potentially mediate an effect of vitamin D on BP levels".

Studies in India have demonstrated the low levels of vitamin D in the Indian population and hypertension, diabetes, vascular disease show high incidence and prevalence in India.[17]

Hence the present study was done at our hospital to assess the relationship between plasma levels of vitamin D and hypertension in this part of our country. Based on this observatation further prospective studies can be taken up on the role of supplementation of vitamin D3 and reduction in blood pressure in hypertensive patients.

MATERIALS AND METHODS

This case control study included outpatients and inpatients at tertiary care center, between October 2016 to august 2018, who were diagnosed as primary hypertension. All patients with primary hypertension, aged more than 18years were included in the studied and patients with secondary hypertension were excluded. A detailed history, general physical examination, systemic examination and investigations were performed on all patients having primary hypertension.

Vitamin D is done in every patient of primary hypertension and other routine investigations to rule out secondary hypertension are done. After considering the inclusion and exclusion criteria, all patients will be interviewed as per the prepared proforma and then complete clinical examination and laboratory investigations will be done.

Inclusion Criteria

- Primary Hypertensive patients
- 18-60 years of both sexes.

Exclusion Criteria

- All identifiable secondary hypertensive patients.
- Cerebro- vascular disease
- Coronary artery disease
- Chronic renal disease
- Diabetes mellitus
- Anti-epileptic drugs
- Smokers

All patients are evaluated with detailed history including age, sex, presenting symptoms, history of co morbid illnesses, smoking history, alcohol consumption and physical parameters like BMI, Waist Hip ratios will be noted, age and sex matched controls will be taken and in both groups plasma vitamin D level will be estimated.

Statistical Analysis

The patients were informed about study in all respects and informed consent was obtained. Statistical analysis of data was done using Mean ± SD, Diagrams, Correlation coefficient, Chi-square test.

RESULTS

Table 1: Distribution of patients according to Age

Age	Cases		Control		P Value
	N	%	N	%	
21-30	0	0	7	14	0.001*
31-40	6	12	16	32	
41-50	21	42	14	28	
51-60	23	46	13	26	
Total	50	100	50	100	
Mean±SD	18.02±6.3		21.2±11.5		

Note: * significant at 5% level of significance (p<0.05)

A hospital based observational case control study was conducted with 100 patients to analyze whether low plasma vitamin D level is risk factor for primary hypertension or not. The patients are divided into two groups of 50 patients each as follows:
Cases: Patients of primary hypertension
Control: Patients that were age and sex matched individuals

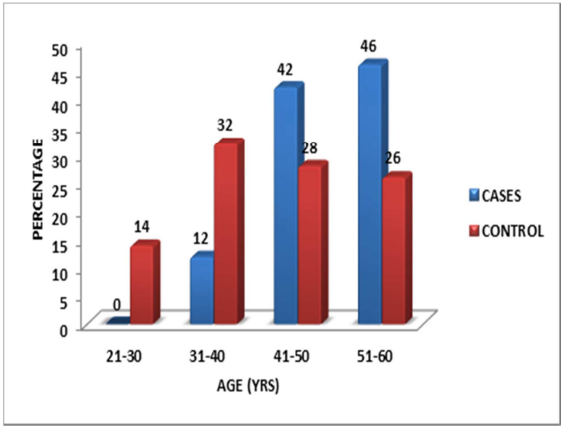

Figure 1: Distribution of patients according to Age

Distribution of patients according to Gender

The number of patients in both the groups was predominantly female (52%) respectively while male patients constituted 48% of the study population.

Table 2: Distribution of patients according to Gender

Sex	Cases		Control		P Value
	N	%	N	%	
Male	24	48	24	48	>0.05
Female	26	52	26	52	
Total	50	100	50	100	
M/f ratio	0.92:1		0.92:1		

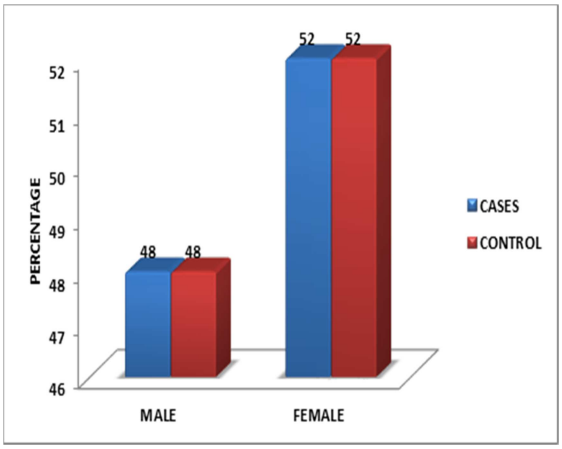

Figure 2: Distribution of patients according to Gender

Comparison of Blood Pressure parameters between groups

The mean systolic blood pressure (SBP) value in controls was significantly lower as compared to cases (116.8 ± 6.7 vs. 155.0 ± 8.4 mmHg).

Table 3: Comparison of Blood Pressure parameters between groups

Parameters	Cases		Control		P Value
	Mean	SD	Mean	SD	
SBP	155.0	8.4	116.8	6.7	<0.001*
DBP	87.6	5.2	74.5	4.8	<0.001*

Note: * significant at 5% level of significance (p<0.05)

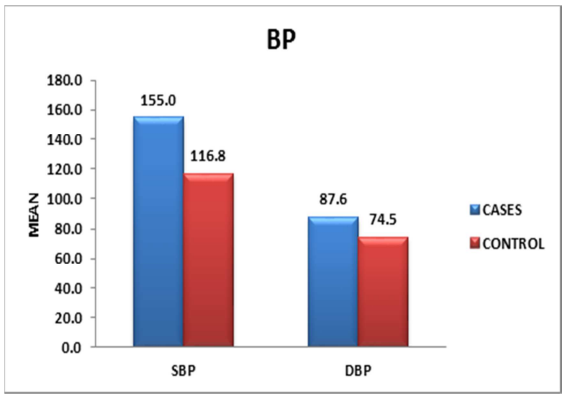

Figure 3: Comparison of Blood Pressure parameters between groups

Comparison of Vitamin D levels between groups

The mean Vitamin D level in controls was higher as compared to cases (21.2± 11.5 vs. 18.0 ± 6.3ng/ml).

Table 4: Comparison of Vitamin D levels between groups

Parameters	Cases		Control		p value
	Mean	SD	Mean	SD	
VIT-D (ng/dl)	18.0	6.3	21.2	11.5	0.093

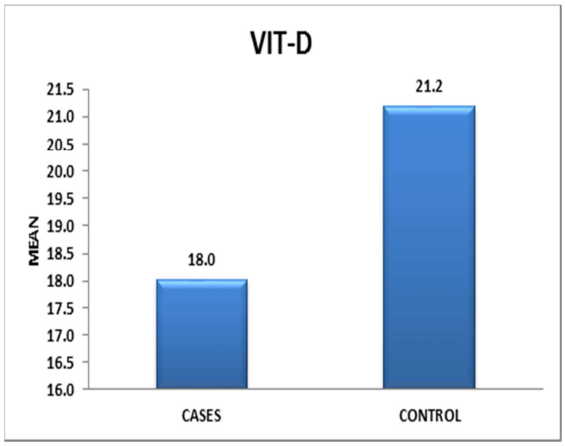

Figure 4: Comparison of Vitamin D levels between groups

Association of Deficiency in Vitamin D levels and Blood Pressure parameters

The systolic and diastolic blood pressure values were significantly higher in cases as compared to controls in Vitamin D deficient, insufficient and sufficient patients. The association of Vitamin D levels was found to be significant with SBP and DBP values (p<0.05).

Table 5: Association of Deficiency in Vitamin D levels and Blood Pressure parameters

VIT-D (ng/dl)	BP	CASES		CONTROL		p value
		Mean	SD	Mean	SD	
Deficiency (<10)	SBP	161.2	5.2	120.0	0.0	<0.001*
	DBP	90.4	0.9	80.0	0.0	<0.001*
Insufficiency (10-30)	SBP	154.3	8.8	117.3	6.9	<0.001*
	DBP	86.9	5.4	74.4	4.8	<0.001*
Sufficiency (>30)	SBP	154.0	2.0	110.0	0.0	<0.001*
	DBP	92.7	3.1	71.2	1.8	<0.001*

Note: * significant at 5% level of significance (p<0.05)

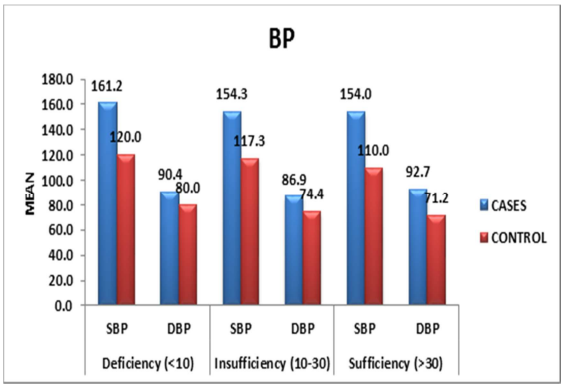

Figure 5: Association of Deficiency in Vitamin D levels and Blood Pressure parameters

DISCUSSION

A hospital based observational case control study was conducted with 100 patients to analyze whether low plasma vitamin D level is risk factor for primary hypertension or not. The patients are divided into two groups of 50 patients each as follows:

Cases: Patients of primary hypertension

Control: Patients that were age and sex matched individuals

Vitamin D deficiency is an emerging risk factor for multiple comorbidities worldwide, despite abundant sunshine. So far, various studies have been done to prove an association between Vitamin D deficiency and HTN. This relationship has already been established in the Western population but needs further validation in the Indian scenario.[18,19]

In the present study, majority of the patients (32%) in controls were from the age group of 31-40 years followed by 28% from the age group of 41-50 years, 26% from the age group of 51-60 years, 14% from the age group of 21-30 years. The mean age in controls was 21.2 ± 11.5 years. Majority of the patients (46%) in cases were from the age group of 51-60 years followed by 42% from the age group of 41-50 and 12% from the age group of 31-40 years. The mean age in cases was 18.02 ± 6.3 years. The difference in mean age of the patients in the two groups was statistically significant as per Student t-test (p<0.05).

The number of patients in both the groups was predominantly female (52%) respectively while male patients constituted 48% of the study population. The distribution of patients between two groups on basis of gender were comparable and statistically not significant as per Chi-Square test (p>0.05). This is similar to the studies of Priya S et al,[22] Reddy VS et al and Akbari R et al.[21,23]

The study of Reddy VS et al,[21] reported Hypertension was detected in 29 of the 407 subjects (prevalence=7.1%), of which the majority were newly diagnosed (76%). The prevalence among men (15.0%) was higher as compared to women (5.0%). In addition, 46.7% of the subjects were found to have blood pressures in the pre-hypertensive range.

It was observed in our study that the mean Vitamin D level in controls was higher as compared to cases (21.2± 11.5 vs. 18.0 ± 6.3ng/ml). However there was no significant difference between the groups as per Student t-test (p>0.05).

Priya S et al,[22] cross sectional case–control study establishing a causal association between Vitamin D deficiency and HTN reported mean level of 25(OH) D among cases was 15.15 ± 12.51 ng/ml, while among controls, the corresponding value was 33.59 ± 16.69 ng/ ml. The difference was statistically significant (P = 0.0001). Among cases, 80.4% were Vitamin D deficient and 9.8% had insufficient levels of Vitamin D. Among controls, 16.2% each had Vitamin D deficiency and insufficiency.

It was observed in the present study that in controls, 8% patients had Vitamin D deficiency while 24% patients had Vitamin D sufficiency. In cases, 10% patients had Vitamin D deficiency while 84% patients had Vitamin D insufficiency. There was significant difference between the groups as per Chi-Square test (p<0.05).

Akbari R et al,[23] case-control study investigating the relationship between serum vitamin D level and hypertension (HTN) in hypertensive subjects reported mean of PTH serum level in two groups showed no significant difference between the men of the two groups; however, this difference was significant between the females of both groups. Serum vitamin D level was significantly higher in patients with HTN than healthy group (P=0.001). Proportion of serum 25-OHD deficiency, insufficiency and sufficiency in patients were 27%, 40% and 33% and in the control group 40%, 53% and 7% respectively.

The systolic and diastolic blood pressure values in our study were significantly higher in cases as compared to controls in Vitamin D deficient, insufficient and sufficient patients. The association of Vitamin D levels was found to be significant with SBP and DBP values (p<0.05). This is comparable

to the studies of Priya S et al,[22] Akbari R et al and Martins D et al.[23.24]

Discrepancies in relationship between serum vit D across various studies may be attributed to several factors including age, sex, ethnic characteristics, and prevalence of coexisted comorbidities particularly HTN and vit D deficiency in the general population and the study groups. Additionally, several common chronic diseases such as vitamin D deficiency, diabetes, obesity, metabolic syndrome, and hypertension are prevalent in this geographic region.[25] These factors affect HTN and vitamin D status differently.

For Vitamin D, a cut off 17.75 had highest sensitivity 42.0% and specificity 40.0%. The area under the ROC curve was low and cannot be a predictor of hypertension. Similar observations were noted in the studies of Priya S et al,[22] Ke L et al,[13] Qi D et al,[18] and O'Callaghan KM et al.[20]

Qi D et al,[18] prospective study and meta-analysis determining the link between vitamin D concentrations and incident hypertension reported during a median follow-up of 2 years, 42.6% of the cohort (n = 1047) developed hypertension. Compared with the 25-hydroxyvitamin D >30ng/ml, 25-hydroxyvitamin D <20 ng/ml was associated with a greater hypertension risk (OR: 1.225 [95% CI: 1.010 to 1.485] p = 0.04).

O'Callaghan KM et al,[20] interventional, observational narrative systematic review evaluating growing evidence of an association between low maternal vitamin D status and increased risk of hypertensive disorders reported conflicting data for an association of vitamin D with gestational hypertensive disorders in observational studies arises from a number of sources including large heterogeneity between study designs, lack of adherence to standardized perinatal outcome definitions, variable quality of analytical data for 25-hydroxyvitamin D (25(OH)D), and inconsistent data reporting of vitamin D status.

CONCLUSION

Low Vitamin D levels are risk factors for primary hypertension. Despite the accumulating evidence of a consistent link between vitamin D and blood pressure, the questions still remain in relation to the causality of this relationship. Further studies are needed to determine whether this represents a causal association. Large randomized controlled trials are also needed to determine whether vitamin supplementation may be beneficial in the prevention or the treatment of hypertension. More research is needed to further determine the role of 25-hydroxyvitamin D in hypertension prevention and therapy.

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