

A STUDY ON PLASMA 25-HYDROXY VITAMIN D LEVELS AS A RISK FACTOR IN PRIMARY HYPERTENSIONRavinandana Gowda H. V¹, Mumtaz Ali Khan²**HOW TO CITE THIS ARTICLE:**

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ABSTRACT: BACKGROUND: Recent research shows that vitamin D deficiency could be a risk factor in many chronic diseases like hypertension, diabetes mellitus, dyslipidemia, cardiovascular disease, some cancers, auto immune disease and tuberculosis. **AIMS AND OBJECTIVES:** To determine serum 25-hydroxy vitamin D levels in patients with primary hypertension. This study also attempts to demonstrate an inverse co-relation between vitamin D levels and primary hypertension. **MATERIALS AND METHODS:** 30 patients who are primary hypertensive were selected, their vitamin D levels measured and the vitamin D levels were compared to age and sex matched non hypertensive controls. **STATISTICAL METHODS:** Descriptive and inferential statistical analysis has been carried out in the present study. ANOVA test and Chi-square test was applied for quantitative and qualitative data respectively to find significant associations between two variables. **RESULTS:** It is seen from this study that serum vitamin D levels was lower in hypertensive patients when compared to non-hypertensive controls. Hypertensive patients had lower levels of vitamin D with vitamin D status of deficiency in 50% of the cases and insufficiency in 43.3% of the cases and normal levels in 6.7% of the cases. Non hypertensive controls showed vitamin D status of normal in 66.7% of controls and insufficiency in 33.3% of the controls without deficiency. 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, number of anti-hypertensive drugs, drug compliance, family history of hypertension and fundus status did not correlate to vitamin D levels. **CONCLUSIONS:** Based on the observations of the study, Vitamin D is an independent risk factor that is associated with primary or essential hypertension. The level of vitamin D also correlated inversely to age, duration of hypertension and systolic and diastolic blood pressure.

KEYWORDS: Vitamin D, hypertension, RAS, 1, 25(OH) vitamin D, Regulation, Atherosclerosis.

INTRODUCTION: Vitamin D deficiency has been traditionally associated with poor bone growth and development and development of rickets in children and osteoporosis in adults. In recent years emphasis has been given to the role of vitamin D in areas beyond those traditionally known. 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, cardiovascular disease, some cancers, auto immune disease and tuberculosis.

Hypertension is a polygenic and multifactorial disease involving many pathways and mechanisms. Many epidemiological studies have demonstrated an inverse relationship between vitamin D levels and blood pressure. Studies in India have demonstrated that the level of vitamin D in the population is low and there is high prevalence of chronic diseases like hypertension, diabetes, cardiovascular disease.

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Endothelial dysfunction is a hallmark of many vascular diseases including cardiovascular disease. Vitamin D deficiency may cause endothelial dysfunction^[1] by itself or by its significant correlation with its risk factors like hypertension, diabetes mellitus and dyslipidemia.

Vitamin D deficiency is also related to increased activity of renin-angiotensin-aldosterone system, cardiac contractility, vascular tone, cardiac collagen content and cardiac tissue maturation and chronic sub-acute inflammation with increase in pro-inflammatory cytokines, loss of suppression of anti-inflammatory cytokine IL-10 and loss of suppression of foam cell formation thereby promoting atherosclerosis.

AIMS AND OBJECTIVES OF THE STUDY: To determine the serum 25-hydroxy vitamin D levels in patients with primary hypertension. This study also attempts to demonstrate an inverse correlation between vitamin D and primary hypertension.

MATERIALS AND METHODS: SOURCE OF DATA: The study was conducted on patients attending the outpatient department (OPD) of hospitals attached to Bangalore medical college and research institute (BMC&RI) i.e. Victoria hospital and Bowring and Lady Curzon hospitals. The study was conducted on 30 hypertensive cases and 30 age and sex matched 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 October 2010 and September 2012.

INCLUSION CRITERIA:

1. Primary hypertension.
2. Age 18-65 years.

EXCLUSION CRITERIA:

1. Secondary hypertension.
2. Cerebrovascular disease.
3. Cardiovascular disease.
4. Diabetes mellitus.
5. Dyslipidemia.
6. Chronic kidney disease.
7. Chronic liver disease.
8. Smoker.
9. Anti-epileptic drugs, steroids, rifampicin, ART, cholestyramine, antacids, orlistat.
10. Osteoporosis.

METHOD OF COLLECTION OF DATA: Complete clinical history and physical examination of 60 patients were done. All patients underwent the following investigations;

1. Electrocardiogram.
2. Random blood sugar.
3. Serum vitamin D₂ level.

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4. Blood urea.
5. Serum creatinine.
6. Ultrasound of the abdomen.
7. Renal Doppler.

STATISTICAL SOFTWARE: The Statistical software namely SAS 9.2, SPSS 15.0, Stata 10.1, MedCalc 9.0.1, Systat 12.0 and R environment ver.2.11.1 were used for the analysis of the data and open office have been used to generate graphs, tables etc.

RESULTS AND ANALYSIS:

Study Design: A cross sectional study done on 30 hypertensive cases and 30 non hypertensive controls is undertaken to know the vitamin D status in them.

Age	Case (%)	Control (%)
18-30	0(0.0)	0(0.0)
31-40	5(16.6)	12(40)
41-50	12(40.0)	7(23.3)
51-60	11(36.6)	11(36.6)
61-65	2(6.6)	0(0.0)
Total	30	30

Table 1: Age distribution of study population

Sex	Case (%)	Control (%)
Male	22(73.4)	23(76.7)
Female	8(26.6)	7(23.3)
Total	30	30

Table 2: Sex distribution of study population

Age	Case		Control	
	Male	Female	Male	Female
18-30	0	0	0	0
31-40	3	2	7	5
41-50	8	4	5	2
51-60	9	2	11	0
61-65	2	0	0	0
Subtotal	22	8	23	7
Total	30	30	30	30

Table 3: Age-sex distribution of study population

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Duration of hypertension	Number of cases (%)
One year or less	11(36.6)
2-5 years	14(46.6)
5-10 years	4(13.3)
More than 10 years	1(3.3)
Total	30

Table 4: Duration of hypertension

Number of anti-hypertensive drugs	Number of cases (%)
0	0(0.0)
1	25(83.3)
2	5(16.7)
3 or more	0(0.0)
Total	30

Table 5: Number of anti-hypertensive drugs

Type of drug	Number of patients (%)
ACE	5(16.7)
ARB	4(14.3)
CCB	10(33.3)
ACE+CCB	1(3.3)
ACE+BB	2(6.6)
ARB+Diuretic	2(6.6)
Total	30

Table 6: Type of anti-hypertensive therapy

ACE – Angiotensin converting enzyme inhibitor, ARB – Angiotensin receptor blocker, BB – Beta blocker, CCB – Calcium channel blocker.

Compliance	Number of cases (%)
Good	16(53.3)
Average	10(33.3)
Poor	4(14.3)
Total	30

Table 7: Compliance to anti-hypertensive drugs

Good – Does not miss drug doses, Average – Misses one dose a week, Poor – Misses more than one dose a week.

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History	Case (%)	Control (%)
Present	11(36.6)	15(50.0)
Absent	19(73.4)	15(50.0)
Total	30	30

Table 8: Family history of hypertension

Family History – History of hypertension in parents or siblings.

Diet	Case (%)	Control (%)
Vegetarian	3(10.0)	4(13.3)
Mixed	27(90.0)	26(86.7)
Total	30	30

Table 9: Type of diet

Alcohol	Case (%)	Control (%)
Does not consume	20(66.6)	20(66.6)
Occasional	8(26.6)	6(20.0)
Regular/ Daily	2(6.6)	4(13.3)
Total	30	30

Table 10: Alcohol consumption

BMI	Case	Control
Less than 20.9	0(0.0)	2(6.6)
21-25.9	28(93.4)	26(86.6)
26-29.9	2(6.6)	2(6.6)
More than 30	0(0.0)	0(0.0)
Total	30	30

Table 11: Body mass index of study population

SBP (mm of Hg)	Case (%)
Less than or equal to 120	0(0.0)
121-130	3(10.0)
131-140	18(60.0)
141-150	7(23.3)
151-160	2(6.6)
More than 160	0(0.0)
Total	30

Table 12: Systolic blood pressure of cases

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DBP (mm of Hg)	Case (%)
Less than or equal to 80	6(20)
81-90	21(70)
91-100	3(10)
> 100	0(0.0)
Total	30

Table 13: Diastolic blood pressure of cases

Fundus grade	Case (%)
Grade 1	5(16.6)
Grade 2	4(13.3)
Grade 3	2(6.6)
Grade 4	2(6.6)
Normal	19(63.3)
Total	30

Table 14: Fundus examination of cases

ECG	Case (%)
Normal	22(73.3)
LVH	8(26.7)
Total	30

Table 15: Electrocardiogram of cases

	Case	Control	P-value
Vitamin D Mean±SD	19.91± 7.0	32.22± 4.0	< 0.001
Vitamin D Median (IQR)	20(15.3, 23.8)	31.6(29.1, 35.6)	<0.001

Table 16: Vitamin d results

IQR - Inter quartile range.

Vitamin D Status	Cases	Control	Total
Deficiency	15(50.0)	0(0.0)	15(25.0)
Insufficient	13(43.3)	10(33.3)	23(38.3)
Normal	2(6.7)	20(66.7)	22(36.7)
Total	30	30	60

Table 17: Vitamin d status

Chi-Square = 30.12 p <0.001.

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Characteristic	Correlation Co-efficient (r)	P – value
Age	- 0.42	0.023*
BMI	- 0.18	0.347
SBP	- 0.37	0.045*
DBP	- 0.41	0.026*
Duration of Hypertension	- 0.39	0.032*

Table 18: Correlation between vitamin d and other parameters

*Indicates statistically significant.

The baseline characteristics of the study population were similar (Table-1 to 11).

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 130mm of Hg, there were no patients with SBP more than 160 or less than 120mm of Hg (Table 12). The Diastolic blood pressure of most patients was between 81 to 90mm of Hg, there were no patients with DBP more than 100mm of Hg (Table 13). The fundus of most of the patients were normal with 5 patients had grade 1 fundus, 4 had grade 2 fundus, 2 patients had grade 3 fundus and none of the patients had grade 4 fundus (Table 14). The ECG of 8 hypertensives showed left ventricular hypertrophy and rest of them had a normal ECG (Table 15).

The mean vitamin D in cases was 19.91 and the median vitamin D in cases was 20. The mean Vitamin D in controls was 32.22 and the median vitamin D in controls was 31.6 (Table 16). The highest vitamin D level in cases was 37.56 and the lowest vitamin D level in cases was 3.94. The highest vitamin D level in controls was 39.41 and the lowest level in controls was 24.54.

Vitamin D deficiency was seen in 15(50%) of the cases and in 0 among controls. Vitamin D insufficiency was seen in 13(43.3%) of the cases and in 10(33.3%) of controls and normal levels was seen in 2(6.7%) of cases and in 20(66.7%) of controls (Table 17). There was significant inverse correlation between vitamin D and hypertension ($p < 0.001$). Vitamin D deficiency and insufficiency was seen in most of the hypertensive cases. Among the controls none of the subjects showed deficiency as most of the subjects had normal levels of vitamin D.

Age showed an inverse correlation with Vitamin D ($p=0.023$), 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 ($p=0.045$). Diastolic blood pressure also increased with lower levels of vitamin D ($p=0.026$). Vitamin D levels tended to be lower in hypertensive cases with longer duration of hypertension ($p = 0.032$).

BMI did not show any significant correlation with hypertension ($p=0.347$). Other characteristics and parameters like diet, alcohol consumption, number of drugs in anti-hypertensive therapy, compliance to therapy, family history of hypertension, fundus status, ECG

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and random blood sugar levels also did not show any significant correlation with the levels of vitamin D (Table 18).

DISCUSSION: Essential or primary hypertension is a major and significant risk factor for cardiovascular disease. The incidence of hypertension is increasing and there is large hypertensive population at risk for cardiovascular morbidity and mortality. Recent studies show that vitamin D plays a key role in influencing various parameters that regulate high blood pressure via various pathways including endothelial cell function, proliferation of vascular smooth muscle cells, regulation of renin-angiotensin pathway and in regulation of blood pressure via increased intracellular calcium leading to decreased renin activity.^[2]

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.^[3] More recently a study by Tomaschitz A et al,^[4] 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.

In addition to potential effects on the RAS and regulation of vascular smooth muscle contractility, vitamin D has also been hypothesized 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.

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.

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° north or south shift of the equator BP increases by 2.5mm of Hg and prevalence of hypertension increases by 2.5%.

Initial retrospective observational studies have shown a significant inverse correlation between vitamin D and systolic blood pressure.^[5,6,7] Duprez et al^[5] 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 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^[8] 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.

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A study involving 613 men from health professionals follow up study^[9] and 1198 women from nurses' health study^[10] 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). Another prospective study in 1448 women demonstrated a 2.21 fold increase in incident hypertension in hypovitaminosis D group versus control groups.^[11] A cross-sectional study^[12] conducted on 4125 subjects showed a significant association between hypovitaminosis D and hypertension.

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%.^[13]

The largest trial to date the women's health initiative (WHI)^[14] 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.

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.

CONCLUSION:

- Hypertensive patients had lower levels of vitamin D with vitamin D status of deficiency in 50% of the cases and insufficiency in 43.3% of the cases and normal levels in 6.7% of the cases.
- Non hypertensive controls showed vitamin D status of normal in 66.7% of controls and insufficiency in 33.3% of the controls without deficiency.
- 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, number of anti-hypertensive drugs, drug compliance, family history of hypertension and fundus status did not correlate to vitamin D levels.
- Vitamin D is an independent risk factor that is associated with primary or essential hypertension.

SUMMARY:

- Recent research and studies show vitamin D may be associated with hypertension, diabetes mellitus, cardiovascular disease, cerebrovascular disease. Dyslipidemia, obesity, increased risk of infections and auto-immune disease.
- 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 vaso-dilators.
- Vitamin D supplementation may have a role in reducing the risk of development of hypertension.

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