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**A STUDY ON PLASMA 25-HYDROXY VITAMIN D LEVELS AS A RISK FACTOR IN  
PRIMARY HYPERTENSION**

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**ABSTRACT**

To determine the serum vitamin D levels in primary hypertensive patients. 30 patients who were primary hypertensive were selected and their vitamin D levels will be measured and compared to age and sex matched non hypertensive controls. It is seen from this study that serum vitamin D levels were lower in hypertensive patients when compared to non hypertensive controls. The levels of vitamin D also inversely correlated to age, duration of hypertension and systolic and diastolic blood pressure. 30 hypertensive cases and 30 non hypertensive controls attending to outpatient department of hospitals attached to J.L.N medical college and Hospital were investigated for evaluation of vitamin D status. Based on the observations made in them the following conclusions were drawn: The 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, and 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.

**Keywords: Serum Vitamin D, Hypertensive**

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## INTRODUCTION

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 [1].

Vitamin D deficiency has been traditionally associated with poor bone growth and development and development of rickets in children and osteoporosis in adults and in recent year's 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 [2-4].

Hypertension is a polygenic and multifactorial disease involving many pathways and mechanisms. 1 in 9 are affected in India, with a population of more than one billion, estimated number of patients may be more than 100 million. There is a significant morbidity, mortality and economic burden on a developing country like India [3, 4].

Many epidemiological studies have demonstrated an inverses 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 [5].

Present study was aimed to determine the serum 25-hydroxy vitamin D levels in patients with primary hypertension. This study attempts to demonstrate an inverse co-relation between vitamin D.

## MATERIALS AND METHODS

### Source of Data

The study was conducted on patients attending the outpatient department (OPD) of hospitals attached to J.L.N medical college and Hospital, Ajmer. 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 2012 and September 2013.

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

### Statistical Methods

Descriptive and inferential statistical analysis has been carried out in the present study. Results on continuous measurements are presented on Mean  $\pm$  SD (Min-Max) and results on categorical measurements are presented in Number (%). Significance is assessed at 5 % level of significance. The following assumptions on data is made,

### Assumptions:

1. Dependent variables should be normally distributed,
2. Samples drawn from the population should be random, Cases of the samples should be independent.

### 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.

### Ethics

This study was conducted after ethical clearance from the medical College Board and University as per standard protocols and guidelines.

### RESULTS

The baseline characteristics of the study population were similar, out 30 of cases 22 were males and 8 were females and out of 30 controls 23 were males and 7females. The majority of the cases were from the 41 to 50 age group followed by the 51 to 60 age group and the control group majority of the population was from 31 to 40 age group followed by 51 to 60 age group. There no patients of less than 30 years in both the groups and there were 2 patients above 60 in case group among the hypertensive 11 of them were diagnosed to be hypertensive less

than or equal to year from the time of study, 14 were diagnosed between 2 to 5 years, 4 of them were diagnosed between 5 to 10 years and only 1 had long standing hypertension of greater than 10 years (**Table 1**). All of them were on anti-hypertensive medications with 25 of them on single drug regimen and 5 of them on combination regimen. Most of the patients were on calcium channel blockers followed by almost equal number of patients on angiotensin converting enzyme inhibitors, angiotensin receptor blockers and beta blockers. Out of the 30 hypertensive who were on treatment 16 of them were having good compliance and were not missing any of their doses and 10 of them were missing 1 dose a week and 4 of them were missing more than 1 dose per week (**Table 2**).

Among the 30 cases 11 of them had family history of hypertension in their parents or siblings and among the 30 controls 15 of them had family history of hypertension. Majority of cases and controls were of mixed diet at 27 and 26 respectively and only 3 and 4 respectively were vegetarians. In both the groups 20 of them did not consume alcohol and 8 in case group and 6 control group were occasional alcohol consumers and 2 in case group and 4 in control group were regular alcohol consumers taking alcohol daily. The body mass index (BMI) of case group was

predominantly in the 21 to 25.9 range and in the control group also were in the same range. 2 each in case group and control group were overweight, there were no obese subjects in both the groups and there were 2 underweight subjects in the control group. 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 (**Table 3, 4**). The systolic blood pressure most of the patients were between 121 to 130 mm of Hg, there were no patients with SBP more than 160 or less than 120 mm of Hg. The Diastolic blood pressure of most of the patients was between 81 to 90 mm of Hg, there were no patients with DBP more than 100 mm of Hg. 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. The ECG of 8 hypertensives showed left ventricular hypertrophy and rest of them had a normal ECG.

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 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 were 24.54 (**Table 5**).

Vitamin D deficiency was seen in 15(50%) of the cases and in 0 of 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. 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 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 and random blood sugar levels did not any significant correlation with the levels of vitamin D (**Table 6**).

**Table 1: Age Distribution of Study Population**

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 2: Duration of Hypertension**

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)

**Table 3: Number of Anti-Hypertensive Drugs**

Number of Anti Hypertensivedrugs	Number of Cases (%)
0	0(0.0)
1	25(83.3)
2	5(16.7)
3	0(0.0)
Total	30

Table 4: Type of Anti-Hypertensive Therapy

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

Note: ACE – Angiotensin Converting Enzyme Inhibitor; ARB – Angiotensin Receptorblocker; BB – Beta Blocker; CCB – Calcium Channel Blocker

Table 5: Vitamin D Status

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

Chi-Square = 30.12 p < 0.001

Table 6: Correlation Between Vitamin D and Other Parameters

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*

Note: \*Indicates Statistically Significant

## 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 [4].

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 [1]. More recently a study [6] 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 juxta glomerular 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 month's blood pressure recordings show higher recording of blood pressure and for each 100 norths 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, 7, 8]. 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 [9] 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.

A study involving 613 men from health professionals follow up study [2] and 1198 women from nurses' health study [10] found that lower serum 25(OH) vitamin D levels of 15 ng/mL (<37 nmol/L) increased the relative risk for hypertension by 6.13 in men and 2.67 in women when compared to vitamin D sufficient population (>75 nmol/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 amount of vitamin D (400IU) with calcium given over 8 week period significantly reduced systolic blood pressure (SBP) by 9% [3]. The largest trial to date the women's health initiative (WHI) [13] 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

30 hypertensive cases and 30 non hypertensive controls attending to outpatient department of hospitals attached to J.L.N medical college and hospital were

investigated for evaluation of vitamin D status. Based on the observations made in them the following conclusions were drawn:

- The 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 antihypertensive drugs, drug compliance, and 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 essential hypertension.

## Summary

- Vitamin D is a lipid soluble vitamin.
- Traditionally vitamin D deficiency is associated with development of rickets and bone disease.

- Vitamin D insufficiency is said to present at vitamin D levels below 30ng/ml and deficiency is said to be present at levels below 20ng/ml.
- 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 rennin 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.
- Vitamin D supplementation may have a role in reduction of blood pressure in hypertensive patients.

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