

A STUDY ON CORRELATION BETWEEN SERUM VITAMIN-D AND ESSENTIAL HYPERTENSION

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Abstract

Background: Vitamin D insufficiency affects almost 50% of the population worldwide. It is associated with an increased risk of cardiovascular events, but whether this association reflects a causal relationship remains unclear. Hence, this study was undertaken to evaluate the relationship between vitamin D and arterial hypertension, and examine the clinical data for this association. The objective is to study the level of vitamin- D in patients with essential hypertension. To identify whether any association exists between age, sex, body mass index, diabetes, and target organ damage and the presence of decreased level of vitamin -D. **Materials and Methods:** A cross sectional study was conducted for a period of six months from April 2021 to September 2021. A total of 60 participants were enrolled in the study. Data was collected and entered in excel and analysed in SPSS using appropriate statistics. **Result:** The mean age of participants in normotensive and hypertensive group is 63 years and 59 years respectively. About 70% and 72.5% are males in normotensive and hypertensive group respectively. The difference in age, gender, weight, height, BMI, smoking, diabetes was not statistically different between the groups. The difference in systolic BP, diastolic BP, ECHO findings, Retinopathy, ECG findings and Vitamin D was statistically different between the groups. The difference in age, gender, height, weight, BMI, urea, phosphate, albumin, serum creatinine and smoking was not statistically different between various levels of vitamin D. The difference in Systolic BP, Diastolic BP, diabetes, calcium, ECG changes, ECHO changes was statistically different between various levels of vitamin D. **Conclusion:** From our study, it was revealed that Hypovitaminosis D was found in 57.5% of hypertensive patients and 10% of the normotensive persons. Hypovitaminosis D was significantly associated with left ventricular hypertrophy. The systolic and diastolic blood pressure exhibit significant association with low levels of vitamin-D.

INTRODUCTION

Vitamin D insufficiency affects almost 50% of the population worldwide.^[1] This pandemic of hypovitaminosis D can mainly be attributed to lifestyle and environmental factors that reduce exposure to sunlight, which is required for ultraviolet-B (UVB)-induced vitamin D production in the skin. Levels of UVB radiation diminish with increasing distance from the earth's equator, during the winter months, and as a result of air pollution. Black people absorb more UVB in the melanin of their skin than do white people and, therefore,

require more sun exposure to produce same amounts of vitamin D.^[2]

Importantly, conditions associated with reduced UVB-induced vitamin D production, such as high latitude, industrialization, and dark skin, have all been associated with increased blood pressure values.^[2] The logical hypothesis that high UVB-induced vitamin D production is associated with low blood pressure was confirmed by a small trial of 18 patients with untreated essential hypertension.^[3] The researchers found that systolic and diastolic blood pressure values were reduced by 6 mmHg after 6 weeks of UVB irradiation three times per week.

UVB irradiation was also associated with a 162% rise in plasma 25-hydroxyvitamin D (25[OH]D) concentrations, but in hypertensive patients who received UVA irradiation, no significant change in 25(OH)D levels or blood pressure occurred.^[3]

The high prevalence of vitamin D insufficiency is a particularly important public health issue because hypovitaminosis D is an independent risk factor for total mortality in the general population.^[4] A meta-analysis published in 2007 showed that vitamin D supplementation was associated with significantly reduced mortality.^[5] Furthermore, vitamin D insufficiency is associated with an increased risk of cardiovascular events, but whether this association reflects a causal relationship remains unclear.^[6-8]

The effect of vitamin D on blood pressure could be one of the potential mechanisms underlying the link between vitamin D and cardiovascular disease. In this Review, we will summarize the mechanisms that are presumed to underlie the relationship between vitamin D and arterial hypertension, and examine the clinical data for this association.

Aims and objectives

1. To study the level of vitamin- D in patients with essential hypertension.
2. To identify whether any association exists between age, sex, body mass index, diabetes, and target organ damage and the presence of decreased level of vitamin -D.

MATERIALS AND METHODS

Study site: This study was conducted in the Department of Biochemistry at Government Madurai Medical College, Madurai

Study population: All the eligible hypertensive patients

Study design: The current study was a cross sectional study

Sample size: Sample size was calculated based on previous study results. The other parameters considered for sample size calculation were 5% absolute precision and 95% confidence level. The sample size was calculated using software and found to be 60. Around 40 cases and 20 controls.

Sampling method: All the eligible subjects were recruited into the study consecutively by convenient sampling till the sample size is reached.

Study duration: The data collection for the study was done between April 2021 and September 2021 for a period of 6 months.

Inclusion Criteria

1. Patients with essential hypertension
2. Patients whose age were above 25 years
3. Both sexes were included.

Exclusion criteria

1. Individuals below 25 years were excluded
2. Patients with renal failure
3. Pregnancy
4. Patients with secondary hypertension

5. Patients who were on calcium or vitamin –D supplements
6. Patients on long term diuretics.
7. Patients receiving any other vitamin D supplementation.

Controls: Subjects whose age were above 25 years and had normal blood pressure and who met the above exclusion criteria.

Ethical considerations: The study was presented in the institutional human ethics committee and got the approval. Informed written consent was obtained and only those who are willing to sign the informed consent were included. The risks and benefits involved and the voluntary nature of participation were actually well explained to the participants before obtaining the consent. The confidentiality of the participants was maintained.

Data collection tools: All the relevant parameters were documented in a structured study proforma.

Methodology: For this study, about 40 cases and 20 controls were included in this study. Selected socio-demographic, clinical and laboratory data were elicited from the patients and recorded in a proforma.

Socio demographic data – Age, Sex

Clinical data - Body mass index, Systolic and diastolic blood pressure, Cardiovascular risk factors, Clinical examination.

Laboratory data

- **Blood urea:** Estimation done manually by using diacetyl monoxime technique
- **Serum Creatinine:** Estimation was done using COBAS autoanalyser.
- **Serum albumin:** Bromo cresol green (end point assay)
- **Serum calcium:** Arsenazo III method.
- **Serum phosphorus:** UV Molybdate (end point assay).
- **Serum uric acid:** Acid enzymatic method.
- **Vitamin D:** Enzyme immune assay

Definitions used in Present study:

Essential hypertension

According to the JNC-VII report, hypertension is defined as systolic blood pressure of 140mm Hg and above and or diastolic blood pressure of 90mmHg and above. In newly detected cases it was the mean of 3 relaxed, seated right arm reading. The diagnosis that the hypertension is essential and not secondary was made on the over all clinical impression only. Laboratory investigations to rule out secondary causes were not done in each case.

Hypovitaminosis-D

Hypovitaminosis-D is defined in this study as serum level of Vitamin – D less than 37.5nmol/l

Diabetes Mellitus

- Already a known case of diabetes mellitus on treatment
- Fasting plasma glucose > 126m g/dl
- Two hour plasma glucose > 200mg/dl
- Symptoms of diabetes plus random blood glucose > 200mg/dl

Left Ventricular hypertrophy

Based on electrocardiographic findings satisfying either sokolon- lyon criteria or cornell voltage criteria.

Hypertensive Retinopathy

Based on keith- wagner – baker grading

Grade I – attenuation of arteries

Grade II - arterio-venous nipping

Grade III - with haemorrhage and exudates Grade

IV – with papilledema.

Statistical Methods

Descriptive analysis was made using frequency and proportion for categorical variables and mean, standard deviation for continuous variables. The mean values were analysed between and within the study groups using Independent t test. Categorical outcomes were analysed between study groups using the Chi-square test. P-value < 0.05 was considered statistically significant. IBM SPSS was used for statistical analysis.

RESULTS

About 60 were enrolled based on the inclusion and exclusion criteria. About 40 were cases and 20 were controls. The results are discussed below.

The mean age of participants in normotensive and hypertensive group is 63 years and 59 years respectively. About 70% and 72.5% are males in normotensive and hypertensive group respectively. The mean height of participants in normotensive and

hypertensive group is 166.1 cm and 163.1 cm respectively. The mean weight of participants in normotensive and hypertensive group is 70.3 kg and 65.9 kg respectively. The mean BMI of participants in normotensive and hypertensive group is 25.46 and 25.1 respectively. The mean systolic BP of participants in normotensive and hypertensive group is 115 and 163 respectively. The diastolic BP of participants in normotensive and hypertensive group is 75 and 95 respectively. The difference in age, gender, weight, height, BMI was not statistically different between the groups. The difference in systolic and diastolic BP was statistically different between the groups. [Table 1]

[Table 2] represents the relation between the risk factors and two groups. The difference in smoking, diabetes status was not statistically different between the groups. The difference in ECHO findings, Retinopathy, ECG findings and Vitamin D levels was statistically different between the groups. [Table 3] represents the relations between various characteristics of participants and vitamin D levels. The difference in age, gender, height, weight, BMI, urea levels, phosphate levels, albumin levels, serum creatinine levels, smoking was not statistically different between the various levels of vitamin D. The difference in Systolic BP, Diastolic BP, DM status, calcium levels, ECG changes, ECHO changes was statistically different between the groups.

Table 1: Basic characteristics of participants

Variable	Category	Normotensive group		Hypertensive group		p value
		N	%	N	%	
Age	Mean	63 years	SD 6 years	59 years	SD 10 years	0.13 (t)
Gender	Male	14	70	29	72.5	0.91 (c)
	Female	6	30	11	27.5	
Height	Mean	166.1 cm	SD 5.9 cm	163.1 cm	SD 6.4 cm	0.11 (t)
Weight	Mean	70.3 kg	SD 7.7 kg	65.9 kg	SD 8.5 kg	0.10 (t)
BMI	Mean	25.46	SD 2.81	25.1	SD 3.07	0.67 (t)
Systolic BP	Mean	115	SD 5.9	163	SD 16.7	0.001* (t)
Diastolic BP	Mean	75	SD 5.1	95	SD 9.3	0.001* (t)

*p <0.05 – The difference between two groups is statistically significant
c- chi square test, t – independent t test

Table 2: Risk factors

Variable	Category	Normotensive group		Hypertensive group		p value
		N	%	N	%	
Smoking among males	Yes	11	78.6	27	93.1	0.18 (c)
	No	3	21.4	2	6.9	
ECHO	Normal	20	100	21	52.5	0.006* (c)
	Abnormal	0	0	19	47.5	
DM	Yes	6	30	13	32.5	0.92 (c)
	No	14	70	27	67.5	
Retinopathy	I	0	0	6	15	0.001* (c)
	II	0	0	8	20	
	III	0	0	7	17.5	
	IV	0	0	7	17.5	
	No	20	100	12	30	
ECG	LAD	1	5	4	10	0.0003* (c)
	LAD, LYH	0	0	19	47.5	
	WNL	19	95	17	42.5	
Vitamin D levels	Level – I - (< 37.5 nmol L-1)	2	10	23	57.5	0.007* (c)
	Level II - (<37.5 – 49.9 nmol L-1)	4	20	3	7.5	
	Level III - (50 – 74.9 nmol L-1)	10	50	8	20.0	

	Level IV- (75 – 100 nmol L-1)	4	20	6	15.0	
*p <0.05 – The difference between two groups is statistically significant c- chi square test						

Table 3: Characteristics of participants Vs Vitamin D levels

Variable	Category	I		II		III		IV		p value
		N	%	N	%	N	%	N	%	
Age	Mean	58.3 years	SD 9.2 years	64.7 years	SD 8.6 years	58.6 years	SD 11.5 years	59.5 years	SD 10.7 years	0.71 (A)
Gender	Male	17	58.6	2	6.9	6	20.7	4	13.8	0.21 (c)
	Female	6	54.5	1	9.1	2	18.2	2	18.2	
Height	Mean	162.3 cm	SD 6.6 cm	159.7 cm	SD 5.7 cm	163.1 cm	SD 7.2 cm	161.5 cm	SD 6.4 cm	0.89 (A)
Weight	Mean	67.6 kg	SD 8.5 kg	63.3 kg	SD 12.7 kg	63.3 kg	SD 5.8 kg	64.7 kg	SD 10 kg	0.41 (A)
BMI	Mean	25.69	SD 2.99	24.6	SD 3.17	23.77	SD 2.8	24.83	SD 3.84	0.51 (A)
Urea	Mean	27.7	SD 7.2	23.3	SD 1.5	28.3	SD 7.4	29	SD 6.8	0.65 (A)
Calcium	Mean	7.65	SD 0.44	7.58	SD 0.43	8.02	SD 0.33	8.5	SD 0.54	0.006* (A)
Phosphate	Mean	3.97	SD 0.74	3.8	SD 1.37	3.86	SD 0.84	3.52	SD 0.51	0.54 (A)
Albumin	Mean	3.51	SD 0.43	3.73	SD 0.25	3.55	SD 0.31	3.4	SD 0.22	0.47 (A)
Serum creatinine	Mean	1.2	SD 0.23	1.07	SD 0.21	1.16	SD 0.14	1.13	SD 0.12	0.72 (A)
ECG	LAD, LVH	20	87	0	0	2	8.7	1	4.3	0.0001* (c)
	WNL	3	17.6	3	17.6	6	35.3	5	29.4	
Smoking among males	Yes	16	59.3	2	7.4	5	18.5	4	14.8	0.66 (c)
	No	1	50	0	0	1	50	0	0	
ECHO	Normal	4	19	3	14.3	8	38.1	6	28.6	0.0001* (c)
	Abnormal	17	89.5	2	10.5	0	0	0	0	
DM	Yes	11	84.6	0	0	2	15.4	0	0	0.038* (c)
	No	12	44.4	3	11.1	6	22.2	6	22.2	
Systolic BP	Mean	176.2	SD 10.9	153.3	SD 3.46	147	SD 3.7	142	SD 2.5	0.001* (A)
Diastolic BP	Mean	101	SD 8.5	96	SD 5.2	88.75	SD 4.1	84.35	SD 4.8	0.001* (A)
*p <0.05 – The difference between two groups is statistically significant c- chi square test, A - ANOVA										

DISCUSSION

Hypertension is one of the leading causes of morbidity and mortality in both developing and developed countries, which is usually found incidentally by healthcare professionals during a routine checkup.^[9]

Several potential mechanisms can explain the association of vitamin D deficiency with higher BP. Although the relationship between circulating levels of vitamin D and renin activity linkage was previously suggested in essential clinical hypertension studies,^[10] it has just recently been demonstrated that 1,25(OH)₂-D directly modulates the renin-angiotensin system.^[11] Vitamin D deficiency is involved in secondary.

Hyperparathyroidism, and parathyroid hormone has been proved to have unfavorable cardiovascular effects, promoting arterial hypertension, left ventricular hypertrophy and cardiac fibrosis.^[12]

Other potential mechanisms could include the effects of vitamin D on the cells of the vessel wall, which include endothelial cells, vascular smooth muscle cells, and macrophages, all of which express the vitamin D receptor (VDR) as well as 1 α -hydroxylase. Therefore an optimal level of circulating 1, 25(OH)₂D which is regulated by

25(OH)₂D concentrations, is thought to be crucial for a normal level of BP. Our results are in line with these mechanisms and Burgaz et al,^[13] indicate that men with vitamin D levels of <37.5 nmol/L have a 3-fold increased risk for hypertension compared to men with normal levels (>75 nmol/L).

An inverse relationship between vitamin D and the renin angiotensin system (RAS) activity suggests that vitamin D may act as an endogenous inhibitor of the RAS. This association has also been observed in other studies. (Formann et al).^[14,15]

The authors of the Health Professionals Follow-Up Study of 38,388 men concluded that the 25(OH)₂D concentration required for normal BP was at least 37.5 nmol/L (Formann et al).^[16] An expert panel has recently recommended a target range for 25(OH)₂D concentrations of 75–100 nmol L) (30–40 ng mL) to reduce chronic disease including hypertension (Souberbille et al).^[17] In our study we included hypertensive patients and found out that their vitamin-D levels were definitely lower than the normotensive counterparts.

The first human study to investigate the association, that an inverse association existed between vitamin-D and hypertension examined 10 normotensive individuals, as well as 51 hypertensive individuals, on ambient diet and found out that all 61

individuals, there was an inverse correlation between PRA and 1,25(OH)2D (r 0.65; P 0.001) (Resnick et al).^[10] In our study around 85% of all hypertensive patients had vitamin –D level below the target level ($< 75\text{nmol/L}$).one study by Jaume Almirall et al showed 86% of the hypertensive patients had vitamin-D level less than 62.5nmol/L .^[18]

In this study age, sex, physical features like BMI were all adjusted between normotensive and hypertensive group. There was no confounding factor as suggested by the ‘ p ’ value. Both group’s random blood sugar and renal functions were also matched.

However serum uric acid was found to be elevated in the hypertensive group as compared to normotensive patients. Similar results of elevated levels of uric acid in hypertensive patients is well documented (Cannon et al).^[19]

Likewise retinopathy, left ventricular hypertrophy on echocardiogram and electrocardiographic changes suggesting left axis deviation and left ventricular hypertrophy were seen in the hypertensive patients as compared to normotensive group.

The mean age in this study is 59. We have not included patients above the age of 70 as Aging decreases the amount of 7-dehydrocholesterol produced in the skin by as much as 75% by the age of 70 years. Therefore, a 70 year old person has approximately 25% of the capacity to produce cholecalciferol compared with a healthy young adult (Holick, et al. 1989).^[20]

We have divided the hypertensive group into four groups based on the vitamin-D level as level-I $<37.5\text{nmol/L}$, level –II 37.5nmol/l to 49.9nmol/L , level –III as 50nmol/L to 74.5nmol/L , and level-IV 75nmol/L to 100 nmol/L . This type of division is similar to that of a study conducted by Burgaz et al.^[13]

By dividing the patients into four groups we try to analyse whether any significance does really exists between decreasing level of vitamin-D and variables like systolic BP, diastolic BP, age, sex, BMI, serum calcium, retinopathy, left ventricular hypertrophy and electrocardiographic changes.

The mean vitamin-D level in male hypertensive was 45.7 and in females 49, which was statistically not significant. This is in contrast to study done by Ian H. de Boer et al in which they have shown that serum vitamin-D level was less in male subjects.

The serum vitamin-D level was significantly lower in hypertensive subjects when compared with normotensive patients. The mean vitamin-D level in cases was 46.6 and in controls was 62.3. Observational studies strongly support an inverse association between plasma 25(OH) D levels and blood pressure and hypertension (Hintzpeter B).^[21]

The serum vitamin-D level was found to significantly associated with ECG changes like LAD, LVH and left ventricular hypertrophy. Two small clinical trials of hemodialysis patients have

shown that treatment with activated vitamin D [1, 25(OH)D or related analogs] may lead to regression of LVH, suggesting a cardioprotective action (Park et al, Kim et al).^[22,23] Cardiac hypertrophy has been observed in the hearts of VDR knockout mice (Xiang et al).^[24] Activated vitamin D has been shown to downregulate proliferation and hypertrophy in cultured cardiomyocytes (Wu et al, Nibbelink et al).^[25,26]

In this study we found out the diabetic status of hypertensive patients and around 13 patients were found to have diabetes mellitus. We associated diabetes with various levels of vitamin-D, and found significant association. In a study done by Mathieu et al,^[27] they found out that Vitamin D deficiency predisposes individuals to type 1 and type 2 diabetes, and receptors for its activated form-1alpha, 25-dihydroxyvitamin D3-have been identified in both beta cells and immune cells.

No statistical significance was observed between vitamin –D level and smoking. The same was observed in the study conducted by Annamari Kilkkinen et al,^[28] were patients were classified based on their daily intake of nicotine level.

In our study we analyzed systolic and diastolic blood pressure as continuous variable and compared with various levels of vitamin-D. There was a significant association between vitamin –D level and both systolic and diastolic blood pressure. This is in line with the study conducted by Jaume Almirall et al,^[19] where the authors demonstrated significant association between vitamin-D and systolic and diastolic blood pressure. Also low 25(OH)-D levels were significantly and independently associated with a 6.6 mmHg increase in systolic BP (95% CI: 1.5–11.6) after controlling for the other variables in the study.

Vitamin-D deficiency has been documented to have elevated rennin level as Resnick et al¹⁸ originally reported that plasma renin activity (PRA) and 1,25-di hydroxy vitamin D (1,25[OH]2D) were inversely correlated (r 0.65) among 61 individuals on an ambient diet. Several years later, Burgess et al,^[29] reported a similar association in 10 hypertensives (r 0.76). Interestingly, in a randomized trial that documented a 14-mm Hg decrease in SBP with vitamin D supplementation compared with placebo, the authors also noted a trend toward a decrease in circulating angiotensin II (Ang II) levels ($_13.1\text{ pg/mL}$; P 0.14) relative to placebo.^[30]

Not only does vitamin-D has an inverse relation with hypertension but studies by Harald Dobnig et al have showed Independent Association of Low Serum 25-Hydroxyvitamin D and 1,25-Dihydroxyvitamin D Levels With All-Cause and Cardiovascular Mortality studies by Mark F. McCarty et al showed that Poor vitamin D status may contribute to high risk for insulin resistance, obesity, and cardiovascular disease in Asian Indians. Although many studies by Burgaz et al and various other authors have demonstrated an inverse relation between vitamin-D and hypertension, few studies

like the one by Formann et al have demonstrated no significant association between vitamin-D level and hypertension. As there are controversies, it is suggested to carry out prospective studies among vitamin-D deficient patients and follow them to ascertain the rate of incident hypertension to ascertain the truth.

Limitations

1. In this study, both newly detected as well as known cases of essential hypertension on treatment were included in the study.
2. The study population included patients with essential hypertension both with and without target organ damage and other cardiovascular risk factor but without renal failure.
3. The study was only an observational study of hypovitaminosis-d in hypertensive patients and controls were included.

CONCLUSION

From our study, it was revealed that Hypovitaminosis D was found in 57.5% of hypertensive patients while only 10% of the normotensive subjects demonstrated low levels of vitamin-D. An inverse relation exists between vitamin-D and essential hypertension. Hypovitaminosis D was significantly associated with left ventricular hypertrophy. While considering systolic and diastolic blood pressure as continuous variables significant association was found with low levels of vitamin-D. There is no correlation between serum vitamin-D level with age, gender, body mass index and smoking.

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