Original Research Article

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Correlation between serum vitamin D3 levels and blood pressure in patients with essential hypertension and normotensive individuals

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ABSTRACT

Background: Vitamin D, a fat-soluble vitamin is produced when ultraviolet rays from sunlight strike the skin. Literature data supports, there is a relationship between low vitamin D and pathogenesis of cardiovascular diseases and arterial hypertension. It had been seen that lower circulating 25(OH)D levels were associated with higher blood pressures. Aim was to study the correlation between serum vitamin D3 levels and blood pressure in patients with essential hypertension and normotensive individuals.

Methods: An observational study was conducted on 60 individuals in the OPD at MGMCRI between January 2018 and December 2018. Based on history and blood pressure values (JNC 7), the population was divided into cases and controls in accordance with the age and sex. Serum Vitamin D levels were measured by chemiluminescence assay and classified into deficiency (<20ng/ml), insufficiency (20-30ng/ml) and sufficiency (30-100ng/ml). Statistical analysis was done using independent t test, one way ANOVA and correlation.

Results: Among the hypertensive individuals, 90% were Vitamin D deficient and 10% had insufficiency. The mean Serum Vitamin D level in essential hypertension was 14.6 ± 4.401 (p value <0.001). Serum Vitamin D levels were affected significantly by increasing BMI (p value <0.001) and less sunlight exposure (p value <0.001) among both cases and controls. There was also a significant negative correlation between serum vitamin D levels and systolic blood pressure (p <0.001).

Conclusions: Isolated systolic hypertension was associated with lower serum Vitamin D levels. Obesity and reduced sunlight exposure are factors associated with lower serum Vitamin D levels.

Keywords: Blood pressure determination, Cardiovascular disorders, Cholecalciferol, Essential hypertension, Hypovitaminosis D, Isolated systolic hypertension, Increased BMI, Renin angiotensin aldosterone system

INTRODUCTION

Hypertension (HTN) is the most prevalent primary diagnosis reported in ambulatory care visits and its management accounts for 30% of office visits for individuals aged 45-65 years and more than 40% among those aged 64years and more. Vitamin D insufficiency affects almost 50% population worldwide. Vitamin D is a fat soluble vitamin produced endogenously when ultraviolet rays from the sunlight strike the skin and trigger Vitamin D synthesis. Vitamin D is biologically

inert and it undergoes to two hydroxylations in the body to undergo activation. Vitamin D is a precursor for reactions involved in metabolism of phosphorus, calcium, bone mineralization and several other biochemical reactions. Unopposed activation of the Renin angiotensin aldosterone system (RAAS) and generation of angiotensin promote arterial stiffening and endothelial dysfunction that precede and contribute to the development of hypertension and are also predictors of Cardiovascular disease (CVD) risk. Observational data supports the concept that Vitamin D is involved in the

pathogenesis of cardiovascular diseases and arterial hypertension (HTN).^{3,4} Hence this study was carried out to find the correlation between essential hypertension and serum vitamin D levels as compared to and normotensive individuals in the south Indian population.

METHODS

This case control study was that conducted in Mahatma Gandhi medical college and research institute during the year 2018-2019. The patients diagnosed with essential hypertension and normotensive controls in the age group of 30-50 years were enrolled into the study. This study was approved by the Institutional Ethical Committee (PG DISSERTATION/12/2017/115). Informed and written consent were obtained from study participants before proceeding with the study. The prevalence of vitamin d deficiency in patients with essential hypertension according to the study conducted by Priya et al was found to be 80%.5 This study was used to calculate the sample size. The sample size for the present study determined by using Epi software version 3.01, The mean levels of Serum Vitamin D levels in patients with essential hypertension is 15.15±12.51ng/ml and in controls as 33.9 ± 16.9 ng/ml1, with $\alpha = 0.01$, power of 80% with confidence interval of 95%, the minimum sample size was estimated to be 30 in each group using the following formula. We would be recruiting 60 patients, 30 as cases and 30 as controls.

Details of the study were explained to the study participants, permission was sought in the form of written consent and the study was conducted. Whenever patients presented to the medicine outpatient clinic, hypertensive clinic and inpatients in the age group of 30 -50 years, history was obtained, diagnosis of essential hypertension was based on blood pressure with 2 or more values of systolic >=140 and or diastolic more than or equal to 90 mm Hg and were considered for the study as per JNC 7 guidelines.⁶

Inclusion criteria

- Patients with essential hypertension and normotensive individuals.
- Age group of 30-50 years.

Exclusion criteria

- Patients suffering from any chronic illness like Diabetes Mellitus, Tuberculosis, chronic kidney disease, thyroid disorders, coronary artery disease or autoimmune diseases.
- Cases of secondary hypertension.
- Patients who had taken Vitamin D supplementation in the last 3 months.

The patients (cases n=30) aged between 30-50 years who did not suffer from any chronic illness such as diabetes mellitus, tuberculosis, chronic kidney disease, thyroid

disorders, coronary artery disease, autoimmune disorders and secondary hypertension were recruited for the study. It was also made sure that the cases recruited for the study did not receive any form of Vitamin D supplementation for the last 3 months. They were seated comfortably with the back supported and the upper arm bared without constrictive clothing, BP was measured by a trained physician after 5mins of rest in the right arm in sitting position with a mercury sphygmomanometer; it was ensured that patient must not have taken either tea or coffee within a period of 30 minutes. The legs were not to be crossed. The arm was supported at the level of the heart, and the bladder of the BP cuff was to encircle at least 80% of the arm circumference. The blood pressure measuring device was deflated at the rate of 2 to 3 mm/sec, and the first and last audible sounds were taken as the systolic and diastolic pressure respectively. Neither the patient nor the observer spoke during the measurement. Normotensive individuals aged between 30-50 years and who were not known cases of diabetes, tuberculosis, chronic kidney disease, or coronary artery disease were recruited for the study as controls(n=30) and they were age and sex matched. Informed consent was obtained and single blood sample of 5ml was collected to estimate Serum vitamin D .Serum Vitamin D was done by chemiluminescence assay by using Cobas e411 by ROCHE DIAGNOSTICS. Result were obtained and analyzed. Serum Vitamin D levels was classified into deficiency where value of vitamin D less than 20ng/ml deficiency, insufficiency (20-30ng/ml), sufficiency $>30 \text{ng/ml.}^2$

Statistical analysis

Statistical analysis was carried out using SPSS version 16.0 software with regression modules installed. Descriptive analyses were reported as mean and standard deviation of continuous variables. It was observed that the scores of all parameters in cases and controls followed the normal distribution curve except Vitamin D3 in control group. Therefore, Independent sample't' test, chi square test and ANOVA were applied for all the other parameters, but for Vitamin D3 levels in the control group Mann Whitney 'U' test and fisher exact test were used .Linear regression analysis was performed to determine the association among serum Vitamin D, age, exposure to sunlight, SBP, DBP, mean arterial pressure (MAP), gender and BMI; the correlation coefficient was reported together with SEE(standard error of estimate), intercept and its standard error, coefficient of independent variable and its standard error and level of significance. The p value was found to be significant at < 0.001.

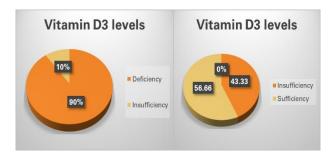
RESULTS

Among the 60 subjects enrolled in the study who were divided as cases and controls and were age and sex matched. The results of our study shown in the Table 1 depicts the mean age of the cases with essential hypertension was 39.87 and that of the normotensive

controls was 40.70 years The gender distribution was equal among both the groups. The participants further classified into two groups based on exposure to sunlight. Among the cases and controls, the percentage with less exposure was 76.7% was 36.7% respectively (p =0.002). The mean BMI among the cases and controls was 28.69 and 24.19 respectively (p=0.001). The mean systolic blood pressure among the cases and controls 166.7 ± 11.65 and 21.33 ± 8.09 respectively (p<0.001). The mean diastolic blood pressure among the cases and controls 86.47 ± 7.22 and 75.47 ± 6.30 respectively (p<0.001). The mean arterial pressure among the cases and controls was 113.6 ± 7.56 and was 91.77 ± 7.39 respectively (p<0.001).

Table 1: Distribution of all demographic characteristic.

Variables	Essential hypertension	Control group	p value	
y ur iu sies	(mean±SD) N (%)	(mean±SD) N (%)		
Age in years	39.87±5.91	40.70±5.91	0.590	
Gender				
Male	15 (50%)	15 (50%)	1	
Female	15 (50%)	15 (50%)	1	
Exposure to	sunlight			
Less	23 (76.7%)	11 (36.7%)	0.002*	
More	7 (23.3%)	19 (63.3%)	0.002	
Weight (Kgs)	72.5±15.44	66.07±12.02	0.075	
Height (cms)	159.97±10.79	164.83±11.55	0.097	
BMI	28.69±6.52	24.19±1.75	0.001*	
SBP (mm of Hg)	166.7±11.65	121.33±8.09	p<0.001*	
DBP (mm of Hg)	86.47±7.22	75.47±6.30	p<0.001*	
MAP(mm of Hg)	113.6±7.56	91.77±7.39	p<0.001*	



Essential Hypertension

Normotensive Controls

Figure 1: Distribution of serum vitamin D3 levels among the cases and controls.

Vitamin D deficiency was prevalent among patients above the age of 40 years, with the distribution of serum

vitamin D3 deficiency depicted in Figure 1. Among the men, 60% had Vitamin D3 insufficiency. Among woman 26.7% of controls had Vitamin D3 deficiency and 73.3% of cases had Vitamin D3 insufficiency (p =0.065).

From the Table 2 it can be inferred that amongst the cases, it is seen that there is a negative correlation of -0.728 between systolic blood pressure and serum vitamin D3 (p<0.001). There is also a negative correlation of -0.348 between diastolic blood pressure and serum Vitamin D3 (p =0.059). Among the controls, it is seen that there is a negative correlation of -0.268 between systolic blood pressure and serum vitamin D (p value = 0.153). There is also a negative correlation of -0.325 between diastolic blood pressure and serum Vitamin D3 (p value= 0.08). The negative correlation between systolic blood pressure and serum Vitamin D3 levels was also evident from Figure 2 which is the scatter plot between systolic blood pressure and the serum Vitamin D3 levels among the cases with essential hypertension.

Table 2: Correlation between systolic and diastolic blood pressure with serum vitamin D3.

Group	Blood pressure	Vitamin D3 levels
Essential hypertension group	Systolic - r (p value)	-0.728 (<0.001)**
	Diastolic - r (p value)	-0.348 (0.059)
Control	Systolic - r (p value)	-0.268 (0.153)
group	Diastolic - r (p value)	-0.325 (0.080)

**. Correlation is significant at the 0.01 level (2-tailed).

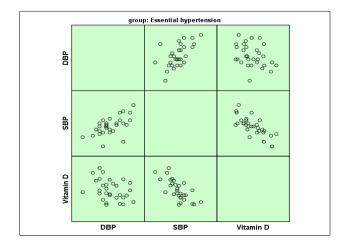


Figure 2: Scatterplot between systolic and diastolic blood pressure with serum vitamin D3 in the essential hypertension group.

In the essential hypertension group, it shows that 50.7% of the variance of serum Vitamin D3 is explained by the other predictors. In the control group, it shows that 85.8% of the variance of serum Vitamin D3 is explained by the other predictors (Table 3).

Table 3: Multiple regression analysis on vitamin D3 dependent variable with all selected demographic and clinical parameters - model summary.

Model summary										
					Std.	Change statistics				
Group	Model	R	R Square	Adjusted R Square	error of the estimate	R square change	F change	df1	df2	Sig. F change
Essential hypertension	1	0.802ª	0.643	0.507	3.0912	0.643	4.725	8	21	0.002
Control group	1	0.947 ^b	0.897	0.858	2.9130	0.897	22.981	8	21	0.000

a. Predictors: (Constant), SBP, DBP, Age, Exposure Sun Light, Gender, MAP, BMI

Table 4: Multiple regression analysis on vitamin D3 dependent variable with all selected demographic and clinical parameters - ANOVA.

ANOVA ^a							
Group	Model		Sum of Squares	df	Mean Square	F	Sig.
Essential hypertension 1		Regression	361.178	8	45.147	4.725	0.002 ^b
	1	Residual	200.662	21	9.555		
		Total	561.840	29			
Control group		Regression	1560.039	8	195.005	22.981	0.000^{c}
	1	Residual	178.196	21	8.486		
	,	Total	1738.235	29			

a. Dependent Variable: Vitamin D

Table 5: Multiple regression analysis on vitamin D3 dependent variable with all selected demographic and clinical parameters - coefficients.

Crown	Model		Unstandardized coefficients		Standardized coefficients	T	G:~	95.0% Confidence Interval for B	
Group			В	Std. error	Beta	1	Sig.	Lower bound	Upper bound
		(Constant)	38.118	21.739		1.753	0.094	-7.092	83.327
		Age	-0.075	0.129	-0.101	-0.583	0.566	-0.344	0.193
		Gender	0.572	1.704	0.066	0.335	0.741	-2.972	4.116
Essential		BMI	0.085	0.293	0.126	0.290	0.775	-0.524	0.694
hypertension	1	Exposure sun light	3.355	1.627	0.328	2.062	0.052	-0.029	6.740
		MAP	0.243	0.156	0.418	1.562	0.133	-0.081	0.567
		SBP	-0.336	0.113	-0.889	-2.961	0.007	-0.572	-0.100
		DBP	0.011	0.211	0.018	0.053	0.958	-0.427	0.449
		(Constant)	-141.818	15.100		9.392	0.000	-399.749	31.337
		Age	0.076	0.116	0.059	0.658	0.518	-0.165	0.318
		Gender	-2.535	2.623	-0.167	-0.967	0.345	-7.991	2.920
Control		BMI	-3.949	0.395	-0.895	-9.995	0.000	-1.497	7.460
group	1	Exposure sun light	0.434	1.254	0.027	0.346	0.733	-2.174	3.041
		MAP	-0.067	0.109	-0.064	-0.611	0.548	-0.294	0.160
		SBP	0.073	0.109	0.076	0.671	0.509	-0.153	0.298
		DBP	-0.405	0.153	-0.329	-2.653	0.015	-0.721	-0.088

a. Dependent variable: Vitamin D

b. Predictors: (Constant), SBP, DBP, Age, Exposure Sun Light, BMI, MAP, Gender

b. Predictors: (Constant), SBP, Age, Exposure Sun Light, Gender, MAP, BMI

c. Predictors: (Constant), SBP, Age, Exposure Sun Light, BMI, MAP, Gender

In the ANOVA table (Table 4), the p value is 0.002 in the essential hypertension group and <0.001 in the control group which is statistically significant. In our study we performed a multiple regression analysis seen in Table 5 which showed that in the essential hypertension group, it was observed that gender, BMI, exposure to sunlight, mean arterial pressure (MAP) and diastolic blood pressure directly influence the serum Vitamin D3 levels whereas age and systolic blood pressure have an inverse relationship with serum Vitamin D3 levels. But only systolic blood pressure significantly affects the serum Vitamin D levels in the essential hypertension group with a p value of 0.007. This can be explained as with every one unit increase in the systolic blood pressure, the serum Vitamin D3 levels fall by 0.336 units which was found to be statistically significant.

In the control group (Table 5), it was observed that age, exposure to sunlight and systolic blood pressure (SBP) directly influence the serum Vitamin D3 levels whereas gender, BMI, diastolic blood pressure and mean arterial pressure have an inverse relationship with serum Vitamin D3 levels. But only BMI significantly affects the serum Vitamin D levels in the control group with a p value of <0.001.With every one unit increase in the BMI, the serum Vitamin D3 levels fall by 3.949 units which was found to be statistically significant. It is seen that diastolic blood pressure also affects serum Vitamin D3 among controls with a p value (0.015) nearing significance. This shows that BMI independently affects serum Vitamin D3 levels irrespective of the blood pressure.

DISCUSSION

The results from our study indicate that prevalence of vitamin d deficiency in 90% of the cases where as only 43.33% of the controls were vitamin d insufficient. This data contributes to a clearer understanding of the prevalence of vitamin d deficiency in the south Indian population. The striking feature amongst the controls is that 56.6% were vitamin d sufficient, which could be due to their increased exposure to sunlight and lower body mass index as described by various observational studies. The data from many observational studies in India and worldwide suggest that the prevalence of vitamin d deficiency ranges from 50-80%. Hence these results provide an contrasting evidence in the prevalence of vitamin d deficiency amongst cases and controls.

The participants in our study were both age and sex matched, vitamin d deficiency was more prevalent amongst males ,there exist a contrasting evidence in the sex predisposition for vitamin D deficiency. Vitamin D deficiency was more prevalent amongst above 40 years, these results build on the existing evidence of higher prevalence of vitamin d deficiency after the age of 40 years. Furthermore the deficiency is multifactorial, one of the existing hypothesis is that it is

due the decreased ability of synthesis of vitamin d in the skin. 15

The data from our results suggest that subjects with indoor professions had lower serum vitamin D3 levels, these results build on the existing evidence. Vitamin D stores are worsened by protecting the skin from sunlight by sunscreens or other methods such as thick clothing, being indoors due to sickness. Whether Vitamin D levels are reduced by use of sunscreens has evidence that is inconsistent.¹⁶

The results from our study indicating that body mass index independently affects the serum vitamin D 3 levels do fit with the theory that, vitamin d had an inverse relationship with the body mass index. 10,17-19 Vitamin D synthesised is cloistered in the adipose tissue in the subcutaneous layer of the skin as vitamin D is fat soluble and therefore vitamin d levels are lower in obese individuals. And hence higher dose of vitamin d need to supplemented in obese individuals. 20

The study demonstrates inverse correlation between serum vitamin d levels and essential hypertension, while the previous research has focused on vitamin deficiency in hypertension caused by various aetiology, here in our study we found that subjects with essential hypertension were vitamin D deficient. 11,17,21,22 Additionally we found that with every 1 unit increase the serum Vitamin D3 levels, the systolic blood pressure decreased by 0.872 units. This data contributes to a clearer understanding of the correlation. These results build on the existing evidence but in the essential hypertensive population. While the previous research focused on blood pressure, in our study results demonstrate a significant association between vitamin D levels and isolated systolic hypertension.

Subjects with hypertension have other chronic conditions and hence may have less exposure to sunlight which is required for vitamin D production. Subjects with higher BMI have low vitamin d levels and increased risk of hypertension, which acts a confounding factor. Extraneous supplementation of vitamin D in essential hypertensive cases was beyond the scope of this study were few study limitations.

CONCLUSION

Based on this results, it can be concluded that there is a significant negative correlation between the serum vitamin D levels and systolic blood pressure. The lower the serum vitamin D levels, more is the severity of hypertension. It was also observed that systolic blood pressure independently affected the serum Vitamin D levels among the hypertensive individuals. However, reduction of blood pressure with the supplementation of extraneous Vitamin D was not done since it was beyond the scope of this study. Hence there is a need from supplementation of calciferol among individuals with sub

optimal serum vitamin D levels in order to reduce the risk of complications due to high blood pressures. Proper guidelines are required which can recommend the apt dosage of supplementation when vitamin D deficiency is diagnosed at different ages.

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Ethical approval: The study was approved by the

Institutional Ethics Committee

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