e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2023; 15(6); 653-663

Original Research Article

Study on Co-Relation between Serum Vitamin D Level and Essential Hypertension

Shiv Purari[1], R. D. Singh[2], Sanjay Kumar[3], K. Kishore[4]

[1]Junior Resident (3rd year), Department of General Medicine, Patna Medical College & Hospital, Patna, Bihar, India

[2]Associate Professor, Department of General Medicine, Patna Medical College & Hospital, Patna, Bihar, India

[3]Assistant Professor, Department of General Medicine, Patna Medical College & Hospital, Patna, Bihar, India

[4]Professor & HOD, Department of Internal Medicine, Patna Medical College & Hospital, Patna, Bihar, India

Received: 22-03-2023 / Revised: 25-04-2023 / Accepted: 30-05-2023

Corresponding author: Dr. Sanjay Kumar

Conflict of interest: Nil

Abstract

Vitamin D insufficiency affects almost 50% of the population worldwide. 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. 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. The aim of this study 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, and, to study Diabetes, and target organ damage and the presence of decreased level of Vitamin-D.

Keywords: Vitamin D, UVB, Dar skin, Industrialization and Sunlight.

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 [6,7,8]. 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.

Method

Source of Data: Patients visiting outdoor and admitted inpatients in the Department of General Medicine in Patna Medical College and Hospital, Patna.

Period of Study: April 2021- November 2022.

Design of Study: Cross-sectional study.

Sample Size: 60 cases and 20 controls.

Inclusion Criteria:

- Patients with essential hypertension
- Patients whose age were above 25 years
- Both sexes were included.

Exclusion Criteria:

- Individuals below 25 years
- C Patients with renal failure
- Pregnancy
- Patients with secondary hypertension
- Patients who were on calcium or vitamin -D supplements
- Patients on long term diuretics.
- Patients receiving any other vitamin D supplementation.

Statistical Analysis: The information collected regarding all the selected cases were recorded in a Master Chart. Data analysis was done with the help of computer using Epidemiological Information Package. Using this software, frequencies, percentage, mean, standard deviation values will be calculated.

Ethical Clearance

The study proposal along with other relevant documents will be submitted to the institutional ethical committee for review and approval.

Investigations Required for the Study:

- Blood urea
- Serum Creatinine
- Serum albumin
- Serum calcium
- Serum phosphorus
- Serum uric acid.
- Serum Vitamin D

Investigations to rule out secondary hypertension

1. Electrocardiography
2. Chest X-ray
3. Echocardiography
4. Renal artery colour dopplar
5. Ultrasonography
6. Renin and aldosterone level
7. Serum TSH
8. 24-hour urinary fractionated metanephrines
9. 24-hour urinary free cortisol

Results

A: Profile of cases studied: Majority of the subjects were from age group 61-70 years. The hypertensive group had an age of 58.9 ± 9.3 years and the normotensive group 63.0 ± 5.5 years. There was no statistically significant difference between the two groups [Table 1].

Table 1: Age wise distribution of studied groups

		Hypertensive	Normotensive	Total
AGE	Up to 50 years	11	1	12
		18.3%	5.0%	15.0%
	51-60 years	22	7	29
		36.7%	35.0%	36.3%
	61-70 years	21	11	32
		35.0%	55.0%	40.0%
	> 70 years	6	1	7
		10.0%	5.0%	8.8%
Total		60	20	80
		100.0%	100.0%	100.0%
Mean ± SD		58.9 ± 9.3	63.0 ± 5.5	
P-value		0.294 (not significant)		

Among 60 hypertensive patients, 44 were male and 16 were female. The Normotensive group had 20 patients of which 14 were male and 6 were female. There was no statistically significant difference between two groups (p= 0.78).

Height (HT), weight (WT) and BMI of the hypertensive and normotensive cases studied did not have any significant difference (p-value above 0.05) [Table 2].

Table 2: Physiological Variables

Group		Mean	Std. Deviation	P-value
HT	Hypertensive	1.6	0.1	0.561 (not significant)
	Normotensive	1.7	0.1	
WT	Hypertensive	67.4	8.6	0.227 (not significant)
	Normotensive	70.3	7.7	
BMI	Hypertensive	25.6	3.1	0.658 (not significant)
	Normotensive	25.5	2.8	

Systolic blood pressures (SBP) and diastolic blood pressures (DBP) of the hypertensive groups (163.9±16.8and 95.6±9.0 respectively) were significantly higher than those of the normotensive group (114.5± 5.1and 75.0+5.1) [Figure 1]

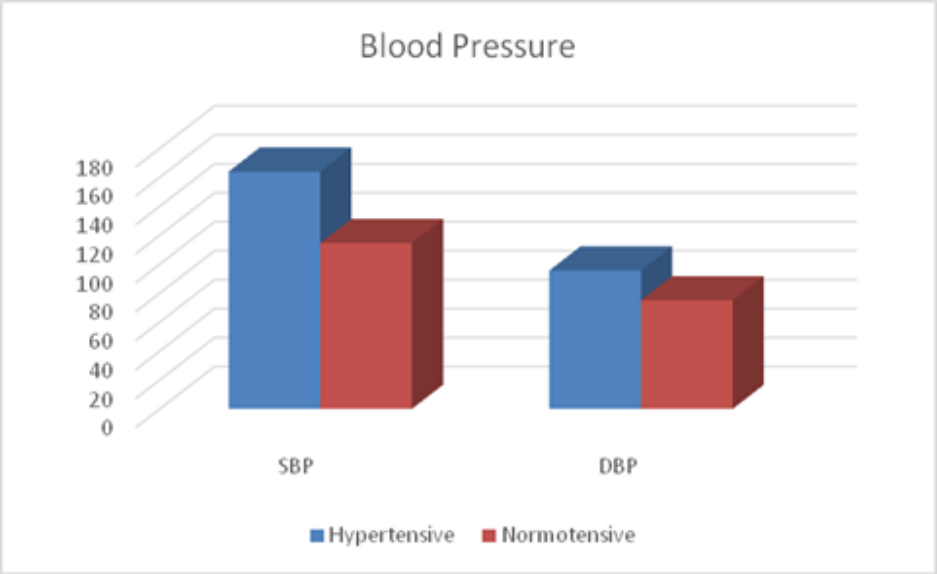


Figure 1: Blood Pressure among the two groups

Frequency of smoking was found higher in the hypertensive group (68.3%) as compared to normotensive group (55%).

Frequency of abnormal ECG findings were significantly higher in the hypertensive group as compared to normotensive group (p- value<0.001) [Table 3].

Table 3: Comparison of ECG findings among the two groups

			Hypertensive	Normotensive	Total
ECG	LAD	Count	6	1	7
		%	10.0%	5.0%	8.8%
	LAD, LVH	Count	28	0	28
		%	46.7%	0.0%	35.0%
	WNL	Count	26	19	45
		%	43.3%	95.0%	56.3%
Total		Count	60	20	80
		%	100.0%	100.0%	100.0%
P-value		<0.001(Significant)			

Frequency of abnormal ECHO findings were significantly higher in the hypertensive group as compared to normotensive group (p-value<0.001).

Frequency of abnormal ECHO findings were significantly higher in the hypertensive group as compared to normotensive group (p-value<0.001) [Figure 2].

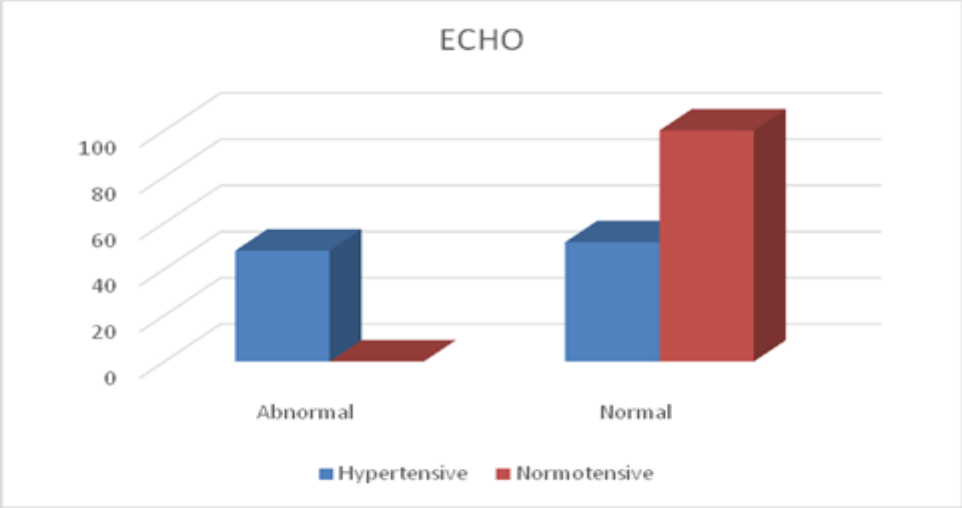


Figure 2: Comparison of ECHO among two groups

Percentage of retinopathy were significantly higher in the hypertensive group as compared to normotensive group (p- value<0.001) [Table 4].

Table 4: Comparison of retinopathy between the two groups

Retinopathy	Hypertensive	Normotensive	Total	P-value
I	10	0	10	<0.001 (Significant)
	16.7%	0.0%	12.5%	
II	13	0	13	
	21.7%	0.0%	16.3%	
III	11	0	11	
	18.3%	0.0%	13.8%	
IV	10	0	10	
	16.7%	0.0%	12.5%	
NO	16	20	36	
	26.7%	100.0%	45.0%	
Total	60	20	80	
	100.0%	100.0%	100.0%	

Frequency of diabetes mellitus (DM) cases were found slightly higher in the hypertensive group (35%) as compared tonormotensive group (30%) [**Figure 3]**.

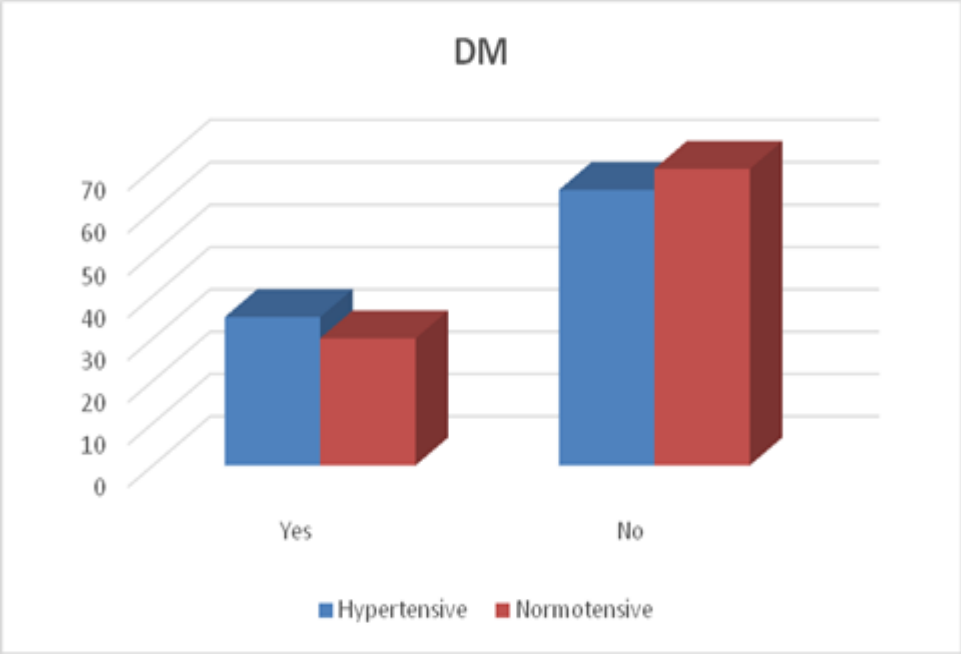


Figure 3: Comparison of Diabetes Mellitus

The mean Vitamin-D value in the hypertensive group and normotensive cases were 45.71nmol L-1and 62.3 nmol L-1 respectively. The mean Vitamin-D was found significantly lower in hypertensive cases compared to control group. (p-value = 0.001) [Table 5]. Vitamin-D levels among males and females did not have any significant difference (p=0.966, p-value above 0.05).

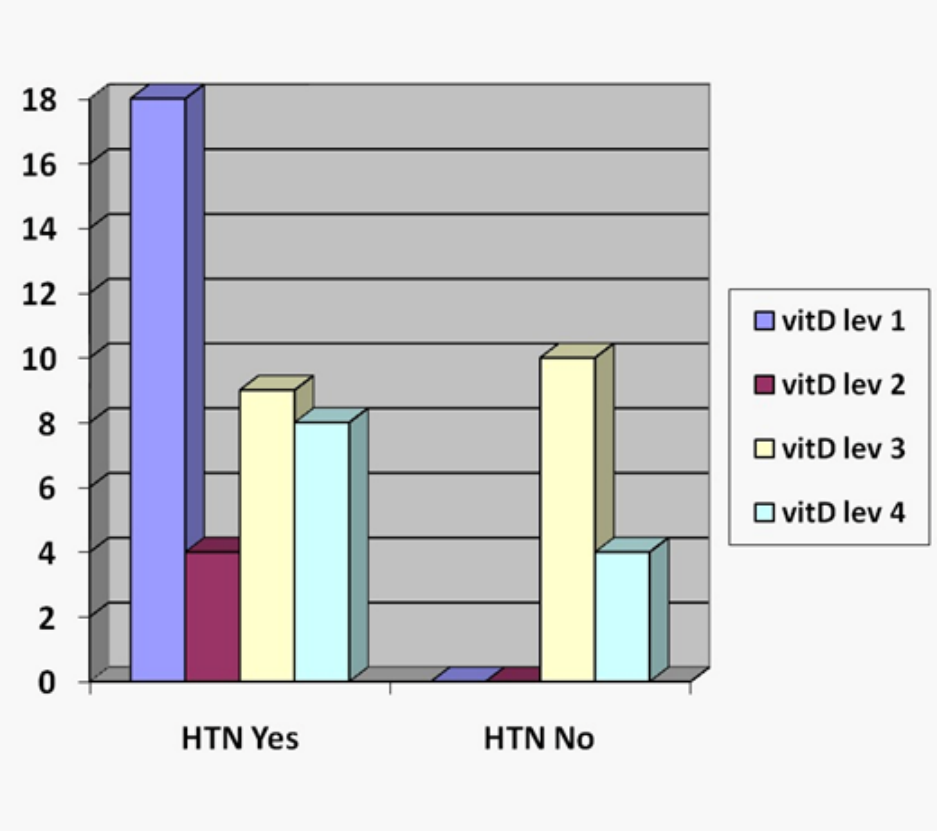
Table 5: Comparison of Vitamin D levels between two groups

Vit - D	**Hypertensive**	**Normotensive**	**Total**
Level I (< 37.5 nmol L^{-1})	36	2	38
	60.0%	10.0%	47.5%
Level II (<37.5 – 49.9 nmol L^{-1})	4	4	8
	6.7%	20.0%	10.0%
Level III (50 – 74.9 nmol L^{-1})	12	10	22
	20.0%	50.0%	27.5%
Level IV (75 – 100 nmol L^{-1})	8	4	12
	13.3%	20.0%	15.0%
Total	60	20	80
	100.0%	100.0%	100.0%
Mean	45.71	62.33	
SD	20.278	18.379	
P-value	**0.001 (Significant)**		

Vitamin-D values and age of the patient did not have any statistically significant relationship (p = 0.947, p-value above 0.05). There were no significantly differences between height, weight and BMI and levels of vitamin-D concentration.

Table 6: Correlation between essential hypertension and vitamin D level. The relation is statistically significant with a p-value of 0.002."

Vitamin D	HTN		Total
	Yes (N=39)	No (N=14)	
I	18	0	18
	46.2%	0.0%	34.0%
II	4	0	4
	10.3%	0.0%	7.5%
III	9	10	19
	23.1%	71.4%	35.8%
IV	8	4	12
	20.5%	28.6%	22.6%
Total	**39**	**14**	**53**
	100%	**100%**	**100%**



The percentage of ECG changes were significantly higher in cases with low vitamin-D concentration (level I) with p-value=0.001. Smoking did not have any significant association in regard with vitamin-D levels (p=0.844). Percentage of abnormal ECHO were significantly higher in cases with low vitamin-D concentration (level I) with p- value<0.001. Percentage of diabetic cases were significantly higher in cases with low levels of vitamin-D (level I) with p-value=0.014. In the hypertensive cases, there was significant association between B.P values and vitamin-D levels ($p< 0.05$).

Discussion:

Vitamin D deficiency is a common health problem worldwide in both children and adults. Low levels of vitamin D have been

associated with an increased risk of hypertension. Vitamin D deficiency may also be linked with preterm births given the immunomodulatory and anti-inflammatory properties of vitamin D [9]. The foetus relies entirely on vitamin D stores of mother, so if the mother is deficient, so is the foetus [10]. Vitamin D may exert a protective effect on spontaneous preterm birth. Vitamin D reduces the response to microbial pathogens by abrogating the production of interleukin-6, interleukin-1, and tumour necrosis factor-alpha by macrophages. Certainly, there is a strong biologic possibility linking vitamin D status and hypertension [11].

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 [12]. Several potential mechanisms can explain the association of vitamin D deficiency with Hypertension. Although the relationship between circulating levels of vitamin D and renin activity linkage was previously suggested in essential clinical hypertension studies, it has just recently been demonstrated that 1.25(OH)2-D directly modulates the renin– angiotensin system. Vitamin D deficiency is involved in secondary Hyperparathyroidism, and parathyroid hormone has been proved to have unfavourable cardiovascular effects, promoting arterial hypertension, left ventricular hypertrophy and cardiac fibrosis [13-15]. 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 1α-hydroxylase. Therefore, an optimal level of circulating 1,25(OH)D which is regulated by 25(OH)D concentrations, is thought to be crucial for a normal level of BP.

Findings of the present study were in line with these mechanisms and another study [16] suggested that patients with vitamin D levels of <37.5 nmol/L have3-fold increased risk for hypertension compared with normal levels (>75 nmol/L).In present study, we included hypertensive patients and found out that their vitamin-D levels were lower than the normotensive counterparts. We found that Vitamin-D deficiency was significantly associated with hypertensive (p-value = 0.001). In present 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 groups 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 [19].

Similarly, retinopathy, ECHO and ECG 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 58.9. We excluded patients above the age of 70 years 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 [20].

In present study, we have divided the hypertensive patients into four groups based on the vitamin-D level as level-I<37.5nmol/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 like that of a study [21].

By grouping we analysed whether any significance does really exist 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 and females was statistically not significant. This contrasts with study done by de Boer et al., in which they have shown that serum vitamin-D level was less in male subjects [22].

In present study, the serum vitamin-D level was significantly lower in hypertensive subjects when compared with normotensive patients. The mean vitamin-D level in cases was 45.71and in controls was 62.3. Observational studies strongly support an inverse association between plasma 25(OH)D levels and blood pressure and hypertension [23].

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 analogues] may lead to regression of LVH, suggesting a cardioprotective action [24]. Cardiac hypertrophy has been observed in the hearts of VDR knockout mice [19]. Activated vitamin D has been shown to downregulate proliferation and hypertrophy in cultured cardiomyocytes [25].

Present study revealed the diabetic status of hypertensive patients and around 21 patients were found to have diabetes mellitus (DM). We also study association between diabetes and levels of vitamin-D, and found significant association. In a study done [26] 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. We have not found statistical significance was observed between vitamin –D level and smoking. The same was observed in the study [27] where patients were classified based on their daily intake of nicotine level.

In present study we also analysed 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 [28] 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 previous study reported that plasma renin activity (PRA) and 1,25-dihydroxyvitamin D (1,25[OH]2D) were inversely correlated (r 0.65) among 61 individuals on an ambient diet. A study [29] reported a similar association in 10 hypertensives. Remarkably, 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 pg/mL; P=0.14) relative to placebo [30].

Vitamin Dsynthesised 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 [28]. Cases with hypertension have other chronic conditions and hence may have less exposure to sunlight which is required for vitamin-D production.

Conclusion

Based on these results, it can be concluded that there is a significant correlation between the vitamin D levels and Hypertension. The lower the vitamin D levels, more is the severity of hypertension. It was also observed that both systolic and diastolic blood pressure affected the Vitamin D levels among the hypertensive individuals. 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.

References

1. Holick, M. F. Vitamin D deficiency. N. Engl. J. Med. 2007;35(7):266–281.
2. Rostand, S. G. Ultraviolet light may contribute to geographic and racial blood pressure differences. Hypertension. 1997; 30: 150–156.
3. Krause, R., Bühring, M., Hopfenmüller, W., Holick, M. F. & Sharma, A. M. Ultraviolet B and blood pressure. Lancet. 1998; 352:709–710.
4. Melamed, M. L., Michos, E. D., Post, W. & Astor, B. 25- hydroxyvitamin D levels and the risk of mortality in the general population. Arch. Intern. Med. 2008; 168:1629–1637.
5. Autier, P. & Gandini, S. Vitamin D supplementation and total mortality: a meta-analysis of randomized controlled trials. Arch. Intern. Med. 2007; 167:1730–1737.
6. Pilz, S. et al. Association of vitamin D deficiency with heart failure and sudden cardiac death in a large cross-sectional study of patients referred for coronary angiography. J. Clin. Endocrinol. Metab. 2008; 93: 3927–3935.
7. Giovannucci, E., Liu, Y., Hollis, B. W. & Rimm, E. B. 25- hydroxyvitamin D and risk of myocardial infarction in men: a prospective study. Arch. Intern. Med. 2008; 168: 1174–1180.
8. Pilz, S. et al. Low vitamin D levels predict stroke in patients referred to coronary angiography. Stroke. 2008; 39: 2611–2613.
9. Harrison's principles of internal medicine; 17th edition,1549. 2008.
10. Davidsons principles and practice of medicine; 20th edition
11. Brenner and rector the kidney; 8th editon. Guyton.
12. Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine, 8th ed.2007.
13. Holick MF. Environmental factors that influence the cutaneous production of vitamin D. Am J Clin Nutr. 1995; 61:63 8S-645S.
14. Wolpowitz D, Gilchrest BA. The vitamin D questions: how much do you need and how should you get it? J Am Acad Dermatol. 2006; 54:301-17.
15. Barysch MJ, Hofbauer GF, Dummer R. Vitamin D, ultraviolet exposure, and skin cancer in elderly. Gerontology. 2010; 56:410-3.
16. Clemens TL, Adams JS, Henderson SL, Holick MF. Increased skin pigment reduces the capacity of skin to synthesise vitamin D3. Lancet. 1982; 1:74-6.
17. Holick MF, Matsuoka LY, Wortsman J. Age, vitamin D, and solar ultraviolet. Lancet. 1989; 2:1104-5.
18. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S. Evidence for alteration of the vitamin D-endocrine system in obese subjects. J Clin Invest. 1985; 76:370-3.
19. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH. Low circulating vitamin D in obesity. Calcif Tissue Int. 1988; 43:199-201.
20. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF. Decreased bioavailability of vitamin D in obesity. Am J Clin Nutr. 2000; 72:690-3.

21. Compston JE, Vedi S, Ledger JE, Webb A, Gazet JC, Pilkington TR. Vitamin D status and bone histomorphometry in gross obesity. Am J Clin Nutr. 1981; 34:2359-63.
22. Park's textbook of preventive and social medicine; 18th edition, 2005;444.
23. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. J Nutr. 2005; 135: 310- 6.
24. Holick MF. Vitamin D deficiency. N Engl J Med. 2007; 357:266-81.
25. Holick MF. Vitamin D and sunlight: strategies for cancer prevention and other health benefits. Clin J Am Soc Nephrol. 2008; 3:1548-54.
26. Karohl C, Su S, Kumari M, et al. Heritability and seasonal variability of vitamin D concentrations in male twins. Am J Clin Nutr. 2010; 92:1393-8.
27. Snellman G, Melhus H, Gedeborg R, et al. Seasonal genetic influence on serum 25-hydroxyvitamin D levels: a twin study. PLoS One. 2009;4: e7747.
28. Andreassen TK. The role of plasma-binding proteins in the cellular uptake of lipophilic vitamins and steroids. Horm Metab Res. 2006; 38:279-90.
29. Speeckaert M, Huang G, Delanghe JR, Taes YE. Biological and clinical aspects of the vitamin D binding protein (Gc- globulin) and its polymer phism 0020. Clin Chim.