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# A study of correlation in between sublingual vitamin D3 and blood pressure

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## ABSTRACT

The present study was aimed to study of correlation in between Sublingual Vitamin D3 and Blood Pressure. This was a non-randomized clinical trial done in collaboration with Department of family and General medicine. All the known cases of essential hypertension coming to the Family and General Medicine department of PRH, Loni were enrolled for the study. The study was registered with the Clinical Trial Registry of India (CTRI). Total of 400 patients were enrolled for the study. All the subjects were screened for the serum 25 (OH) D levels. Subjects fulfilling the eligibility criteria with serum 25 (OH) D levels less than 20 ng/ml, having history of hypertension were included in the study. At the end of the study, 49 patients (24 from Test and 25 from control group) dropped out of the study due to their personal reasons and finally 351 patients participated till the end of the study. The subject's serum 25(OH) D levels were estimated before and after treatment of sublingual vitamin D3. There was statistically significant difference in serum vitamin D3 level before 16.61±6.71 ng/ml and after 35.80±7.80 ng/ml after treatment with Sublingual Vitamin D3. Six doses of 60,000IU of Vitamin D3 sublingual route having improved role of serum 25(OH)D levels in treatment of Vitamin D3 deficiency patients, whereas in the control group decreased from baseline 16.40±3.63ng/ml to 14.96±4.94 ng/ml.There was a significant decrease in SBP associated with increasing 25(OH)D levels in response to supplementation. This intervention trail clarified Sublingual Vitamin D3 prevent the hypertension in the general population.

**Keywords:** Sublingual Vitamin D3, Systolic Blood Pressure, Diastolic Blood Pressure.

## INTRODUCTION

Approximately 30 million subjects (14.1 million in urban Areas, and 15.7 million in rural areas) are likely to be affected with Cardio Vascular Disease (CVD) in India [1]. Hypertension is a polygenic and multifactorial disease involving many pathways and

mechanisms, One in Nine are affected in India, with a population of more than one billion, the estimated number of patients were more than 100 million. Hypertension is more prevalent in urban area 20-40% and 12-17% in rural adults. There is significant morbidity, mortality and economic burden on a developing country like India [2, 3]. It is estimated that 1.56 billion adults will be living with high blood pressure in 2025 and one in three adults has hypertension in the world [4].The prevalence of hypertension in this elderly rural population is extremely high (89%). However, despite the levels of awareness and treatment of hypertension being similarly high (approximately 89%), Blood Pressure (BP) was poorly controlled at only 32%. The proportion of those taking combined therapies in the study was also relatively high (70%) [5].

Vitamin D deficiency is also associated with various chronic diseases including cardiovascular diseases, which are the leading causes of death [6, 7]. However, it is now known that adequate vitamin D status is important for the optimal function of many organs and tissues throughout the body, including the cardiovascular system. Vitamin D deficiency is playing an important key role in the genesis of coronary risk factors and cardiovascular diseases [8]. Reduction in blood pressure has been found in various studies when administered Vitamin D evidence points to vitamin D is having an important association with blood pressure. Data from animal studies showed circulating active vitamin D as an inhibitor of rennin expression in the juxtaglomerular apparatus as well as an inhibitor of vascular smooth muscle cell proliferation [9, 10].

Several Studies conducted over the last decade have suggested that vitamin D may play a role in blood pressure regulation. Receptors for 1, 25-dihydroxyvitamin D (calcitriol) are found in target tissues closely connected with blood pressure regulation11. Furthermore, calcitriol has been found to suppress the in vitro secretion of PTH, which has been associated with blood pressure levels [12, 13]. These works can clarify the physiological seasonal changes in blood pressure that is not completely explained by fluctuations in environmental temperature. Because vitamin D status is lowest and blood pressure is high in winter [14].

Vitamin D deficiency can activate the renin-angiotensin system [15]. Li and co-authors found that rennin expression and plasma angiotensin -II production were increased several-folds in vitamin D receptor-null mice They concluded that vitamin D was a novel negative endocrine regulator of the rennin angiotensin system [9]. Thus, in view of the above role of Vitamin D3 in regulation of blood pressure through vasodilatation and Rennin Angiotensin System (RAS), it was thought prudent to evaluate efficacy of Vitamin D3 as an add on therapy with novel route of administration. Availability of vitamin D3 sublingual tablets was thought to be the best and quickest alternative.

### Aim

To find out the correlation in between sublingual vitamin D3 and blood pressure.

### Objectives

1. Test group of correlation in between Baseline Vitamin VD3 and Baseline-SBP and DBP
2. Test group of correlation in between 6th visit vitaminD3 and 6th visit-SBP and DBP
3. Control group of correlation in between baseline Vitamin D3 & baseline-SBP and DBP
4. Control group of correlation in between Visit 6 vitamin D3 and 6th visit -SBP and DBP

## MATERIALS &METHOD

This was a non-randomized clinical trial done in collaboration with Department Family and General Medicine. All the known cases of Essential hypertension coming to the Family and General Medicine department of PRH, Loni enrolled for the study. The study was registered with Clinical Trial Registry of India (CTRI), it is available on the Website: CTRI Website URL - http://ctri.nic.in; Registration number: CTRI/2017/03/008033 [Registered on: 07/03/2017].

**Study Duration**: 2 Years

## INCLUSION CRITERIA

- Adult patients between age group of 18-60 Years.
- Patients of either sex
- All the patients of Essential hypertension.
- Patient ready to give written inform consent and willing to participant in the study.

## EXCLUSION CRITERIA

- Normal Vitamin D levels of hypertensive patients were excluded.
- The patient suffering from Gestational hypertension.
- Patients with a history of any tumours and Patients on medication which may lead to hypercalcemia.
- Patients suffering from genetic disorders, taking antiepileptic drugs.
- Patients on chronic medications other than antihypertensive.

## STUDY GROUP

All the patients satisfied with the inclusion and exclusion criteria were estimated of Serum Vitamin D3 below the normal (Deficiency = <20ng/ml) level taken grouped as under: following.

### Group-I (n=200)

- Patients on add on Vitamin D3 60,000 IU sublingual

### Group-II (n=200)

- Patients on only antihypertensive drugs without add on Vitamin D3 therapy

### Vitamin D therapy

**Drug name:** Dura D3 (Cholecalciferol Vitamin D3)

**Dose:** 60,000 IU

**Dosing Schedule**

| Tab-1 | Tab-2 | Tab-3 | Tab-4 | Tab-5 | Tab-6 |
|---|---|---|---|---|---|
| 15 days | 30 days | 45 days | 60 days | 75 days | 90 days |

**Route:** Sublingually

### Investigated Profile

- Estimated of Serum Vitamin D3 level at the baseline visit and at the 6th Visit (end of the study)
- Renal function test (RFT) at the baseline visit and at the 6th Visit (end of the study)
  - ✓ Serum Urea
  - ✓ Serum creatine
  - ✓ S. Na+
  - ✓ S. K+

## DATA ANALYSIS

Data coding and entry was done in Microsoft Excel spread sheets and descriptive and inferential statistical analysis was done by using SPSS version 21 (Statistical Package for Social Sciences) software. Linear relationship was established using Pearson's correlation test.

## RESULTS

**Table 01: Distribution of participants according to estimate of serum Vitamin D level**

| | Baseline Visit | | Test Group | | Control Group | |
|---|---|---|---|---|---|---|
| | Test | Control | Baseline | 6thF. P | Baseline | 6thF. P |
| Mean ± SD | 16.61±6.71 | 16.40±3.63 | 16.61±6.71 | 35.80±7.80 | 16.40±3.63 | 14.96±4.94 |
| Median | 15.60 | 15.90 | 15.60 | 36.00 | 15.90 | 15.16 |
| test | Mann Whitney U Test: P:0.55 Non-Significant | | Wilcoxon matched-pairs test P<0.0001 Significant | | Wilcoxon matched-pairs test P<0.0001 Significant | |

**Graph No: 01**

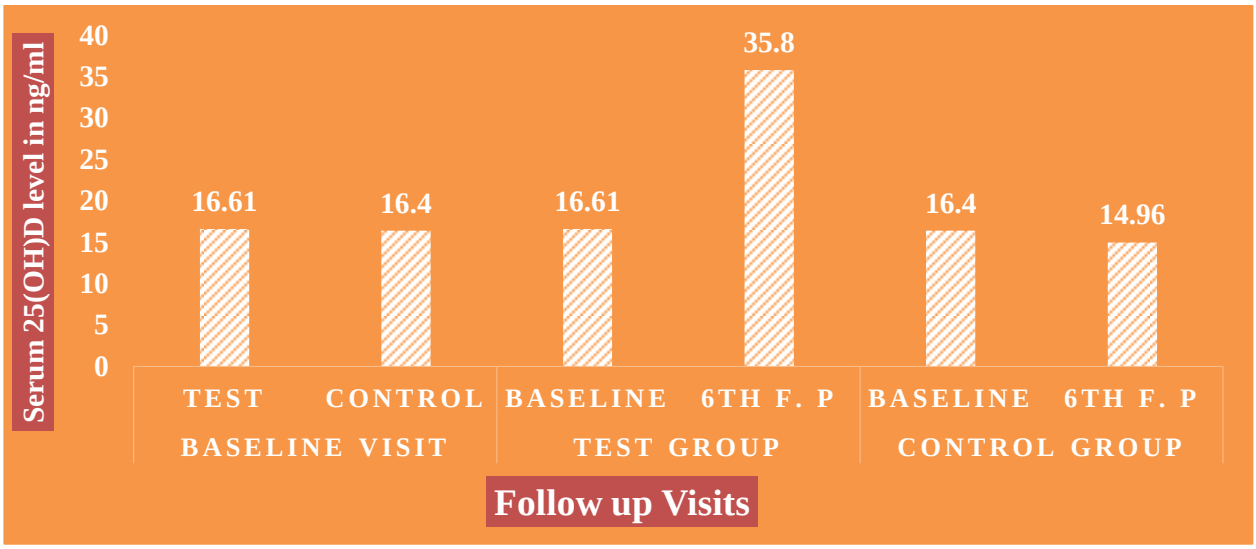


**Table :01 and Graph no:01 shows significant increase in serum vitamin D level(ng/ml) was seen in test group whereas the vitamin D level(ng/ml) was decreased in control group.**

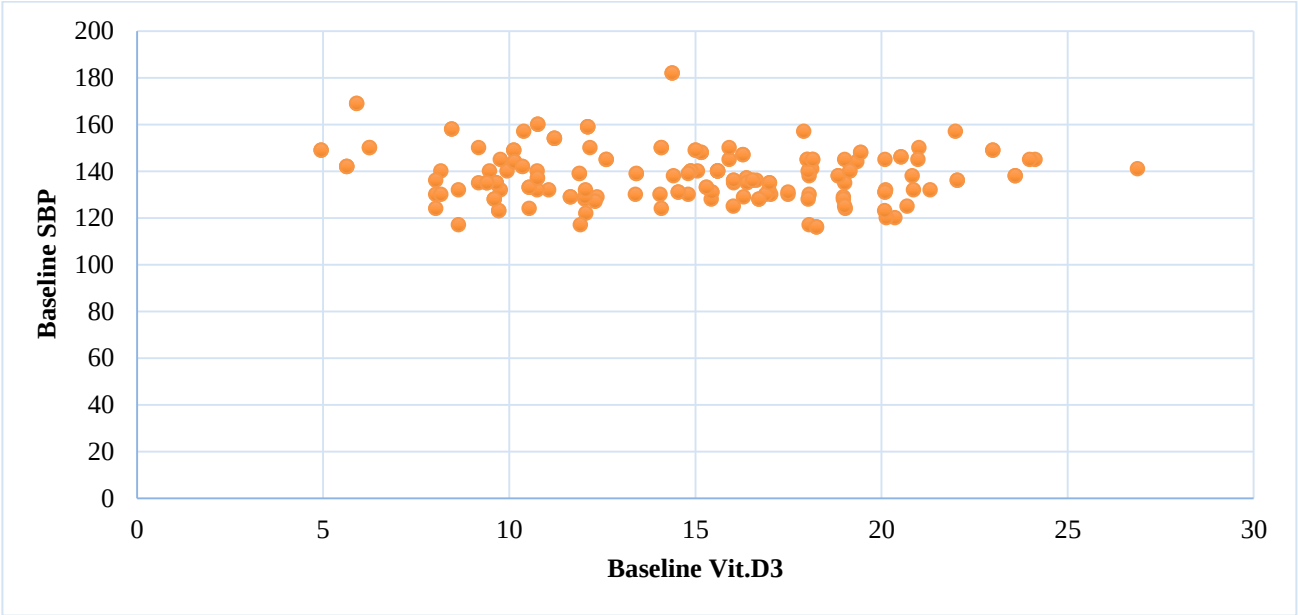


**Figure 02: Test group of correlation in between Baseline Vit.VD3 and Baseline-SBP**

Figure 02 shows on Pearson correlation (weak) negative correlation was observed between decreased Vitamin D3 level with increased SBP.

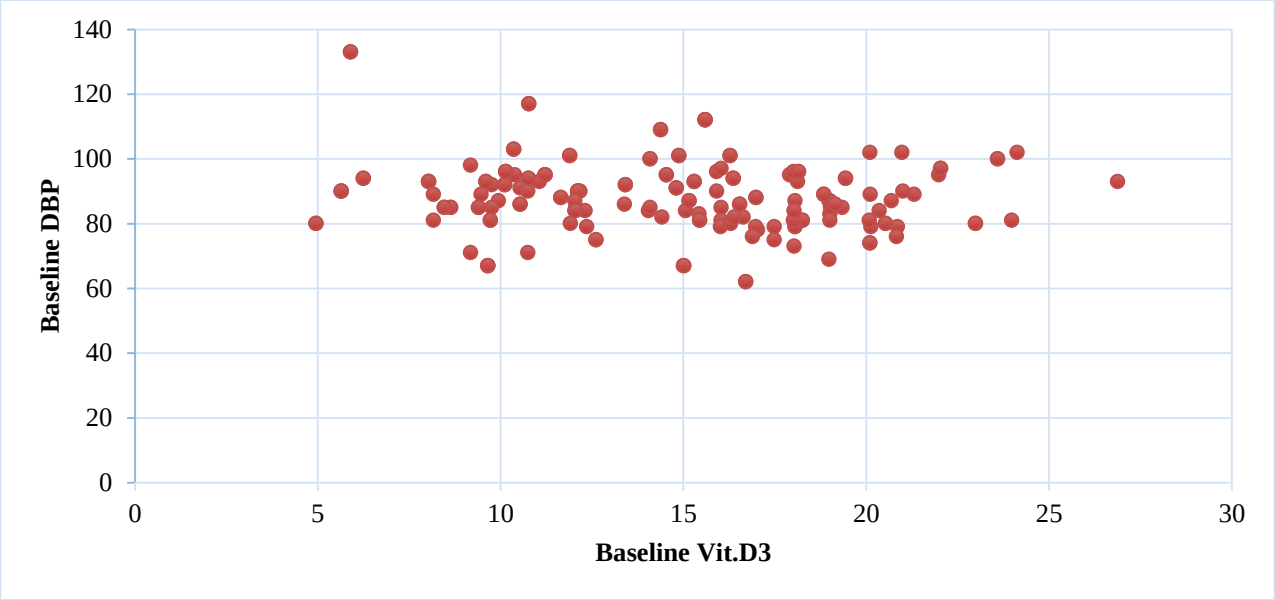


**Figure 03: Test group of correlation in between Baseline Vit.VD3 and Baseline-DBP**

Figure 03 shows on Pearson correlation (weak) negative correlation was observed between decreased Vitamin D3 level with increased DBP.

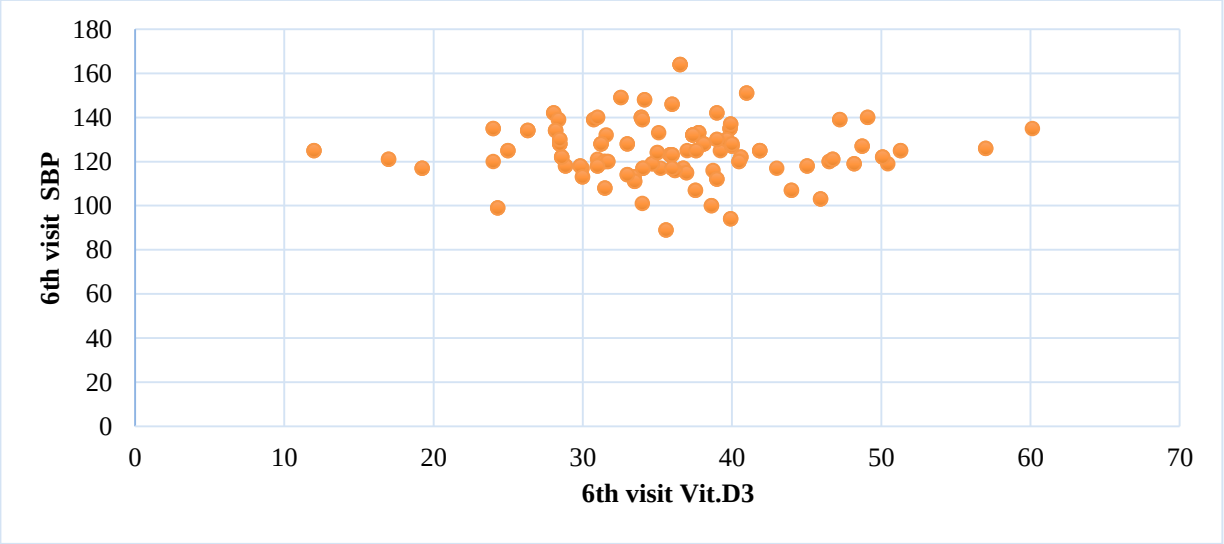


**Figure 04: Test group of correlation in between 6th visit vitaminD3 and 6th visit-SBP**

Figure 04shows on correlation in between vitamin D3 6th visit with 6th visits SBP (weak) negative correlation was observed, increased VitminD3 level was associated with decreased SBP.

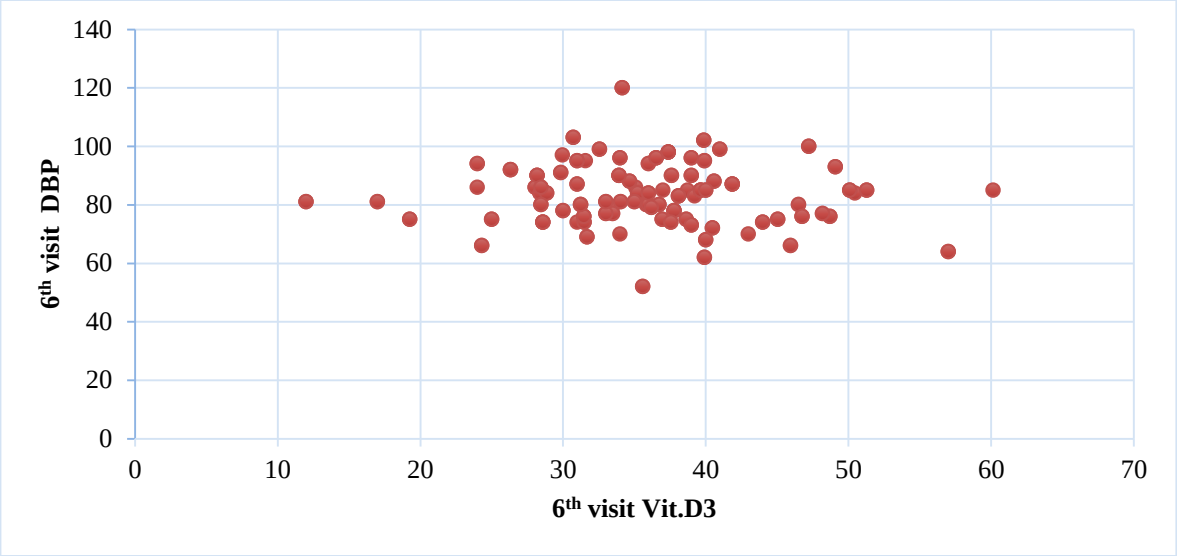


**Figure 05: Test group of correlation in between 6th visit vitaminD3 and 6th visit- DBP**

Figure 05shows on correlation in between vitamin D3 6th visit with 6th visits DBP (weak) negative correlation was observed, increased VitminD3 level was associated with decreased DBP.

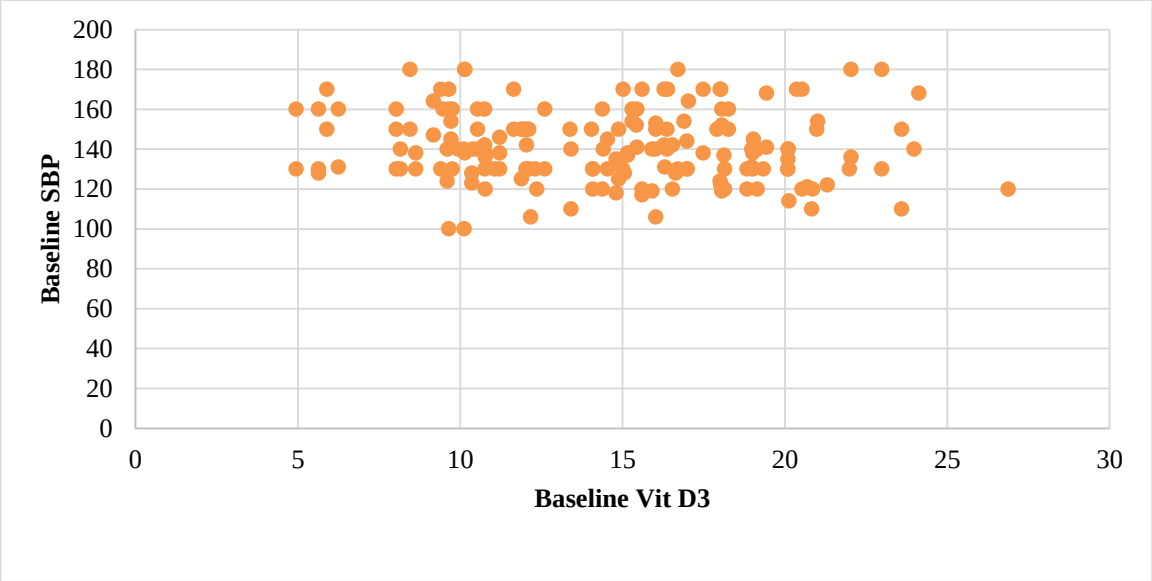


**Figure 06: Control group of correlation in between baseline Vit.D3 & baseline-SBP**

Figure 06: Shows on Pearson correlation in between baseline visit vitamin D3 and baseline- SBP (weak) positive correlation was observed between decreased VitminD3 Level with increased SBP.

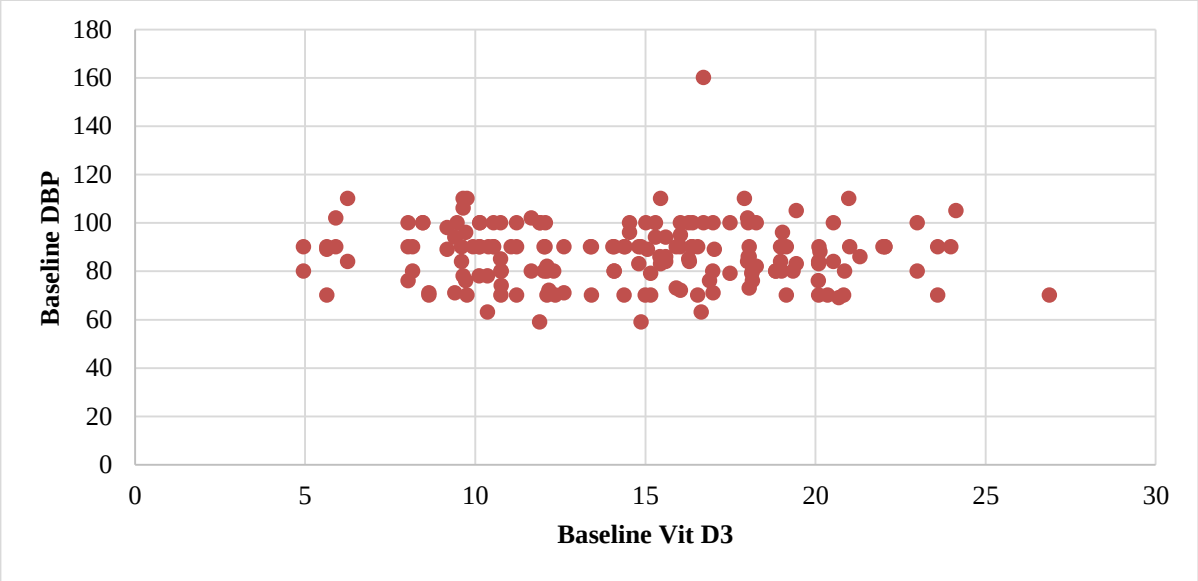


**Figure 07: Control group of correlation in between baseline Vit.D3 & baseline DBP**

Figure 07shows on Pearson correlation in between baseline visit vitamin D3 and baseline- DBP (weak) positive correlation was observed between decreased VitminD3 Level with increased DBP

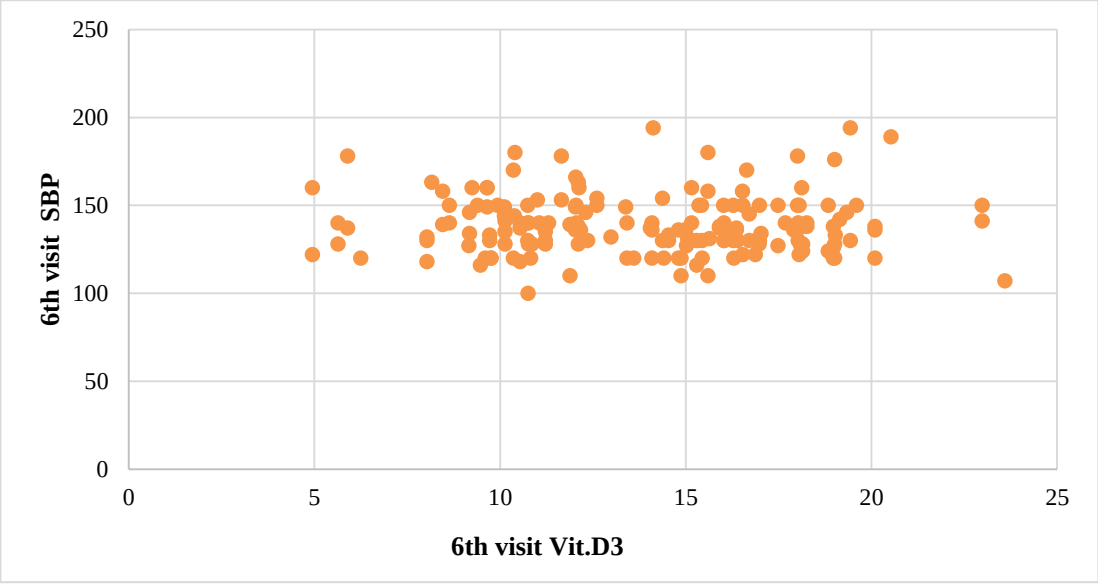


**Figure 08: Control group of correlation in between Visit 6 vit. D3 and 6th visitSBP**

Figure 08: shows on Pearson correlation in between 6$^{th}$visit vitamin D3 and 6$^{th}$visit SBP (weak) negative correlation was observed between decreased VitminD3 Level with increased SBP.

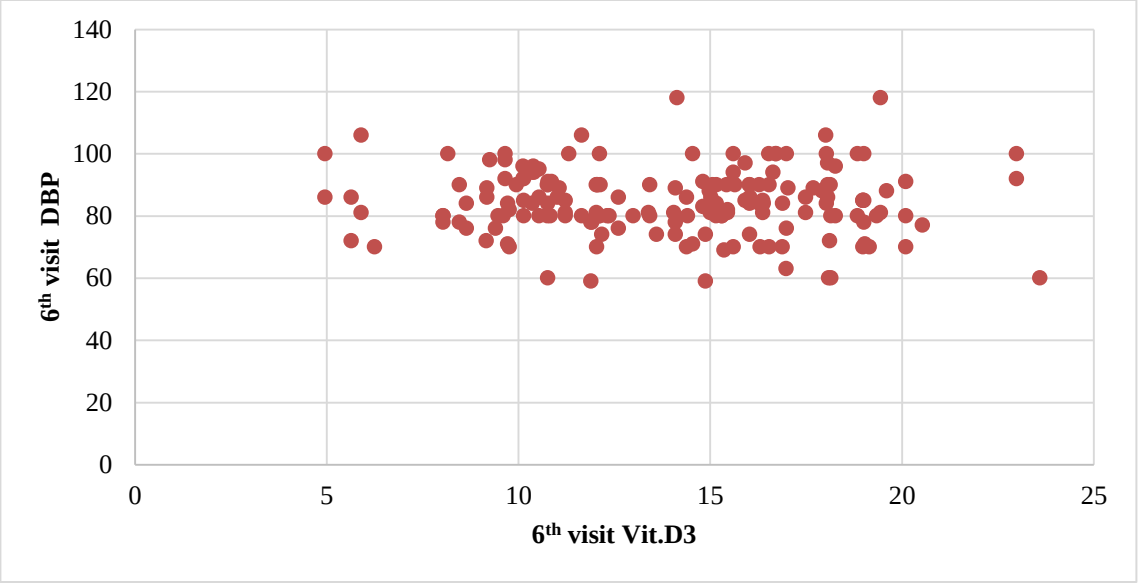


**Figure 09: Control group of correlation in between Visit 6 vit. D3 and 6th visitDBP**

Figure 09shows on Pearson correlation in between 6th visit vitamin D3 and 6th visit DBP (weak) negative correlation was observed between decreased VitminD3 level with increased DBP**.**

## DISCUSSION

This was a non-randomized clinical trial done in collaboration with Department of family and General medicine. All the known cases of essential hypertension coming to the Family and General Medicine department of PRH, Loni were enrolled for the study. The study was registered with the Clinical Trial Registry of India (CTRI). Total of 400 patients were enrolled for the study. All the subjects were screened for the serum 25(OH) D level. Subjects fulfilling the eligibility criteria with serum 25(OH)D level less than 20 ng/ml, having history of hypertension were included in the study. At the end of the study, 49 patients (24 from Test and 25 from control group) dropped out of the study due to their personal reasons and finally 351 patients participated till the end of the study.

Estimation of the Serum level of Vitamin D before and after the sublingual treatment with Vitamin D in Test Group and without add on therapy of Vitamin D in Control Group was compared in our study. 60,000IU dose of sublingual Vitamin D3 was prescribed at an interval of 15 days for 3 months, the mean serum Vitamin D levels raised from baseline 16.61±6.71 ng/ml to 35.80 ±7.80ng/ml in the test group which was found to be highly significant as analyzed byWilcoxon matched-pairs testwhereas in the control group the mean serum Vitamin D levels decreased from baseline 16.40±3.63ng/ml to 14.96±4.94ng/ml after 3 months which was found to be non-significant as analyzed byWilcoxon matched-pairs test **(Table number -01& Graph No :01)**. This finding is in accordance with other studies done by Wei Ren Chen et al[196], Hamid Nasri et al[195] and Miles D. Witham et al[190]where vitamin D was administered orally and was given for longerduration. In these studies, vitamin D 2000 IU was given daily orally as tablet form whereas in our study vitamin D was given sublingually at a duration of 15 days in tablet form. These results are showing the effectivity of sublingual administration of vitamin D and in fact this is the novelty of our study. This might improve compliance of the patient as there is no need of daily administration of vitamin D and also faster results with sublingual route as it bypasses first pass metabolism.

On Pearson correlation in between baseline visit vitamin D3 and baseline visit -SBP, DBP, we observed a negative correlation between decreased VitaminD3 level with increased SBP, DBP in the Test group**(Figure number -02&03)**.On Pearson's correlation in between 6th visit vitamin D3 level and at 6th visit - SBP, DBP ,we observed negative correlation between increased Vitamin D3 level was associated with decreased SBP, DBP in the Test group **(Figure number -04 &05)**.On Pearson

correlation in between baseline visit vitamin D3 and baseline-SBP, DBP, we observed a weak positive correlation between decreased VitminD3 level with increased SBP, DBP in the control group **(Figure number -06&07)**.On Pearson correlation in between $6^{th}$visit vitamin D3 and $6^{th}$ visit - SBP, DBP, we observed (weak) negative correlation between decreased Vitamin D3 level with increased SBP, DBP in the control group **(Figure number -08&09).**

Our finding was similar with Jooyoung Kim et al [16] which reported that serum 25 (OH) D level was negatively correlated with SBP. Also, there was significant negative correlation between pulse pressure and serum 25 (OH) D levels. Thus, level of 25(OH) Dmight is factors that affect blood pressure in middle-aged males. Therefore, an increase in theintake of vitamin D may be an effective way to prevent the elevation of blood pressure [16]. As per Qureshi D et al [17] and Ravinandana Gowda et al [18], there was a significant negative correlation between vitamin D and SBP, DBP. Duprez et al in a study conducted on 25 hypertensive patients demonstrated that vitamin D levels inversely correlated with systolic blood pressure [19]. Several studies reported negative correlations of serum 25(OH)D levelswith both SBP and DBP like Liudmila Yankouskaya et al [20] Forouhi NG et al [21], Smotkin TangorraM, etal [22], Gannage Yared MH et al [23]. At the same time, many cross-over studies did not reveal any correlations between blood pressure values and serum25 (OH) D levels [24-27]. Other studies showed positive correlations between SBP, DBP, and the serum level of 25(OH) D [28,29]. It is possible that the correlations between serum vitamin D levels and SBP, DBP were caused by the effect of vitamin D and on vascular endothelial function, which was already demonstrated by experimental studies [30-32]. In our study Sublingual vitamin D3 was found to be effective in reducing the systolic and diastolic blood pressure, the novelty of our study lies in the sublingual route of administration which was proven to be very effective, however multicentre trials with large sample size are required to come to a conclusion.

## Acknowledgement

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## CONCLUSION

There was a significant decrease in SBP associated with increasing 25(OH) D levels in response to supplementation. This intervention trail clarified Sublingual vitamin D3 prevents the hypertension in the general population. In view of the costs and side-effects associated with antihypertensive drugs, the potential to reduce hypertension by vitamin D is very attractive. Similarly, in view of the multiple health benefits of vitamin D and the high prevalence of vitamin D deficiency, as well as the easy, safe, and inexpensive ways in which vitamin D can be supplemented.

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