Effect of Vitamin-D supplementation on blood pressure in post-menopausal women: A community based interventional study

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Introduction

It has been estimated that 1 billion people worldwide have Vitamin-D deficiency or insufficiency.[1] There is wide spread prevalence of varying degrees (50 – 90%) of Vitamin-D deficiency with low dietary calcium intake in the Indian population.[2] Besides its role in bone metabolism Vitamin-D has additional effects on the immune system, neuromuscular function, cancer & cardio-vascular system including hypertension. Hypertension affects nearly 26% of the adult population worldwide.[3] In India, the prevalence of hypertension in the last six decades has increased from 2% to 25% among urban residents and from 2% to 15% among the rural residents. According to Directorate General of Health Services, Ministry of Health and Family Welfare, Government of India, the overall prevalence of hypertension in India by 2020 will be 159.46/1000 population.[4] Emerging evidence suggest an inverse relation between Vitamin-D and hypertension.

Vitamin-D regulates the renin – angiotensin – aldosterone system, suppresses vascular smooth muscle proliferation, inhibits secretion of Parathyroid hormone (PTH) and regulates calcium and phosphorous levels, which are all mechanisms by which Vitamin-D is believed to have an impact on blood pressure.[5,6] An interventional study in Vitamin-D deficient elderly women found that a combination of calcium and Vitamin-D supplementation had a greater blood pressure lowering effect than calcium supplementation alone.[7] Up to 9% reduction in the systolic blood pressure was seen after two weeks of calcitriol supplementation in hypertensive adults in another study.[8]

However, findings from various randomized trials of Vitamin-D supplementation to lower blood pressure are inconsistent, possibly due to variability in study population, sample size, Vitamin-D dose and duration. If Vitamin-D supplementation lowers blood pressure, its wide- spread use would be of significant clinical implication as hypertension is one of the leading non-communicable disease of the present generation.

Aims and Objectives

***Primary Objective*:** To find out the effect of Vitamin-D supplementation on blood pressure in post-menopausal women in the study population.

***Secondary Objective*:** To determine the prevalence of hypertension in the post-menopausal women in the study population.

Materials and Methods

Study design: A community based interventional study.

Study setting: The study was conducted in Jamalpur, a field practice area of the Department of Community Medicine, Christian Medical College, Ludhiana, Punjab. The Department provides primary health care services to approximately 10,000 population in this area through its Urban Training Centre, and has a well-established system of constant community monitoring by the use of the Family Folder methodology, a health information system wherein each family in the population served has a Family Folder containing the demographic and health profile of the members of the family. The homes are visited regularly in a beat visit fashion by a health team consisting of a female Multi-purpose Health Worker (MPHW) and a medical intern to provide targeted, home-based primary health care and advice, and to update the demographic and health information. Information regarding women who are in the menopausal age group was available from the database of the study area which is regularly updated by the department.

Reference population: Post-menopausal women residing in the study area.

Study population: 290 post-menopausal women in the area.

Sample size estimation: As per the departmental data-base, there were 820 post-menopausal women in the study area. Considering the lowest prevalence of Vitamin-D deficiency of 50%[2] the minimum sample size at 95% confidence limit and 10% allowable error, was calculated to be 262 (Epi Info v6, Statcalc). Allowing for 10% loss to follow-up, a total of 290

women were selected for the study by systematic random sampling. Family folders were screened and a line-list of all the post-menopausal women was made. By dividing the total number of eligible women of the area by the sample size, the sampling interval obtained in this study was 820/290=2.8~3. A random number was chosen (using the last three digits in a 100 rupee note). The random number came out to be 432. The first respondent to participate in the study was selected from the line-list by this random number. The sampling interval of 3 was then used as the constant difference between subjects.

Study period: 12 months

Inclusion Criteria:

1. Post-menopausal women
2. Consent to participate in the study

Exclusion criteria:

1. Subjects on calcium or Vitamin-D supplements presently or within the past 3 months.
2. Terminally ill.
3. History of heart disease/stroke.
4. Known case of chronic liver disease/ renal failure.
5. Current treatment for cancer.
6. Current use of more than three anti-hypertensive medications
7. Known cases of secondary hypertension.

Study tools and data collection: Two hundred ninety post-menopausal women were included in the study after obtaining their signed informed consent on the consent form. Menopause was defined as cessation of menstruation for 12 months. At induction, the subjects were interviewed to obtain their demographic, lifestyle and chronic diseases details. Height, weight, Body Mass Index (BMI) and blood pressure (BP) of each individual was recorded during the house visits using portable electronic scales/monitors, as per WHO-STEPS methodology.[9]

The participants were then supplemented with Vitamin-D 60,000IU weekly for a total period of 8 weeks. This was made available to them in the form of sachets which contained cholecalciferol granules. Compliance was ensured by reinforcement through weekly personal visits by the investigator. The pre- and post-intervention Vitamin-D levels were estimated for a randomly selected 25% sample of all those found to be having hypertension. This was done to see if Vitamin-D has any role to play in the control of blood pressure. We did not intervene in any way in the management of hypertension in these subjects. The Vitamin-D estimation was done using DIA source 25OH Vitamin D Total ELISA Kit. This FDA approved kit is manufactured by DIA source Immuno Assays S.A, Belgium.

Out of the 290 women who were enrolled into the study, 271 successfully completed the study.

Data Analysis

The data was analyzed using EpiInfo version 6 software. Analysis included comparison of the mean pre- and post-intervention blood pressure of the subjects. Analysis also included comparison of the pre & post-intervention Vitamin-D levels in 25% of the sample of hypertensive women. Chi-square test and Paired t-test was applied, where appropriate, to assess the statistical significance of observed differences.

Results

Table 1: Socio-demographic profile of the participants (n=271)

Characteristics	No.	%
Age (yrs)		
• 40-49	73	26.9
• 50-59	95	35.1
• 60-69	58	21.4
• 70-79	39	14.4
• 80-89	6	0.02
Education		
• Illiterate	102	37.6
• Literate	169	62.4
Occupation		
• Housewife	239	88.2
• Working	32	11.8
Type of family		
• Joint	179	66.1
• Nuclear	86	31.7
• Single	6	2.2
Physical activity		
• Sedentary	247	91.1
• Moderate	24	8.9
• Heavy	0	0.0
BMI		
• Under weight (<18.50)	13	4.8
• Normal (18.50-24.99)	94	34.7
• Pre-obese (25.0-29.99)	95	35.0
• Obese ≥ 30	69	25.5
Hypertension		
• Pre-hypertensive/ Normotensive	86	31.7
• Hypertensive	185	68.3

The mean age of the participants was 56.5 years with standard deviation of 10.01 (95% CI 55.36 – 57.76). Maximum number of women was in the age group of 50 – 59 years (35.1%) **(Table 1).**

Table 2: History of chronic disease in the participants (n=271)

Disease	No.	%
Hypertension	86	31.7
Arthritis	53	19.5
Diabetes	46	16.9
Hypothyroidism	5	1.8
Respiratory Illness	4	1.4
Psychiatric Illness	2	0.7
None	139	51.3
(*Total = 335, as few subjects had reported more than one chronic illness.)		

Hypertension (31.7%) was the most commonly reported chronic disease in the study subjects, followed by arthritis (19.5%) and diabetes mellitus (16.9%). The percentage of women who had both hypertension and diabetes was 4.4%. Almost half of the subjects (51.3%) did not give any history of chronic disease. It was seen that 185/271 subjects had hypertension (including already diagnosed cases) as per the JNC-7 criteria. Thus the prevalence of hypertension among post-menopausal women in the study was 68.3% **(Table 2)**.

A reduction in the mean systolic blood pressure by 3.0% was observed in the subjects following supplementation with Vitamin-D for 8 weeks, but this was not statistically significant (p = 0.0705). The mean diastolic blood pressure was also seen to be reduced by 3.2% and this was statistically significant (p = 0.0419) (**Table 3a)**.

Table 3a: Effect of Vitamin-D supplementation on blood pressure (n = 271)

	Mean SBP	Mean DBP
Pre-intervention	143.75±29.89	93.26±17.62
	F-stat=3.28; p=0.0705	
Post-intervention	139.37±26.26	90.26±16.61
	F-stat=4.16; p=0.0419	

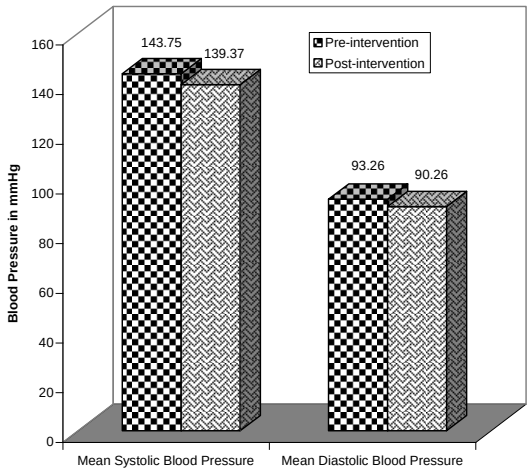

Fig. 1: Difference in Blood Pressure (mmHg)

Among the hypertensive subjects, a reduction in both the mean systolic and diastolic blood pressure was noted following Vitamin-D supplementation. But this reduction was not statistically significant (Table 3b).

Table 3b: Effect of Vitamin-D on Mean Blood Pressure of Hypertensive women (n=47)

	Mean SBP	Mean DBP
Pre-intervention	161.68±25.14	104.60±17.67
	F-stat=1.89; p=0.1723	
Post-intervention	153.85±29.87	100.19±20.76
	F-stat=1.23; p=0.2701	

A significant reduction in blood pressure was seen among the 47 hypertensive women who were studied for the effect of Vitamin-D on blood pressure. Following intervention, 9 out of 47 subjects (19.1%) were found to be in the normal/pre-hypertensive stage (p=0.0068) (**Table 4)**.

Table 4: Effect of Vitamin-D on stage of hypertension (n=47)

Hypertension	Pre-intervention		Post-intervention	
	No.	%	No.	%
Normal/ Pre-HTN	0	0.0	9	19.1
Stage- 1	18	32.3	15	31.9
Stage- 2	29	61.7	23	48.9
	$\chi2$=9.97; df=1; p=0.0068			

There were 18 patients who had Stage 1 hypertension, of which 77.8% were Vitamin-D deficient /insufficient and 22.2% - normal. Among 32 women who had Stage 2 hypertension, 87.5% were found to be deficient. Thus Stage 2 hypertensives were more deficient as compared to stage 1 hypertensive, but this association was not statistically significant **(Table 5a)**.

Table 5a: Association between pre-intervention Blood pressure and Vitamin-D level (n=50)

Hypertension	Vitamin- D Level (n=50)			
	Deficient/ Insufficient		Normal	
	No.	%	No.	%
Stage 1	14	77.8	4	22.2
Stage 2	28	87.5	4	12.5

Yate's corrected $\chi2$= 0.25, df = 1, p = 0.618

Out of the 50 randomly selected hypertensive subjects whose serum Vitamin D levels were estimated pre-intervention, 3 were lost to follow up. So we compared the pre- and post-supplementation values of 47 hypertensive subjects. At baseline, 83.0% of the women were found to have deficient or insufficient

serum Vitamin-D levels. Post-intervention, the proportion of women deficient or insufficient in serum Vitamin-D levels reduced to 29.8%. Those with sufficient levels of serum Vitamin-D increased from 17.0% pre-intervention to 61.7% post-intervention, while and 4/47 (8.5%) subjects had levels in the toxic range **(Table 5b).**

Table 5b: Pre & post-intervention Vitamin-D levels (n=47)

Vitamin-D levels	Pre-intervention		Post-intervention	
	No.	%	No.	%
Deficient	29	61.7	9	19.1
Insufficient	10	21.3	5	10.6
Sufficient	8	17.0	29	61.7
High	0	0.0	4	8.5
Total	47	100	47	100

$\chi 2 = 28.11$, df = 3, p = 0.000

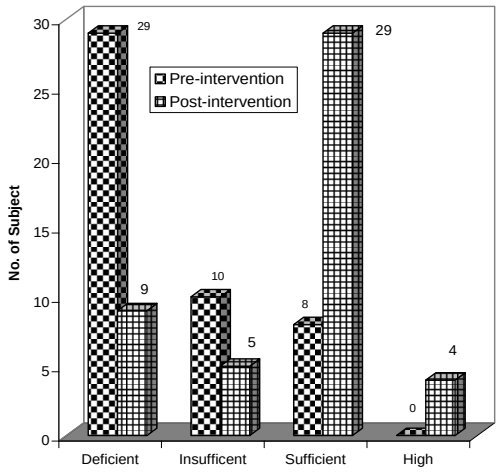

Fig. 2: Comparison of Serum Vitamin-D levels (n=47)

Discussion

A total of 290 post-menopausal women residing in Jamalpur were enrolled into the study after taking their written consent, out of which 271 completed the study. The mean age of the participants in this study was 56.5±10.01 years with the youngest subject in the study being 40 years old and oldest subject 85 years old **(Table 1).**

In our study, Hypertension (31.7%) was the most commonly reported chronic disease in the study subjects, followed by arthritis (19.5%) and diabetes mellitus (16.9%) **(Table 2).** The blood pressure of all the subjects who consented to take part in the study was recorded and it was seen that 185/271 subjects had hypertension (including already diagnosed cases) as per the JNC-7 criteria. Thus the prevalence of hypertension among post-menopausal women in our study was 68.3%. This was similar to the finding from a study done in China where the prevalence of hypertension among post- menopausal women was 62.4%.[10] The prevalence of hypertension in this study was found to be higher than the prevalence reported from a study done in Delhi (39.6%) among urban post-menopausal women and 56% among rural post-menopausal women.[11] In another study also prevalence of hypertension in rural post-menopausal women was observed to be higher.[12] We have come to a stage when the load of communicable diseases have been taking a backseat and other newer diseases or non-communicable illness, are occurring. It's high time we find a way towards Universal Health Coverage than treating the illnesses.[13]

The blood pressure of all the study subjects was recorded in their homes both pre-intervention and after supplementation of Vitamin-D for a total of 8 weeks. Pre-intervention, the mean systolic blood pressure (SBP) was 143.75±29.89 mmHg and the mean diastolic blood pressure (DBP) was 93.26±17.62 mmHg. Post-intervention the mean systolic blood pressure (SBP) was 139.37±26.26 mmHg and the mean diastolic blood pressure (DBP) was 90.26±16.61 mmHg. Though a reduction in both the mean systolic (3.0%) and diastolic blood pressure (3.2%) was seen after 8 weeks, the reduction in diastolic blood pressure was found to be statistically significant (p = 0.0419). (Table-3a) Our findings varied from similar studies done abroad where, in a randomized, placebo-controlled study done in 148 elderly women it was seen that 800 IU of Vitamin-D3 plus 1200 mg of calcium significantly reduced blood pressure by 9.3% after 8weeks, whereas treatment with 1200 mg of calcium alone reduced blood pressure by only 4.0% (P = 0.02).[14] In another experiment in 2013 which looked at the effects of Vitamin-D on blood pressure in African Americans, the researchers assigned 250 people to receive either 1,000 IU per day, 2,000 IU per day, 4,000 IU per day of Vitamin-D, or a placebo for 3 months. They found that for each 1ng/mL increase in plasma 25-hydroxyvitamin D, there was a significant 0.2mm Hg reduction in systolic pressure (P=0.02), but there was no effect on diastolic pressure (P=0.37).[15] In the Women's health initiative randomized trial, it was seen that calcium plus vitamin D3 supplementation did not reduce either blood pressure or the risk of developing hypertension over 7 years of follow-up in post-menopausal women.[16]

Following Vitamin-D supplementation for 8 weeks, it was observed that out of the 47 hypertensives who had either stage 1 or stage 2 hypertension prior to supple-mentation, 9 had their blood pressure lowered to the normotensive/pre-hypertensive range and this was statistically significant (p=0.0068). **(Table 4)** This was despite the fact that they were under routine care and no treatment was started to control the hypertension. Among the 47 hypertensive patients, a reduction in the

mean systolic and diastolic blood pressure was seen following Vitamin-D supplementation. The mean systolic and diastolic blood pressures were found to be lowered by 4.8% and 4.2% respectively. However, this was not statistically significant **(Table 3b**). A probable explanation for this would be the smaller sample size (n=47) used for this comparison. RCTs on Vitamin-D supplementation and blood pressure as a primary outcome have produced mixed results, with some studies showing no significant result whereas others reporting antihypertensive Vitamin-D effects. More deficiency/insufficiency was found in the study women with stage 2 hypertension as compared to those with stage 1 hypertension (87.5% vs 77.8%), but this was not statistically significant **(Table 5a).** Bhandari SK et al demonstrated similar results in their study where hypertension rates were 52%, 41%, 27%, and 20% in 25-hydroxyvitamin D quartiles <15 ng/mL, 15 to 29 ng/mL, 30 to 39 ng/mL, and ≥40 ng/mL, respectively (P<.001).[17]

In a study performed in 130 hypertensive patients in Denmark, patients were randomly allocated to either placebo or 3000 IU Vitamin-D per day over 12 weeks during winter. Using 24 h ambulatory blood pressure measurements, there was only a moderate trend for a reduction in systolic (-3 mm Hg; *P*=0.26) and diastolic (-1 mmHg; *P*=0.18) blood pressure in the treatment compared to the placebo group. In analyses restricted to patients with 25(OH)D levels below 32 ng/ml (80 nmol/l) there was a reduction in systolic blood pressure by -4 mmHg (*P*=0.05) and in diastolic blood pressure by -3 mmHg (*P*=0.01) in the Vitamin-D supplementation group. This result suggests that if antihypertensive effects of Vitamin-D are actually present, these may only be observed in groups with both low Vitamin-D levels and high blood pressure.[18]

Conclusions

Vitamin-D supplementation was seen to reduce the blood pressure among post-menopausal women (n=271), of which, the reduction in the diastolic blood pressure was statistically significant. Among the 47 hypertensive subjects, though a reduction in both the mean systolic and diastolic blood pressure was noted following Vitamin-D supple-mentation, this was not significant. This could possibly be due to the smaller sample size (n=47) used for this comparison. Hypertension was the most common chronic disease followed by arthritis and diabetes, among post-menopausal women in this community. The prevalence of hypertension was alarmingly high (68.3%). This can be attributed to aging and the loss of endogenous estrogen production after menopause. The prevalence of Vitamin-D deficiency was quite high (83%) among these hypertensive post-menopausal women who were tested and supplementation was found to be beneficial to this group too as it led to a significant improvement in their levels.

Limitations

- We could not control for all potential confounders.
- The pre-intervention and post-intervention serum Vitamin-D levels of all the subjects could not be estimated due to financial constraints.

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