Vitamin D Levels and its Relation to Blood Pressure among Saudi Postmenopausal women: A Cross-Sectional Study

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Abstract: Background: Vitamin D deficiency and hypertension are common health problems among the Saudi population. Mounting evidence points to the role of optimal 25-hydroxyvitamin D [25(OH)D] status in the prevention of many chronic disorders including hypertension. Data on the correlation between hypovitaminosis D and blood pressure (BP) level in the Saudi population are lacking. **Objective:** The aim of the present study was to assess the correlation between vitamin D status and BP in a group of Saudi postmenopausal women. **Methods:** A cross sectional study conducted in the "Center of Excellence for Osteoporosis Research" (CEOR) during the year 2013. The study included 31 Saudi postmenopausal women (aged 52-70 years), randomly selected from "Primary Health Care" centers in Jeddah, Saudi Arabia. Serum 25(OH) D and parathyroid hormone (PTH) were measured by sandwich chemiluminescence immunoassay. Blood pressure was recorded with an automated BP monitor (BpTRU) according to a standardized protocol. Linear regression was performed to find out if 25(OH)D was independently associated with BP in this group of women. **Results:** A high prevalence of vitamin D deficiency was found with 68% of the women having levels <50 nmol/L. There was a significant inverse association between 25(OH)D and both systolic and diastolic BP. However, multiple linear regression analysis showed that 25(OH)D level was independently associated with diastolic BP only.**Conclusions:** In Saudi postmenopausal women, 25(OH)D level was inversely and independently associated with diastolic BP. Correction of vitamin D deficiency may improve BP control in hypertensive postmenopausal women. Interventional studies to evaluate if attainment of optimal vitamin D status may prevent hypertension are necessary.

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1. Introduction:

The role of optimal vitamin D status in skeletal and extra skeletal health had recently been the subject of extensive research. One of the consequences of vitamin D deficiency is cardiovascular disorders including hypertension. Vitamin D deficiency and hypertension are common health problems that on the long-term may lead to more serious health problems. Vitamin D deficiency is highly prevalent worldwide (30-50%)[(1)] and in the Saudi population, in particular among Saudi women with a prevalence of (68-76%) in premenopausal women, and (80-85%) in postmenopausal women[(2)]. Studies also reported that the group at risk the most is postmenopausal women[(3-5)], deficiency among that group increased the risk of hypertension and fractures, thus contributing to early mortality.

Cross sectional studies had clearly demonstrated the presence of an association between 25(OH)D levels and blood pressure, however longitudinal studies and randomized clinical trials showed a weak evidence to support this finding and more research is required to draw final conclusions.

Bhandari, *et al.* conducted a cross sectional study in 2011 that included 2722 patients aged 18 years and above. They confirmed the inverse association between 25(OH)D levels and hypertension. Patients were classified according to their 25(OH)D serum concentration, and the study showed increased rates of hypertension in patients with lower 25(OH)D concentrations[(6)]. Burgaz, *et al.* in another cross sectional study confirmed the presence of an association between low levels of 25(OH) D and hypertension in elderly men[(7)].

Results from the "Third National and Health Examination Survey" (NHANES III) (1988-1992) found a negative correlation between 25(OH)D concentrations and BP in white subjects involving both genders[(8)]. However, after controlling for age, this association was lost. Although black subjects had lower concentrations of 25(OH)D, no association was found between 25(OH)D levels and blood pressure in both sexes.

Experimental studies on animal models found that 25(OH)D inhibits renin gene expression. Moreover, mice lacking vitamin D receptor (VDR) developed uncontrolled expression of the renin gene and over

production of angiotensin II, leading to increased blood pressure[9].

Another study in humans by Forman, *et al.* suggested that higher blood pressure in subjects with deficient or insufficient levels of 25(OH)Dmight be related to the up-regulation of renin-angiotensin system (RAS)[10].

Studies addressing the association between vitamin D status and hypertension in the Saudi population are lacking, therefore, the aim of this study was to determine the correlation between vitamin D status and blood pressure level in Saudi postmenopausal women.

2. Subjects and Methods:

Saudi postmenopausal women (aged 52 and above) were randomly selected from "Primary Health Care" centers. Those who agreed to participate (n=31) were asked to attend the "Center of Excellence for Osteoporosis Research" (CEOR) at "King Abdulaziz University" (KAU) in Jeddah, Saudi Arabia.

Each subject was interviewed using a standardized questionnaire and information on lifestyle, extent of physical activity, sun exposure, dietary habits, calcium and vitamin D supplementations, medication use, and history of diseases was collected.

Subjects with renal disease, liver disease, thyroid disease, or on medications that may alter bone metabolism such as steroids and antiepileptic medications, were excluded from the study.

An informed consent was taken from all enrolled women, and the Ethics Committee of CEOR in "King Abdulaziz University" approved the study.

Anthropometric measurements:

Weight was measured using an electrical scale to the nearest half-kilogram. Subjects were wearing light clothes and were bare footed when weighed. Height was measured using a stadiometer to the nearest half-centimeter. Body mass index (BMI) was calculated as weight (kg)/height (m^2). Waist circumference (midway between the lower rib margin and the iliac crest) and hip circumference (the maximal circumference over the buttocks) were measured as well, and waist to hip ratio (WHR) was also calculated.

Blood Pressure Measurement:

Blood pressure was recorded with an automated blood pressure monitor (BpTRU) that was previously validated by the "British Hypertension Society"(BHS). The blood pressure was recorded in a private room where subjects were asked to sit and relax for 5 minutes before the measurement. Women were also asked to refrain from talking or making any other effort while waiting for the measurement to be taken. Appropriately sized cuff was placed on the right upper arm. Three readings were recorded; the first was after taking rest for 5 minutes, and the second and third were after a one-minute resting period from the first and second reading, respectively. The average of the last 2 readings was used for analysis.

Blood Samples:

A venous blood sample was obtained from each subject and centrifuged at 2500g for 10 minutes within 30 minutes of sample collection. Serum was stored at -80ºC until analyzed for the biochemical and hormone determinations. Serum 25(OH)D and parathyroid hormone were measured by sandwich chemiluminescence immunoassay method using commercial kits from DiaSorin (Italy) and the tests were performed on LIASON auto analyzer [DiaSorin Inc, Stillwater, MN, USA]. Postmenopausal status was confirmed biochemically in all women (FSH>20 IU/L).

Statistical Analysis:

The statistical analysis was performed using the latest version of SPSS program (SPSS Statistics 20). Normal distribution of the different variables was checked using "Kolmogorov-Smirnov" test. PTH was the only variable that was not normally distributed; therefore log PTH was used in the analysis. All results were expressed as means ± SD. Women were grouped into 2 groups according to their 25(OH)D level. The significance of differences in blood pressure between the two groups was assessed using the unpaired student t-test. The association between blood pressure and vitamin D level was assessed with Pearson's correlation. Linear regression analysis was performed to find out if 25(OH)D level was independently associated with BP. P values < 0.05 were considered significant.

3. Results:

The study included 31 postmenopausal Saudi women. Sixteen of the studied women were known hypertensive and receiving antihypertensive medications, 10 of these women were also diabetic. Age and anthropometric data of the studied women are presented in Table 1.

Table 1: General characteristics of the study group (n=31).

Variable	Mean±SD
Age (years)	60 ± 3.9
Weight (kg)	81.5 ± 13.2
Height (cm)	152.2 ± 5.3
Waist circumference (cm)	102.7 ± 9.4
Hip circumference (cm)	115.7 ± 10.8
WHR	0.893 ± 0.092
BMI (Kg/m^2)	35.2 ± 5.5

"SD; standard deviation, WHR; waist to hip ratio, BMI; body mass index"

The mean BMI of the study group was in the

obese range. None of the women studied had a BMI within the normal range (i.e. <25kg/m^2). The prevalence of overweight (BMI 25-<30 kg/m^2) in the study group was 13%, while obesity (≥ 30 kg/m^2) was prevalent in the majority of women (87%).

The biochemical characteristics of the studied women are presented in Table 2. Mean 25(OH)D was in the deficient range (<50 nmol/L) with levels as low as 7 nmol/L were found in some women.

Table 2: Biochemical characteristics of the study group.

Variable	Mean±SD
25(OH)D (nmol/L)	40.1 ± 30.4
PTH (pmol/L)	6.3 ± 4
Ca (mmol/L)	2.3 ± 0.1
PO_4 (mmol/L)	1.3 ± 0.2

"SD; standard deviation,25(OH)D; 25-hydroxyvitamin D, PTH; parathyroid hormone, Ca; total serum calcium, PO_4; inorganic phosphate"

High prevalence of vitamin D deficiency was found among the studied women, with almost 39% having levels below 25 nmol/L (Figure 1).

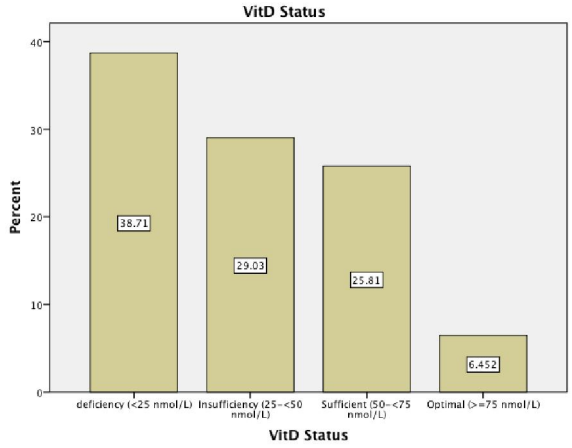

Figure 1: 25(OH)D status among the study subjects.

Blood pressure in the study group:

The mean systolic blood pressure (SBP) for the study group was 129.8 ± 19.3 mm/Hg and the mean diastolic blood pressure (DBP) was 74.7± 8.7 mm/Hg. Women were grouped into two groups according to 25(OH)D status (those with vitamin D level <25 nmol/L and those ≥ 25nmol/L). Comparisons between the blood pressure and other variables in the 2 groups are presented in Table 3.

Blood pressure (both SBP and DBP) was higher in the group with 25(OH)D level <25 nmol/L compared to those with 25(OH)D level ≥ 25nmol/L, although the difference was not statistically significant.

Correlation studies:

A statistically significant inverse correlation was observed between 25(OH)D and blood pressures, both systolic (r=-0.39, P=0.028) and diastolic (r=-39, P=0.030). However, because of the known correlation between blood pressure and BMI, age, and PTH, linear regression analysis was performed to control for these confounding factors.

Regression analysis:

Multiple linear regression analysis was done to assess the independent correlation between 25(OH)D level and blood pressure among the study group. Table 4 shows the regression coefficients for each predictor.

Table 3: Differences in blood pressure and other variables between women with 25(OH)D level <25nmol/L and those ≥ 25 nmol/L.

Variables	25(OH)D level		*P* value
	<25 nmol/L n=12 Mean±SD	≥25 nmol/L n=19 Mean±SD	
Age (years)	60.3±2.2	59.8±4.8	0.670
BMI (kg/m^2)	35.1±5.8	35.2±5.5	0.951
WC (cm)	101.6±10.0	103.5±9.3	0.589
SBP (mmHg)	133.9±15.6	127.3±21.3	0.358
DBP (mmHg)	76.8±7.6	73.3±9.3	0.286
25(OH)D (nmol/L)	16.1±4.7	55.2±30.0	<0.001
PTH (pmol/L)	7.98±4.92	5.17±2.81	0.091
Serum Ca (mmol/L)	2.37±0.13	2.34±0.13	0.536
PO_4 (mmol/L)	1.29±.021	1.37±0.15	0.215

"SD; standard deviation, BMI; body mass index; WC, waist circumference, SBP; systolic blood pressure, DBP; diastolic blood pressure, 25(OH)D; 25-hydroxyvitamin D, PTH; parathyroid hormone, Ca; total serum calcium, PO_4; inorganic phosphate".

Table 4: Linear regression analysis showing correlation coefficients for predictors of both SBP and DBP.

Predictor of SBP	**B**	**SE**	***P* value**
Age (years)	2.634	0.768	0.002
Predictor of DBP	B	SE	P value
25(OH)D (nmol/L)	-0.113	0.049	0.030

"SE; standard error, SBP; systolic blood pressure, DBP; diastolic blood pressure, 25(OH)D; 25-hydroxyvitamin D"

Linear regression analysis showed that age was the main predictor of SBP and 25(OH)D level was the main predictor for DBP.

4. Discussion:

This study showed the presence of a negative and independent association between serum 25(OH)D and diastolic blood pressure in Saudi postmenopausal women. A high rate of serum 25(OH)D deficiency was also observed among those women (68% had serum 25(OH)D levels <50 nmol/L). Another remarkable finding was the high rate of obesity (87% of the study group).

Low serum 25(OH)D was linked to higher blood pressure levels in many cross sectional studies. Judd, *et al.* (2008) in a cross sectional study recruiting 7699 subjects, of both genders, reported a significant inverse association between 25(OH)D and systolic BP in white men and women only, and no presence of association in black men or women[(11)]. While some of the postmenopausal women of the present study were hypertensive, that of Judd, *et al.* were non-hypertensive young subjects with age variation from 18 to 50 years old.

Another cross sectional study conducted by Jorde *et al.*(2010) with a sample of 4125 including both genders, found a significant negative association between quartiles of serum 25(OH)D and SBP, but not DBP[(12)].

The "Third National Health and Examination Survey" (2007), confirmed the increased prevalence of hypertension among blacks in relation to the other ethnic groups, and the inverse relation between 25(OH)D with SBP[(13)]. Two main differences from the present study were the age range of the recruited subjects (from 20 and above), and the exclusion of subjects on hypertensive medications.

Another study from Germany conducted by Hintzpeter *et al.*(2008) with a total of 1763 men and 2267 women, aged between (18-79 years old), found that reduced levels of 25(OH)D was associated with increased risk of hypertension in both genders, with a higher prevalence in women[(14)]. This study differed from the present study in the age variation (18-79 years old) and gender variation.

Presence of a relationship between serum 25(OH)D and diastolic blood pressure in this study, might be explained by the high prevalence of vitamin D deficiency, most of the studied women (39%) were having serum levels <25 nmol/L. Another explanation is that it is common to find vitamin D deficiency and hypertension in the elderly, especially when there's a high rate of obesity. 87% of the study subjects were obese; this might have a strong impact on both the increased blood pressure and the deficiency of 25(OH)D. In addition, the presence of association between serum 25(OH)D and blood pressure might be due to the fact that only some women had elevated serum levels of PTH as a response to 25(OH)D deficiency (9 out of 31); this might have strengthened the association between 25(OH)D levels and blood pressure.

Limitations:

The main limitation of this cross sectional study is the problem of temporality. Another limitation was the small sample size. In addition, the inclusion of diabetic women (13 out of 31) was a limitation as well. Most study subjects were also obese (27 out of 31), and this might have contributed to the relation between 25(OH)D and an elevated blood pressure. Therefore, these results cannot be generalized because the sample is not representative of the whole population (Saudi postmenopausal women).

Conclusion:

To conclude, this is the first study that assesses the correlation between 25(OH)D status and blood pressure in Saudi postmenopausal women. 25(OH)D was found to be independently associated with diastolic BP only. Hypertension is a common issue especially in the elderly, thus correcting the situation with vitamin D supplements is an easy, safe, and inexpensive measure that will have an impact on the prevention of many complications and improving the quality of life. Future studies with a larger sample, including both genders, with wide age variation are recommended to confirm the findings of this study. Intervention studies assessing the role of optimal vitamin D status in preventing hypertension are also needed.

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