VITAMIN D STATUS AND ITS CORRELATION WITH BLOOD PRESSURE IN PREMENOPAUSAL SAUDI WOMEN: A CROSS-SECTIONAL STUDY

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ABSTRACT

Vitamin D deficiency is a major health problem in the Saudi population. A negative association between blood pressure and vitamin D level has been suggested in several clinical and epidemiological studies and evidence for an effect of vitamin D in lowering blood pressure was reported. These findings indicate that 1,25(OH)₂D₃ deficiency may play a role in the pathogenesis of hypertension through its effect on the renin-angiotensin system. We are the first to investigate the correlation between blood pressure or renin concentration and vitamin D status in the Saudi population. METHODS: we included 201 healthy Saudi premenopausal females (20-45 years old). Blood pressure was measured by a standardized method using an automated blood pressure monitor (BPTru). Fasting blood samples were collected from each participant after 20 minutes of rest in the seated position. Serum cholecalciferol, PTH and renin concentration were measured by sandwich chemiluminescence immunoassay method (DiaSorin, Italy). RESULTS: The analysis included 192 subjects who were normotensive (blood pressure <140/90 mmHg). A total of 34% of women had a severe deficiency (vitamin D ≤ 12.5 nmol/L); 41% had moderate deficiency (vitamin D levels between 12.5 - 25 nmol/L); 23% had mild deficiency (vitamin D level ≥ 25 - < 50 nmol/L); and 2% had insufficiency (vitamin D level ≥ 50 - ≤ 75 nmol/L). None had a sufficient level of ≥75 nmol/L. The systolic blood pressure ranged from 79-130.5 mmHg and the diastolic from 48.5-85.5 mmHg. Both systolic and diastolic blood pressures were significantly higher in women that were in the lower 2 quartiles of vitamin D. However, linear regression analysis adjusting for potential confounders showed that 25(OH)D level was not a predictor of either systolic or diastolic blood pressures. A negative correlation (although not significant) was found between vitamin D level and plasma renin concentration in this study group. CONCLUSION: Vitamin D deficiency was highly prevalent among the study group. Vitamin D was not a predictor of either systolic or diastolic blood pressure. There was a negative correlation between vitamin D level and renin concentration although not statically significant. It is possible that any underlying relationship was obscured by the relatively young age group or due to the narrow blood pressure range of the studied population. A larger sample size including hypertensive subjects may be needed.

UDC CODE & KEYWORDS

■ UDC: 615.8, 612 ■ Vitamin D ■ Blood pressure ■ Renin hormone

INTRODUCTION

Vitamin D deficiency is a worldwide health problem (Holick, 2010). Apart from its major role in calcium homeostasis and skeletal development, vitamin D was found to have extra skeletal functions (DeLuca, 2004). Moreover, vitamin D deficiency had been linked to many chronic disorders such as cancer, chronic infections, autoimmune diseases, metabolic and cardiovascular disorders including hypertension (Peterlik and Cross, 2009).

Subsequent experimental work showed that vitamin D inhibits renin gene expression. Thus, correction of vitamin D deficiency may prevent or reduce the cardiovascular risk associated with hypertension. Therefore, the aims of this study were to 1) investigate the effect of poor vitamin D status on blood pressure level in Saudi women and 2) to determine the association between vitamin D level and plasma renin concentration.

Methods

This is a cross sectional study, including 192 apparently healthy Saudi premenopausal women aged between 20 to 45 years old. Sample size was calculated using the Epi-Info Statistical Package. The study subjects were randomly selected from women attending the center of excellence for osteoporosis research (CEOR) at King Abdulaziz University, for evaluation of bone health during June-July 2010.

Each woman was medically examined and interviewed using a standardized validated questionnaire provided by CEOR to collect information on socioeconomic status, lifestyle, smoking habits, and level of physical activity in leisure time, the use of vitamins and medications, and intake of calcium and vitamin D supplementation.

Informed consent was obtained from all women and the study was approved by the Human Research and Ethics committee at CEOR.

Women with hypertension, diabetes, renal, liver, or thyroid diseases were excluded. Pregnant women, and those on medications that affects bone metabolism such as steroids and antiepileptic medications were also excluded. All women had regular menstrual cycles and were considered premenopausal (confirmed by FSH level) and those with FSH level > 15 IU/L were excluded.

Anthropometric Measurements

Weight in kilograms was measured using a balance beam scale. Women were weighed to the nearest half kilogram while wearing light clothes and without shoes. Height to the nearest centimeter was measured using a stadiometer. Body mass

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index (BMI) was calculated as weight (kg)/height (m²). The World Health Organization (WHO) 1998 clinical guidelines (NHLBI Obesity Education Initiative., 2000) were used to define overweight (BMI 25-29.9 kg/m²) and obesity (BMI ≥30 kg/m²).

Waist circumference (WC) (midway between the lower rib margin and the iliac crest) and hip circumference (HC) (the maximal circumference over the buttocks) were also measured to the nearest 1.0 cm using a measuring tape. Additionally, waist to hip ratio (WHR) was calculated (WC/HC).

Blood Pressure Measurements

Blood pressure was measured using an automated blood pressure monitor (BPTru, model BPM 2000) that had been validated by the British Hypertension Society (BHS) (Mattu et al., 2001).

Instructions to Women Studied

All women were instructed not to eat or smoke at least 8 hours before their appointments. Blood pressure measurement was performed in a quiet room that was specifically allocated for blood pressure measurements to ensure the privacy of the women studied. All women were seated in an armed chair with their back supported and were instructed to relax completely, keeping their legs uncrossed and in a comfortable position. They were also asked to refrain from talking and to keep their mobiles silent throughout the procedure.

The procedure was explained prior to blood pressure recording to avoid the rise in blood pressure associated with the anxiety of measurement. After 5 minutes of rest, three readings were recorded 1 minute apart, and the average of the last 2 readings was used for analysis.

The appropriate cuff size was applied to the right upper arm (British Heart Society, 2001) and any restrictive clothing covering the upper arm at the time of blood pressure cuff application was removed.

Blood Sampling

Blood samples were obtained from each woman after at least 8 hours overnight fasting and 20 minutes rest and centrifuged at 2500 g for 10 minutes within 30 minutes of sample collection. Serum was stored at - 80°C until analyzed for the biochemical analyses and hormone determinations. Serum 25(OH)D, parathyroid hormone (PTH) and renin hormone were measured by sandwich chemiluminescence immunoassay method using commercial kits supplied by DiaSorin and the tests were performed on a LIASON autoanalyzer [DiaSorinInc, Stillwater, MN, USA].

Statistical Analysis

The statistical analysis was performed using SPSS program (version 16). Raw data were checked for any inaccuracies. Minimum and maximum values for all continuous variables were checked and all identified entry errors (if any) were corrected before starting statistical analysis. A similar process was applied to categorical variables.

Data were examined for normal distribution by Kolmogorov-Smirnov statistic. Continuous variables were expressed as means and standard deviation (SD) or median and interquartile range (IQR) according to their distribution, while categorical variables were expressed as frequencies and percentages. Correlation studies between different continuous variables were assessed using Pearson's or Spearman's correlation as appropriate. Independent student t-test was done to compare blood pressure readings between two groups (grouped according to vitamin D status). Vitamin D status was classified as Desirable Vitamin D level 100-250 nmol/L, Sufficient Vitamin D level 75-99.9 nmol/L, Insufficient Vitamin D level 50-74.9 nmol/L, Mild Vitamin D Deficiency 25-49.9 nmol/L, Moderate Vitamin D Deficiency 12.5- 24.9 nmol/L, Severe Vitamin D Deficiency < 12.5 nmol/L (Ardawi et al., 2005).

Multiple regression analysis (stepwise method) was performed to find out the explanatory variables (predictors) for the blood pressure readings. A 'p' value < 0.05 was considered as significant.

Results

A total of 201 apparently healthy premenopausal women (aged between 20-45 years old) were initially recruited. Six women were found to have a systolic blood pressure (SBP) of 140 mmHg or more and/or a diastolic blood pressure of 90 mmHg or more and therefore were excluded from the study. In addition, FSH level of 3 women were more than 15 mIU/L and were also excluded from the analysis. Therefore, the final study group included 192 women.

Age and Anthropometric Characteristics of the Study Population

Table 1 demonstrates the anthropometric measurements of the study group.

Table 1: Age and anthropometric characteristics of the study population (n = 192)

Variable	Mean (SD)
Age (year)	31.8 (8.6)
Weight (kg)	67.8 (16.2)
Height (cm)	156.4 (7.0)
BMI (kg/m ²)	27.8 (7.1)
WC (cm)	79.0 (15.5)
HC (cm)	98.8 (12.8)
WHR	0.79 (0.09)

BMI = body mass index, WC = waist circumference, HC = hip circumference, WHR = waist-to-hip ratio

Source: Authors

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Characteristics of the Study Population

Table 2 illustrates socioeconomic and lifestyle characteristics of the study population. Most of the studied women (75%) had a university degree. Out of 192 women, 83 (43.2%) were unemployed and 55 (28.7%) were students. Only 30 (15.7%) were exercising regularly (mainly walking > 3 times a week for 30 minutes) and 11 (5.7%) were smokers (more than 90% were smoking meassel).

Table 2: Characteristics of the study population (n = 192)

Number (Percentage)	Number (Percentage)
Education	
Post graduate	5 (2.6%)
University	144 (75%)
High school	26 (13.5%)
Intermediate – Elementary	15 (7.8%)
Illiterate	2 (1.1%)
Income in SR/month	
< 5,000	83 (43.5%)
> 5,000 - < 10,000	33 (17.4%)
>10,000 - < 15,000	36 (18.8%)
>15,000	39 (20.3%)
Occupation	
Unemployed	83 (43.2%)
Employed	52 (28.1%)
Students	55 (28.7%)
Parity	
Multipara	102 (53.1%)
Nullipara	90 (46.9%)
Physical Activity	
Yes	30 (15.7%)
No	161 (84.3%)
Smoking	
Yes	11 (5.7%)
No	181 (94.3%)
Vitamin D supplementation	
Yes	24 (12.5%)
No	168 (87.5%)
Calcium supplementation	
Yes	32 (16.7%)
No	160 (83.3%)

Source: Authors

The Prevalence of Obesity in the Study Population

Using the BMI, the study participants were grouped into underweight, normal weight, overweight and obese according to WHO definitions (NHLBI Obesity Education Initiative, 2000). The percentage within each group is shown in figure 1. It can be seen that almost a third of the study population was overweight and a third was obese.

Figure 1: Percentage of women (shown on bars) who were underweight (BMI: <18.5 kg/m²), normal weight (BMI: 18.5-24.9 kg/m²), overweight (BMI: 25-29.9 kg/m²), and obese (BMI: ≥ 30 kg/m²), according to WHO criteria

Source: Authors

Blood Pressure Readings of the Study Population

Table 3 shows the mean and SD of blood pressure readings. All women were normotensive.

Table 3: Mean and SD of blood pressure reading of the study group (n = 192)

Variable	Mean (SD)
SBP	104.40 (8.97)
DBP	67.51 (7.75)

SBP: Systolic Blood Pressure, DBP: Diastolic Blood Pressure, SD: Standard deviation

Source: Authors

Bone Mineral Characteristics of the Study Population

Table 4 presents the mean (SD) of the serum level of different bone minerals that were measured. Calculated ionized calcium was determined using the following equation:

Calculated ionized calcium = $(0.8 * (\text{Normal albumin} - \text{Women albumin})) - \text{Total serum calcium}$ (Sava et al., 2005).

Table 4: Biochemical characteristics (bone minerals) of the study group

Type of Test	Variable	N	Mean (SD)
Bone minerals	Serum Ca (mmol/L)	191	2.48 (0.20)
	Serum Pi (mmol/L)	186	1.28 (0.20)
	Ionized Ca (mmol/L)	172	1.73 (0.19)
	Serum magnesium	190	0.80 (0.22)

Ca = Calcium, Pi = Inorganic Phosphate, N: Number of tested samples, SD: Standard Deviation

Source: Authors

Hormonal Characteristic of the Study Population

Table 5 represents the median and IQR of the different hormones that were measured in all women.

Table 5: Hormonal characteristics of the study population (n = 192)

Variable	N	Median	IQR
25(OH)D (nmol/L)	192	15.7	(10.5 – 25.7)
PTH (pmol/L)	192	9.5	(7.12 – 12.4)
Renin (mIU/L)	187	16.1	(8.8 – 24.5)

PTH = parathyroid hormone, IQR = Interquartile range

Source: Authors

Vitamin D Status of the Study Group- Prevalence of Vitamin D Deficiency

Figure 2 shows vitamin D status in the women who participated in this study. Although the cut-off value for vitamin D deficiency differs from one laboratory to another, based on the literature, a value of less than 12.5 nmol/L is considered to represent severe deficiency (to convert units to ng/ml, the value is divided by 2.5); moderate deficiency: 12.5 - 25 nmol/L; mild deficiency: $\geq 25 - < 50$ nmol/L; insufficiency: $\geq 50 - \leq 75$ nmol/L; adequate or sufficient: > 75 nmol respectively (Ardawi et al., 2005). None of the studied women had a sufficient vitamin D value > 75 nmol/L.

Figure 2: Vitamin D status in the study population (severe deficiency ≤ 12.5 nmol/L; moderate deficiency 12.5 - 25 nmol/L; mild deficiency $\geq 25 - < 50$ nmol/L; insufficiency $\geq 50 - \leq 75$ nmol/L)

Source: Authors

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Quartiles of 25(OH)D level were calculated and comparison of blood pressure readings was made between the upper and lower two quartiles. Table 6 shows the differences between the two groups. Both SBP and DBP were significantly higher in women in the lower two quartiles of vitamin D, although there were no significant differences in age, BMI or WC in both groups.

Table 6: Characteristics of women in the lower 25(OH)D quartiles as compared to those in the upper 25(OH)D quartiles. Results are presented as mean and + SD

Variable	Lower 25(OH)D Q. Mean (SD) n = 96	Upper 25(OH)D Q. Mean (SD) n = 96	P-value
Age	31.3(8.5)	32.2(8.8)	0.494
BMI	28.5(6.7)	27.1(7.5)	0.172
WC	81.2(16.4)	76.9 (14.4)	0.057
SBP	105.7(8.7)	103 (9.03)	0.034
DBP	68.9 (7.8)	66.1 (7.5)	0.01
Serum 25(OH)D	10.3 (3.2)	27.6 (10.7)	0
Serum PTH	12.1 (7.03)	9.4 (4.0)	0.001
Serum calcium	2.5 (0.2)	2.5 (0.22)	0.594
Ionized Ca	1.7 (0.2)	1.7 (0.2)	0.913
Serum PO ₄	1.2(0.2)	1.3 (0.2)	0.015
Plasma Renin	20.2(15.9)	18.3 (14.7)	0.404

25(OH)D Q = Vitamin D Quartile; SD = Standard deviation; BMI = Body Mass Index; WC = Waist Circumference; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; PTH = Parathyroid Hormone; Ca = Calcium, PO₄ = Inorganic Phosphate

Source: Authors

Correlation of Vitamin D Status with Blood Pressure

Correlation studies showed that there was a negative correlation between vitamin D status and both systolic and diastolic blood pressure, however, this correlation was only significant for the diastolic blood pressure readings ($P=0.025$). The correlation between blood pressure and other variables known to affect blood pressure was also done (Table 7). There was a significant positive correlation between both SBP and DBP and PTH, BMI, WC and age. DBP was also inversely correlated with serum calcium.

Table 7: Correlation between blood pressure and different variables known to affect it

Variables	SBP		DBP	
	r	p	r	p
25(OH)D	-0.125	0.084	-0.162	0.025
PTH	0.203	0.005	0.157	0.03
BMI	0.363	0	0.25	0
WC	0.352	0	0.213	0.003
Age	0.249	0.001	0.148	0.041
Ca (Total)	-0.138	0.056	-0.15	0.038
Ca (ionized)	-0.034	0.661	-0.121	0.115
Renin	-0.137	0.061	-0.084	0.253

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; PTH = Parathyroid hormone, BMI = Body Mass Index, WC = Waist circumference; Ca = Calcium

Source: Authors

Multiple regression analysis (stepwise method) was performed to find out the explanatory variables (predictors) for the SBP and DBP (Table 8). In addition to 25(OH)D, variables that showed significant correlation with blood pressure were entered as independent variables into the regression model. These included age, BMI, WC, PTH and level of education for the systolic blood pressure and age, BMI, WC, PTH and total serum calcium for the diastolic blood pressure.

Both age and WC were positive predictors for SBP, while WC only was a positive predictor for DBP.

Table 8: Multiple regression analysis with systolic and diastolic blood pressure as dependant variables

Dependant Variables	Predictors	β estimate	SE	p
SBP	Constant	84.316	3.33	0
	WC	0.191	0.043	0
	Age	0.159	0.077	0.039
DBP	Constant	56.94	2.812	0
	WC	0.136	0.035	0

SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; WC = Waist Circumference

Source: Authors

Correlation between 25(OH)D and renin

There was an inverse relationship between 25(OH)D and renin which was not significant ($r = -0.062$, $p = 0.398$). Figure 3 shows a scatter plot of the relationship between plasma renin concentration and 25(OH)D level.

Figure 3: A scatter plot showing the correlation between 25(OH)D and renin hormone

Source: Authors

Discussion

Up to our knowledge this is the first study that examines the association between blood pressure readings and vitamin D status in Saudi premenopausal women.

The present study confirmed the inverse relationship between vitamin D status and blood pressure readings although this relationship was not statistically significant.

Another main finding in this study is the high prevalence of vitamin D deficiency among this relatively young and healthy population ($n = 192$), where 98% of these women were vitamin D deficient. About 34% of them had severe deficiency (levels of 25(OH)D < 12.5 nmol/L). This is in agreement with other studies that were conducted in Saudi Arabia on the prevalence of vitamin D deficiency. A recent community-based study that was done by Ardawi and associates and included 2,369 women, reported that 80% of the Saudi women studied were vitamin D deficient (Ardawi et al., 2011).

Possible risk factors for vitamin D deficiency in Saudi Arabia includes conservative clothing, reduced outdoor activities due to hot weather, and low calcium and vitamin D dietary intakes (Holick, 2010). Moreover, vitamin D deficiency was found to be more prevalent among obese individuals (Ardawi et al., 2011). This is due to the decreased bioavailability of 25(OH)D in obese people (Wortsman et al., 2000). In the present study, almost one third of the studied population was overweight and one third was obese according to WHO definition of obesity (NH&LBI Obesity Education Initiative., 2000). In addition, when vitamin D was correlated to body mass index, results showed that 84% of obese women were severely vitamin D deficient ($P = 0.046$) compared to non-obese women (data not shown in the results section).

In addition to high prevalence of vitamin D in Saudi population, hypertension affects more than one fourth of the Saudi population (Saeed et al., 2011). Although in 90% of hypertension cases it is essential hypertension, possible risk factors might be due to the unhealthy eating habits and sedentary life-style (Holick, 2010). Studies reported that other causes of hypertension in Saudi Arabia include the high prevalence of obesity (Al-Nozha et al., 2007). In this study, only 15.6% of the studied women were exercising, 33% were obese and 28% were overweight. Although 23.9% of women in Saudi Arabia are suffering from hypertension according to a community based study that included 17,230 subjects of different age groups (Saeed et al., 2011), less than 3% of the initial study population ($n = 201$) were hypertensive. This is probably because of the healthy and relatively young age of the studied women.

Recent evidence indicated that higher blood pressure was associated with lower 25(OH)D levels. Some of these studies found an inverse relationship between vitamin D and blood pressure (Pfeifer et al., 2001, Krause et al., 1998, Sugden et al., 2008, Kimura et al., 1999, Yuan et al., 2007, Li et al., 2004), while others found no relationship (Forman et al., 2005, Margolis et al., 2008).

In the present study, both systolic and diastolic blood pressures were significantly higher in women that were in the lower 2 quartiles of vitamin D. However, linear regression analysis adjusting for potential confounders showed that 25(OH)D level was not a predictor of either systolic or diastolic blood pressures. This relation might be due to the normotensive women studied and that almost all of the women studied were vitamin D deficient. These results were in agreement to a study that was conducted in Lebanon on college students (180 women and 201 men) and found that in women, 25(OH)D level, although was inversely associated with both SBP and DBP, it was not a predictor of either pressures (Gannage-Yared et al., 2009). However, and in contrast to our results, vitamin D sufficiency (25(OH)D = 77.5 ± 31 nmol/L) was prevalent among both sexes. This is probably due to the different lifestyle factors in this young Lebanese population.

On the other hand, Morgolis and associates found no relation between vitamin D levels and blood pressure readings (Margolis et al., 2008). This might be due to the low vitamin D dose given to the studied population (400 IU) which is less than the recommended daily intake (2,000 IU (Holick, 2009)). In addition, having a relatively old population (50-79 years-old) might affected the 25(OH)D levels.

Limitations of the Present Study

This is a cross section study and a causal relationship cannot be concluded from these results. Data on dietary intake of calcium and vitamin D were not collected.

Study Strength

All the studied subjects were apparently healthy. Premenopausal status was confirmed by hormonal analysis (FSH levels). Blood pressure measurements were only conducted by the main investigator using standardized validated methodology.

Future Work

Possible future work includes the conduction of prospective large population-based cohort studies to investigate the effect of low vitamin D status on the risk of developing hypertension, and the effect of vitamin D supplements in lowering blood pressure in hypertensive and vitamin D deficient subjects.

CONCLUSION

Results of this study confirmed the high prevalence of vitamin D deficiency in young Saudi women. In addition, correlation studies showed a significant inverse relationship between vitamin D status and diastolic blood pressure. However, linear regression analysis adjusting for potential confounders showed that 25(OH)D level was not a predictor of either systolic or diastolic blood pressures. It is possible that any underlying relationship was obscured due to the narrow and normal blood pressure range of the studied population in addition to the high prevalence of vitamin D deficiency where all of the studied women were vitamin D deficient. Larger population based cohort studies including hypertensive subjects are needed to confirm our findings.

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