The Relation between Serum Vitamin D Levels and Blood Pressure: A Population-Based Study

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Abstract- Vitamin D deficiency has been proposed as an associating factor with increased blood pressure. We studied the relationship between serum vitamin D and blood pressure in a large representative sample of Iranian population. In this cross-sectional study, based on the data of 2508 adults (aged between 20 and 70 years) from the Iran Multicenter Osteoporosis Study (IMOS), the association between serum vitamin D and blood pressure was investigated. There was a significant difference between mean (±SD) vitamin D levels of the individuals with stage I hypertension and that of the three other groups (Normal: 32.9 (±27.5); Prehypertension: 34.4 (±27.2); Stage-I: 38.7 (±29.2); Stage-II: 34.7 (±24.0) ng/ml; $P<0.05$. In multivariate regression models, the weak positive association of vitamin D and systolic blood pressure values disappeared after age and Body Mass Index (BMI) adjustment. We found a statistically positive but weak association between vitamin D serum concentration and systolic blood pressure. Considering the difference noted between our results and previous studies, further research is needed to assess the potential effect of ethnicity and genetic factors on these findings.

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Keywords: Hypertension; Systolic blood pressure; Vitamin D; Vitamin D deficiency

Introduction

It is important to understand various risk factors contributing to hypertension, which imposes a huge burden on the health system (1). To date, the list of known risk factors for hypertension includes: old age, genetics, stressful lifestyle, low physical activity, obesity, and diabetes (2,3). Vitamin D deficiency as a well-known risk factor for osteoporosis (4) has also been presented as an influential factor in the metabolic diseases (5,6) and cardiovascular system (7), particularly hypertension (8).

According to previous studies, the effect of serum levels of vitamin D on hypertension is not clear. The fact that $1,25(OH)_2D_3$ suppresses the expression of the renin gene (9) could provide an explanation for the documented inverse relationship between vitamin D and blood pressure (10). However, some trials have failed to support the impact of vitamin D on reducing hypertension (11,12). Besides, there is a study that indicates a positive correlation between blood pressure and 25(OH)D levels (13).

Despite the fact that hypertension is quite prevalent worldwide (14) and among the Iranians (3,15), limited studies have investigated the relation between vitamin D deficiency which is common in Iran (16-20) and blood pressure status. In this regard, the present study is one of the largest cross-sectional population based study in the Middle East which investigates the correlation between blood pressure and vitamin D levels in the Iranian population.

Materials and Methods

To assess the correlation between serum 25(OH)D and blood pressure levels among Iranian adults, the data of 2451 subjects were extracted from the Iranian Multi-centric Osteoporosis Study (IMOS). Details on the study design and methods have been reported previously (21). Briefly, the study was conducted in the urban areas of

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five great cities from different geographical regions (Tehran, Tabriz, Mashhad, Shiraz and Booshehr) in late winter 2001 (February-March). All the recruited individuals were healthy Iranians aged between 20 and 70 years. None of them took any medications, which could affect bone metabolism, had hepatic or renal disorders, metabolic bone disease, hypercortisolism, malabsorption, sterility, oligomenorrhea, type I diabetes, type II diabetes, or malignancy. The smokers, immobile subjects for more than 1 week, alcoholics, and infertile individuals were excluded based on the report.

An informed consent was obtained from each participant before the investigation. The study was approved by the Medical Ethics Committee of Tehran University of Medical Sciences and the Endocrine and Metabolism Research Center (EMRC).

The anthropometric measurements including weight and height were obtained while individuals were in light cloths and without shoes. The measurements were done by trained technicians using a similar instrument based on the same technique following international guidelines (22). Quality control for all the measurements was performed regularly based on the study protocols.

The height and weight were measured using a wall-mounted stadiometer (Seca) and a mobile digital scale (Seca, Hamburg, Germany), respectively. The Body Mass Index (BMI) was calculated by dividing body weight by squared height (kg/m^2). The individuals were then categorized according to their baseline BMI values (underweight <18.5, normal weight 18.5-25, overweight 25-29.9, and obese ≥30 kg/m^2) (23).

Blood pressure measurement was done after a 10-minute rest, on dominant arm in a sitting position by trained nurses using a mercury sphygmomanometer (Riester, Germany; provided with an appropriate cuff size according to the subject's arm circumference) for two time. The subjects were asked not to smoke or consume caffeine within 30 minutes prior to the measurements.

Systolic blood pressure (SBP) was defined at the level of first korotkoff sound whereas diastolic blood pressure (DBP) was the point of last (fifth) Korotkoff sounds (24). Blood pressure classification was based on the Joint National Committee on the detection and evaluation of high blood pressure (25): Normal ≤ (120/80 mmHg), pre-hypertension (120-139/80-89 mmHg), stage I hypertension (140-159/90-99 mmHg), and stage II hypertension ≥ (160/100 mmHg).

Blood samples were drawn in a fasting state (10 ml of venous blood) from all the participants at their residence place. Blood samples were centrifuged and the serum was extracted in the field. The samples were then frozen and sent to the EMRC laboratory. Serum levels of 25(OH) D were measured by radioimmunoassay (BioSource-Europe). To define an appropriate threshold for vitamin D deficiency, the classification was based on data retrieved from our previous studies (17): severely deficient (<12.5 ng/ml), moderately deficient (12.5 to 25 ng/ml), insufficient or mild deficient (25 to 35 ng/ml), and sufficient or normal (>35 ng/ml).

Statistical analysis

In this study to present standard descriptive statistics Mean ± SD was used. Categorical variables were expressed as numbers and percentages and compared using Chi-square test. The two-sided Student's t-test was used to compare the mean of age, systolic and diastolic blood pressure, serum levels of vitamin D, parathyroid hormone (PTH) and BMI values between males and females.

As the distribution of vitamin D and PTH values showed a positively skewed pattern, we performed a transformation of those values into their Naperian Logarithm. The output showed an acceptable normal distribution.

In order to compare mean vitamin D levels, we divided the population into four different strata for blood pressure. We compared the mean transformed (Naperian Logarithms-Ln) values of serum levels of vitamin D across different stages of blood pressure using One-way ANOVA test and evaluated the significance of the differences with post-hoc test. We also retransformed each group's mean of Ln of vitamin D value into its true value for better clarification of vitamin D differences across blood pressure groups.

To evaluate the influence of various factors on the changes in systolic blood pressure, we fitted the categories of vitamin D, age, BMI and also the interaction of vitamin D with BMI and Age into 5 univariate and multivariate linear regression models. The effects of interactions between vitamin D and BMI and also between vitamin D and age on SBP were significant at 5% level. All the regression analyses were done separately for males and females. Regression coefficient was defined as any change in SBP (mmHg) along with that in the predictor categories. Standardized beta coefficients were also calculated for each model.

Statistical analyses were conducted using statistical software; STATA version 11 (StataCorp LP) to analyze linear regression models. Statistical significance was defined as *P*-values less than 5 percent.

Results

A total of 2451 participants from the Iranian Multicenter Osteoporosis Study with the mean age of 42.43 ± 13.9 years were enrolled in this study (Table 1). The majority of the participants aged less than 50 years (70%) and the vitamin D status was increased by aging (data not shown). Women accounted for more than 54.5% of the entire population. The mean 25(OH) D levels were 34.1±21.2 and 35.3±31.7 ng/ml in men and women, respectively. Vitamin D deficiency was more common in males compared with females (66.6% vs. 51.5%). However, moderate to severe vitamin D deficiency was more prevalent among the females (P<0.05). PTH mean level was 28.4±20.3 in males compared to 30.4±18.5 in those of females. In addition, 17.7% and 9.6% of the studied samples suffered from stage one and two hypertension, respectively. Mean systolic and diastolic blood pressure levels were approximately 5 and 3 mmHg lower in females compared with males (P<0.05). After dividing the population into four groups based on their blood pressure levels, we found a significant difference between mean Naperian Logarithm values of vitamin D in individuals with stage I hypertension and the three other groups (Figure 1). In this regard, those with stage I hypertension had the highest level of 25(OH) D compared with the others (P<0.05).

Table 1. Distribution of demographic characteristics for men and women who had blood pressure measurement in the Iranian Multicenter Osteoporosis Study (IMOS)

Variables	Men 45.5% (n=1114)	Women 54.5% (n=1337)	Total (n=2451)	*P*-value
Age groups %(n)				
<50	42.7 (732)	57.3 (983)	70.0 (1715)	<0.001
50-60	49.4 (216)	50.6 (221)	17.8 (437)	<0.001
60<	55.5 (166)	44.5 (133)	12.3 (299)	<0.001
Mean age (SD)	42.9 (14.9)	41.8 (13.0)	42.3 (13.9)	0.06
BMI categories %(n)				
20-25 kg/m^2	56.3 (535)	43.7 (416)	38.8 (951)	<0.001
25-30 kg/m^2	45.6 (440)	54.4 (525)	39.4 (965)	<0.001
> 30 kg/m^2	26.0 (139)	74.0 (396)	21.8 (535)	<0.001
Mean BMI (SD)	25.4 (4.0)	27.6 (5.1)	26.6 (4.7)	<0.001
Sun exposed area % (n)				
No area	37.6 (245)	62.4 (407)	26.6 (652)	<0.001
Face and hand	52.9 (745)	47.1 (664)	57.5 (1410)	<0.001
More than face and hand	38.0 (148)	62.0 (241)	15.9 (389)	<0.001
Blood pressure categories % (n)				
Normal	33.4 (216)	66.6 (430)	26.4 (646)	<0.001
Prehypertension	47.1 (546)	51.9 (599)	46.3 (1135)	<0.001
Stage I hypertension	53.0 (230)	47.0 (204)	17.7 (434)	<0.001
Stage II hypertension	51.7 (122)	48.3 (114)	9.6 (236)	<0.001
Blood pressure (SD)				
Systolic (mmHg)	123.2 (19.2)	118.1 (20.2)	120.4 (19.9)	<0.001
Diastolic (mmHg)	80.9 (10.6)	77.9 (11.5)	79.2 (11.2)	<0.001
Vitamin D Categories % (n)				
Normal	47.4 (376)	52.6 (417)	32.4 (793)	<0.001
Mild Deficiency	56.2 (296)	43.8 (231)	21.5 (527)	<0.001
Moderate Deficiency	40.9 (409)	51.9 (590)	40.8 (999)	<0.001
Severe Deficiency	25.0 (33)	75.0 (99)	5.3 (132)	<0.001
Mean Serum levels (SD)				
25(OH)D (ng/ml)	34.1 (21.2)	35.3 (31.7)	34.7 (27.5)	<0.001
PTH (pg/ml)	28.4 (20.3)	30.4 (18.5)	29.5 (19.4)	<0.001

- SD: Standard Deviation, pg: picogram, ng: nanogram, BMI: Body Mass Index, ml: milliliter, %: percentage, PTH: Parathyroid hormone
- Chi-Square test was done for all categorical variables
- Student's t-test used to compare means of quantitative variables

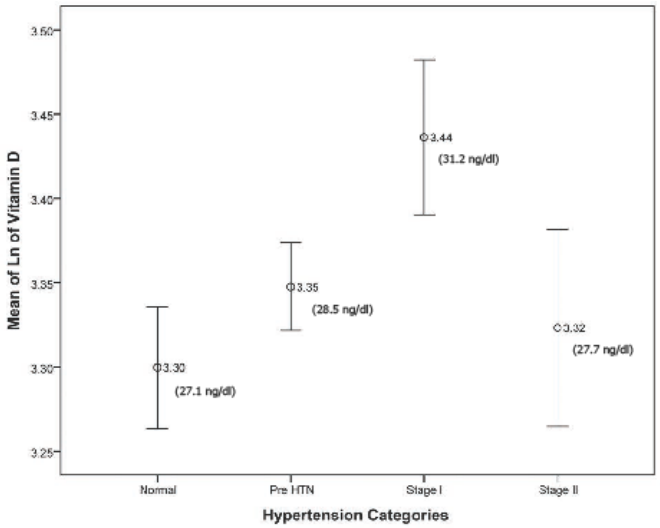

Figure 1. Error bar chart depicting mean and 95% confidence intervals of the mean for Naperian Logarithm (Ln) (as transformed values) of vitamin D in different blood pressure groups categorized based on JNC-7. We also calculated retransformed numbers for better understanding of true value differences (written below and right to each mean number). Mean vitamin D reached a peak in stage I hypertension and was different from other groups tested by post-hoc ANOVA (P<0.05). Serum levels of vitamin D decreased significantly when moving from stage I to stage II and pre hypertension stages

Table 2. Univariate and multivariate linear regression analysis between Systolic Blood Pressure and age, BMI and vitamin D level as predictors in different fitted models[1]

	Unadjusted		Model A		Model B	
Predictors	**Male**	**female**	**Male**	**female**	**Male**	**female**
VD categories:						
Normal (Ref.)						
Mild	-1.83 (-0.04)	-4.16 (-0.08)**	-1.149 (-0.03)	-1.15 (0.02)	-2.19 (-0.05)	-4.29 (0.08)**
Moderate	-0.19 (-0.005)	-3.96 (-0.10)**	-0.007 (-0.00)	-0.24 (0.01)	-0.43 (-0.01)	-2.86 (-0.07)**
Severe	-1.73 (-0.02)	-8.99 (-0.12)**	-2.94 (-0.03)	-3.36 (0.04)	-2.23 (-0.02)	-6.98 (-0.09)**
Age categories:						
Age ≤ 50 y/o (Ref.)						
Age: 50-60	11.03 (0.24)**	15.24 (0.30)**	11.83 (.24)**	16.64 (.30)**		
Age ≥ 60	18.80 (0.36)**	23.36 (0.37)**	20.29 (.38)**	25.23 (.37)**		
BMI categories:						
Normal (Ref.)						
Overweight	4.59 (0.12)**	7.71 (0.19)**			4.70 (0.12)**	7.15 (0.17)**
Obese	12.94 (0.23)*	14.48 (0.34)**			13.55 (0.23)**	15.28 (0.35)**
VD × age Interaction:						
NL VD × age < 50 (Ref.)						
Mild def × age 50-60						
Mild def × age ≥ 60						
Mod def × age 50-60						
Mod def × age ≥ 60						
Severe def × age 50-60						
Severe def × age ≥ 60						
VD × BMI interaction:						
NL VD × NL BMI (Ref.)						
Mild def × overweight						
Mild def × obese						
Mod def × overweight						
Mod def × obese						
Severe def × overweight						
Severe def × obese						

Table 2. (continue) Univariate and multivariate linear regression analysis between Systolic Blood Pressure and age, BMI and vitamin D level as predictors in different fitted models[1]

	Model C		Model D		Model E	
Predictors	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
VD categories:						
Normal (Ref.)						
Mild	-1.55 (-0.04)	-1.48 (-0.03)	-1.31 (-0.03)	-3.18 (-0.06)	-5.94 (-0.14)**	-4.15 (-0.08)
Moderate	-0.28 (-0.01)	0.34 (0.01)	-.83 (-0.03)	-2.09 (-0.05)	-4.72 (-0.12)*	-2.52 (-0.06)
Severe	-3.35 (0.03)	-2.13 (-0.03)	-1.04 (-0.01)	-4.76 (-0.06)*	-1.13 (-0.01)	-5.69 (-0.07)
Age categories:						
Age ≤ 50 y/o (Ref.)						
Age: 50-60	10.84 (0.22)**	14.86 (0.27)**	12.17 (0.25)**	12.24 (0.22)**		
Age ≥ 60	19.99 (0.37)**	24.43 (0.36)**	17.97 (0.33)**	22.96 (0.34)**		
BMI categories:						
Normal (Ref.)						
Overweight	3.82 (0.10)**	5.29 (0.13)**				
Obese	12.73 (0.22)**	13.29 (0.30)**				
VD × age Interaction:						
NL VD × age < 50 (Ref.)						
Mild def × age 50-60			-.48 (-0.01)	7.27 (0.08)*		
Mild def × age ≥ 60			1.47 (0.01)	4.21 (0.02)		
Mod def × age 50-60			0.19 (0.002)	7.07 (0.08)*		
Mod def × age ≥ 60			5.00 (0.07)	4.21 (0.04)		
Severe def × age 50-60			-8.42 (-0.04)	7.71 (0.03)		
Severe def × age ≥ 60			0.53 (0.002)	-6.349 (-0.02)		
VD × BMI interaction:						
NL VD × NL BMI (Ref.)						
Mild def × overweight					7.13 (.11)*	-.71 (-.01)
Mild def × obese					7.96 (.08)	.52 (.01)
Mod def × overweight					6.96 (.12)*	-2.83 (-.05)
Mod def × obese					12.65 (.14)**	-2.69 (.04)
Severe def × overweight					-5.44 (.03)	-2.15 (-.02)
Severe def × obese					8.80 (.02)	-2.25 (-.02)

Model A: Adjusted for age; Model B: Adjusted for BMI; Model C: Adjusted for age and BMI; Model D: Adjusted for age, Vitamin D and vitamin D interaction with age (age × Vitamin D); Model E: Adjusted for BMI, Vitamin D and vitamin D interaction with BMI (BMI ×Vitamin D); VD: Vitamin D; BMI: Body Mass Index; NL: Normal; Ref: Reference; Def: Deficiency; Mod: moderate.

1 All values are regression coefficients; regression coefficient represents the change in SBP (mmHg) compared with the reference category as base value. Standardized β coefficients were shown in parentheses.

* Coefficient was significant (P-value <0.05)

** Coefficient was significant (P-value <0.001)

We examined the correlation between SBP and vitamin D, age and BMI with univariate and multivariate linear regression analysis (Table 3). We also evaluated these correlations in fitted models for the interaction of vitamin D with age and BMI separately. There was a significant (P<0.001) positive association between systolic blood pressure and vitamin D levels in women in the unadjusted model. Adding BMI to the regression models did not change the significance of the correlation (Model B). Whereas by controlling the BMI and vitamin D interaction, the association faded away in females, as for the men, in mild and moderate vitamin D deficiency groups the significant but negative association between SBP and vitamin D can be seen (Model E). It is noteworthy that the association between SBP and vitamin D became insignificant after age adjustment (Model A). However, by taking to account the age and also the interaction of vitamin D and age the positive association between vitamin D and SBP became significant (P<0.05) only in females with severe vitamin D deficiency (Model D).

Discussion

About 67% of the participants in this study suffered from vitamin D deficiency. Serum levels of vitamin D

decreased significantly when comparing the stage I hypertension with other groups of stage II hypertension, pre hypertension and normal blood pressure.

In this investigation, the impact of age on the correlation of blood pressure and vitamin D levels was significant and the association disappeared after age adjustment. In addition, this study revealed the important effect of the interaction between BMI and vitamin D on systolic blood pressure levels in the adjusted model. While the association between vitamin D and SBP was only significant in females in the unadjusted model, after adjusting for BMI and also taking into account the interaction of BMI and vitamin D, the negative association of vitamin D with SBP was only significant in males with mild to moderate vitamin D deficiency.

There are various studies suggesting the considerable effect of vitamin D on blood pressure levels (13,25). As a basic rule, vitamin D indirectly influences smooth muscle and endothelial vessel cells via activating vitamin D receptors (VDR). Also the effect of vitamin D on blood pressure levels is believed to be secondary to reduced inflammation (26) and increased endothelial cell function (27). On the other hand, Kruse *et al.* explained that any increase in the endogenous release of vitamin D is associated with a mild decrease in blood pressure levels (28). This comes while many studies have demonstrated that vitamin D can increase induce vascular resistance and consequently may cause hypertension by altering the sensitivity of vascular muscle cells to vasoconstrictive factors (29-31).

Our findings did not support the presence of reverse association between vitamin D and blood pressure noted in previous studies (10,32,33). We mainly noticed that mean vitamin D levels were lower in stage II compared with stage I hypertension. Although this finding is not in agreement with most of the existing studies, the recent meta-analysis on 8 RCTs (Randomized Control Trials) revealed that the vitamin D effects is not the same in decreasing the blood pressure in non-hypertensive patients compared to hypertensive individuals. According to this study the vitamin D supplementation in patients with stage II hypertension and lower vitamin D status had the better impact on reducing blood pressure compare to those with mild hypertension. As can be seen from this study in hypertensive category, higher blood pressure levels are is accompanied with the lower vitamin D status. However in non-hypertensive group (normal hypertension or prehypertension) by rising in blood pressure level the blood vitamin D concentration increased (34).

We found that the relation between blood pressure and vitamin D levels is strongly affected by age and BMI and their interaction with vitamin D serum levels. It is noteworthy that Judd *et al*. (35) mentioned the effect of age on the correlation between blood pressure and vitamin D in NHANCE survey in terms of the age and systolic blood pressure interaction .The results of this study demonstrated that by including the age in the model, the BP and vitamin D association decreased significantly. Scragg *et al*. (10) also showed a strong inverse association between blood pressure and vitamin D levels in the elderly, stressing the important effect of age in this regard. Furthermore, similar to our results, this study reported that adding BMI to the model attenuates the relationship between vitamin D and systolic blood pressure (10). Overall, our study indicated a statistically positive significant association between blood pressure and vitamin D that disappeared after age and BMI adjustment. This finding is in line with the recent meta-analysis which revealed vitamin D supplementation has no significant impact on blood pressure in the existing trials (36).

It may be argued that this discrepancy may be due to the ethnical variation in vitamin D receptor polymorphism, which was reported previously. Muray *et al*. demonstrated a positive association between blood pressure and vitamin D status in special VDR genotype (13). Although , VDR polymorphism's effect on type II diabetes (37,38) and osteoporosis (39) in the Iranian population has been confirmed, its effect on blood pressure levels is not clear. In line with the hypothesis of the ethnical variation in VDR polymorphism's influence on blood pressure, Judd *et al*. reported that the black Americans are more vitamin D deficient compared with the white Americans. This may contribute to the non-significant correlation between vitamin D serum levels and blood pressure in the black American group; however, in the white Americans the high vitamin D concentration results in a negative but significant correlation (35). Moreover, it is demonstrated that vitamin D supplementation in the black Americans increases the risk of developing systolic hypertension (40). It seems that the association between blood pressure and vitamin D levels in highly vitamin D deficient population such as the Iranians and the black Americans differs considerably. Moreover in the current study, the blood pressures were examined by highly experienced and educated nurses that helped us to find the hypertension prevalence and blood pressure status accurately, while, there are many studies which relied on the self-reported hypertension subjective history (32,33).

The limitations of this study include: first, considering the cross-sectional nature of the study, a causal relationship could not be defined between serum levels of vitamin D and blood pressure. Second, based on the exclusion criteria of the study, the individuals who had taken vitamin D supplements (oral or injection) were not recruited. This comes while as the data was gathered through self-report questionnaires and therefore, recall bias is possible. Third, several factors like: diabetes, positive family history of hypertension and dyslidemia are known to affect blood pressure which we could not consider them all. Finally, we did not use any diet questionnaire to find out the amount of vitamin D intake in detail.

In conclusion, it could be argued that vitamin D has a mild positive effect on blood pressure that, putting forward the hypothesis of "VDR hypersensitivity" in our population. At last, to clearly demonstrate the effect of vitamin D on blood pressure, further large scale interventional studies are needed to assess the effects of vitamin D supplements on blood pressure of hypertensive patients with low vitamin D concentrations.

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