Both Low and Upper Normal Levels of 25-Hydroxy Vitamin D Relates to Risk Factors of Metabolic Syndrome and Cardiovascular Diseases

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Abstract

Background: Vitamin D deficiency is implicated in a wide range of pathological situations including cardiovascular diseases. This study aimed to investigate the association between serum 25-hydroxy vitamin D (25(OH)D) and risk factors of metabolic syndrome and cardiovascular diseases.

Methods: The cross-sectional study was conducted on 169 adults (88 males, 81 females) aged 19-52 years living in Shiraz, Iran. Anthropometric characteristics and blood pressure were measured using standard methods. Blood samples were collected in fasting state for determination of blood glucose, lipids, and 25(OH)D. Data were analyzed with one-way analysis of variance and linear regression using SPSS software.

Results: Serum 25(OH)D concentrations were considerably higher in males. One third of females had vitamin D deficiency (25(OH)D <10 ng/ml) while one third of males exhibited 25(OH)D levels >50 ng/ml. In males, systolic and diastolic blood pressure, triglycerides, and metabolic syndrome score increased and high-density lipoprotein (HDL) cholesterol decreased across tertiles of serum 25(OH)D. On the contrary, in females body mass index (BMI) and metabolic syndrome score decreased and HDL cholesterol increased across tertiles of 25(OH)D. Linear regression, after controlling for confounding factors, showed that diastolic blood pressure (B=0.07; 95% CI: 0.02, 0.11; P=0.006), triglycerides (B=0.54; 95% CI: 0.22, 0.85; P=0.001), and metabolic syndrome score (B=0.01; 95% CI: 0.001, 0.01; P=0.02) positively and HDL cholesterol (B=-0.05; 95% CI: -0.09, -0.01; P=0.02) inversely associated with tertiles of 25(OH) D concentrations in males. In contrast, BMI (B=-0.06; 95% CI: -0.11, -0.02; P=0.01), waist circumference (B= -0.12; 95% CI:-0.23, -0.01; p=0.04), and metabolic syndrome score (B=-0.02; 95% CI:-0.03, -0.01; P=0.01) were inversely and HDL-C (B=0.16; 95% CI: 0.02, 0.31; P=0.02) positively associated with 25(OH) D tertiles in females.

Conclusion: The results suggest that both low and upper normal levels of 25(OH)D are associated with increased risk of cardiovascular diseases and metabolic syndrome.

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Keywords: Vitamin D, Metabolic syndrome, Cardiovascular diseases

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Introduction

Metabolic syndrome and cardiovascular diseases are important metabolic disorders in many parts of the world,[1] and in Iran.[2] Based on definitions of Adult Treatment Panel III, 34.7% (>11 millions) of Iranians have metabolic syndrome,[3] and cardiovascular diseases are still the leading cause of death consisting 43.7% of total mortality rate in this country.[4] Numerous factors are implicated in the pathogenesis of these non-communicable diseases, with nutrition being one of determinative factors.

Vitamin D is a fat-soluble vitamin with numerous biological activities including skeletal and non-skeletal activities.[5] The role of vitamin D in calcium homeostasis and skeletal health has long been recognized, but its function in non-skeletal tissues is just being elucidated.[6] Growing evidence suggests that vitamin D deficiency is implicated in a wide range of pathological situations such as obesity, insulin resistance, diabetes mellitus, dyslipidemia, hypertension, and as a result metabolic syndrome and cardiovascular diseases (CVD).[7,8] A number of previous studies demonstrated a graded increase in the risk of cardiovascular events across decreasing categories of 25(OH)D levels,[9] and decreases in the risk of metabolic syndrome along with increments in 25(OH)D levels.[10] a

The aim of the present study was to investigate the association between serum 25(OH)D and risk factors of CVD and metabolic syndrome. Given the high prevalence of vitamin D deficiency in Shiraz,[11,12] and the high rate of CVD and metabolic syndrome in Iran,[3,4] we hypothesized that the negative association between serum 25(OH)D and risk factors of CVD and metabolic syndrome also exists among adults living in Shiraz.

Materials and Methods

Study subjects. This cross-sectional study was conducted between November 2013 and March 2014 on adults aged 19-52 years in Shiraz, Iran. Participants (88 males and 81 females) were selected by stratified random sampling from households living in 9 municipal districts of Shiraz, Iran. Sample size was calculated according to a previous publication using the margin of error of 5% and the confidence level of 95%.[13] Samples were taken from all districts according to the population size of the districts. Then, within each district, using a map, houses were selected by random sampling from blocks located on that district. In each selected house, all adults who met the inclusion criteria were included. Subjects were included if they were apparently healthy, aged 19-52 y, without morbidities like cancer, organ failure, hypo- or hyper-thyroidism, anorexia or physiological conditions like pregnancy and lactation. Also, participants were not taking medications for control of diabetes, dyslipidemia, and hypertension, appetite-enhancing or -suppressive agents, and nutritional supplements. An informed written consent was obtained from all participants. The project was approved by the Ethics Committee of Shiraz University of Medical Sciences (Approval No. 92-01-87-7025).

Data collection. Data were collected by expert nutritionists. A questionnaire was used to collect the data on demographic information including age, marital status, and education. Family welfare was evaluated by using family affluence scale as described previously.[14] Physical activity was measured in metabolic equivalent task (MET)-min/week by self-reported International Physical Activity Questionnaire (IPAQ).[15] This questionnaire which has been tested for validity and reliability among 18 to 65 year old adults in many countries estimates physical activity as MET intensity × duration × frequency per week.

Anthropometric measures. Anthropometric and blood pressure measurements were performed by trained expert personnel. Weight was measured with minimal clothing to the nearest 0.1 kg using a digital scale (Glamor BS-801, Hitachi, China) and height was measured without shoes to the nearest 0.1 cm with a non-stretchable tape. Body mass index (BMI) was calculated by dividing weight in kilograms by height squared in meters. Waist circumference was measured with a non-stretchable tape to the nearest 0.1 cm at the midpoint between the lower border of the last rib and the upper border of the iliac crest.[16] Hip was measured over light clothing at the maximum circumference over the buttocks.[16]

Blood pressure. Blood pressure was measured after 5 minutes rest with the use of a standing mercury sphygmomanometer (Alpk2, Japan) according to the standard procedure.[17] Participants were seated and blood pressure was measured twice with at least 1 min interval in between. The mean of two measurements was considered as the participant's blood pressure.

Biochemical measures. Blood was taken on consecutive days from 8 to 10 a.m. after 12-h fasting. The samples were then centrifuged at 2500 g for 10 min, serum was separated, and glucose, triglycerides, low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C) were quantified by using enzymatic procedures (Pars-Azmun, Tehran, Iran) and an auto-analyzer (ChemWell autoanalyzer, Awareness Technology Inc., USA) on the same day of bleeding. The autoanalyzer was calibrated every day. Metabolic syndrome was scored based on the criteria defined by Adult Treatment Panel III.[18] According to the American Heart Association, quantitative risk factors of CVD include obesity, in particular abdominal obesity, hypertriglyceridemia, hypercholesterolemia, high LDL cholesterol, low

HDL cholesterol levels, high blood pressure, and elevated levels of fasting glucose.[18]

Serum 25-hydroxy vitamin D (25(OH)D) was measured with an enzyme-linked immunosorbant assay (ELISA) kit (DRG, DRG Instruments GmbH, Germany) with inter- and intra-assay coefficient variations (CV)s of 9.7% and 4.7%, respectively. Vitamin D deficiency, insufficiency, and adequacy were defined as serum 25(OH)D of less than 12 ng/ml, 12 to less than 20 ng/ml, and equal to 20 ng/ml and higher, respectively.[19]

Statistical analysis. Data were analyzed using SPSS, version 16.0. Normality of data was tested with Kolmogorov-Smirnov. Non-parametric tests were used for non-normally distributed data. For comparisons of vitamin D concentrations between demographic, socioeconomic, and lifestyle categories, independent t-test (for binary groups) or one-way ANOVA (for triad cases) was used. Also, values of CVD and metabolic syndrome characteristics between tertiles of 25(OH) D were compared with one-way ANOVA with LSD as the post-hoc test. For linear regression, adjustments were performed for age, marital status, education, family welfare, physical activity, and smoking. A $P<0.05$ was set as the statistical significance.

Results

Fifty percent of the study subjects (30.7% of males and 71.6% of females) possessed low levels of 25(OH)D (serum 25(OH)D concentration <20 ng/ml). There was a considerable difference in mean serum concentrations of 25(OH)D between the two sexes. No statistical difference in concentrations of 25(OH)D between various demographic, socioeconomic, and lifestyle categories was observed (Table 1).

Mean values of CVD and metabolic syndrome risk factors across tertiles of 25(OH)D concentrations are illustrated in Table 2. In males, the increase in systolic (P=0.02) and diastolic blood pressure (P=0.004), triglycerides (P=0.002), triglycerides/HDL-C (P=0.003), and metabolic syndrome score P=0.02) and the decrease in HDL-C P=0.02) was associated with increasing tertiles of 25(OH)D. In contrast, in females the decrease in BMI (P=0.03) and metabolic syndrome score (P=0.002) and the increase in HDL-C (P=0.01) were associated with increasing tertiles of 25(OH)D.

To see whether the association between tertiles of serum 25(OH)D concentrations and risk factors of CVD and metabolic syndrome components exists independently of age, marital status, education, family welfare, physical activity, and smoking, these variables were entered in a regression model. Linear regression analysis showed that the associations between risk factors of metabolic syndrome and serum levels of 25(OH)D occurred independent of confounding factors (Table 3). After adjustments for age, marital status, educational level, family affluence, physical

Table 1: Mean serum 25(OH)D concentrations (ng/ml) in different demographic, socioeconomic, and lifestyle categories[1]

Categories	Serum 25(OH)D concentrations (ng/ml)					
	Males (n=88)	P value[2]	Females (n=81)	P value	Total (n=169)	P value
Sex	38.1±23.1	-	16.7±17.4	-	27.9±23.2	-
Age (y)						
19-29 (n=46)	36.1±22.8	0.7	10.6±11.0	0.3	27.8±23.0	0.6
30-39 (n=67)	37.6±24.7		17.5±16.3		25.9±22.4	
40-52 (n=56)	40.9±22.4		18.9±21.2		30.3±24.3	
Marital status						
Single (n=45)	37.8±20.3	0.9	13.9±15.8	0.5	30.9±21.9	0.3
Married (n=124)	38.4±24.8		17.3±17.7		26.8±23.6	
Education						
School (n=101)	36.8±24.6	0.6	17.9±18.8	0.4	26.6±23.5	0.4
College (n=68)	39.6±21.5		14.2±14.0		29.9±22.6	
Family affluence scale						
Low (0-4) (n=122)	40.4±22.1	0.2	17.7±18.1	0.3	28.1±22.9	0.7
High (5-7) (n=46)	33.3±24.4		12.3±13.7		26.5±23.5	
Physical activity (Met-min/wk)						
Low (<600) (n=101)	40.2±24.2	0.4	17.7±17.9	0.4	27.5±23.6	0.8
High (≥600) (n=68)	36.1±22.0		14.3±16.2		28.4±22.6	
BMI (kg/m^2)						
<25 (n=66)	35.6±22.5	0.8	16.7±15.2	0.4	25.3±30.0	0.4
25-29.9 (n=62)	39.2±23.4		19.6±19.3		31.0±23.7	
≥30 (n=41)	39.9±24.2		12.7±18.9		27.3±25.6	

[1]Values are means of serum 25(OH)D concentrations±standard deviation (SD). [2]Comparisons were performed for each sex or for total values between mean 25(OH)D concentrations of different categories using one-way ANOVA (for age and BMI) or independent t-test (for others).

Table 2: Mean values of CVD and metabolic syndrome risk factors across tertiles of serum 25(OH)D concentrations[1]

	Males (n=88)			P value	Females (n=81)			P value
	Tertiles of serum 25(OH)D				Tertiles of serum 25(OH)D			
	Tertile 1 (n=29)	Tertile 2 (n=30)	Tertile 3 (n=29)		Tertile 1 (n=27)	Tertile 2 (n=27)	Tertile 3 (n=27)	
BMI (kg/m^2)	26.6±4.6	26.9±5.6	26.9±4.3	0.9	28.4±5.8^a	25.1±3.7^b	25.8±4.6^{ab}	0.03
WC (cm)	93.7±13.0	94.3±14.8	94.9±13.4	0.9	87.4±14.2	80.2±9.6	82.5±10.9	0.08
WHR	0.91±0.07	0.93±0.08	0.94±0.07	0.4	0.84±0.08	0.81±0.07	0.80±0.11	0.2
SBP (mm Hg)	122.5±13.6^a	131.7±15.9^b	132.5±16.1^b	0.02	107.4±18.1	103.7±15.5	106.2±17.3	0.7
DBP (mm Hg)	75.7±10.6^a	84.3±14.0^b	86.8±13.6^b	0.004	72.9±15.0	70.3±11.9	75.0±13.8	0.4
Glucose (mg/dl)	89.5±10.6	92.6±28.8	92.1±14.0	0.8	95.0±19.5	86.1±8.5	91.5±16.2	0.1
TG (mg/dl)	139.3±78.6^a	140.3±66.9^a	210.6±108.4^b	0.002	140.2±86.5	109.2±54.3	120.0±91.6	0.4
LDL-C (mg/dl)	113.5±26.7	106.1±25.9	108.0±30.7	0.6	100.0±23.8	100.1±24.1	107.7±31.4	0.5
HDL-C (mg/dl)	46.1±10.2^a	40.7±10.1^b	38.8±10.5^b	0.02	45.3±12.0^a	53.2±8.2^b	52.6±11.4^b	0.01
Total-C/HDL-C	4.2±1.6	4.6±1.5	5.1±1.2	0.09	4.0±1.0	3.5±0.8	3.6±1.1	0.08
TG/HDL-C	3.5±2.9^a	3.8±2.3^a	6.1±3.9^b	0.003	3.5±2.6	2.2±1.3	2.7±2.9	0.1
Metabolic score[3]	1.6±1.6^a	2.0±1.7^{ab}	2.9±1.7^b	0.02	1.9±1.4^a	0.7±1.2^b	1.1±1.7^b	0.002

[1]Values are means±SD. [2]Comparisons were performed using one-way ANOVA with LSD as the post hoc test. Different letters demonstrate significant differences. [3]Metabolic syndrome risk was scored according to the criteria proposed by National Iranian Committee of Obesity as described in the Methods. BMI, body mass index; WC, waist circumference; WHR, waist/hip circumference ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglyceride; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Total-C, total cholesterol.

Table 3: Linear regression analysis of the association between CVD and metabolic syndrome components and serum concentrations of 25(OH)D in males and females

Risk factors	Males (n=88)				Females (n=81)			
	Unadjusted B Coefficient (95% CI)	P value	Adjusted B Coefficient (95% CI)[1]	P value	Unadjusted B Coefficient (95% CI)	P value	Adjusted B Coefficient (95% CI)[2]	P value
BMI (kg/m^2)	0.004 (-0.01 0.02)	0.7	0.002 (-0.02 0.02)	0.8	-0.09 (-0.15 -0.03)	0.005	-0.06 (-0.11 -0.02)	0.01
WC (cm)	0.01 (-0.04 0.06)	0.6	0.002 (-0.04 0.05)	0.9	-0.16 (-0.29 -0.02)	0.02	-0.12 (-0.23 -0.01)	0.04
WHR	0.001 (-0.01 0.01)	0.2	0.001 (-0.01 0.03)	0.4	-0.01 (-0.01 0.01)	0.1	0.01 (-0.01 0.01)	0.2
SBP (mm Hg)	0.08 (0.02 0.13)	0.009	0.05 (-0.01 0.10)	0.08	0.04 (-0.05 0.12)	0.4	0.007 (-0.07 0.08)	0.8
DBP (mm Hg)	0.08 (0.04 0.13)	0.001	0.07 (0.02 0.11)	0.006	0.06 (-0.01 0.12)	0.1	0.03 (-0.03 0.09)	0.3
FBG (mg/dl)	0.009 (-0.06 0.08)	0.8	-0.01 (-0.09 0.06)	0.7	0.04 (-0.04 0.12)	0.4	0.03 (-0.05 0.11)	0.4
TG (mg/dl)	0.6 (0.25 0.89)	0.001	0.54 (0.22 0.85)	0.001	0.14 (-0.27 0.54)	0.5	0.06 (-0.31 0.44)	0.7
LDL-C (mg/dl)	-0.06 (-0.16 0.04)	0.3	-0.09 (-0.19 0.01)	0.07	0.09 (-0.05 0.22)	0.2	0.06 (-0.07 0.19)	0.4
HDL-C (mg/dl)	-0.05 (-0.08 -0.01)	0.02	-0.05 (-0.09 -0.01)	0.02	0.20 (0.06 0.33)	0.006	0.16 (0.02 0.31)	0.02
Total-C/HDL-C	0.005 (-0.01 0.01)	0.08	0.003 (-0.01 0.01))	0.2	-0.01 (-0.02 0.001)	0.1	-0.01 (-0.02 0.001)	0.07
TG/HDL-C	0.02 (0.01 0.03)	0.001	0.02 (0.01 0.03)	0.001	-0.02 (-0.04 0.01)	0.2	-0.01 (-0.03 0.01)	0.3
Metabolic score	0.009 (0.003 0.01)	0.003	0.01 (0.001 0.01)	0.02	-0.03 (-0.05 -0.01)	0.001	-0.02 (-0.03 -0.01)	0.01

[1]Adjusted for age, marital status, education, family affluence, physical activity, and smoking. BMI, body mass index; WC, waist circumference; WHR, waist/hip circumference ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBG, fasting blood glucose; TG, triglycerides; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; Total-C, total cholesterol.

activity, and smoking habits diastolic blood pressure (B=0.07; 95% CI: 0.02, 0.11; P=0.006), triglycerides (B=0.54; 95% CI: 0.22, 0.85; P=0.001), and metabolic syndrome score (B=0.01; 95% CI: 0.001, 0.01; P=0.02) were positively and HDL-C (B=-0.05; 95% CI: -0.09, -0.01; P=0.02) inversely associated with 25(OH)D concentrations in males. In contrast, BMI (B=-0.06; 95% CI: -0.11, -0.02; P=0.01), waist circumference (B=-0.12; 95% CI:-0.23, -0.01; P=0.04), and metabolic syndrome score (B=-0.02; 95% CI:-0.03, -0.01; P=0.01) were inversely and HDL-C (B=0.16; 95% CI: 0.02, 0.31; P=0.02) positively associated with 25(OH)D concentrations in females. Figure 1 illustrates how serum 25(OH)D levels differed between subjects with and without metabolic syndrome

Discussion

In the current study, significant associations were found between serum 25(OH)D concentrations and risk factors

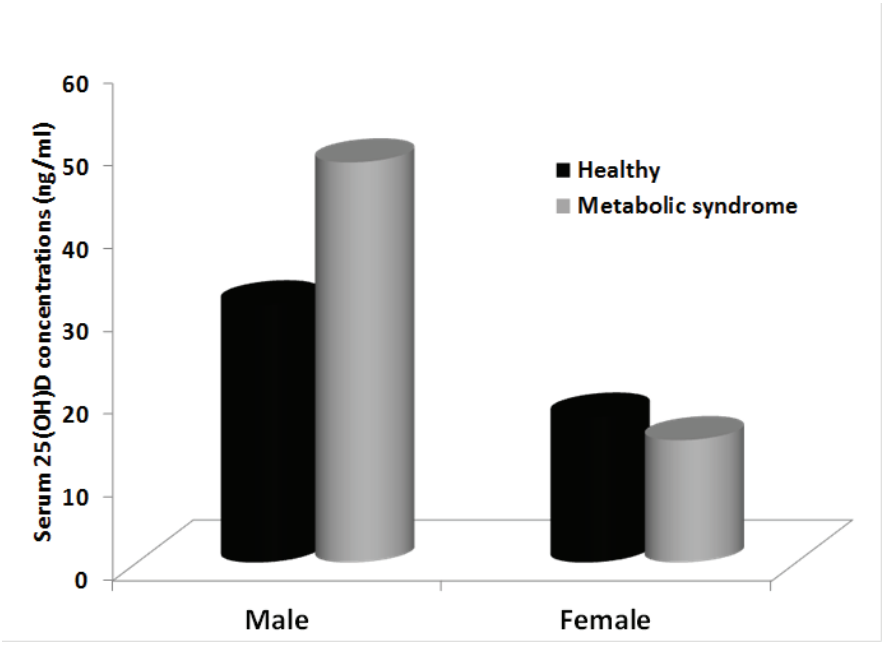

Figure 1: Shows mean levels of serum 25(OH)D in healthy subjects and subjects with metabolic syndrome. Black bars show healthy subjects (score of metabolic syndrome=0, 1, or 2) and gray bars illustrate subjects with metabolic syndrome (score of metabolic syndrome=3, 4, or 5). Metabolic syndrome was scored according to the definition proposed by National Iranian Committee of Obesity as described in Methods.

of CVD and metabolic syndrome. Different patterns were observed in males and females owning to different levels of 25(OH)D in the two sexes. In females, who possessed low concentrations of 25(OH)D, higher BMI and waist circumference and lower HDL-C were significantly associated with lower levels of serum 25(OH)D, while in males, who had higher levels of serum 25(OH)D, higher diastolic blood pressure and triglycerides and lower HDL-C were associated with higher concentrations of 25(OH)D, suggesting that both lower and higher concentrations of vitamin D are associated with increasing risk of CVD and metabolic syndrome.

Previous studies are in accordance with our results for females. It has been reported that serum 25(OH) D concentrations are inversely correlated with the risk of metabolic syndrome,[20,21] and cardiovascular diseases.[22,23] This association is mainly attributed to obesity,[23] and insulin resistance,[24,25] but is also reported for fasting blood glucose,[26-28] waist circumference,[25,29] triglycerides,[28] and reduced HDL-C.[28-30] Interestingly, an association has been found between vitamin D receptor gene polymorphisms and metabolic syndrome.[31,32]

In contrast to the abundant reports on the negative association of vitamin D and CVD risk factors, reports of the positive relationship between vitamin D and CVD risk factors are scarce. Recently, a few studies have reported this kind of association. For instance, in a retrospective cross-sectional study on 1110 subjects in Mashhad, a positive and significant relationship was found between serum lipids and vitamin D.[33] Recently, it has been shown that vitamin D receptor promotes lipogenesis and inhibits lipid oxidation pathways in hepatocytes while low vitamin D receptor ligand concentration (i.e. vitamin D deficiency) should have a protective effect on liver steatosis.[34] Given that hepatic lipogenesis (liver steatosis or non-alcoholic fatty liver) is the cause of metabolic disturbances in glucose and lipid profile,[35] assuming a role for high vitamin D levels in increasing the risk of CVD is plausible.

Increased levels of 25(OH)D can also promote hypertension, as an important risk factor of CVD. In a cross-sectional study on 2500 adults in Ahvaz, individuals with stage 1 hypertension had higher levels of serum vitamin D compared to individuals with prehypertension and normal blood pressure.[36] The active form of vitamin D has shown to enhance resistance artery contractile function in rats.[37] In addition, hypertension may result from vascular calcification following high levels of serum vitamin D for prolonged periods. High levels of serum vitamin D may be a promoter of vascular calcification and a risk factor for subclinical atherosclerosis.[38] Vitamin D elevates the absorption of calcium and phosphorus in the intestine, and, therefore, the increased calcium and phosphorus load may stimulate the development of vascular calcification. In this regard, in a study on 180,000 Koran subjects, high levels of serum vitamin D were associated with higher risk of coronary artery calcification in men, although such association was not seen in women.[38]

We suppose that the relatively high concentrations of 25(OH)D which was observed in the current study have resulted from vitamin D synthesis in the

skin; such levels of 25(OH)D are common in sunny countries.[39] The difference in 25(OH)D concentrations between men and women of this study could be due to the religion and culture of the people. In sunny Moslem countries, like Iran, males usually have higher levels of 25(OH)D than females and lower rates of vitamin D deficiency because females wear veils, such as Neqab and Hijab, which prevent vitamin D synthesis in the skin.[40] For example, in a study on Bahrainis adults, the prevalence of vitamin D deficiency among males and females was 31.2% and 67.6%, respectively.[41] Similarly, in Jordanian adults, 5.1% and 37.3% of males and females were vitamin D deficient (<30 ng/ml).[40] Also, in two studies in Iran 18.3% and 72.1% of boys and girls aged 14-18 years,[42] and 51.2% of male and 95.2% of female university students[11] had vitamin D levels of <20 ng/ml, respectively. The type of job is also an important factor in the difference in vitamin D levels between the two sexes. Because of their job, males spend times of the day out of home and so are more exposed to sunlight than females. In our study, 74.1% of females were housekeepers.

In recent years, a limited number of studies reported a U-shaped relationship between serum 25(OH)D levels and the incidence of certain types of cancer,[43,44] cardiovascular events, and all-cause mortality.[45,9] However, this type of association has not been found between serum 25(OH)D levels and BMI, dyslipidemia, or blood pressure.[43] However, due to the sex difference in serum concentrations of 25(OH)D, the results herein are not sufficient to suggest a U-shaped association between 25(OH)D levels and the risk of CVD and metabolic syndrome; such association is plausible if the association between low and relatively higher levels of 25(OH)D and risk factors of metabolic syndrome is considered regardless of the gender.

The cross-sectional design of this study did not allow us to draw conclusions on the causality of the associations. Because of ethical issues examining this kind of association is difficult; however, large scale cross-sectional studies or well-designed cohort or case-control investigations should to be conducted before a firm conclusion can be made. Financial limitations hindered us from using a larger sample size to improve the power of the results. Our study also lacked information on serum calcium and possible hypercalcemia in higher concentrations of 25(OH) D, something that should be determined in future investigations.

Conclusion

According to the results herein, low serum 25(OH)D in females and upper normal levels of serum 25(OH)D in males may have associations with risk factors of CVD and metabolic syndrome.

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