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Association of Serum 25-Hydroxyvitamin D Levels and Vitamin D Dietary Intake with Metabolic Syndrome: A Case Control Study

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ABSTRACT

Background: Association between the vitamin D deficiency and metabolic syndrome (MetS) has previously been noted and reported to be controversial. The aim of this study was to determine the association of serum 25 (OH) D Level and Vitamin D dietary intake with MetS among Iranian population.

Methods: This analytical study was conducted on 122 patients with MetS based on the ATPIII criteria and 128 subjects without MetS as control from September 2010 to April 2011. Serum levels of calcium, phosphorus and 25(OH) D were compared between the two groups. A food frequency questionnaire (FFQ) was used to calculate dietary intake. Data were analyzed using Chi- square test, *t*-test, Mann-Whitney U test and logistic regression analysis.

Results: Serum concentrations of 25 (OH) D, calcium and phosphorus and calcium intake were significantly lower in subjects with MetS compared to the subjects without MetS. 98.4% of subjects with MetS and 88.3% without MetS had Vit. D deficiency and this difference was statistically significant (P=0.005). In regression analysis, lower concentration of serum 25 (OH) D, calcium and phosphorus and lower calcium and diary intake were predictors of MetS.

Conclusions: Serum 25 (OH) D Level, calcium and phosphorus and calcium intake are associated with metabolic syndrome. However, the mechanism of this association requires further studies.

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Introduction

Vitamin D (Vit. D) has various roles in human life including bone and muscle functions, and normal growth[1]. Its roles in bone mineralization, promoting intestinal absorption of calcium and phosphorus, prevention of cancer, both through genomic and non-genomic mechanisms, adjustment of immune system functions, and glucose homeostasis has been confirmed. Vit. D deficiency would result in various diseases such as rickets, osteoporosis, bone fracture, certain types of cancers, hypertension, cardiovascular diseases, multiple sclerosis, type 1 diabetes mellitus, autoimmune diseases, and dental diseases[2-4]. 1, 25 $(OH)_2$ Vit. D mediates function of more than 200 genes; include genes responsible for synthesis of renin, insulin, and cytokines[2].

Despite its importance in body homeostasis, Vit. D deficiency is highly prevalent worldwide[5, 6]. It has been claimed that 30-50% of children and adults in different parts of the world suffer from Vit. D deficiency[6-8]. It has even been about twice more prevalent in Chinese elderly and Korean menopaused women[9, 10]. The same is true for Iranian[6, 11, 12].

Metabolic syndrome (MetS) is defined as; central obesity, insulin resistance, abnormal glucose tolerance test, hypertriglyceridemia, low level of high density lipoprotein cholesterol (HDL), and hypertension. It is associated with risks of diabetes, cardiovascular diseases, and their resultant morbidity and mortality. Its prevalence is increasing, currently known as an epidemic disease worldwide[13]. Various causative factors have been suggested for MetS; including Vit. D deficiency. There are some studies that have proposed negative relationship between serum concentration of 25 (OH) D and occurrence of MetS or its components[14,15]. However, other studies have not supported this relationship[16,17]. Theoretically, the roles of Vit. D in normal function of beta- cells of pancreas and insulin secretion and regulation of lipolysis explain the relationship between the serum concentration of 25 (OH) D and occurrence of MetS, reported to be so5, 18 but this relationship, is not found in another study[19].

Both MetS and Vit. D deficiency are prevalent in Iran as other Asian countries. Metabolism of Vit. D and prevalence of MetS are partly affected by ethnicity and lifestyle. The aim of this study was to determine the association of serum 25 (OH) D Level and Vit. D dietary intake with metabolic syndrome among Iranian population.

Methods

This analytical study was conducted on 250 subjects (122 with MetS and 128 as control group) identified in the Qazvin Metabolic Diseases Study (QMDS), Iran.

The research project was approved by the Medical Research Ethics Committee of Qazvin University of Medical Sciences. All subjects gave their written informed consent form.

Details of sampling method and data collection of the QMDS have been published elsewhere[20]. All households of the Minoodar district had profiles at the health center and the sampling unit was the household. Subjects were invited by phone call to attend the health center and after being fully explained, their written informed consent for the participation was obtained. Overall, 1107 subjects aged >20 yr old were selected by multistage cluster random sampling methods from residents of this district of Qazvin because of their similar socioeconomic status. The subjects were studied in a cross sectional design from September 2010 to April 2011. A self-reported questionnaire was used for social and demographic information. Two practitioners recorded medical history, family history, medication, and physical examination for all subjects. Waist circumference (WC), weight, height and body mass index (BMI) were measured after 12-14 h overnight fasting. In a seated position, blood pressure (BP) was measured three times by a mercury sphygmomanometer and after a 15 min rest on a single occasion. Blood levels of glucose, insulin, triglycerides (TGs), total cholesterol, high-density lipoprotein cholesterol (HDL) and low-density lipoprotein cholesterol (LDL) were measured for all subjects after 12-14 h overnight fasting and in the same laboratory. Oral glucose tolerance test (OGTT) by 75 g glucose was performed on subjects without previous diagnosis of diabetes.

MetS was defined according to the ATP III criteria if at least three of the following conditions were met: WC > 102 cm in men and > 88 cm in women, fasting plasma glucose (FPG) ≥ 100 mg/dl (includes diabetes), TGs > 150 mg/dl, HDL < 40 mg/dl in men and < 50 mg/dl in women, systolic blood pressure > 130 mmHg or diastolic blood pressure > 85 mmHg[21]. Given this information, presence or absence of MetS was known for all study subjects and 328 (30.6%) of them had MetS.

Totally, 122 subjects with MetS were selected and 128 subjects without MetS were matched for age, gender, marital status, education level and occupation as control group. Subjects with diseases related to Vit. D (such as rickets), cancer, hepatic and renal disease or on treatment with drugs that could affect the Vit. D metabolism (such as phenytoin) were excluded from this study. Serum concentrations of 25 (OH) Vit. D, Calcium and Phosphorus were measured. 25 (OH) Vit D levels were measured by ELISA using reagent (IDS Company, Germany). Mean intra- and interassay coefficients of variation were 5.3 and 4.6, respectively. 25 (OH) D concentrations above 30 ng/ml were considered as Vit. D sufficiency. Vit. D insufficiency was defined as 20< 25 (OH) D <30 ng/ml and25 (OH) D lower than 20 ng/mlwas considered as Vit. D deficiency[2]. A 168-item semi-quantitative food frequency questionnaire (FFQ) was used to calculate dietary intake. Validity and reliability of this questionnaire were confirmed previously[22]. A list of foods has been developed in this questionnaire with a standard serving size. Food consumption frequency was self-reported by study subjects on a daily, weekly or monthly basis. The food intake was analyzed using "Nutrition 4, version 3.5.2" software (Nutrition 4, 2011).

The normality of variables was examined by Kolmogorov Smirnov test. Categorical variables were described as number (percent). Quantitative variables were described as mean ± SD. Independent samples *t*-test and Mann-Whitney U test were used to compare quantitative parameters with normal and abnormal distribution between the two groups. Chi-square test was used to compare qualitative variables. Multiple logistic regression analysis was performed to investigate the independent association of MetS, Vit. D and other potential risk factors. SPSS software version 16.0 was used for statistical analysis. *P*-value less than 0.05 were considered significant.

Results

Overall, 122 subjects with MetS and 128 subjects without MetS were evaluated. Mean age was 46.3±11.8 yr in subjects with MetS and 45.3±12.3 in subjects without MetS and the difference was not statistically significant (*P*= 0.464). The groups had no statistically significant difference in their demographic characteristics (Table 1). BMI was 24.8± 3.7 kg/m^2 (18.1-37.2) in subjects without MetS, while it was 28.3± 3.7 kg/m^2 (18.4-37) in subjects with MetS and this difference was statistically significant (*P*< 0.001).

Table 1: Demographic characteristics of the study subjects

	Cases with MetS (n= 122)		Controls without MetS (n= 128)		
Variables	**Number**	**Percent**	**Number**	**Percent**	***P* value**
Gender					0.267
Male	62	50.8	74	57.8	
Female	60	49.2	54	42.2	
Marital status					0.486
Single	8	6.6	12	9.5	
Married	109	89.3	112	88.9	
Divorced	1	0.8	0	0.0	
Widow	4	3.3	2	1.6	
Education level					0.358
Illiterate	11	9.2	5	4.2	
Less than high school	67	55.8	64	53.3	
High school diploma	28	23.3	35	29.9	
College education	14	11.7	16	13.3	
Occupation					0.571
Employed	32	26.2	32	25.0	
Unemployed	4	3.2	4	3.1	
Retired	34	27.8	46	35.9	
Housewife	52	42.6	46	35.9	

According to the ATP III criteria, 28 (21.9%), 19 (14.8%), 60 (46.9%), 18 (14.1%) and 35 (27.3%) of subjects without MetS had High WC, high BP, low HDL, high TGs and high FPG, respectively. Seventy-eight (63.9%), 62 (50.8%), 111 (91%), 96 (78.7%) and 92 (75.4%) of subjects with MetS had high WC, high BP, low HDL, high TGs and high FPG, respectively. Thirty-seven subjects with MetS and four subjects without MetS were diabetic. Of them, 25 subjects with MetS and 3 without MetS were on anti-diabetic treatment.

Clinical and laboratory characteristics of the subjects are shown in Table 2. The groups had statistically significant differences in all components of MetS. Serum concentrations of 25 (OH) D, calcium and phosphorus and calcium intake were significantly different between two groups (Table 2). Distribution of Vit. D in subjects with and without MetS has been showed in figure 1. 98.4% of subjects with MetS and 88.3% of subjects without MetS had Vit. D deficiency while 1.6% of subjects with MetS and 6.2% of subjects without MetS had Vit. D sufficiency and this difference was statistically significant (*P*=0.005). Eighty percent of subjects with MetS had vitamin D concentration less than 10 ng/ml, while the corresponding number was 41.7% in subjects without MetS.

In multiple logistic regression analysis, lower concentration of serum 25 (OH) D, calcium and phosphorus and lower calcium and diary intake were predictors of MetS (Table 3). We evaluated the studied groups for their WC, presence of hypertension, HDL levels, TG levels, and FPG; while categorizing them according to their Vit. D concentrations. The differences were statistically significant for WC, HDL and TG levels (*P*= 0.001, *P*=0.001, and *P*=0.012, respectively); but not for hypertension, and FPG.

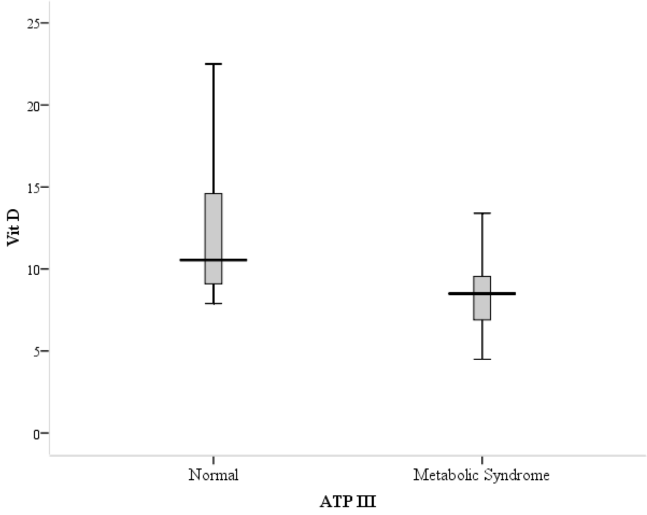

Figure 1: Distribution of vitamin D in subjects with and without metabolic syndrome

Table 2: Clinical and laboratory characteristics of the study subjects

Variables	Cases with MetS (n= 122)		Controls without MetS (n= 128)		*P* value
	Mean	SD	Mean	SD	
Systolic blood pressure (mmHg)	121.0	18.0	112.3	15.0	0.001
Diastolic blood pressure (mmHg)	76.8	12.2	70.2	10.4	0.001
Waist circumference (cm), male	99.0	8.6	89.3	8.0	0.001
Waist circumference (cm), female	96.2	9.6	88.1	11.6	0.001
Fasting plasma glucose (mg/dL)	113.1	45.1	94.7	16.6	0.001
Triglycerides (mg/dL)	213.2	92.2	116.5	46.2	0.001
LDL (mg/dL)	116.1	26.3	105.9	21.4	0.001
HDL (mg/dL), male	34.4	6.5	41.9	7.7	0.001
HDL (mg/dL), female	40.4	5.6	47.0	9.9	0.001
Serum calcium (mg/dL)	8.7	0.3	9.1	0.4	0.001
Serum phosphorus (mg/dL)	3.3	0.2	3.9	0.3	0.001
Serum 25(OH) D (ng/ml)	9.6	5.4	14.5	10.5	0.001
Vitamin D intake (μg/day)	3.5	11.1	4.2	11.1	0.205
Calcium intake (mg/day)	686.9	263.5	785.7	286.7	0.008
Phosphorus intake (mg/day)	1336.0	485.5	1439.6	372.1	0.084
Dairy intake (servings/day)	1.1	0.6	1.4	0.9	0.001

Table 3: Multiple Logistic regression analysis of metabolic syndrome predictors

Variables	Cases with MetS	Controls without MetS	Unadjusted OR (95% CI)	*P* value	Adjusted OR[a] (95% CI)	*P* value
Serum Calcium (mg/dl)						
8.5-10.6	93	122	1.00		1.00	
<8.5 or >10.6	29	6	0.16 (0.06, 0.40)	0.001	0.14 (0.03, 0.70)	0.016
Serum Phosphorus (mg/dl)						
3.3-5.5	66	119	1.00		1.00	
<3.3	54	1	0.01 (0.00, 0.08)	0.001	0.00 (0.00, 0.01)	0.001
Serum 25(OH) D (ng/ml)						
>30	2	8	1.00		1.00	
<30	120	120	0.25 (0.05, 1.20)	0.084	0.78 (0.67, 0.91)	0.002
Vitamin D intake	-	-	0.99 (0.97, 1.02)	0.686	0.99 (0.95, 1.04)	0.874
Calcium intake	-	-	0.99 (0.99, 1.00)	0.015	1.00 (0.99, 1.01)	0.171
Phosphorus intake	-	-	0.99 (0.99, 1.00)	0.088	0.99 (0.99, 1.00)	0.212
Diary intake	-	-	0.46 (0.29, 0.72)	0.001	0.27 (0.08, 0.88)	0.030

[a]ORs adjusted for serum Calcium, serum Phosphorus, serum 25(OH) D, vitamin D intake, Calcium intake, Phosphorus intake and diary intake.

Discussion

The current study was designed to determine association between Vit. D deficiency and MetS. Results showed that Vit. D concentration was notably lower in subjects with MetS compared to subjects without MetS. High prevalence of Vit. D deficiency was considerable.

Both Vit. D deficiency and MetS cause most important health problems. Vit. D deficiency may lead to various dysfunctions in body metabolism while MetS may also increase the risk of cardiovascular diseases. Recent advances in technology and welfare, changes in lifestyle and nutritional habits have exposed Asian countries including Iran with side effects of so- called western lifestyle, such as MetS and its associated increased risk of cardiovascular diseases.

On the other hand, Vit. D deficiency has become prevalent despite improvements in the socioeconomic status. In Tehran, the capital city of Iran, in 2004; 9.5, 57.6, and 14.2 percent of studied individuals suffered from severe, moderate, and mild Vit. D deficiency, respectively[12]. In Isfahan City, 26.9, 23.9, and 19.6% prevalence for severe, moderate, and mild Vit. D deficiency, respectively in 2011 has been reported [6] while another study conducted in five large cities of Iran has reported that more than 40% of the studied individuals (in various gender and age groups) had Vit. D deficiency[11]. We found that 88.3% of subjects without MetS and 98.4% of subjects with MetS had Vit. D deficiency. It seems that Vit. D deficiency becomes a frightening issue among Iranians.

There are controversial reports about the relation between Vit. D deficiency and MetS or its components. Many studies have suggested relationship between Vit. D and MetS. However, their findings are not satisfactory and comparable. They differ in their methodology, studied population, study design, model of report, and method of analysis of Vit. D. Some of them are not matched for some imperative variables and some are performed on certain age or population groups, hence their results cannot be extrapolated to general population[19].

Serum concentration of 25 (OH) D is widely accepted as a standard measure for the evaluation of Vit. D adequacy in human; however, there is no consensus on it[23, 24]. Nevertheless, we considered levels higher than 30 ng/ml as normal serum concentration of 25 (OH) D. It is shown that this concentration of Vit. D is associated with optimal health status, minimum level of parathyroid hormone, and the least probability of bone fracture [8, 25].

Cheng et al. have studied relationship between the serum concentrations of Vit. D and obesity, as well as its cadiometabloic risks on 3890 non-diabetic persons[15]. Accordingly, serum concentration of Vit. D had reverse association with WC, serum insulin concentration, subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). They found that serum concentration of Vit. D was indirectly proportional to the fat content of body; even in individuals with BMI less than 25 kg/m^2. They also found that frequency of Vit. D deficiency (serum concentration of Vit. D less than 20 ng/ml) is 3-fold in persons with high SAT and VAT; compared to persons with low SAT and VAT. They believed that Vit. D deficiency is related to body fat content, particularly visceral fat. Lender et al. have reported that serum concentration of 25 (OH) D decreases 0.46±0.22 with every 1% increase in body fat mass, alongside with decrease in PTH level 0.78±0.29 [26]. Their findings are in favor of the effect of body fat content on distribution of Vit. D. Chiu et al. have found independent association between serum concentration of 25 (OH) D and insulin sensitivity index; but no similar association is found between Vit. D and response to insulin[5]. They have reported that components of MetS are more frequently seen in patients with low serum Vit. D (< 20 ng/ml). They have concluded that Vit. D deficiency has negative effect on function of beta cells of pancreas. McGill et al. have found significant negative relationship between serum level of Vit. D_3 and body weight, BMI, and WC; but not with body fat content[16]. They believed that every 1 kg/m^2 rise in BMI decreased vitamin D by 0.75 nmol/l, while every increase in WC decreased it by 0.29 nmol/l. There are other studies that have also found significant relation between serum levels of 25 (OH) D and MetS, as well as LDL concentration[23, 27]. In Iran MetS is more prevalent in men with Vit. D deficiency when compared to men with normal level of Vit. D[28]. The authors believed that Vit. D deficiency was an independent predictive variable for the occurrence of MetS. Findings of the present study about negative relationship between the occurrence of MetS and serum concentration of Vit D are in accordance with above-mentioned studies.

On the other hand, there are some contradictory studies. Kim et al. have not found any relation between serum concentrations of Vit. D and MetS among Korean[1]. Nevertheless, they have found negative relation between serum concentrations of Vit. D and HDL level. Khader et al. have performed similar study in west Asia [19] and they did not found any significant relation between serum concentrations of Vit. D and MetS or its components. These studies might imply that the relation between serum concentration of Vit. D and MetS may not be factual among Asian people, particularly in west Asia. However, current study confirmed that the association is present even in this geographic area.

Vit. D intake from animal sources is very low among Iranians [25] and this study claimed that 90-95% of them had Vit. D intake less than 10 micrograms/day and our findings in this study confirm this too.

The authors chose subjects without MetS from same area as subjects with MetS and assessed them at the same time to avoid confounding factors such as sun exposure, socioeconomic status and seasonal variation. However, we had some limitations in the present study as we did not measure duration of the sunlight exposure in the subjects to estimate the severity of Vit. D deficiency among exposed and non-exposed individuals. Another limitation for interpretation of the results was the high prevalence of Vit. D deficiency in this population. It might also help to clarify causes of Vit. D deficiency among studied population.

Conclusions

Vit. D deficiency is associated with MetS, however their cause and effect relation needs other studies. Design of clinical trials to treat patients with concurrent Vit. D deficiency and MetS with Vit. D supplementation and assessment of their response can be helpful.

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Conflict of interest statement

The authors declare that they have no conflicts of interest.

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