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The relationship between serum vitamin D levels and ankle-brachial index in patients with metabolic syndrome

Davoud Kazemisaleh[1], Keivan Kiani[2], Masoumeh Sadeghi[3], Hamidreza Roohafza[4], Minoo Dianatkhah[5], Nizal Sarrafzadegan[6]

Original Article

Abstract

BACKGROUND: Vitamin D deficiency is a prevalent condition in Iran and previous studies have shown that a low level of serum vitamin D is related to low ankle-brachial index (ABI). In the present study, the relationship of the serum level of vitamin D with ABI, as an index for atherosclerosis of peripheral arteries, was evaluated.

METHODS: In this cross-sectional study, data on 91 patients with metabolic syndrome (Mets) from the Isfahan Cohort Study (ICS) were analyzed in order to evaluate the association between serum 25(OH) vitamin D level and ABI. The participants were divided into two groups; group A with desirable serum vitamin D level and group B with abnormal serum vitamin D level. ABI was measured and compared between these groups.

RESULTS: A crude and adjusted model showed no association between vitamin D level and ABI in patients with MetS.

CONCLUSION: It can be concluded that serum vitamin D level could not affect ABI in patients with MetS.

Keywords: Vitamin D, Ankle Brachial Index, Metabolic Syndrome

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Introduction

Metabolic syndrome (MetS) is characterized by the clustering of cardiovascular risk factors including adiposity, hyperglycemia, hypertension, and dyslipidemia. It has become one of the major public health challenges in developed and developing countries and the management of these risk factors can change with community trial.[1] MetS has been linked to increased arterial stiffness and thickness.[2] Different studies show that the stage of arterial stiffness was significantly more pronounced in patients with MetS.[3] The majority of literature have demonstrated that diverse inflammatory and oxidative stress markers correlate with arterial damage leading to arterial stiffness and thickness.[4-5]

Vitamin D is a secosteroid which is attained by the body through exposure to sunlight and dietary sources. Although 1,25 (OH)2D has been recognized as the active form of vitamin D, the 25(OH)D level is a marker of more clinical importance.[6] Studies have provided evidence of the involvement of vitamin D in bone metabolism. There is also evidence of the role of vitamin D in glucose levels, insulin resistance (IR), and prevalence of type 2 diabetes mellitus (DM).[7] Other studies have found that vitamin D plays a role in systemic inflammation, the immune system, and lipid metabolism to reduce the risk of cardiovascular diseases (CVD).[8] However, few investigations have reported an association between vitamin D and ankle-brachial index (ABI) in MetS. Hence, it is necessary to investigate the relationship between vitamin D and ABI.

Both MetS and abnormal vitamin D serum level are prevalent in our community.[9-13] Therefore, this study was designed to investigate the possible association between vitamin D and ABI as an indicator of peripheral artery atherosclerosis in patients with MetS.

1- Associate Professor, Atherosclerosis Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran
2- Resident, Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
3- Professor, Cardiac Rehabilitation Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
4- Associate Professor, Psychosomatic Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
5- Heart Failure Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
6- Professor, Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran
Correspondence to: Masoumeh Sadeghi, Email: m_sadeghi@crc.mui.ac.ir

Materials and Methods

This cross-sectional study was conducted in Isfahan Cardiovascular Research Center, Iran, in 2014. Patients with MetS were enrolled to participate in the study. MetS was diagnosed based on the National Cholesterol Education Program/Adult Treatment Panel, based on the presence of at least three of the factors of central obesity (i.e., waist circumference [WC] > 102 cm for men and > 88 cm for women), high blood pressure (BP) (i.e., systolic BP [SBP] ≥ 130 mmHg or diastolic BP [DBP] ≥ 85 mmHg), hyperglycemia (i.e., fasting glucose ≥ 110 mg/dl), hypertriglyceridemia (i.e., fasting triglycerides [TGs] ≥ 150 mg/dl), and low high-density lipoprotein (HDL)-cholesterol (i.e., HDL-cholesterol < 40 mg/dl for men and < 50 for women).[14-15] The exclusion criteria were chronic renal failure, prior grafting or stenting of lower limb arteries, and abnormal coronary or peripheral angiography.

The study participants consisted of 91 patients from Isfahan Cohort Study (ICS).[16] Patients with MetS diagnosed by an endocrinologist were included in the study based on the inclusion and exclusion criteria. The data on all 91 patients with MetS was complete. The study was approved by the Ethics Committee of Isfahan Cardiovascular Research Center, and written informed consent forms were obtained from all participants.

The diet of the participants consisted of a balanced diet for 3 days and fasting overnight for 12 hours. Body mass index (BMI) was calculated through the division of weight by height squared (kg/m^2). The participants' systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured. The collected blood samples were frozen and reserved at -80 °C until analysis. Using an automatic biochemical analyzer, fasting blood sugar (FBS), total cholesterol (TC), TG, low-density lipoprotein (LDL), and HDL were measured. Moreover, some variables such as sex, age, physical activity, smoking, and education were evaluated as confounding variables.

25(OH)D was measured using an Elisa Kit (Calbiotech Inc, USA) and automated analyzer. The various states of serum vitamin D levels were defined as abnormal (< 75 nmol/l) and desirable (≥ 75 nmol/l).

To perform ABI measurements, the subjects were asked to lie in the supine position. The Doppler instrument was used for this purpose. The blood pressure cuff of the Doppler device was wrapped around the patient's upper arm and was inflated until no brachial pulse was detected. Then, the cuff was slowly deflated until the pulse returned to measure brachial systolic blood pressure (BSBP). The cuff was then placed on the distal calf and the Doppler device was placed over the dorsalis pedis or the posterior tibial artery to measure ankle systolic blood pressure (ASBP) and the same measures were repeated on the leg.[17]

Descriptive statistics such as mean ± standard deviation (SD) and absolute number (percentage) for categorical variables are reported in the present text for continuous and categorical variables. Chi-square and independent t tests were used to evaluate differences between the two groups for categorical and continues variables, respectively. Moreover, logistic regression analysis was used to evaluate the relationship between ABI and vitamin D. All statistical analyses were performed in SPSS software (version 22, IBM Corporation, Armonk, NY, USA). All P-values of less than 0.05 were considered significant.

Results

91 patients completed the study. The patients were divided into two groups. Group A with desirable vitamin D level and group B with abnormal vitamin D level. These groups were compared in terms of demographic and clinical variables. The mean age in group A was greater than group B [59.8 ± 10.1 v 54.9 ± 7.4 years; P = 0.010]. Furthermore, the number of patients with high LDL level in group A were more than group B [7 (21.9%) vs. 3 (5.1%); P = 0.014]. However, there was no significant difference between the two groups in terms of the other variables such as ABI (low ABI was 23.7% in group B and 28.1% in group A) (P = 0.645) (Table 1).

Each group (A and B) was evaluated in terms of ABI and they were divided into normal ABI and low ABI. Other variables were evaluated in the two groups. It was found that in group A, mean age was greater in individuals with low ABI [66.5 ± 9.4 v 57.1 ± 9.3 (years); P = 0.016] and also BMI was greater in this group than individuals with normal ABI [35.9 ± 10.5 v 30.5 ± 3.5 kg/m^2; P = 0.036]. Nevertheless, high TG (≥ 150 mg/dl) was more prevalent in individuals with normal ABI than individuals with low ABI, but no significant difference was observed between normal ABI and low ABI in terms of the other variables. In group B, abnormal BP was more prevalent in individuals with normal ABI [31 (68.9%) v 14 (100%); P = 0.017], but there was no significant difference in terms of other variables between individuals with normal ABI and low ABI (Table 2).

Table 1. The frequency of studied variables based on vitamin D levels

Variable		Group A Vitamin D ≥ 75 (nmol/dl) (n = 32)	Group B Vitamin D < 75 (nmol/dl) (n = 59)	P
		Mean ± SD	Mean ± SD	
Age (year)		59.8 ± 10.1	54.9 ± 7.4	0.010*
BMI (kg/m^2)		32.0 ± 6.6	30.9 ± 4.3	0.332
Physical activity(MetS/week)		803.1 ± 669.5	758.8 ± 418.9	0.699
		n (%)	n (%)	
Sex (Man)		8 (25.0)	18 (30.5)	0.579
Education	Illiterate	4 (12.5)	9 (15.3)	0.088
	Primary school	20 (62.5)	23 (39.0)	
	Higher than primary school	8 (25.0)	27 (45.8)	
Low ABI (< 0.9)		9 (28.1)	14 (23.7)	0.645
Smoking		1 (3.1)	5 (8.5)	0.419
High BS [FBS ≥ 110 (mg/dl)]		7 (21.9)	19 (32.2)	0.298
Triglyceride ≥ 150 (mg/dl)		30 (93.8)	55 (93.2)	0.923
High density lipoprotein (≤ 40 mg/dl for men or ≤ 50 for women)		24 (75.0)	45 (76.3)	0.892
LDL ≥ 100 (mg/dl)		7 (21.9)	3 (5.1)	0.014*
Total cholesterol ≥ 200 (mg/dl)		12 (37.5)	22 (37.3)	0.984
Systolic blood pressure ≥ 130 (mmHg) or Diastolic blood pressure ≥ 85 (mmHg)		25 (78.1)	45 (76.3)	0.841
Waist circumference [men ≥ 102 (cm) or women ≥ 88 (cm)]		25 (78.1)	42 (71.2)	0.473

* P < 0.050

ABI: Ankle-brachial index; BMI: Body mass index; FBS: Fasting blood sugar; LDL: Low-density lipoprotein; MetS: Metabolic syndrome

The results of logistic regression showed no significant association between ABI and vitamin D levels even after adjustment for age, sex, physical activity, and smoking (P = 0.875) (Table 3).

Table 2. The frequency of studied variables based on low ankle-brachial index and normal ankle-brachial index and vitamin D levels

Variables		Group B Vitamin D < 75 (nmol/dl)			Group A Vitamin D ≥ 75 (nmol/dl)		
		Low ABI (n = 14)	Normal ABI (n = 45)	P	Low ABI (n = 9)	Normal ABI (n = 23)	P
		Mean ± SD	Mean ± SD		Mean ± SD	Mean ± SD	
Age (year)		57.7 ± 7.3	54.0 ± 7.3	0.101	66.5 ± 9.4	57.1 ± 9.3	0.016*
Physical activity (MetS/week)		811.3 ± 482.0	742.4 ± 401.9	0.595	667.3 ± 416.1	856.2 ± 747.1	0.482
BMI (kg/m^2)		29.5 ± 3.2	31.3 ± 4.5	0.171	35.9 ± 10.5	30.5 ± 3.5	0.036*
		n (%)	n (%)		n (%)	n (%)	
Sex (Man)		7 (50.0)	11 (24.4)	0.070	3 (33.3)	5 (21.7)	0.496
Education	Illiterate	3 (21.4)	6 (13.3)	0.762	2 (22.2)	2 (8.7)	0.378
	Primary school	5 (35.7)	18 (40.0)		6 (66.7)	14 (60.9)	
	Higher than primary school	6 (42.9)	21 (46.7)		1 (11.1)	7 (30.4)	
Smoking		2 (14.3)	3 (6.7)	0.583	0	1 (4.3)	> 0.999
High BS [FBS ≥ 110 (mg/dl)]		6 (42.9)	13 (28.9)	0.329	3 (33.3)	4 (17.4)	0.327
Triglyceride ≥ 150 (mg/dl)		12 (85.7)	43(95.6)	0.201	7(77.8)	23(100)	0.020*
HDL [≤ 40 (mg/dl) for men or ≤ 50 (mg/dl) for women]		9 (64.3)	36 (80.0)	0.227	7 (77.8)	17 (73.9)	0.820
LDL ≥ 100 (mg/dl)		1 (7.1)	2 (4.4)	0.564	2 (22.2)	5 (21.7)	0.976
Total cholesterol ≥ 200 (mg/dl)		6 (42.9)	16 (35.6)	0.622	3 (33.3)	9 (39.1)	0.761
SBP ≥ 130 or DBP ≥ 85 (mmHg)		14 (100)	31 (68.9)	0.017*	9 (100)	16 (69.6)	0.073
Waist circumference [men ≥ 102 (cm) or women ≥ 88 (cm)]		8 (57.1)	34 (75.6)	0.184	9 (100)	16 (69.6)	0.061

SBP: Systolic blood pressure, DBP: Diastolic blood pressure, ABI: Ankle-brachial index; BMI: Body mass index; FBS: Fasting blood sugar; LDL: Low-density lipoprotein; HDL: High-density lipoproteins

* P < 0.050

Table 3. The association of ankle-brachial index level and vitamin D serum levels

Logistic regression model	Odds ratio (95% CI)		P
	Vitamin D > 75 (nmol/dl)	Vitamin D ≤ 75 (nmol/dl)	
Crude	1	0.795 (0.299-2.110)	0.645
Model 1	1	1.180 (0.386-3.604)	0.722
Model 2	1	1.096 (0.350-3.432)	0.875

Model 1: adjusted based on sex and age; Model 2: adjusted based on sex and age; CI: Confidence interval

Discussion

In the present study, it was found that MetS is not significantly related to low ABI. Moreover, in the Edinburgh Artery Study (EAS), no association was reported between MetS and peripheral artery disease (PAD) incidence.[18] The present study findings were not in agreement with that of the Women's Health Study, a cohort clinical trial on women free of baseline cardiovascular disease, which showed that MetS was associated with an increased risk of PAD.[19]

The present study showed high level of LDL was more prevalent in patients with desirable levels of vitamin D. However, many studies, such as that by Saedisomeolia et al., have reported a negative relationship between vitamin D deficiency and LDL level.[20]

Scragg et al. in their epidemiological study, reported that blood pressure has an inverse association with vitamin D levels.[21] Rostand also conducted an epidemiological study in this regard and found a direct association between increasing latitude, as a surrogate of low vitamin D levels, and blood pressure.[22] Pfeifer et al. performed a small clinical trial the results of which suggested that systolic blood pressure was reduced as a result of oral vitamin D supplementation.[23] However, in the present study, a significant difference was not observed between group A and B in terms of abnormal blood pressure, but there was a higher rate of abnormal blood pressure in normal ABI patients of group B. In addition, Scragg et al. did not find any relationship between vitamin D and blood pressure, which was in agreement with the present study findings.[24]

A potential mechanism for increased risk of CVD is the association of 25(OH)D deficiency with glucose intolerance[25] and MetS.[26] However, this relationship was not observed in the current study.

Some studies have reported a relationship between low 25(OH)D levels and increased prevalence of coronary heart disease (CHD), stroke,[27] and congestive heart failure.[28] However, some other studies have found inverse relationships between these factors and higher than normal levels of 25(OH)D. Rajasree et al. conducted a case-control study on 143 patients with CHD and 25(OH)D levels of higher than 89 ng/ml.[29] They obtained a multivariable-adjusted odds ratio of 3.18 (95% CI: 1.31, 7.73) for CHD.[29] The case-control study by Scragg et al. on patients with acute myocardial infarction (AMI) showed the protective effect of higher than the median levels of 25(OH)D (≥ 12.8 ng/ml) against CHD (multivariable adjusted odds ratio = 0.43, 95% CI: 0.27, 0.69).[30]

The Framingham Offspring Study was performed on 1739 participants free of CVD at baseline; an association was observed between 25(OH)D level of lower than 15 ng/ml and a multivariable-adjusted 62% higher hazard of first cardiovascular event.[31]

There is evidence of the possibility of the role of vitamin D in the pathogenesis of CVD. Cardiac myocytes possess vitamin D receptors.[32] Xiang et al., in their in-vitro study, found that cardiac myocyte hypertrophy can be inhibited by active vitamin D.[33] Bodyak et al. evaluated the development of left ventricular hypertrophy in Dahl salt-sensitive rats and found that paricalcitol, an active vitamin D compound, weakened its development.[34] Li .et al reported that vitamin D is an inhibitor of the renin-angiotensin system.[35] In addition, Timms et al.[36] and Schleithoff et al.[37] reported improvement in the cytokine profile [C-reactive protein (CRP) and tumor necrotizing factor-alpha (TNF-α) levels] of patients with vitamin D deficiency[36] and congestive heart failure,[37] respectively, as a result of supplementation with various forms of vitamin D. The anticoagulant activity of active vitamin D and its analogs have been shown in cellular experiments. Furthermore, Kasuga et al. found that aortic atherosclerosis is developed in transgenic rats which expressed the vitamin D-25-hydroxylase gene, a model of vitamin D deficiency attributable to continuous degradation of active vitamin D.[38]

The present clinical study was conducted on a small sample by evaluating a limited number of variables; therefore, this might be a preliminary conclusion. It is suggested that future population-based studies be performed with a larger sample size and by measuring a higher number of related

factors to confirm the role of vitamin D in the development of MetS.

Conclusion

In summary, it can be concluded that low 25(OH) D levels in Iranian adults with MetS had no significant relationship with cardiovascular risk factors and ABI. No association was found between the studied variables even after adjustment for age, sex, physical activity, and smoking. To confirm these conclusions, further prospective and mechanistic studies are necessary.

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Conflict of Interests

Authors have no conflict of interests.

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