

Evaluation of the relationship between vitamin D levels and metabolic syndrome components.

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Abstract

Objective: Metabolic Syndrome (MS) is a metabolic disorder with several cardiovascular risk factors such as insulin resistance, impaired glucose tolerance, Diabetes Mellitus (DM), obesity, abdominal fat accumulation, dyslipidemia and hypertension (HT). Recently, excessive emphasis has been put on the relationship between Vitamin D (Vit D) deficiency and MS. However, studies are limited. The aim of this study is to investigate the prevalence of vitamin D deficiency and its association with metabolic syndrome and its components in Turkish women.

Methods: This cross-sectional study was conducted at Ankara Training and Research Hospital Internal Diseases Polyclinic between February 2012 and August 2012. Patients were questioned about the use of medication for HT, DM and dyslipidemia as well as Calcium-Vit D. Blood pressure and anthropometric measurements (height, body weight, waist circumference, and hip circumference) were evaluated. Biochemical parameters related to Metabolic Syndrome such as the levels of fasting plasma glucose (mg/dl), 2-h postprandial blood glucose (mg/dl), fasting insulin, glycated hemoglobin (HbA1c) and 25 (OH) Vit D were studied. Levels of insulin and 25 (OH) Vit D were measured using DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits and Tandem MassSpectrometer (Tandem-MS), respectively. Patients were assessed for MS according to the IDF (International Diabetes Foundation) criteria. Insulin sensitivity was assessed using the HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) method. The data were analyzed using SPSS for Windows 11.5 software package. $p < 0.05$ was considered statistically significant for the results.

Results: The study included 191 adult female cases among patients presenting at the Internal Diseases Polyclinic, who met the inclusion criteria. The mean age of the patients was 47.1 ± 9.8 (22-73) y. There was no statistically significant difference in Vit D levels between the women with and without MS diagnosis based on IDF criteria ($p > 0.05$). The results from the analysis of correlation between fasting blood glucose and Vit D levels were similar ($p = 0.447$, $p = 0.255$). There was a statistically significant correlation between fasting insulin levels, HOMA-IR and HDL ($p < 0.05$). The group with insulin resistance had statistically significantly higher levels of Vit D compared to those without insulin resistance ($p = 0.036$). However, there was not any statistically significant correlation between DM status and Vit D levels ($p > 0.05$). The correlation between TG levels and Vit D levels were similar ($p : 0.299$). Components of the MS that were not associated with serum Vit D levels including waist circumference and blood pressure ($p : 0.259$; $p : 0.621$).

Conclusions: Vitamin D deficiency is prevalent in this Turkish women population. Presence of metabolic syndrome was not associated with presence of vitamin D deficiency. We concluded that long-term and detailed studies with broad case series are required to investigate the relationship between Vit D deficiency and MS components.

Keywords: Metabolic syndrome, Diabetes mellitus, Vitamin D, Insulin.

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Introduction

Metabolic Syndrome (MS) is a metabolic disorder characterized by several cardiovascular risk factors, such as insulin resistance, impaired glucose tolerance, Diabetes Mellitus (DM), obesity, abdominal fat accumulation, dyslipidemia and hypertension [1-3]. The rapidly increasing prevalence of MS and MS components including obesity, dysglycemia, hypertension, and dyslipidemia in recent years has increased the recognition of this disease as a public health issue and the multi-perspective investigation of possible underlying factors. The leading causes of increasing prevalence are advanced age, sedentary lifestyle, unhealthy nutrition and gaining weight both in developed and developing countries [4]. In metabolic syndrome, the complications with high morbidity and mortality can be prevented if the risk factors are known and measures are taken before.

In recent years, the possible relationship between Vitamin D (Vit D) and insulin secretion, peripheral insulin resistance and MS has gained interest. The term Vit D is used for both Vit D2 (ergocalciferol) that is vegetative and VitD3 (cholecalciferol) that can be synthesized endogenously from subcutaneous tissue with ultraviolet lights [5].

Some studies showed that Vit D enables the conversion of proinsulin to insulin using calcium-dependent endopeptidases by stimulating insulin exocytosis through a significant increase in calcium amount as mediated by Vit D receptor (VDR) in the cytosol of the pancreatic beta cells [6-8]. It has a protective effect on beta cells by regulating inflammatory cytokine release with an immunomodulatory effect [9,10]. Vitamin D effects might be directly relevant for growth and differentiation of beta-cells [11]. There is also evidence that Vit D may improve insulin resistance in peripheral tissues such as muscles, liver, and adipose tissue [12]. Some studies reported a high prevalence of Vit D deficiency in patients with Type 1 DM [13-15]. There are many studies which have reported the association between Vitamin D and metabolic syndrome while others have not confirmed this observation [16-21].

As a result, Vit D deficiency results in impaired insulin secretion [6]. Therefore, the present study aimed to examine whether the levels of Vit D has an effect on MS and its components in adult women.

Materials and Methods

The study was approved by the Regional Committee for Medical and Health Research Ethics in our hospital (reference number: 2011/3416).

A written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

This cross-sectional study was conducted at Ankara Training and Research Hospital Internal Diseases Polyclinic between February 2012 and August 2012. The study included patients aged above 18 y. Patients with an impaired general condition, cirrhosis, nephrotic syndrome, hypopituitarism, adrenal

tumors, hypothyroidism, alcoholism, pacemakers, platinum in any part of the body, decompensated heart failure and conditions that might affect anthropometric measurements (acid, pregnancy, orthopedic problems and ect.) were excluded from the study. All patients were questioned about the use of medication for hypertension, DM and dyslipidemia as well as calcium (Ca)-Vit D. Blood pressure and anthropometric measurements (height, body weight, waist circumference and hip circumference) were evaluated. Blood pressure was measured using a mercury sphygmomanometer at the right arm in the erect sitting position after a minimum 5-min rest. For patients with the Korotkoff sounds not heard well, the blood pressure was measured again at both arms and the results were averaged. The height and weight measurements were conducted with shoes taken off and light clothes worn. Body mass index was calculated by dividing weight in kg by the square of height in meters (kg/m^2). Waist circumference was measured in the upright position and by the end of expiration, in parallel to the floor at the middle of lower rib edge and upper iliac spine. Hip circumference was measured at the widest area of the hip. Height, waist and hip circumferences were recorded in cm, while weight was recorded in kg with a single decimal.

A number of biochemical parameters related to metabolic syndrome were requested. Within this scope, the blood samples were taken between 09:00 am and 11:00 am after a minimum of 12-h nightlong fasting. The levels of fasting plasma glucose (FPG) (mg/dl), 2-h postprandial blood glucose (PBG) (mg/dl), fasting insulin, glycated hemoglobin (HbA1c) and 25 (OH) Vit D were studied using fasting blood. The measurements were performed using original Roche Diagnostic's kits in the RocheModuler analyzer at Ankara Training and Research Hospital Central Biochemistry Laboratory. The insulin levels were measured using DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits. The levels of 25 (OH) Vit D were studied using Tandem Mass Spectrometer (Tandem-MS). Patients were evaluated for MS based on and IDF (International Diabetes Federations) criteria specified in the general information part [8]. Insulin sensitivity was assessed using the HOMA-IR (Homeostatic Model Assessment of Insulin Resistance) method. For this purpose, the HOMA values of all cases were calculated using the formula (Fasting serum insulin ($\mu\text{IU}/\text{ml}$) \times Fasting plasma glucose (mg/dl)/405).

Statistical analysis

The data were analyzed using SPSS for Windows version 11.5 software package (SPSS Inc., Chicago, IL, USA). The normality of the continuous variables was analyzed using the Shapiro-Wilk test. Descriptive statistics were expressed in mean \pm standard deviation or median (interquartile range) for continuous variables, and in number of cases for categorical variables. The significance of the difference in mean values between the groups was evaluated by the Student's t test, while the significance of the difference in median values was analyzed by the Mann-Whitney U test when there were two independent groups and by the Kruskal-Wallis test when there were more than two groups. Categorical variables were

evaluated using the Pearson's chi-Square test. The Spearman's correlation test was used to examine whether there was a statistically significant correlation between the continuous variables. A p value of <0.05 was considered statistically significant.

Results

The study included a total of 191 adult females presenting at the internal diseases polyclinic, who met the inclusion criteria. The mean age of the patients was 47.1 ± 9.8 (range: 22 to 73) y. The distribution of patients by Body Mass Index (BMI) revealed that 16 (8.4%) normal-weight women (BMI: 18.5-24.99), 42 (22%) were overweight (BMI: 25-29.99), 113 (59.1%) were obese (BMI: 30-39.99) and 20 (10.5%) were morbid obese (BMI>40.0). The distribution of patients by the levels of Vit D showed that the great majority had low levels of Vit D. Regarding the vitamin D status, 48.7% had a Vit D deficiency, 38.2% a Vit D insufficiency, and 13.1% had sufficient Vit D levels. The distribution of patients by the levels of Vit D is summarized in Table 1.

Table 1. The distribution of patients by the levels of vitamin D.

Vitamin D	n (%)
<20 ng/ml	93 (48.7)
20.0-29.9 ng/ml	73 (38.2)
≥ 30 ng/ml	25 (13.1)

The group that was MS (+) based on the IDF criteria had significantly higher levels of insulin, HOMA-IR and HbA1c (Glycatedhaemoglobin) compared to the MS (-) group (p<0.05) (Table 2). There was no statistically significant difference in Vit D levels between the women with and without MS diagnosis based on the IDF criteria (p>0.05) (Table 3).

Table 2. Demographic and clinic characteristics of the cases by the group with and without metabolic syndrome based on the IDF criteria.

Variables	MS ^{***} (-) (n=49)	MS ^{***} (+) (n=142)	p-value
Insulin (µU/ml)	8.2 ± (4.9)	12.6 ± (7.7)	<0.001 ^a
Homa-IR [*]	2.0 ± (0.9)	3.5 ± (2.0)	<0.001 ^a
HbA1C ^{**} (%)	5.7 ± (0.4)	5.9 ± (0.7)	0.027 ^a

Homa-IR^{*}: Homeostatic model assesment of Insulin Resistance; HbA1C^{**}: Glycatedhaemoglobin; MS^{***}: Metabolic Syndrome; ^aMann Whitney U test.

Table 3. Comparison of the cases with and without metabolic syndrome diagnosis based on the IDF criteria.

MS	Vitamin D (ng/ml)	P-value
No	17.3 ± (16.4)	
Yes	21.3 ± (11.1)	0.061 ^a

^aStudent's t-test.

The Spearman's correlation test was used to evaluate whether there was a significant correlation between the Vit D levels and MS components; the anthropometric measurements (BMI, waist circumference) and laboratory measurements (fasting blood glucose, postprandial blood glucose, HbA1c, fasting insulin levels, insulin resistance and lipid profile) and the systolic-diastolic blood pressure levels. There was a statistically significant correlation between fasting insulin levels, HOMA-IR and HDL (p<0.05). The correlation between TG levels and Vit D levels were similar (p:0.299). Components of the MS that were not associated with serum Vit D levels including waist circumference, fasting blood glucose and blood pressure (p:0.259; p:0.353; p:0.621) (Table 4).

Table 4. The coefficient of correlation between vitamin D levels and anthropometric and laboratory measurements and the levels of significance.

Variables	Correlation coefficient	p-value ^a
Age (y)	0.079	0.284
Mass body index (kg/m ²)	0.089	0.222
Waist circumference (cm)	-0.082	0.259
Hip circumference (cm)	-0.064	0.375
Systolic blood pressure (mmHg)	-0.036	0.621
Diastolic blood pressure (mmHg)	-0.123	0.091
Fasting blood glucose (mg/dl)	0.068	0.353
Postprandial blood glucose (mg/dl)	0.135	0.063
Insulin (µU/ml)	0.153	0.036
HOMA-IR [*]	0.178	0.014
HbA1C ^{**} (%)	0.038	0.602
Total cholesterol (mg/dl)	0.034	0.64
High density lipoprotein (mg/dl)	-0.239	<0.001
Low density lipoprotein (mg/dl)	0.129	0.075
Triglycerides (mg/dl)	0.076	0.299

^aStudent's t-test; Homa-IR^{*}: Homeostatic model assesment of Insulin Resistance; HbA1C^{**}: Glycatedhaemoglobin.

Table 5. Vitamin D levels of cases in terms of insulin resistance and diabetes mellitus status.

Variables	Vitamin D (ng/ml)	p-value
Insulin resistance		
No	18.4 ± (14.3)	0.036 ^a
Yes	21.3 ± (11.0)	
Diabetes mellitus status		
Normoglycemic	18.2 ± (15.3)	0.280 ^b

Impaired fasting glucose	21.2 ± (10.9)
Overt diabetes mellitus	19.0 ± (14.8)

^aStudent's t-test; ^bMann Whitney U-test.

There was no statistically significant difference between insulin resistance and Vit D levels of the patients divided into subgroups according to Vit D deficiency. The study cases were evaluated using Vit D levels in terms of insulin resistance and DM status, and the insulin resistance group had statistically significantly higher levels of Vit D compared to the non-insulin resistance group ($p=0.036$). However, there was not any statistically significant correlation between DM status and Vit D levels ($p>0.05$) (Table 5).

Discussion

In this study, we have investigated the relationship between Vit D levels and metabolic syndrome components. Vit D levels demonstrated relationship with insulin resistance (HOMA-IR) and HDL. The relationship between Vit D and insulin resistance was unexpectedly positive. Vit D correlated significantly and inversely with HDL. We didn't find association between Vit D levels and other metabolic syndrome components.

Today, besides insulin resistance, Type 2 DM and the known risk factors related to MS; different potential risk factors that can be associated with these parameters and thereby that can be treated are under investigation. In recent years, the possible relationship between Vit D and insulin secretion, peripheral insulin resistance and MS has gained interest. Additionally, the conflicting results from various studies contribute to the continuing interest in Vit D [22,23]. For the first time in 1985, Vit D was shown to have a possible regulating effect on hormone synthesis and release from endocrine glands [24]. In 1998, Vit D was reported to be a risk factor for developing glucose intolerance, DM, myocardial infarction and MS (formerly named as Syndrome X) [25]. Stimulating insulin exocytosis by significantly increasing calcium amount as mediated by VDR in the cytosol of the pancreatic beta cells, enabling the conversion of proinsulin to insulin using calcium-dependent endopeptidases and having a protective effect on beta cells by regulating inflammatory cytokine release with an immunomodulatory effect are only a few of the causes of insulin secretion disorder that occurs in the presence of Vit D deficiency [6-8]. Insulin resistance, particularly in the peripheral tissues cause these patients to be faced with developing Type 2 DM and dyslipidemia, and increased cardiovascular risk. This risk profile associated with Vit D deficiency has been investigated in different age groups, different ethnicities and both genders; the relationship between Vit D deficiency and insulin resistance and MS development has been studied. Although previous studies reported some conflicting results, most of them confirmed the relationship between Vit D deficiency and insulin resistance and dyslipidemia development [26-30].

We classified our study patients into two separate groups with and without MS diagnosis based on the IDF criteria and examined whether there was a difference in Vit D levels between the groups. There was not any significant difference in Vit D levels between MS (+) and MS (-) groups ($p>0.05$).

Among study cases, the relationship of Vit D levels with FBG, PBG, HbA1c, fasting insulin levels, HOMA-IR, total cholesterol, HDL, LDL, TG and systolic-diastolic blood pressures was investigated and a statistically significant relationship was found between Vit D levels and HOMA-IR and HDL ($p<0.05$). It was a significant but paradoxical relationship. Although most of the domestic and foreign studies have supported the link between Vit D and insulin resistance, some of the previous studies could not demonstrate a significant association [31-33]. The NHANES (National Health and Nutrition Examination Survey) study, which is accepted as the largest-scale research examining the relationship between Vit D and insulin resistance and DM, compared heterogeneous groups consisted of cases with different ethnicities such as non-Hispanic whites, non-Hispanic blacks and Mexican-Americans, and established high levels of Vit D in non-Hispanic whites, moderate levels in Mexican-Americans and low levels in non-Hispanic blacks. Additionally, a significant and negative relationship was found between Vit D levels and insulin resistance and DM in non-Hispanic whites and Mexican-Americans, and individuals with Vit D deficiency were reported to have an increased prevalence of insulin resistance and DM [34,35]. In the present study, the significant and unexpectedly positive relationship between Vit D levels and insulin resistance can be explained by the Vit D deficiency in almost all of our cases (86.9%), the Vit D metabolism and efficacy varying by ethnicity, similar to the black group in the NHANES III study. Also this significant and positive relationship between Vit D levels and fasting insulin levels and HOMA-IR, which are suggestive of insulin resistance; might be confounded by other independent variables like gynaecological conditions (Polycystic ovarian syndrome (PCOS) or endometriosis), menopausal status and timing of the menstrual cycle which may affect the insulin resistance indices. The significant and negatively relationship between Vit D and HDL can be explained by other confounding factors like physical activity, smoking or dietary style.

After the study cases were divided into two groups as diagnosed and not diagnosed by MS through each one of the MS diagnosis criteria of IDF; waist circumference, blood pressure, TG, HDL and fasting blood glucose, the difference in Vit D levels were examined. There was no significant difference in Vit D levels in terms of waist circumference, blood pressure, TG and fasting blood glucose between MS (+) and MS (-) groups, whereas Vit D levels were significantly different in terms of HDL between MS (+) and MS (-) groups.

In our patient group that can be considered homogeneous with Vit D deficiency in 86.9%. Our finding of deficient levels of vitamin D could be partly explained by the fact that our studied subjects were nearly all overweight and obese as many studies

have shown that low 25 (OH) D levels are associated with obesity in adults [36-39].

In conclusion, not all but, most of several studies evaluating metabolic syndrome and MS-related hypertension, blood glucose, blood lipids together have found blood levels of Vit D associated with aforementioned diseases [40-42]. However, the results indicate that Vit D supplement usually does not contribute to the reduced occurrence of such issues. The findings of many studies suggest that the Vit D levels may be linked with glycemic control in diabetic individuals, but broader studies are required to clearly establish the relationship between glycemic control and Vit D. Further investigations are needed to better understand the role of vitamin D in the occurrence of insulin resistance and MS.

Study Limitations

1. The menopausal status of female patients was not questioned.
2. Physical activity, smoking and dietary style were not questioned.
3. As we could not foresee in our patient group with Vit D deficiency (86.9%), secondary hyperparathyroidism affecting insulin resistance is also a factor with negative effect on the results.

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