Relationship Between Levels of Vitamin D and Metabolic Syndrome Parameters in Patients with Metabolic Syndrome and Healthy Individuals

Metabolik Sendromlu ve Sağlıklı Olgularda Vitamin D Düzeyleri ve Metabolik Sendrom Parametreleri Arasındaki İlişki

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ABSTRACT Objective: Hypovitaminosis D and metabolic syndrome are worldwide common problems. The link between them was unresolved. We planned to define the relation between Vitamin D levels and metabolic syndrome and also their parameters. **Material and Methods:** We evaluated all the demographic and anthropometric parameters of 79 healthy participants and 95 patients with metabolic syndrome and compared those parameters and vitamin D levels. We classified 25(OH)D serum levels; <10ng/mL as serious deficiency, 10-20 ng/mL as deficiency, 20-30 ng/mL insufficiency and > 30 ng/mL as normal status. We searched the correlation of vitamin D levels with metabolic syndrome parameters. We also examined the relation of various Vitamin D levels with demographic and anthropometric findings of metabolic syndrome patients. **Results:** Vitamin D levels were low in all the individuals (12.8 ± 6.7ng/mL in patients and 19.0 ± 10.0ng/mL in controls. p<0.001). In metabolic syndrome patients, serious deficiency was high and normal Vit D status was significantly low especially in females. In metabolic syndrome group vitamin D levels were negatively correlated with body mass index, waist circumference, blood glucose, hemoglobin A1c, fasting insulin, insulin resistance index (p <0.012, <0.040, <0.002, <0.008, <0.006, <0.001 respectively). We found that vitamin D levels of the patients without hypertension, diabetes mellitus, dyslipidemia or obesity were higher than that of the patients with those diseases among metabolic syndrome group (all p<0.001). We also demonstrated as Vitamin D levels decreased, rate of obesity, hypertension and diabetes mellitus increased, (p<.0.029, <0.035 and <0.001 respectively). **Conclusion:** In patients with metabolic syndrome hypovitaminosis D is frequent especially in women. As Vitamin D levels are in negative correlation with obesity, diabetes and insulin resistance indices and also with metabolic syndrome parameters, we concluded that Vitamin D supplementation is important in hypovitaminosis D cases with metabolic syndrome.

Key Words: Metabolic Syndrome; Vitamin D

ÖZET Amaç: Hipovitaminozis D and metabolik sendrom dünya çapında sık görülen problemlerdir. Aralarındaki bağlantı tam olarak çözülmemiştir. Çalışmamızda Vitamin D düzeyleri ile metabolik sendrom ve parametreleri arasındaki ilişkiyi tanımlamayı planladık. **Gereç ve Yöntemler:** 79 sağlıklı kişide ve 95 metabolik sendromlu hastada demografik ve antropometrik parametreler değerlendirildi ve bu parametreler ile Vitamin D seviyeleri kıyaslandı. 25(OH)D serum seviyelerini; <10ng/mL ciddi eksiklik, 10-20 ng/mL eksiklik, 20-30 ng/mL yetersizlik and > 30 ng/mL as normal durum olarak sınıflandırdık. Metabolik sendrom parametreleri ile Vitamin D seviyeleri arasındaki korelasyonu inceledik. Ayrıca farklı Vitamin D seviyeleri ile metabolik sendromlu hastalarda demografik ve antropometrik bulgular arasındaki ilişkiyi araştırdık. **Bulgular:** Vitamin D seviyeleri tüm bireylerde düşüktü (12,8±6,7 ng/mL hastalarda ve 19,0±10,0 ng/mL kontrollerde, p<0.001). Metabolik sendromlu hastalarda ciddi eksiklik yüksek orandaydı ve normal Vitamin D durumu belirgin düşüktü, özellikle kadınlarda. Metabolik sendrom grubunda Vitamin D seviyeleri vücut kitle indeksi, bel çevresi, kan şekeri, hemoglobin A1c, açlık insülini, insülin rezistans indeksi ile negatif korele idi (sırasıyla p <0.012, <0.040, <0.002, <0.008, <0.006, <0.001). Metabolik sendrom grubu içinde hipertansiyon, diabetes mellitus, dislipidemi veya obezitesi olmayan hastalarda bu hastalıkları olanlara göre daha yüksek Vitamin D seviyeleri saptadık (tümü p<0.001). Vitamin D seviyelerinin azaldıkça, obezite, hipertansiyon ve diabetes mellitus oranının arttığını da gösterdik (sırasıyla p<.0.029, <0,035 ve <0,001). **Sonuç:** Metabolik sendromlu hastalarda, özellikle kadınlarda hipovitaminozis D sıktır. Vitamin D seviyeleri obezite, diabetes ve insülin rezistansı indeksleri ve metabolik sendrom ve parametreleri ile negatif ilişki içinde olduğundan Vitamin D tedavisinin metabolik sendrom vakalarında önemli olduğu sonucuna vardık.

Anahtar Kelimeler: Metabolik sendrom; Vitamin D

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Metabolic syndrome (MS) is an important endocrinopathy, characterized by obesity, different stages of glucose intolerance, dyslipidemia and hypertension. The components of the metabolic syndrome are also related with insulin resistance, and endothelial dysfunction. MS is one of major problems of public health all over the world. With at least 20 to 30% prevalence rate among the adult population of most countries, it is considered a pandemic problem.[1,2] In Turkey its prevalence was determined to be 33.9%, in women 39.6%, in men 28%.[3] It has been shown that patients with MS are at twice the risk for cardiovascular diseases (CVD) and they may have the risk of having type 2 diabetes mellitus (T2DM) about 5 fold.[4] Patients with MS are also at 3-4 fold increased risk of myocardial infarction (MI), 2-4 fold increased risk of stroke and 2 fold increased risk of dying from a non-cardiovascular event.[5]

Vitamin D (Vit D) has effects on many physiological processes beyond its role on calcium and bone metabolism. There are studies about vitamin D deficiency being a risk factor for hypertension, type 1 diabetes mellitus (T1DM), T2DM, CVD and various cancers.[6-21] A protective effect of high Vit D against CVD and an inverse association between Vitamin D and cardiovascular risks was also suggested.[22,23]

Keeping in mind the various effects of Vit D on many vital processes we wanted to determine Vit D levels in patients with and without metabolic syndrome, see the difference of various Vit D levels in all groups and evaluate the relation of Vit D levels with metabolic syndrome parameters.

MATERIAL AND METHODS

PATIENTS

A total of 95 patients with metabolic syndrome [56 female (58.9%), 39 male (41.1%)], aged from 25-65 years, were recruited from the Clinic of Ankara Training and Research Hospital from January to April 2013. Seventy nine aged matched normal people [45 female (57.0%), 34 male (43.0%)] examined in outpatient Clinic of Ankara Training and Research Hospital were chosen as the control group, individuals without metabolic syndrome.

Our exclusion criteria were women having doubt of pregnancy, patients having heart failure, active infection, acute or chronic inflammatory disease, uncontrolled hypertension, history of cardiovascular or cerebrovascular event, chronic renal disease, thyroid or parathyroid disease (in history or nowadays). Subjects with chronic diseases of renal and liver, skin disorders, malabsorption, inflammatory bowel or Celiac disease (in history or nowadays), and ones taking medications that may interfere serum levels of Vit D were also excluded.

After detailed physical examination, in all subjects body weight and height were measured. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m^2). Waist circumference was measured when fasting, in standing position halfway between costal edge and iliac crest by a non-elastic measure.

Blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), fasting insulin (FI), serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and hemoglobin A1c (HbA1c), blood urea nitrogen (BUN), creatinine, calcium (Ca), phosphorus (P), thyroid stimulating hormone (TSH), parathyroid hormone (PTH), high sensitivity C-reactive protein (CRP) levels. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol –HDL-TG/5). Another blood sample was taken for postprandial plasma glucose (PPPG) 2 h. after breakfast.

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 minute rest in the semi-sitting position with a sphygmomanometer. Blood pressure was determined at least three times at the right upper arm, and the mean was used in the analysis.

Dyslipidemia (DL) was defined as having hypolipidaemic treatment or presence of TC levels ≥ 200 mg/dl, and/or LDL-C levels ≥ 130 mg/dl, and/or TG levels ≥ 150 mg/dL and/or HDL-C levels ≤ 40 mg/dl for men and ≤ 50 mg/dl for women.[24] We accepted diagnostic criteria of World Health Organ-

TABLE 1: Clinical identification of metabolic syndrome.

Waist circumference	Men	≥ 102 cm
	Women	≥ 88 cm
Triglycerides	≥ 150 mg/d L or using medication	
HDL cholesterol	Men	< 50 mg/dL
	Women	< 40 mg/dL or using medication
Blood pressure	≥ 130 / ≥ 85 mm Hg or using medication	
Fasting glucose	≥ 100 mg/dL or using medication	

isation (WHO) for the diagnosis of diabetes mellitus.[25] The current WHO diagnostic criteria for diabetes was recommended as-fasting plasma glucose ≥ 126 mg/dl or 2-h plasma glucose ≥ 200 mg/dl.

The patients who were taking antihypertensive drugs or patients whose determined mean blood pressure levels ≥ 140/90 mmHg were diagnosed as having hypertension (HT).[26] Obesity was defined as the presence of BMI ≥ 30 kg/m^2).[27] An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μunite / ml) x fasting plasma glucose (mmol/l) / 22.5 formula as homeostasis model assessment- insulin resistance (HOMA-IR). Individuals with HOMA-IR < 2.7 were accepted as without insulin resistance(IR) and HOMA-IR ≥ 2.7 as having IR.[28]

Metabolic syndrome diagnosis was based on the criteria of National Cholesterol Education Program (NCEP)-Adult Treatment Panel III (ATP III) (Table 1).[29] When 3 of 5 of the listed characteristics were present, a diagnosis of metabolic syndrome was made.

This study was performed according to the Helsinki decleration 2008. The local ethics comitee approved this study and all the subjects gave written informed consent.

LABORATORY METHODS

Plasma glucose, total cholesterol, TG, creatinine, Ca, P, albumin and HDL-C concentrations were determined by enzymocalorimetric spectrophotometric method in a Roche/Hitachi molecular PP autoanalyser. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol-HDL-TG/5). FI was measured by means of DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits and HbA1c by TOSOH G7 HPLC system. High sensitivity C-reactive protein (CRP) was measured by immunoflowmetric tests by Beckman-Cutler device, TSH and PTH were determined with Advia Sentor XP device by chemoluminescence method.

As serum concentration of 25-hydroxy vitamin D3 (25(OH)D) is the best indicator of vitamin D status we measured D3 (25(OH)D levels. For the measurements of 25(OH)D, Tandem Gold device liquid chromatography mass spectrometry was used. We classified 25(OH)D serum levels; <10 ng/mL as serious deficiency, 10-20 ng/mL as deficiency, 20-30 ng/mL insufficiency and > 30 ng/mL as normal status.

STATISTICAL ANALYSIS

Calculations were performed using program of NCSS (Number Cruncher Statistical System) 2007& Pass (Power analysis and Sample Size) 2008 Statistical Software (Utah, USA). When evaluating the study data, besides definitive statistical methods (median, Standard deviation etc.) for the comparison of quantitative results, Student-t test was used in comparing normal distributed parameters, Oneway Anova test was used in comparing groups and Tukey HSD test was used to find which group was the cause of the difference. In order to compare the parameters without normal distribution we used Kruskal Wallis test and Mann Whitney U test. Pearson Ki-Square test was also performed for the comparison of qualitative results. Data are presented as mean ± SD. A p value of < 0.05 and $p< 0.01$ was considered as statistically significant.

RESULTS

A total 95 patients with MS and 79 control person without MS were recruited for the study. Our groups were formed as; MS and control. The demographic and laboratory parameters of all the groups and their comparisons were shown in Table 2.

TABLE 2: The demographic and clinical characteristics of the groups.

	MS (n:95)	Control (n:79)	p
Age (year)	53.8 ± 10.4	50.1 ± 12.2	NS
FBG (mg/dL)	128.8 ± 56.1	89.0 ± 7.5	₹0.001
HbA1c (%)	6.9 ± 1.9	5.6 ± 0.5	₹0.01
Creatinine (mg/dL)	0.9 ± 0.1	0.9 ± 0.1	NS
BMI (kg/m2)	31.5 ± 5.4	23.2 ± 2.6	₹0.001
W. circum.(cm)	106.1 ± 13.5	84.3 ± 9.3	₹0.001
T.C (mg/dL)	200.2 ± 32.1	169.2 ± 40.4	₹0.001
LDL-C (mg/dL)	133.5 ± 35.9	114.6 ± 29.5	₹0.001
HDL-C (mg/dL)	48.0 ± 10.6	55.7 ± 10.3	₹0.001
TG (mg/dL)	184.2 ± 85.9	105.8 ± 30.1	₹0.001
SBP (mm/Hg)	135.9 ± 11.2	122.4 ± 22.1	<0.01
DBP(mm/Hg)	87.1 ± 8.1	87.4 ± 13.3	<0.01
Ca (mg/dL)	9.7 ± 0.4	9.7 ± 0.4	NS
P (mg/dL)	3.2 ± 0.5	3.2 ± 0.4	NS
Albumin (g/dL)	4.3 ± 0.3	4.4 ± 0.3	NS
PTH (pg/mL)	48.6 ± 17.1	48.1 ± 19.8	NS
TSH (µIU/ mL)	1.9 ± 1.3	1.8 ± 1.0	NS
CRP (mg/dL)	4.7 ± 3.5	1.4 ± 1.3	<0.001
FI (µU/ ml)	10.2 ± 6.8	7.4 ± 5.3	<0.001
HOMA-IR	3.3 ± 2.7	1.6 ± 1.2	<0.001
Vit D (ng/mL)	12.8 ± 6.7	19.0 ± 10.0	<0.001

MS: Metabolic syndrome, BMI: Body mass index, W. circum: Waist circumference, FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, FI: Fasting insulin, HOMA-IR: Homeostasis model assessment- insulin resistance index, Vit D: Vitamin D. Data are presented as mean ± SD.

When we compared the 2 groups we found that FBG, HbA1c, BMI, waist circumference, TC, LDL-C, TG, SBP, DBP, CRP, FI, HOMA-IR levels of MS group were statistically higher and HDL-C and Vit D levels were statistically lower than the control group.

Then we classified Vit D levels of our groups as < 10 ng/mL, 10-20 ng/mL, 20-30 ng/mL and > 30 ng/mL. We found that in MS group 36 patient (37.9%) had serious deficiency, 44 patient (46.3%) had deficiency, 13 patient (13.7%) had insufficiency and only 2 patient (2.1%) had normal Vit D levels. In control group, 14 person (17.7%) had serious deficiency, 37 person (46.8%) had deficiency, 17 person (21.5%) had insufficiency and 11 person (13.7%) had normal Vit D status. When we compared Vit D levels in MS and control groups, there was a significant difference only in Vit D levels < 10 ng/m L and ≥ 30 ng/mL (p<0.01 both).

In MS patients, serious deficiency was statistically high and normal Vit D status was significantly low. Vit D levels of 10-20 ng/mL and 20-30 ng/mL did not differ in individuls with MS (+) or (-).

When we classified our groups according to their gender we demonstrated that in MS group 56 females had 10.9 ± 5.6 ng/mL and 39 males had 15.4 ± 7.2 ng/mL Vit D levels. In this group Vit D levels of males were statistically higher than those of females (p<0.001). There was not a gender difference in Vit D levels of control group. 45 females had 18.0 ± 9.8 ng/mL and 34 males had 17.0 ± 6.8 ng/mL Vit D levels.

Then we evaluated gender differences according to values of Vit D in the MS group. Among MS group percentage of female patients were higher than males in patients with Vit D levels < 10 ng/mL (20 female -74.1%, 7 male 25.9%) and 10-20 (23 female -57.5%, 17 male 42.5%) ng/mL and percentage of male patients were higher than females in patients with Vit D levels 20-30 ng/mL (10 female -47.6%, 11 male 52.4%) and > 30 ng/mL (3 female -42.9%, 4 male 57.1%).

Then we evaluated characteristics of the patients according to Vit D levels (Table 3).

Statistically significant difference was obtained in BMIs and waist circumferences classified according to Vit D groups. In Vit D < 10 ng/mL and 10-20 ng/mL groups BMI were significantly higher than Vit D > 30 ng/mL group (p=0.006, p=0.045, p <0.05 respectively). In Vit D < 10 ng/mL and 10-20 ng/mL groups waist circumferences were significantly higher than Vit D > 30 ng/mL group (p=0.040, p=0.050, p <0.05 respectively). As Vit D levels were increasing, BMI and waist circumference levels were seen to be significantly decreased.

Statistically significant difference was obtained in SBP and DBP values classified according to Vit D groups. In Vit D < 10 ng/mL and 10-20 ng/mL groups both SBP and DBP values were significantly higher than Vit D > 30 ng/mL group (p=0.006, p=0.045, p <0.05 respectively). As Vit D levels were

TABLE 3: Evaluation of characteristics according to Vit D levels in MS group.

	Vitamin D levels				
	< 10ng/mL	10-20 ng/mL	20-30 ng/mL	> 30 ng/mL	P
BMI (kg/m²)	29.2 ± 6.5	27.7 ± 5.8	27.3 ± 5.4	23.1 ± 4.2	0.012
W.circum (cm)	97.6 ± 16.7	97.2 ± 15.3	96.2 ± 16.3	84.9 ± 14.4	0.040
FBG (mg/dL)	131.2 ± 63.2	105.0 ± 35.3	99.2 ± 25.9	94.5 ± 42.9	0.002
HbA1c (%)	7.2 ± 2.0	6.1 ± 1.3	5.9 ± 0.8	5.2 ± 2.4	0.008
SBP (mm/Hg)	139.9 ± 12.2	136.5 ± 11.2	126.5 ± 10.2	121.4 ± 10.1	0.007
DBP (mm/Hg)	88.1 ± 9.1	86.1 ± 9.0	85.1 ± 8.8	85.4 ± 7.9	0.007
T.C (mg/dL)	199.2 ± 34.6	201.5 ± 55.4	187.3 ± 31.5	199.5 ± 22.7	0.126
LDL-C (mg/dL)	132.5 ± 35.4	122.5 ± 33.9	140.2 ± 22.6	129.0 ± 34.9	0.117
HDL-C (mg/dL)	53.0 ± 10.6	51.5 ± 10.4	49.7 ± 14.1	50.4 ± 9.5	0.626
TG (mg/dL)	164.2 ± 85.6	146.6 ± 77.9	141.6 ± 60.6	117.6 ± 65.1	0.117
FI (µU/ ml)	11.0 ± 6.2	8.4 ± 7.1	7.8 ± 3.3	6.5 ± 4.4	0.006
HOMA-IR	3.5 ± 2.8	2.3 ± 3.0	1.9 ± 0.8	1.6 ± 1.3	0.001

MS: Metabolic syndrome, BMI: Body mass index, W. circum: Waist circumference, FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, TC: Total cholesterol, LDL-C: Low density lipoprotein cholesterol, HDL-C: High density lipoprotein cholesterol, TG: Triglyceride, FI: Fasting insulin, HOMA-IR: Homeostasis model assessment- insulin resistance index, Vit D: Vitamin D. Data are presented as mean ± SD.

increasing, SBP and DBP levels were seen to be significantly decreased.

Statistically significant difference was obtained in FBG and HbA1c levels classified according to Vit D groups ($p < 0.01$ both). FBG levels of the group with Vit D < 10 ng/mL were significantly higher than the groups with Vit D 10-20 ng/mL, 20-30 ng/mL and > 30 ng/mL ($p=0.007$, $p=0.012$, $p=0.044$, $p <0.05$ respectively). As Vit D levels were increasing, FBG levels were seen to be significantly decreased. HbA1c levels of the group with Vit D < 10ng/mL were significantly higher than the groups with Vit D 10-20 ng/mL, 20-30 ng/mL and > 30 ng/mL ($p= 0.011$, $p= 0.022$, $p < 0.05$, $p< 0.05$ respectively). As Vit D levels were increasing, FBG and HbA1c levels were seen to be significantly decreased.

Statistically significant difference was not obtained in T.C, LDL-C, HDL-C and TG levels when MS patients were classified according to Vit D groups ($p <0.05$ all).

Statistically significant difference was obtained in FI and HOMA-IR levels when MS patients were classified according to Vit D groups ($p < 0.01$ both). FI levels of the group with Vit D < 10ng/mL were significantly higher than the groups with Vit D 10-20 ng/mL, 20-30 ng/mL and > 30 ng/mL ($p= 0.002$, $p= 0.048$, $p= 0.008$, $p < 0.05$ respectively). HOMA-IR levels of the group with Vit D < 10 ng/mL were significantly higher than the groups with Vit D 10-20 ng/mL, 20-30 ng/mL and > 30 ng/mL ($p= 0.001$, $p= 0.004$, $p= 0.004$, $p < 0.01$ respectively).

Then we evaluated our MS patients according to their MS parameters and their Vit D levels (Table 4). We found that there was statistically significant difference between Vit D levels of the MS patients when classified according to the presence of HT, DM, dyslipidemia or obesity ($p < 0.01$ all).

TABLE 4: Vit D levels in MS patients evaluated according to MS parameters.

	n (%)	Vit D (ng/mL)	p
Obesity	(+) 78 (82.1%)	13.2 ± 6.6	0.001
	(-) 17 (17.9%)	17.5 ± 9.9	
HT	(+) 70 (73.6%)	12.6 ± 7.0	0.001
	(-) 25 (26.4%)	17.8 ± 9.7	
DM	(+) 74 (77.8%)	12.3 ± 6.4	0.001
	(-) 21 (22.2%)	17.6 ± 9.4	
Dyslipidemia	(+) 78 (82.1%)	12.9 ± 6.8	0.001
	(-) 17 (17.9%)	17.8 ± 9.7	

Vit D: Vitamin D, HT: Hypertension, DM: Diabetes mellitus, MS: Metabolic syndrome. Data are presented as mean ± SD.

TABLE 5: Evaluation of Vit D levels according to MS parameters.

		Vitamin D levels				
		< 10 ng/mL	10-20 ng/mL	20-30 ng/mL	> 30 ng/mL	P
Obesity	(n:78)	27 (34.6 %)	37 (47.4 %)	13 (16.7 %)	1 (1.3 %)	0.029
HT	(n:70)	26 (37.2 %)	34 (48.6 %)	8 (11.4 %)	2 (2.8 %)	0.035
DM	(n:74)	32 (43.3 %)	31 (41.9 %)	10 (13.5 %)	1 (1.3 %)	0.001
Dyslipidemia	(n:78)	28 (35.8 %)	37 (47.5 %)	11 (14.2 %)	2 (2.5 %)	0.068

Vit D: Vitamin D, HT: Hypertension, DM: Diabetes mellitus, MS: Metabolic syndrome. Data are presented as mean ± SD.

Vit D levels of the patients without HT, DM, dyslipidemia or obesity were higher than that of the patients with HT DM, dyslipidemia or obesity.

Afterwards we calculated Vit D levels of MS patients according to MS parameters (Table 5). We demonstrated that as Vit D levels increased, presence of HT decreased ($p < 0.05$). This relationship was also found in DM ($p < 0.01$), and obesity ($p < 0.05$), but not in dyslipidemia.

CONCLUSION

Hypovitaminosis D is common, its prevelance was determined to be 30-50%.[30] In Turkey, hypovitaminosis D rate was 59.4-65.0 %.[31,32] Low levels of Vit D has been implicated in various diseases, including neoplastic, inflammatory, demyelinating, cardiovascular and diabetic ones. Some authors has focused on association between levels of Vit D and MS and found that low serum Vit D concentrations were associated with the development of MS.[33-35] In our study we compared Vit D levels in individulas with and without MS. Vit D concentrations were statistically lower in our patients with MS than individuals without MS. This result was in concordance with previous studies.[36-38]

It was not surprising than in our control group Vit D levels were also low (19 ng/mL). In almost all sudies with normal Turkish individuals vitamin D levels were below normal.[39,40] In a study of ours we found 14.3 ng/mL Vit D levels in controls.[41] Several explanations are possible to describe the reason of such decrease. First the season we had performed our study might affect the levels; we made our examinations between January and April. Second in our small group of Turkish population genetical variations had to be considered. Third, our clothing style may have affected sun exposure. Fourth, limited intake of foods high in Vit D may be another factor. Last, lack of outdoor physical activity due to the season must be considered. In order to properly compare the control patients with the patients according to Vit D levels, multiple centered large scaled studies with individuals having standardized clothing, same seasonal factors, same sunlight exposure time and period, and not having serious differences of socioeconomical life conditions and diet factors are needed.

In the present study, the rate of having Vit D below 10 ng/mL was statistically higher in MS patients than in control group. But there was not a diffence in having Vit D 10-20 ng/mL and 20-30 ng/mL in people with or without MS. The rate of having Vit D above 30 ng/mL was statistically higher in the control group than in patients with MS. The higher portion of patients having Vit D levels below 10 ng/mL in individuals with MS and the higher portion patients having Vit D levels above 30 ng/mL in individuals without MS were expected results and were concordant with previous studies performed on the basis of quantiles of Vit D to ascertain whether the portion of the population with or without MS differed by Vit D status.[37,42]

In MS group, women had statistically lower Vit D levels than men. Also in control group women had lower Vit D levels than men, but this difference was not statistically significant. Several authors demonstrated indifferent gender results in their studies with MS patients.[37,43] Our results can be explained by traditional clothing style of the women where our study was performed. It was

found that in Turkish regions where women wore clothes with covered arms, Vit D levels were lower than the other parts of Turkey.[44] We also got a similar result when we compared quantiles of Vit D in MS group. We found than high number of females had lower Vit D levels such as <10 ng/mL and 10-20 ng/mL than males. Moreover number of male patients were higher than the females who had Vit D levels 20-30 ng/mL and >30 ng/mL.

As Vit D is a fat soluble vitamin, it is sequestered and stored in fat tissues and then slowly released into the circulation. Moreover, obese individuals with less mobility and more cosmetic problems might have less exposure to sunlight, they consume foods having less Vit D. It have also been thought that in obese patients renal 1 alpha hdroxylase activity was increased and there was a passing defect of Vitamin D from the skin into the circulation.[45] In our study in patients with MS, BMI and waist circumference were higher than in individuals without MS. We also showed that as Vit D levels increased BMI and waist circumference values decreased. In Vit D <10ng/mL and 10-20 ng/mL groups BMI and waist circumference were significantly higher than Vit D > 30 ng/mL group. As MS parameters were evaluated one by one, MS patients who were obese had statistically lower Vit D levels than MS patients who were not obese. When we classified our MS patients according to Vit D levels, we demonstrated that as Vit D levels increased, presence of obesity decreased. The findings concerning the relation of obesity defined by body weight, BMI, waist circumference or fat mass with low Vit D levels were supported by various studies.[46-49] It is interesting that there are not strong evidence that restoration of Vit D levels is not likely to have important affect on obesity but may reduce the obesity associated cardiovascular disease.[50,51]

The inverse relationship between levels of Vit D and hypertension has been assessed in several studies.[52-54] It is slightly more clear whether supplementation of Vit D decreases arterial pressure.[55,56] In our study, SBP and DBP levels were higher in individuals with MS than without MS. Moreover both systolic and diastolic blood pressure levels reduced as Vit D levels increased. In patients with MS who had HT, Vit D levels lower than in the patients who did not have HT. We also showed that in MS patients as the levels of Vit D increased both HT rates decreased. Several potential mechanisms implicating Vit D in the regulation of blood pressure have been suggested. Vit D may regulate blood pressure by renin- angiotensin system. The presence of 1-α hydroxylase activity in vascular smooth muscle and endothelial cells as well as vit D receptors in the endothelial cells suggest a direct effcet ofVit D. Hypovitaminosis D may also affect blood pressure by decreasing production of prostacyclin, nitric oxide, increasing sensitivity to vasoconstructors, affecting PTH and IR and may be associated with endothelial dysfunction.[57,58]

Vit D receptor is present in the pancreas. Studies support a role for vit D in both secretion and sensitivity of insulin.[59,60] In a study of ours we demonstrated significantly lower Vit D levels in type 2 DM patients than the controls[41]. Likewise in the present study FBG and HbA1c levels were higher in individuals with MS than without MS. FBG levels of the group with Vit D <10 ng/mL were significantly higher than the groups with Vit D 10-20 ng/mL, 20-30 ng/mL and D > 30 ng/mL. HbA1c levels of the group with Vit D <10 ng/mL were significantly higher than the groups with Vit D 10-20 ng/mL and 20-30 ng/mL. In patients with MS who had DM, Vit D levels lower than in the patients who did not have DM. We also showed that in MS patients as the levels of Vit D increased DM rates decreased. Authors suggested that an increae in Vit D levels could improve both insulin sensitivity and secretion.[61,62]

Insulin resistance has been associated with systemic inflammation, cytokines seem to play a role in β cell dysfunction. Vit D may improve insulin sensitivity and promote β cell surviving by modulating the actions and generations of cytokines.[63] Liu and coworkers found that, compared with the participants in the lowest tertile category of plasma 25(OH)D, those in the highest tertile category had 12.7% lower HOMA-IR score.[64] Ford et al. also demonstrated that vitamin D status was inversely associated with insulin resistance.[37] Similar to those

studies, in our study patients with MS had higher HOMA-IR than control subjects. Among MS group, as Vit D values increased HOMA-IR lessened.

Dyslipidemia and proinflammatory state are main components of MS. It was demonstrated that Vit D status can effect cytokine production and immunity. Vit D inhibits proinflammatory cytokines such as interleukin-1,2,6, tumor necrosis factor α.[65] Although low Vit D levels have been demonstrated in patients with dyslipidemia there is little evidence suggesting a possible mechanism by which Vit D status can effect the development of dyslipidemia.[66] In the present study in MS group, TC, LDL-C, and TG levels were higher and HDL-C levels were statistically lower than the control group, where Vit D levels were lower than the control group. Statistically significant difference was not obtained in T.C, LDL-C, HDL-C and TG levels when MS patients were classified according to Vit D groups. As Vit D levels lessened lipid levels did not changed. Then we evaluated our MS patients according to their MS parameters and their Vit D levels, we found that there was statistically significant difference between Vit D levels of the MS patients when classified according to the presence dyslipidemia. Vit D levels of the patients without dyslipidemia were higher than that of the patients with dyslipidemia. When we calculated Vit D levels of MS patients according to MS parameters, we demonstrated that as Vit D levels increased, presence of dyslipidemia decreased. Like our study there are conflicting results about the relationship of hypovitaminosis D and levels of TC, LDL-C, HDL-C, TG and apoliporotein A-1 and the effect of Vit D supplementation on lipid levels.[36,67,68] Further large studies are needed.

There are a few limitations of this study. One is the moderate sample size. Second, laboratory values evaluated in this study represents only one point in time. Third, we performed the study in winter season, it is obvious that seasonal variations could have influenced the results. Fourth, some of our patients were having statins. Interestingly it was shown that this class of hyperlipemic treatment increased Vit D levels. As this drug group might have effected Vit D levels, a new study is now being planned with patients who will not receive statins. Fifth, the gold standard for the measurement of insulin sensitivity is the use of the euglycemic clamp; we demonstrated insulin resistance by an indirect method; HOMA-IR. Sixth, although the effect of Vit D supplementation on MS parameters were controversial we did not have the chance of practicing all MS components after Vit D was given. Finally, the findings are limited to our groups, which included only adults from our district, so our results may not be applicable to all our country or other nationalities.

In conclusion we demonstrated that Vit D levels were associated with MS and all its components especially in women. There is also an a strong inverse relationship between Vit D levels and HT, DM, obesity and a weak inverse relationship between Vit D levels and dyslipidemia in a group of Turkish population. As considering these relationship and low Vit D levels both in Turkish individuals with and without MS, Vit D supplementation must be considered more seriously in Turkey.

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Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Design: *Nuray Evrin, Eray Atalay, Gül Gürsoy;* ***Analysis and interpretation of the data:*** *Nuray Evrin, Eray Atalay, Gül Gürsoy, Murat Bayram, Reyhan Bilici Salman;* ***Final approval of the article:*** *Nuray Evrin, Gül Gürsoy,Eray Atalay;* ***Statistical expertise:*** *Eray Atalay;* ***Collection of data:*** *Nuray Evrin, Murat Bayram, Reyhan Bilici Salman.*

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