Relation of Obesity with Serum 25 Hydroxy-Vitamin D3 Levels in Type 2 Diabetic Patients

Tip 2 Diyabetik Hastalarda Obezite ile Serum 25 Hidroksi Vitamin D3 İlişkisi

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ABSTRACT Objective: Hypovitaminosis D is associated with diabetes mellitus. Aim of our study was to determine the relation of obesity with 25 hydroxy-vitamin D3 levels in type 2 diabetic patients. **Material and Methods:** We examined obesity, glucose, lipid parameters, calcium, phosporous, parathyroid hormone, insulin resistance indices, thyroid stimulating hormone, homocysteine, C-reactive protein, insulin, vitamin D levels and blood pressure of 101 type 2 diabetic patients and made correlation analysis in all parameters. Then we classified our diabetics according to their body mass indices and compared their 25 hydroxy-vitamin D3 levels. **Results:** We found negative correlation between 25 hydroxy-vitamin D3 levels and body mass index (p:<0.001, r:-0.23). 25 hydroxy-vitamin D3 levels of our patients were low. When we classified our diabetics according to their body mass indices as normal, overweight and obese, and compared their 25 hydroxy-vitamin D3 levels, we determined that in every body mass index groups 25 hydroxy-vitamin D3 levels were not found to be significantly different. **Conclusion:** These results suggest that at least in a Turkish population with type 2 diabetes mellitus 25 hydroxy-vitamin D3 levels are low and these levels correlate with body mass index. But when vitamin D levels are so low, as obesity gets worse 25 hydroxy-vitamin D3 levels does not lessen.

Key Words: Diabetes mellitus, type 2; obesity; vitamin D

ÖZET Amaç: Hipovitaminozis D diabetes mellitus ile ilişkilidir. Çalışmamızın amacı tip 2 diabetes mellitus hastalarında obezite ve 25 hidroksi vitamin D3 düzeylerinin ilişkisini belirlemektir. **Gereç ve Yöntemler:** Yüz bir tip 2 diyabetik hastada obezite ile ilgili parametreleri, glikoz, lipid parametreleri, kalsiyum, fosfor, parathormon, insulin rezistansı indeksi, tiroid stimüle edici hormon, homosistein, C- reaktif protein, insülin, 25 hidroksi vitamin D3 düzeylerini ve kan basıncını inceledik ve korelasyon analizi yaptık. Daha sonra diyabetikleri beden kitle indekslerine göre sınıflandırdık ve 25 hidroksi vitamin D3 seviyelerini kıyasladık. **Bulgular:** 25 hidroksi vitamin D3 ve vücut kitle indeksi arasında negatif korelasyon bulduk (p:<0,001, r:-0,23). Hastalarımızda 25 hidroksi vitamin D3 seviyeleri düşüktü. Diyabetikleri beden kitle indekslerine göre normal, fazla kilolu ve obez olarak sınıflandırıp 25 hidroksi vitamin D3 seviyelerini kıyasladığımızda tüm beden kitle indeksi gruplarında 25 hidroksi vitamin D3 seviyelerinin istatistiksel olarak farklı olmadığını bulduk. **Sonuç:** Bu sonuçlar en azından tip 2 diabetes mellitusu olan bizim çalıştığımız Türk popülasyonunda 25 hidroksi vitamin D3 seviyelerinin düşük olduğunu ve beden kitle indeksi ile negatif korelasyon gösterdiğini ama, 25 hidroksi vitamin D3 seviyeleri bu kadar düşük olduğunda obezite arttıkça vitamin seviyelerinin daha fazla düşmediğini gösterdi.

Anahtar Kelimeler: Diabetes mellitus, tip 2; obezite; vitamin D

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Hyperglycemia was shown to be independently associated with low vitamin D levels.[1] The relationship between vitamin D deficiency and risk of diabetes both type 1 and type 2 has also been reported in the literature.[2-10]

A high prevalence of hipovitaminosis D was noted in diabetics.[11-16] One of the reasons for this is stated to be obesity besides diet, lack of sun exposure, renal impairment and genetic predisposition. Studies have suggested that vitamin D insufficiency is associated with increased obesity.[17-26]

It has been shown that in Turkey vitamin D deficiency is an important problem.[27-30] There have been rare studies about obesity and vitamin D levels in Turkish population. Aim of this study was to show the relation of obesity with vitamin D levels in type 2 diabetic patients.[26,27,31]

MATERIAL AND METHODS

PATIENTS

A total of 101 T2DM patients, aged from 30-80 years, were recruited from the outpatient Clinic of Ankara Training and Research Hospital from January 2011 to February 2012. Sixty one of them were female (60%), 40 of them were male (40%).

We excluded patients 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 25 hydroxy vitamin D3 (25(OH)D3) such as steroids, antiepileptics, orlistat, ketoconazole.

After detailed physical examination, we measured body weight and height of all the patients. Waist was measured when fasting, in standing position halfway between costal edge and iliac crest, whereas hip was measured at the greatest circumference around the buttocks, by a non elastic measure. We calculated body mass index (BMI) as weight in kilograms divided by the square of height in meters (kg/m^2).

Blood was withdrawn after 12 hour of overnight fasting, at 08.30 a.m. for fasting plasma glucose (FPG), hemoglobin A1c (HbA1c), fasting insulin (FI), serum total (Total-C) and HDL cholesterol (HDL-C), triglyceride (TG), creatinine, calcium (Ca), phosporous (P), parathyroid hormone (PTH), thyroid stimulating hormone (TSH), C-reactive protein (CRP), homocysteine (Hcy), and 25(OH)D3 levels.

An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μ unite/mL) x fasting plasma glucose (mmol/l) /22.5 formula as homeostasis model assessment-insulin resistance (HOMA-IR).

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

LABORATORY METHODS

Plasma glucose, Total-C, TG and HDL-C, Ca, P 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).[32] Insulin was measured by means of DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits and FI was measured by TOSOH G7 HPLC system. HbA1c level was determined by TOSOH G7 HPLC system. PTH and TSH were determined with Advia Sentor XP device by chemoluminescence method. High sensitivity C-reactive protein (hs-CRP) was measured by immunoflowmetric tests by Beckman-Cutler device. Hcy concentrations were determined according to the method of HPLC using Agilend 1100 device. For the measurements of 25(OH)D3, Waters LC-MS/MS device liquid chromatography mass spectrometry was used.

METHODS

We made correlation analysis between parameters in type 2 diabetics, then made the comparison of 25(OH)D3 levels in three BMI groups. We grouped the patients as normal (BMI <25 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obese (BMI >30 kg/m^2).

This study was performed according to the Helsinki decleration 2008. The local ethics commi-

tee approved this study and all the subjects gave written informed consent .

STATISTICAL ANALYSIS

Correlation between variables was calculated by Pearson correlation analysis. For the comparison of the groups ANOVA test was used. Data are presented as mean±SD. A p value of <0.05 was considered as statistically significant.

RESULTS

We performed the study with 101 T2DM patients. All the demographic and laboratory findings of the patients were presented in Table 1.

When we made correlation analysis in diabetic patients we found positive correlations between 25OHD3 and creatinin (p:<0.05, r:0.18) and negative correlations between 25OHD3 and BMI (p:<0.001, r:-0.23), HbA1c (p:<0.05, r:-0.21), FI (p:<0.05, r:-0.01), HOMA-IR (p:<0.05, r:-0.20), PTH levels (p:<0.05, r:-0.18).

After we classified our T2DM patients according to their BMI's, as normal (BMI<25 kg/m^2), overweight (BMI 25-29.9 kg/m^2) and obese (BMI >30 kg/m^2) and compared their vitamin D levels. We did not notice any statistically significant difference in 25(OH)D3 levels of the patients according to their BMI's (Table 2).

DISCUSSION

Vitamin D status is best assessed by serum 25(OH)D3 than 1.25 dihydroxy vitamin D3 (1.25$(OH)_2$D3), because 1.25$(OH)_2$D3 has a short half life of 15 hours and serum concentrations are closely regulated by PTH, Ca and P.[33] Some variation exits related to cut-off values for insufficiency and deficiency due to differences in assay methods and population variations. Normal 25(OH)D3 levels should be 30 to 60 ng/mL.[33] Vitamin D insufficiency has been reported to range from levels of 16 to 30 ng/mL.[34] Vitamin D deficiency varies from <11 to <20 ng/mL, but is generally defined as levels of <15 ng/ mL.[35-37] Whatever value is accepted, it is evident that our diabetics has low values of vitamin D, either totally or when classified according to their BMI's. These results are relevant to those of the studies about diabetes mellitus and decreased serum vitamin D levels.[11-16]

TABLE 1: Demographic and laboratory findings of type 2 diabetic patients.

Findings	T2DM n: 101
Age (year)	55.8±7.5
BMI (kg/m^2)	29.8± 4.1
Waist Circumference (cm)	97.4±10.6
Hip Circumference (cm)	105.6±9.5
FBG (mg/dL)	172.1±68.6
HbA1c (%)	8.2±2.1
FI (µU/mL)	13.0±6.4
HOMA-IR	5.4±3.6
LDL-C (mg/dL)	127.7±38.4
HDL-C (mg/dL)	44.8±10.0
TG (mg/dL)	202.9±23.5
Creatinine (mg/dL)	1.0±0.04
Ca (mg/dL)	9.4±0.3
P (mg/dL)	3.3±0.4
PTH (pg/mL)	53.6±25.2
TSH (µIU/MI)	1.6±1.0
hs-CRP (mg/dL)	8.4±5.3
Hcy (µmol/mL)	11.2±6.2
SBP (mm Hg)	140.1±10.1
DBP (mm Hg)	92.6±11.5
25(OH)D3 (ng/mL)	9.9±7.6

BMI: Body mass index; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; FI: Fasting insulin; HOMA-IR: Homeostasis model assesment index-insulin resistance; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; Ca: Calcium; P: Phosphorous; PTH: Parathyroid hormone; TSH: Thyroid stimulating hormone; hs-CRP: C-reactive protein; Hcy: Homocysteine; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; 25(OH)D3: 25-hydroxy vitamin D3. Data are presented as mean±SD. NS: Nonsignificant.

TABLE 2: Comparison of 25(OH)D3 levels of T2DM patients according to their body mass indices.

BMI	Number of patients	25(OH)D3 Levels
Normal	16	13.1±12.7
Overweight	41	8.5±4.7
Obese	44	10.5±5.9
p	NS	

BMI: Body mass index; 25(OH)D3: 25-hydroxy vitamin D3; Normal: BMI <25 kg/m^2; Overweight: BMI 25-29.9 kg/m^2; Obese: BMI >30 kg/m^2. Data were presented as mean±SD. NS: Nonsignificant.

People with diabetes are at significant risk for vitamin D insufficiency or deficiency. Reasons for this include limited intake of foods high in vitamin D, less sun exposure due to possible fatigue, obesity or mobility issues- renal impairment, that results in less biologically active vitamin D, since conversion to the active form occurs in the kidneys and genetic predisposition such as polymorphisms of vitamin D binding protein or polymorphisms of CYP2R1 gene (which is necessary to catalyze the formation of the main circulating vitamin D metabolite).[38] The last reason may be obesity. More vitamin D is stored in the fatty tissues and less is biologically active in the serum. Obesity is also associated with inflammation and low vitamin D levels are related to inflammation. Cytokines and other inflammatory agents have been linked to beta cell damage which then impaires insulin synthesis and secretion. In studies with diabetic mice high doses of 1.25(OH)D3 have been shown to delay the onset of diabetes.[39] This active form has been shown to protect beta cell function caused by inflammatory cytokines; interleukine-6 and tumor necrosis factor-alpha.[40] Regardless of the possible underlying mechanisms about the relation of vitamin D3 with obesity, it is relevant to take into account obesity when dealing with low vitamin D3 levels in diabetes. In our study according to correlation analysis we found that vitamin D3 levels were negatively correlated with BMI.

Hypönen and Power showed that in their normal, overweight, obese and severely obese subjects serum 25(OH)D3 levels decreased with increasing BMI.[14] Al-Daghri et al. also determined that BMI was a significant predictor of 25(OH)D3.[41] Barchetta et al. when classified their patients according to serum 25(OH)D3 quartiles, found increasing BMI and waist circumference results, in accordance with decreasing vitamin D3 levels.[42] Finding a negative correlation between vitamin D3 levels and body mass indices of our patients we hoped to find statistically significant difference in 25(OH)D3 levels of our normal, overweight and obese diabetic groups. However we could not be able to demonstrate any difference in 25(OH)D3 levels of our patients according to their BMI's. Relatively small sizes of our groups may be a reason. We are also curious that once vitamin D3 levels are so low, whether there may not be a statistical difference in their levels while patients are put into varying BMI groups.

Present study has some limitations. First, we carried out our study between January and February. Because the primary source of this vitamin is through skin production and seasonal variations in vitamin D status is well known we plan to reperform this study in summer. Second, in our type 2 diabetic patients therapy modalities were not mentioned. Third, enlargement of sizes of the groups are needed. Fourth, as our examination is a cross-sectional one and we randomized our patients from a part of capital city we cannot apply our results to all the Turkish population.

In conclusion, grave vitamin D3 levels were present in type 2 diabetic patients in Turkey. A negative correlation was determined in vitamin D3 levels and body mass index, but as vitamin D3 deficiency was so low, 25(OH)D3 levels did not worsen as obesity increased.

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