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

Tip 2 Diyabetik Hastalarda 25 Hidroksi Vitamin D3 Seviyeleri ile Nefropati Arasındaki İlişki

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ABSTRACT Objective: Recent evidence suggests that vitamin D and calcium status may also be important for a variety of nonskeletal outcome. Vitamin D has long been suspected to be related with type 1 and type 2 diabetes mellitus and also with macro and microvascular diabetic complications. Aim of our study was to test the hypothesis of an association between hypovitaminosis D and diabetic nephropathy in type 2 diabetic patients. **Material and Methods:** We studied 101 type 2 diabetic patients. We classified our diabetics as they were with or without nepropathy. After their physical examination, their blood were withdrawn, obesity and insulin resistance indices were measured. Then all parameters of the groups were compared including 25 hidroxy vitamin D3 levels and correlation analysis was made. **Results:** In diabetic group with nephropathy fasting blood glucose and HbA1c levels were significantly higher than the diabetic group without nephropathy. Both in diabetic groups with and without nephropathy 25 hydroxy vitamin D levels were not found to be significantly different. Neither positive nor negative correlations were obtained between any of the parameters. **Conclusion:** These results suggests that at least in a Turkish population with type 2 diabetes mellitus vitamin D levels are not associated with nephropathy. As vitamin D levels of diabetics were very low, either in patients with or without nephropathy, we recommend vitamin D supplementation in diabetics in Turkey.

Key Words: Diabetes mellitus, type 2; vitamin D; diabetic nephropathies

ÖZET Amaç: Vitamin D ve kalsiyumun bir grup iskelet dışı olayda önemli olduğu konusunda deliller artmaktadır. Vitamin D'nin tip 1- tip 2 diyabetes mellitus ve makro-mikrovasküler diyabetik komplikasyonlar ile ilişkili olduğundan uzun zamandır şüphelenilmektedir. Çalışmamızın amacı, tip 2 diyabetik hastalarda hipovitaminozis D ile diyabetik nefropati ilişkisini araştırmaktır. **Gereç ve Yöntemler:** Yüz bir tip 2 diyabetik hastayı inceledik. Tüm diyabetik hastalarımızı nefropatisiz ve nefropatili olarak sınıflandırdık. Fizik muayenelerinden sonra hastaların kanları alındı, obezite ve insülin rezistans indeksleri hesaplandı. Daha sonra her iki grubun 25 hidroksi vitamin D3 seviyeleri de dahil olmak üzere tüm parametreleri kıyaslandı ve korelasyon analizi yapıldı. **Bulgular:** Nefropatili diyabetik grupta açlık kan şekeri ve HbA1c seviyeleri nefropatisiz diyabetik gruptan belirgin olarak yüksek bulundu. Nefropatisiz ve nefropatili diyabetik hastalarımızda 25 hidroksi vitamin D seviyelerini istatistiksel olarak farklı bulmadık. Korelasyon analizinde hiçbir parametre arasında korelasyon saptanmadı. **Sonuç:** Bu sonuçlar en azından küçük bir Türk tip 2 diabetes mellitus popülasyonunda vitamin D seviyeleri ile nefropatinin ilişkisi olmadığını düşündürdü. Hem nefropatili hem de nefropatisiz diyabetik hastalarda vitamin D seviyeleri çok düşük saptandığından, Türkiye'de diyabetik hastalara vitamin D tedavisinin eklenmesini tavsiye ediyoruz.

Anahtar Kelimeler: Diabetes mellitus, tip 2; vitamin D; diyabetik nefropati

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The major and most well-known function of vitamin D is to maintain calcium (Ca) and phosphorus (P) homeostasis and promote bone mineralization. However recent evidence suggests that vitamin D and Ca

status may also be important for a variety of nonskeletal outcome including neuromuscular function, psoriasis, multiple sclerosis, demantia and cancers.[1-6] Vitamin D also has long been suspected as a risk factor in type 1 and type 2 diabetes mellitus (T2DM).[7-13] Studies have investigated the relationship of vitamin D concentration with macro and microvascular diabetic complications. Authors suggested that low levels of vitamin D were associated with a greater risk of cardiovascular disease and correction of vitamin D deficiency may be important for prevention of cardiovascular disease.[14-17] There were rare studies about the relation of vitamin D with diabetic neuropathy and retinopathy.[18-23]

Renal insufficency is also one of unfortunate complications of living with diabetes mellitus. As there were rare studies about levels of vitamin D and diabetic nephropathy, in our study we planned to compare the levels 25 hydroxy vitamin D [25(OH)D3] in our type 2 diabetic patients who were with or without nephropathy.

MATERIAL AND METHODS

PATIENTS

For our cross-sectional study a total of type 2 diabetics, 33 with nephropathy and 68 without nephropathy, aged from 30-80 years, were randomly recruited from the outpatient Clinic of Ankara Training and Research Hospital from January 2011 to February 2011.

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 25(OH)D3 were excluded.

After detailed physical examination, in all subjects body weight and height were measured. Waist circumference was measured when fasting, in standing position halfway between costal edge and iliac crest, whereas hip circumference was measured at the greatest circumference around the buttocks, by a non elastic measure. Body mass index (BMI) was calculated 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), creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), calcium (Ca), phosphorus (P), parathyroid hormone (PTH), thyroid stimulating hormone (TSH), fasting insulin (FI), serum total and HDL cholesterol (HDL-C), triglyceride (TG), and 25 hydroxy vitamin D [25(OH)D3] levels.

An indirect measure of insulin resistance was calculated from the fasting plasma insulin (μunite /mL)xfasting plasma glucose (mmol/l)/22.5 formula as homeostasis model assessment-insulin resistance (HOMA-IR).[24]

Systolic and diastolic blood pressure (SBP and DBP) were measured after a 5 min 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.

Diabetic nephropathy was defined as urinary albumin to creatinine ratio ≥30 mg/g in a random spot urine sample.

LABORATORY METHODS

Plasma glucose, creatinine, AST, ALT, Ca, P, albumin, total cholesterol, TG 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). Insulin was measured by means of DRG Diagnostics (DRG Instruments GmbH, Germany) ELISA kits and FI was measured by TOSOH G7 HPLC system. HbA1c was measured by turbidometric inhibition immunoassay in otoanalyser. PTH and TSH were determined with Advia Sentor XP device by chemoluminescence method. For the measurements of 25(OH)D3, Waters LC-MS/MS device liquid chromatography mass spectrometry was used. Microalbuminuria was determined with nepholometric method.

STATISTICAL ANALYSIS

Calculations were performed using SPSS version 10.1. Student's t-test was used to compare the

groups in a parametric way (for data showing homogenous dispersion) and Mann Whitney U test was used in a non-parametric way (for data showing non-homogenous dispersion). Pearson correlation coefficient was used for the correlation analysis. Data are presented as mean±SD. A p value of <0.05 was considered as statistically significant.

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.

RESULTS

Out of 101 type 2 diabetic patients 61 of them were female (61%), 40 of them were male (29%). All the demographic and laboratory findings of diabetic patients with and without nephropathy were compared and illustrated in Table 1. We found that FBG and HbA1c levels of T2DM patients with nephropathy were significantly higher compared to T2DM patients without nephropathy (p <0.02 and <0.001 respectively). In two groups we did not observe any difference in other parameters including 25(OH)D3 levels (Table 1).

Then we made the correlation analysis among the paremeters in diabetic patients with and without nephropathy. Neither negative nor positive correlations were obtained among all the parameters.

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

	Nephropathy (+) n: 33	Nephropathy (-) n: 68	p
Age (year)	49.6±7.8	55.4±7.3	NS
BMI (kg/m^2)	30.4±4.7	29.5±3.8	NS
Waist cir. (cm)	96.8±10.1	98.4±10.9	NS
Hip Cir.(cm)	106.5±9.5	100.5±10.5	NS
FBG (mg/dL)	**193.0±67.4**	**161.5±67.1**	**<0.02**
HbA1c (%)	**9.8±2.3**	**7.4±1.5**	**<0.001**
FI (µU/mL)	11.5±5.6	13.7±6.6	NS
HOMA-IR	5.5±4.2	5.3±3.4	NS
Creat. (mg/dL)	0.9±0.1	0.8±0.1	NS
CRP (mg/dl)	9.7±5.7	7.7±6.7	NS
Hcy (µmol/ ml)	10.8±4.0	11.4±7.0	NS
SBP (mm Hg)	130.0±10.1	124.0±10.5	NS
DBP (mm Hg)	99.6±12.5	89.8±9.3	NS
LDL-C (mg/dL)	126.7±36.5	121.5±39.6	NS
HDL-C (mg/dL)	44.7±8.4	44.8±10.8	NS
TG (mg/dL)	190.9±96.0	209.1±135.4	NS
AST(U/L)	20.9±5.9	23.4±6.4	NS
ALT(U/L)	23.4±9.5	25.5±9.8	NS
Ca (mg/dL)	9.2±0.2	9.3±0.2	NS
P (mg/dL)	3.3±0.4	3.3±0.4	NS
PTH (pg/mL)	54.1±21.9	53.4±24.0	NS
TSH (µIU/Ml)	1.4±0.8	1.7±1.0	NS
Albumin (g/dL)	4.2±0.2	4.3±0.2	NS
25(OH)D3 (ng/mL)	9.0±6.3	10.3±8.2	NS

BMI: Body mass index; Waist cir: Waist circumference; Hip cir: Hip circumference; FBG: Fasting blood glucose; HbA1c: Hemoglobin A1c; FI: Fasting insulin; HOMA-IR: Homeostasis model assesment -insulin resistance; Creat.: Creatinine; CRP: C-reactive protein; Hcy: Homocysteine; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low density lipoprotein cholesterol; HDL-C: High density lipoprotein cholesterol; TG: Triglyceride; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; Ca: Calcium; P: Phosphorus; PTH: Parathyroid hormone; TSH: Thyroid stimulating hormone; 25(OH)D3: 25-hydroxy vitamin D. Data are presented as mean±SD. NS: non-significant.

DISCUSSION

A high prevalence of hipovitaminosis D was noted in diabetics.[14,25-30] Hypovitaminosis D was defined as serum 25(OH)D3 concentration <20 ng/mL.[12,31,32] As serum concentration of 25(OH)D3 is the best indicator of vitamin D status, not 1,25(OH)D2, we examined the levels of 25(OH)D3. All our type 2 diabetic patients had very low vitamin D levels consistent with previous studies.[2]

The last step in the activation of vitamin D, the hydroxylation on carbon 1, takes place mainly in the kidney. Extrarenal sites having 1alpha-hydroxylase activity have also been demonstrated.[2,3] The hormonally active form of vitamin D mediates its biological effects by binding to the vitamin D receptor, which then translocates to the nuclei of the cell and binds to specific DNA sites to modify the expression of target genes.[2] Although the endocrine effects of vitamin D are widely recognized, somewhat less appreciated is that vitamin D may serve paracrine functions and thus maintain immunity, vascular function, cardiomyocyte health, and abrogate inflammation and insulin resistance.[31,33-41] In the kidney, vitamin D may be important for maintaining podocyte health, preventing epithelial-to-mesenchymal transformation, and suppressing

renin-angiotensin-aldosterone system inhibition and inflammation.[42-47]

Decreased levels of 25(OH)D3 have been reported in patients with diabetic nephropathy.[48-50] Although 25(OH)D3 levels of both our type 2 diabetic patients were low, we could not be able to demonstrate lower vitamin D levels in individuals with nepropathy than individuals without nephropahy. We think that, so low vitamin D levels encountered in both groups may explain the indifference.

The renin-angiotensin system (RAS) is a major mediator of progressive renal injury in diabetic nephropathy, and RAS inhibitors have been used as the mainstay treatment. One major problem limiting the efficacy of the RAS inhibitors is the compensatory renin increase caused by disruption of renin feedback inhibition. Vitamin D negatively regulates the RAS by suppressing renin expression and thus plays a renoprotective role in diabetic nephropathy.[45,51,52] Replacement with pharmacologic dosages of vitamin D receptor agonists (VDRA) have also been used to reduce albuminuria, abrogate glomerulosclerosis, glomerulomegaly, and glomerular inflammation and prevent tubulointerstitial fibrosis and prevent the progression of kidney failure.[53,54] In order to ascertain whether vitamin D or VDRA may be used in diabetic nephropathy randomized, controlled trials are needed. We did not have the chance of compairing different treatment modalities in our patients with T2DM, but we are planning to continue to study our patients with vitamin D supplementation.

In our nephropathic patients compared to non-nephropathic ones, FBG and HbA1c levels were statistically high. In those patients with diabetic regulation not so well, obesity, lipid and insulin resistance indices were not different. Also PTH levels did not significantly differ in two groups. It may be thought that although the presence of nephropathy may promote lower vitamin D levels, in order to talk about low vitamin D levels in nepropathic patients other parameters mentioned must have been present too. The smaller size of our patient groups may be another reason.

Our study has some limitations. First, because it is a cross-sectional study we cannot be certain that indifferent vitamin D levels in our patients with and without nephropathy affect all the Turkish population. Second, we performed this study in winter season, when sun exposure was limited. This may explain why we determined so low vitamin D levels in both groups. Third, our subject number of the groups were small. Fourth, we did not mention the therapy the patients received for their diabetic nephropathy, such as medical treatment, hemodialysis or peritoneal dialysis. Last, we did not have the chance of studying the role of supplementation of vitamin D on nephropathy.

In conclusion, we found that in type 2 diabetics at least in a small Turkish population, the presence of nephropathy did not affect levels of vitamin D. As vitamin D levels of diabetics were very low, both in patients with and without nephropathy, we recommend vitamin D supplementation in diabetics in Turkey.

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