ORIGINAL RESEARCH

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The Possible Effect of Vitamin D on Uric Acid Levels in Diabetic Patients

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ABSTRACT Objective: Low serum levels of Vitamin D and hyperuricemis may be associated with various problems including diabetes mellitus and cardiovascular disease. The connection of serum uric acid levels and cardiovascular events, and also diabetes mellitus has been debated for decades. There have been evidence that both Vitamin D and uric acid levels are related. In this study we aimed to investigate the relation between serum vitamin D and uric acid levels in patients with type 2 diabetes mellitus. **Material and Methods:** We evaluated 100 patients who were diagnosed as type 2 diabetes mellitus at least 1 year ago. Patients were divided into two groups of fifty patients with serum 25 hydroxy vitamin D levels below and above 20 ng/ ml. After evaluating the biochemical and anthropometric parameters of the groups, we compared them. We also searched correlation of Vitamin D with uric acid levels. **Results:** In patients with deficient Vitamin D levels, fasting blood glucose (164.6 ± 62.3 and 141.0 ± 38.6 respectively, $p<0.022$), body mass index (31.3 ± 4.2 and 27.5 ± 3.6 respectively, $p<0.001$) and uric acid levels 6.8 ± 1.0 and 4.6 ± 0.8 respectively, $p<0.001$) were higher than in diabetic patients with non-deficient Vitamin D levels. We also demonstrated a negative correlation between Vitamin D and uric acid levels (r: 0.488, $p<0.001$). **Conclusion:** Potential cardiovascular risk factors such as Vitamin D and uric acid are inversely related to each other. Diabetic patients who have low Vitamin D levels, have also high levels of serum fasting blood glucose and body mass index. These findings may imply that treatment of Vitamin D deficiency in diabetic patients may help the regulation of diabetes and obesity and reduction in uric acid levels and may may lessen cardiovascular events in diabetic patients.

Keywords: Diabetes mellitus; Vitamin D; uric acid

The essential role of Vitamin D (Vit D) in bone and calcium metabolism is well known.[1] Besides, it is clear that Vit D has additional physiological functions. There are studies about vitamin D deficiency being a risk factor for hypertension (HTA), type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), and various cancers.[2-18] A protective effect of high Vit D against CVD and an inverse correlation between Vitamin D and cardiovascular risks were also suggested.[19,20]

Uric Acid (UA) is the product of oxidation of xanthine and hypoxanthine oxidoreductase. Although some authorities believed that elevated UA is beneficial since it can be an antioxidant, recent studies objected to this

viewpoint.[21] There are conflicting reports about its protective effect on carcinogenesis.[21-23] However, it is obvious that UA takes part in various metabolic, homeostatic and hemodynamic processes such as insulin resistance, obesity, dyslipidemia and metabolic syndrome(MS) HTA, for CVD.[24-28] cerebrovascular disease, preeclampsia, and kidney disease.[29-31] UA has also a key role in oxidative stress, inflammatory response, endothelial function and vascular remodelling.[32]

Following rapid economic growth, increase in life expectancy, and changes in lifestyle, diabetes became one of the major public health issues worldwide and also in Turkey. A cross-sectional survey, TURDEP-I showed that the prevalence of diabetes was 7.2% in 2002, but TURDEP II published in 2013 demonstrated that the prevalence increased up to 13.7%.[33,34] DM is thought to be responsible for two-four fold rise in the occurence of CVD and almost all studies revealed that DM was a CVD equivalent.[35]

VitD deficiency has been associated with numerous health outcomes, including diabetes mellitus (DM). Similarly, both clinical and experimental studies link hyperuricemia with the development of DM. Both disorders and DM are related directly and indirectly to a number of cardiometabolic risk factors. The possibility of a direct casual relationship between UA and Vit D levels is twofold. Although a small number of studies have shown no such association there have been accumulated evidence that hyperuricemia may cause hypovitaminosis D and also visa versa.[36]

In diabetic patients by also being probable cardiovascular risk factors both Vit D and UA levels may affect the regulation of diabetes and progression of its complications. It may be said that if a casual association between Vit D and UA exists, treatment of one condition may alleviate the other disorder and also DM.

Bearing in mind the complex relationship among diabetes mellitus (DM), CVD, Vit D and UA in this study we aimed to explore the association of Vit D and UA in T2DM patients.

MATERIALS AND METHODS

PATIENTS

A total of 100 patients with T2DM having medication for at least one year [64 female (64.09%), 36 male (36.0%)], aged from 32-83 years, were recruited from the outpatient clinic of Internal Medicine of Kafkas University from February to April 2015. As Vit D levels below 20 ng/ml were defined as deficiency, we grouped our diabetic patients as having Vit D levels <20 ng/ml (Group I) and Vit D levels >20 ng/ml (Group II).

Our inclusion criteria were T2DM patients having oral antidiabetic agents or insulin for at least 1 year. Our exclusion criteria were patients having T1 DM, 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 malignity, tumor lysis syndrome, 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(like steroids and anticovulsants) and UA(like tiazide, furosemide- and salicylates) 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).

After 12 hours of overnight fasting blood was withdrawn, at 08.30 a.m. for fasting plasma glucose (FPG), urea, creatinine, serum total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C), triglyceride (TG), and hemoglobin A1c (HbA1c), aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubine and UA.

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.

We accepted diagnostic criteria of World Health Organisation for the diagnosis of DM.[37]

This study was performed according to the Helsinki decleration 2008. The local ethics committee approved this study and informed consent was obtained from all individual participants included in the study.

LABORATORY METHODS

Plasma glucose, urea, creatinine, TC, HDL-C, TG, AST, ALT, total bilirubine concentrations were determined by hexokinase enzymometric reference system. Low density lipoprotein cholesterol (LDL-C) was calculated by the Friedewald Formula (LDL: Total cholesterol-HDL-TG/5). HbA1c was measured by immunoturbidimetric inhibition system. Serum UA levels were determined by Cobas 6000 C51 biochemical analysis device (Roche Diagnostics GmBH, Manheim, Germany)

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, Cobas e 41 (Roche Diagnostics GmBH, Manheim, Germany) was used. We determined 25(OH)D serum levels < 20 ng/ml as deficiency.

STATISTICAL ANALYSIS

Calculations were performed using programme of SPSS (Statistical Package for Social Sciences) for Windows 22.0 programme (SPSS Inc. Chicago, IL). Normal distribution of the variables was tested by Kolmogorov Smirnov test, and variance equation by Levene test. As data showed normal distribution, all analysis were completed by parametric tests. Continuous variables were presented as mean ± standard deviation (SD) and categoric variables as percentage (%). When comparing the mean of the groups, for numeric variables independent group t test, and for categoric variables Ki-Square test were used. For the correlation between Vit D and UA levels, we used partial correlation analysis corrected for BMI. A p value of < 0.05 was considered as statistically significant.

RESULTS

Fifty patients had Vit D levels ≤ 20 ng/ml (Group I) and 50 of them had Vit D levels >20 ng/ml (Group II). The demographical and clinical characteristics and their comparison were presented (Table 1). In Table 2, FBG, HbA1c, BMI, Vit D and UA levels of the groups were presented and compared.

Group I: Diabetic patients with Vit D levels ≤ 20 ng/ml, Group II: Diabetic patients with Vit D levels > 20 ng/ml, AST: aspartate aminotransferase

TABLE 1: The demographical and clinical characteristics of the groups.

	Group I (n: 50)	Group II (n: 50)	P
Age (year)	61.9 ± 11.1	57.9 ± 10.6	NS
Gender(male)(n -%)	21(40.4%)	15(28.3%)	NS
Duration of DM(year)	8.1 ± 4.4	6.7 ± 4.9	NS
Urea(mg/dL)	38.0 ± 17.2	34.6 ± 10.8	NS
Creatinine (mg/dL)	0.8 ± 0.2	0.7 ± 0.1	NS
T.C(mg/dL)	207.4 ± 52.9	199.0 ± 41.2	NS
LDL-C(mg/dL)	129.3 ± 44.3	123.0 ± 38.2	NS
HDL-C(mg/dL)	48.2 ± 10.8	49.3 ± 10.4	NS
TG(mg/dL)	183.5 ± 83.8	156.0 ± 80.3	NS
SBP (mm/Hg)	123.5 ± 8.9	122.1± 11.2	NS
DBP(mm/Hg)	80.6 ± 9.9	79.9 ± 8.8	NS
AST(U/l)	19.9 ± 8.8	18.8 ± 6.6	NS
ALT(U/l)	21.8 ± 14.3	21.5 ± 10.9	NS
T.bil. (mg/dL)	0.8 ± 0.1	0.8 ± 0.2	NS

TABLE 2: FBG, HbA1c, BMI, Vit D and UA levels of the groups and their comparisons.

	Group I (n: 50)	Group II (n: 50)	P
FBG(mg/dL)	164.6 ± 62.3	141.0 ± 38.6	0.022
HbA1c (%)	7.6 ± 1.8	7.5 ± 1.5	NS
BMI (kg/m2)	31.3 ± 4.2	27.5 ± 3.6	ŧ0.001
Vit D(ng/mL)	10.0 ± 3.7	35.4 ± 15.0	<0.001
UA(mg/dL)	6.8 ± 1.0	4.6 ± 0.8	<0.001

ALT: alanine aminotransferase T.bil: Total bilirubin, NS: Nonsignificant. Data are presented as mean ± SD.

The groups had the same percentage of women and men. Age, duration of diabetes, urea, creatinine, TC, LDL-C, HDL-C, TG, SBP, DBP, AST, ALT, total bilirubine values did not differ in the groups.

Group I: Diabetic patients with Vit D levels ≤ 20 ng/ml, Group II: Diabetic patients with Vit D levels > 20 ng/ml, FBG: Fasting blood glucose, HbA1c: Hemoglobin A1c, BMI: Body mass index, Vit D: Vitamin D, UA: Uric acid. NS: Nonsignificant. Data are presented as mean ± SD.

FBG, BMI, and UA levels were higher and Vit D levels were lower in Group I than Group II. HbA1c levels of the groups were not different.

When we decided to examine the relation of Vit D and UA levels, in order to the eliminate the effect of BMI we made partial correlation analysis corrected according to BMI. We found an inverse correlation (r: 0.488, p <0.001) between Vit D and UA levels.

DISCUSSION

Previous evidence have shown a reverse association between Vit D status and serum UA in various situation including patients with DM.[38] Vit D, UA and DM all were supposed to be related with cardiovascular events. Expecting to find a relationship between two probable risk factors in CVD; Vit D and UA, we wanted to determine UA levels in our diabetic patients with two different Vit D levels. We found that UA levels of our T2DM patients with hypovitaminosis D were higher than the patients with high Vit D levels. These results brought us to the conclusion that VitD levels are somehow related with UA levels.

The idea of a direct relationship between hyperuricemia and Vit D metabolism was initially raised more than 20 years ago.[39] Takagashi showed that patients with gout had lower 1,25(OH)2 D levels than controls, and later the treatment of hyperuricemia increased 1,25(OH)2 D levels with no change in 25(OH) D.[40,41] It was suggested that hyperuricemia might have a suppressive effect on 1α hydroxylase activity possibly by nuclear factor κ - B(NF κ B).[42] On the other hand, previous studies suggested a negative association between parathyroid hormone (PTH) and serum UA.[43,44] In addition, low levels of Vit D can lead to hyperuricemia by PTH.

Serum UA and Vit D may also be inversely correlated. Peng and colleagues showed that Vit D insufficiency was significantly associated with elevated UA among postmenopausal Chinese women.[45]

There is also an interesting hypothesis about high UA levels. As UA has a known antioxidant activity in the serum, it may be risen as a compensatory mechanism to counteract the increased oxidative stress under conditions of DM and also hypovitaminosis D. Another antioxidant, bilirubin was also found to be associated with atherosclerosis.[46] In our study, bilirubin levels were found to be unchanged in 2 groups where Vit D levels differred. It is also well known that cigarette smoking is a cause of oxidative stress, although we did not considered it in the present study. A causal or resultant relationship of UA with Vit D levels in diabetic patients must be examined thoroughly in the future.

Vit D seems to effect glucose induced insulin response directly and indirectly. Direct effects are mediated by binding of 1,25(OH)2 D3 to β cell Vit D receptors or within β cell by 1 α hydroxylase.[47,48] Indirect effects seem to be related to Ca flux to β cells.[49] Vit D may also directly stimulate insulin responsiveness by increasing the expression of insulin receptors and by regulating free fatty acid metabo-

lism and may indirectly via Ca related pathways.[50,51] It was also shown that PTH was inversely related to insulin sensitivity.[52] Observational studies showed an inverse correlation between Vit D levels and glucose concentrations as well as Hb A1c.[53,54] In our study, we also demonstrated higher FBG values in our diabetic patients with low Vit D levels. Interestingly, we were not able to get the same result with HbA1c like Janner's study where HbA1c levels did not change in T1DM patients with and without Vit D deficiency.[55] The discrepancy of Vit D being inversely related to FBG but not to HBA1c in our study, may be explained with our relatively small sample size or with relatively lower FBG values. We know that in high HbA1c levels, the effect of FBG is more extensive, however at lower HbA1c levels, as in our study, postprandial blood glucose (PPBG) may increase HbA1c more effectively. We think that if we also considered PPBG levels we might have proved our hypothesis.

Besides, glycemic control, diabetes duration was also found to be another factor causing negative effects on serum Vit D levels.[56] Again like Janner's study, we did not find a difference of diabetes duration in our diabetic groups where Vit D levels were different.[55]

In our groups where hypovitaminosis D was present or absent, we found statistically significant difference in BMI levels. Vit D is a fat soluble vitamin, it was shown that it was sequestered, stored in fat tissues and then slowly released into the circulation. Obese patients who have less mobility and more cosmetic problems, may have less exposure to sunlight and consume food having less Vit D. It was also been shown 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.[57] The idea of Vit D being inversely related to obesity was also supported by various studies like ours.[58,59] But as Vit D supplementation is not likely to lead weight loss we think that this relationship is not in a casual manner.[60,61] On the other hand, treatment with Vit D in obese patients was shown to be beneficial in obesity associated CVD risk.[61] So, future large prospective studies are needed where Vit D supplementation will be prescribed.

In almost all studies, with normal Turkish individuals, Vit D levels were found to be below normal limits.[62,63] The season when the study was performed, genetical variations, our clothing style, limited intake of food high in Vit D, lack of outdoor physical activity due to the season must be considered as the reason of hypovitaminosis D in our country. In another study of ours we found 14.3 ng/mL Vit D levels in normal people64. Keeping in mind these low levels of Vit D in Turkey, it may be surprising to see a high level of vit D (35.4 ± 15.0 ng/mL) in our second diabetic group. Probably these patients with high Vit D levels, were our former patients who have been in long-standing control and our study group might have included them on purpose into our second group where Vit D levels were high.

Our study has some limitations. Firstly there is moderate sample size. Secondly, laboratory values evaluated in this study represent only one point at a time. Thirdly, we performed the study in winter season, it is obvious that seasonal variations could have influenced the results. Fourthly, the gold standard for the measurement of insulin sensitivity is the use of the euglycemic clamp; but we demonstrated insulin resistance by an indirect method; HOMA-IR. Fifthly, we did not examine the effect of smoking on our patients. 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 think that there is a strong relationship between Vit D levels and UA in T2DM patients. Obesity is also associated with hypovitaminosis D. As all four conditions, hypovitaminosis D, high UA levels, obesity and DM are related to CVD, in the patients having those problems, treatment of low Vit D and high UA levels may be lifesaving. In order to support this hypothesis future studies including cell culture and animal studies with large epidemiological ones will be helpful.

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Conflict of Interest

Authors declared no conflict of interest or financial support.

Authorship Contributions

Design: *Eray Atalay, Gül Gürsoy, Fırat Korlaelçi;* ***Analysis and Interpretation of the Data:*** *Fırat Korlaelçi, Halil İbrahim Erdoğdu, Eray Atalay;* ***Final Approval of the Article:*** *Gül Gürsoy, Mehmet Yıldız;* ***Statistical Expertise:*** *Eray Atalay;* ***Collection of Data:*** *Fırat Korlaelçi, Halil İbrahim Erdoğdu.*

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