

The effect of vitamin D level on blood glucose regulation, lipid profile and inflammation markers in diabetic patients: a retrospective cross-sectional study

Relationship between vitamin D level and diabetes control

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Abstract

Aim: Vitamin D is known to have functions related to the immune, endocrine, and cardiovascular systems, in addition to its essential role in calcium metabolism and bone health. In our study, we aimed to investigate the relationship between vitamin D levels and metabolic and inflammatory parameters in diabetic patients.

Materials and Methods: The study included 80 patients diagnosed with type 2 diabetes. Patients who were followed up with a diagnosis of type 2 diabetes in the internal medicine outpatient clinics between 01/02/2021 and 01/11/2021 were scanned retrospectively from the hospital archives. From this patient group, patients whose vitamin D levels were checked, whose diabetes treatment was not changed, and who were not given lipid-lowering treatment were included in the study. Demographic data, first and sixth month laboratory data were recorded. Patients were divided into two groups according to their vitamin D levels (Group1: VitD < 20 ng/mL; Group2: VitD ≥ 20 ng/mL). The results obtained at the first and second visits were statistically compared.

Results: At the first visit, HbA1c, HDL cholesterol, and CRP values were statistically significantly different between both groups ($p < 0.05$). In Group 2, lower HbA1c, CRP; but higher HDL cholesterol levels were detected. At the second visit, HbA1c, HDL cholesterol, triglycerides, LDL cholesterol, and CRP values were statistically significantly different between both groups ($p < 0.05$). In Group 2, lower HbA1c, LDL cholesterol, triglyceride, and CRP, but higher HDL cholesterol levels were noted. In the correlation test, vitamin D levels were inversely correlated with HbA1c, CRP, triglyceride, and LDL cholesterol, but directly correlated with HDL cholesterol levels in both visits ($p < 0.05$). Again, HOMA- β index was significantly higher in the group with higher vitamin D levels ($p < 0.05$).

Discussion: High vitamin D levels in diabetic patients are associated with better glycemic control, improved lipid profile, and reduced inflammation.

Keywords

dyslipidemias, inflammation, diabetes mellitus type 2, vitamin D deficiency

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This study was approved by the Ethics Committee of Kütahya Health Sciences University (Date: 2022-02-07, No: 2022.02.13).

Introduction

Vitamin D deficiency is widely observed worldwide and is recognized as a public health problem [1]. It is estimated that nearly one billion people in the world have vitamin D deficiency. Vitamin D is a fat-soluble vitamin with many functions in the human body, especially in the calcium-phosphorus balance and bone health. Vitamin D is also known to have regulatory effects on the immune system and protective effects against hypertension and heart diseases. Serum vitamin D level above 30 ng/ml is normal in healthy individuals. A level between 20-29 ng/ml is defined as insufficient and a level below 20 ng/ml as deficiency [2]. Vitamin D deficiency may develop due to limited exposure to sunlight, use of sunscreen cream, dark skin pigmentation, inadequate intake of vitamin D-containing foods, malabsorption, chronic liver and kidney disease, aging, obesity, and use of drugs that may affect absorption or metabolism of vitamin D [3].

Recent studies have shown that vitamin D deficiency is associated with many chronic diseases including various types of cancer, cardiovascular diseases, metabolic syndrome, infectious diseases, and inflammation [4]. Immune system cells have active vitamin D receptors. Reportedly, these cells can locally activate vitamin D. Therefore vitamin D deficiency is known to be associated with infections or autoimmune diseases and this issue continues to be investigated [5].

Based on literature data, low vitamin D levels impair pancreatic β -cell function, insulin resistance, and induce glucose intolerance. All of these entities may be associated with the risk of diabetes development that may be prevented with vitamin D supplementation [6]. In addition, in cases with vitamin D deficiency, higher LDL cholesterol. But lower HDL cholesterol levels with dramatic decreases in LDL-C/HDL-C ratios exert a positive impact on lipid profile [7]. Vitamin D deficiency presumably affects the lipid profile directly or indirectly by modifying the balance between serum parathormone and calcium levels.

In this study we aimed to investigate the relationship between vitamin D and regulation of type 2 diabetes mellitus (T2DM), lipid profile, and inflammation parameters.

Materials and Methods

Study Design

The data of a total of 80 diabetic patients who were followed up for 6 months in the Internal Medicine and endocrine outpatient clinics of Kütahya Evliya Çelebi Training and Research Hospital between 01.02.2021 and 01.01.2021 were retrospectively analyzed.

Study Population

Eighty T2DM patients were included in our study.

The patients who fulfilled the following criteria were included in the study.

- T 2 DM patients over 18 years of age.
- Patients whose treatment for T2DM remained the same.
- Patients who did not receive any treatment for hyperlipidemia (HL).
- Patients with available control data at the 6th month after the first control visit.

The patients with the following characteristic features were not included in the study:

- Under 18 years of age.
- Type 1 diabetes patients.
- Patients diagnosed with malignancy and were receiving active treatment.
- Patients with pancreatitis, chronic liver disease and chronic renal failure.
- Patients who had undergone pancreatic surgery.
- Chronic alcohol users.
- Patients whose diabetes treatment was changed and those receiving antihyperlipidemic treatment.

Laboratory Parameters

Serum levels of 25(OH)D below 20 ng/ml were considered as vitamin D deficiency. Patients were divided into two groups according to their serum vitamin D levels as follows: Group 1: < 20 ng/ml and Group 2: > 20 ng/ml. Vitamin 25(OH)D, HbA1c, fasting plasma glucose (FPG), lipid profile (LDL-C, HDL-C, triglyceride, total cholesterol), ferritin, C- reactive protein (CRP) levels, white blood cell (WBC) counts, and erythrocyte sedimentation rates (ESRs) were retrospectively retrieved and recorded twice at six-month intervals in both groups. The correlation of all parameters with vitamin D levels was evaluated. Analyses of these laboratory parameters were performed at the Central Laboratory of Kütahya Health Sciences University Evliya Çelebi Training and Research Hospital. Data related to age, gender, BMI (body mass index), duration of diabetes, medications used, and comorbidities of the patients were gathered from their hospital files.

HbA1C levels were measured immediately after blood sampling. Measurements were performed by high pressure liquid chromatography (HPLC) method using Tosoh G8 HPLC Analyzer (Tosoh Bioscience. Inc. San Francisco. CA). Fasting blood glucose (FBG) and lipid parameters (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides) were measured on the day the blood samples were collected. Fasting plasma glucose (FPG) and lipid panel tests were performed using original kits and a Beckman Coulter AU680 Clinical Chemistry Analyzer (Beckman Coulter. Miami. FL. USA). The reference ranges of biochemical parameters were as follows: FBG: 74-106 mg/d; total cholesterol: < 200 mg/dl; HDL-cholesterol: > 40 mg/dL; LDL-cholesterol: < 100 mg/dl, and triglycerides: < 150 mg/dl. HOMA- β was calculated using the following formula based on baseline plasma insulin (FPI). and glucose (FPG) levels [8]. HOMA- β =FPI concentration (μ U/ml) \times 20/FPG (mmol/L)-3.5.

Statistical Analysis

Statistical analyses were performed with the help of the SPSS version 22.0 program. The conformity of the variables to normal distribution was examined by histogram plots and Kolmogorov-Smirnov test. Mean, standard deviation, median, and percentage values were used to present descriptive analyses. Categorical data were compared by chi-square test and quantitative data by non-parametric Mann-Whitney U test. Non-parametric Wilcoxon test was used for variables with two different measurement values. The relationship between variables was analyzed by the Spearman's rho correlation test. A value of $p < 0.05$ was considered statistically significant for

all tests.

Ethical Approval

This study was approved by the Ethics Committee of Kütahya Health Sciences University (Date: 2022-02-07, No: 2022.02.13). The study was conducted in accordance with the latest version of the World Medical Association (WMA) Declaration of Helsinki Good Clinical Practice Guidelines.

Results

The study population consisted of 53 female and 27 male patients. Demographic and clinical characteristics of all patients are given in Tables 1.1 and 1.2.

The mean age of the study population was 56.59 years. The mean age of the patients was 55.24 years in Group 1 and 58.23 years in Group 2. BMI was 30.33 kg/m² in Group 1 and 29.77 kg/m² in Group 2. There was no statistically significant difference between the groups in terms of age, gender, BMI values of the patients, duration of diabetes, and existing comorbidities ($p > 0.05$).

At the first visit in Group 1; the mean \pm SD ($8.1 \pm 1.62\%$) and median HbA1c (8%); the mean (48.27 mg/dL), and median (46 mg/dL) HDL-C, the mean (10.67 mg/L) and median (8.5 mg/L) CRP values were as indicated. In Group 2; the mean \pm SD ($6.88 \pm 1.56\%$), and median (6.35%) HbA1c, the mean (54.25 mg/L), and median (52.5 mg/L) HDL, the mean (4.3 mg/L) and median (3.31 mg/L) CRP values were as indicated. HbA1c, HDL-C and CRP values were statistically significantly different between both groups ($p < 0.05$). FBG, total cholesterol, triglyceride, ferritin values and sedimentation rates were lower while HDL-C values were higher in Group 2 without any statistically significant intergroup difference ($p > 0.05$). At the second visit, the mean HbA1c, LDL-C, triglyceride, and CRP values for Group 1 were 7.8 %, 134.74 mg/L, 219.46 mg/dL, and 5.94 mg/L, respectively. For Group 2; the mean HbA1c, triglyceride, and CRP values were 6.81%, 143.81 mg/L, and 2.71 mg/L, respectively. There was a statistically significant difference between both groups in terms of HbA1c, LDL-C, triglyceride, and CRP values. ($p < 0.05$). FPG, total cholesterol, triglyceride, ferritin values, and sedimentation rates were lower in Group 2 without any statistically significant intergroup difference ($p > 0.05$). When the insulin level and Homa- β results, which is a beta cell function assessment test, were compared at the second visit, Homa- β was found to be significantly higher in group 2 ($p < 0.05$).

The correlation test between vitamin D values, metabolic and inflammatory parameters is shown in Tables 3.

At the first visit, a statistically significant negative correlation was detected between vitamin D and HbA1c, LDL-C, and CRP values ($p < 0.05$). A positive correlation existed between vitamin D and HDL-C values. At the second visit, a statistically significant positive correlation was found between vitamin D and HOMA - β ($p < 0.01$). A statistically significant negative correlation was noted between vitamin D and LDL cholesterol, Triglyceride, CRP, and ferritin values ($p < 0.05$).

Discussion

Our study conducted to evaluate the relationship between vitamin D and diabetes, lipid profile, and inflammatory parameters indicated the presence of a direct relationship

between vitamin D levels and glycemic control and pancreatic beta cell reserve while an inverse relationship existed among LDL-cholesterol, triglyceride, and CRP levels.

Vitamin D deficiency is a commonly detected condition. It is thought to have negative effects on glycemic control and inflammation. For this reason, extensive studies have been, and are being conducted concerning the relationship between vitamin D levels and diabetes. development and control of diabetes. The rationale of these studies is that vitamin D affects insulin sensitivity and insulin secretion. Many studies investigating the relationship between vitamin D levels and incidence of diabetes have been published. In a meta-analysis of prospective studies including healthy adults, Khan et al. reported a significant inverse relationship between baseline vitamin D levels and the incidence of type 2 DM and metabolic syndrome [9]. In a study involving 28258 older adults followed up for more than 7 years. Lucato et al. showed that low vitamin D levels were associated with a 31% higher risk of development of diabetes mellitus in the future [10]. In the relevant studies cited in the literature, an increase in the incidence of diabetes is observed in cases with vitamin D deficiency. A meta-analysis of 23 studies evaluated the effect of vitamin D replacement on glycemic control. Despite a significant improvement in fasting plasma glucose levels, its replacement had not exert a significant impact on HbA1c [11]. In another study on vitamin D levels and glycemic control, Chen W et al. revealed a significant improvement in HbA1c levels with vitamin D replacement and a significant inverse relationship between vitamin D levels and HbA1c values [12]. Other study, an inverse relationship between vitamin D levels and HbA1c values was reported [13]. Our study found an inverse relationship between vitamin D and HbA1c levels. HbA1c was significantly lower in patients with increased vitamin D levels with resultant more improved glycemic control. However some studies in the literature could not demonstrate a relationship between vitamin D replacement, serum vitamin D and HbA1c values [14]. It was thought that more detailed studies should be performed to clarify the effect of vitamin D replacement on glycemic control and its mechanism of action. Vitamin D is thought to affect insulin secretion. Some studies have shown that vitamin D replacement improved beta-cell function and increased insulin sensitivity in people at high risk for diabetes without any effect in people with normal baseline fasting glucose levels [15]. Homeostasis assessment model- β cell (HOMA- β) has been defined and used in clinical practice to evaluate insulin secretion and pancreatic β -cell function [8]. Ozcan et al., and also Corica et al reported the presence of a linear relationship between vitamin D levels and HOMA- β indices [16,17]. In our study, similar to the literature data, increased HOMA- β indices were noted in the group with higher vitamin D levels. This result was interpreted as indicative of a better pancreatic beta cell function in type 2 DM patients with high vitamin D levels.

Vitamin D receptors have been detected in many immune system cells. Presumably, vitamin D may have an impact on the immune system and affect the development of the inflammatory process [4]. In studies investigating the relationship between vitamin D deficiency and inflammation, most frequently erythrocyte sedimentation rate (ESR) and

CRP are being used as inflammatory markers. Our study found an inverse relationship between vitamin D and CRP levels. Some studies in the literature reported a negative correlation between vitamin D and CRP levels. In a study conducted with 30 hyperemesis gravidarum patients with vitamin D deficiency and 30 healthy controls, Yilmaz et al. reported that CRP levels were higher in the group with vitamin D deficiency [18]. Alrefai et al. indicated that vitamin D levels decreased and CRP levels increased as disease activity increased in 201 patients with Crohn's disease [19]. Mathur et al. demonstrated that CRP levels decreased in response to vitamin D supplementation in vitamin D deficient patients with ulcerative colitis [20]. It is known that long- lasting, low-intensity inflammation is an important factor in the pathophysiology of type 2 DM, and it has been thought that the inflammation-enhancing effect of vitamin D deficiency may have a negative effect on glycemic regulation and contribute to the development of chronic complications. However, some studies cited in the literature contradicted our results. Yıldırım et al. reported that there was no relationship between vitamin D levels and inflammation markers in patients with and without chronic kidney disease [21]. In another study, Kim et al. investigated the relationship between vitamin D and factors underlying cardiovascular disease and found no relationship between vitamin D and CRP and interleukin-6 [22]. The impact of the mechanism of action of vitamin D on lipid profile is not clear. Presumably hepatic triglyceride synthesis and its secretion may decrease with increased intestinal calcium absorption affected by vitamin D levels, and increased intestinal calcium levels may decrease intestinal absorption of fatty acids due to formation of insoluble calcium-fat complexes [23]. There are studies in the literature showing that lipid profile is negatively affected in the presence of low serum vitamin D levels. A study conducted on 1475 patients in Beijing has shown the existence of a strong negative correlation between serum vitamin D levels and triglyceride and cholesterol levels in male participants [24]. In another study, Karhämä et al. found that serum vitamin D levels were negatively correlated with total cholesterol, triglycerides, and LDL cholesterol in middle-aged Finnish men [25]. In our study, in accordance with the literature data, high vitamin D levels were found to be associated with low LDL-C and triglyceride, but increased HDL-C levels. These results suggest that associations between vitamin D levels and serum lipid profiles exist among different populations and that normal levels of vitamin D have a beneficial effect on serum lipids. Its favorable effect on lipid profile may restrict the development of atherosclerosis.

The most important limitation of our study is the relatively low number of patients. In addition, it is not known whether or not the patients included in the study were taking vitamin D supplements.

Limitations

This study has some limitations. First, due to the observational and retrospective design of the study, causality cannot be established in the relationships between vitamin D levels and glycemic control, lipid profile and inflammation markers. Therefore, the findings should be interpreted with caution. Second, the relatively small number of patients may limit the generalizability of the results and reduce statistical power

in subgroup analyses. Third, there is no data on whether the patients used vitamin D supplements, which may have a confounding effect on the findings. Finally, due to the single-time nature of the biochemical measurements, changes in the metabolic status of the patients over time could not be reflected.

Conclusion

Our study reinforces the fact that vitamin D has an anti-inflammatory effect and that glycemic control and lipid profile are adversely affected in vitamin D deficiency. Interventions aimed at preventing vitamin D deficiency as well as maintaining adequate vitamin D levels may be useful in preventing the development of metabolic disorders.

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Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content, including study design, data collection, analysis and interpretation, writing, and some of the main line, or all of the preparation and scientific review of the contents, and approval of the final version of the article.

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Data Availability Statement

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

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Conflict of Interest

The authors declare that there is no conflict of interest.

Ethics Declarations

This study was approved by the Ethics Committee of Kütahya Health Sciences University (Date: 2022-02-07, No: 2022.02.13).

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