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25 - Hydroxyvitamin D Status in Type 1 Diabetic Adults and its Relationship with Glycemic Control

Tip 1 Diyabetli Yetişkinlerde 25 - Hidroksivitamin D Durumu ve Glisemik Kontrol ile İlişkisi

ABSTRACT

Objective:

To assess the vitamin D levels between adults with type 1 diabetes mellitus and the healthy control group and evaluate the relationship between HbA1c levels and vitamin D status in the diabetic group.

Material and Methods:

Our cross-sectional, descriptive study included 98 type 1 diabetic patients over 18 years old who applied to the Endocrinology Outpatient Clinic and 95 age- and sex-matched individuals without chronic disease. Patients with advanced renal or liver disorders, primary hyperparathyroidism, metabolic bone disorders, or using medications that might change vitamin D concentrations were excluded from the study. HbA1c and 25(OH) Vitamin-D3 levels were measured three times in nine months, and the average of the measurements was used. Diabetic patients and control individuals were separated into three groups according to their vitamin D levels as follows: deficiency (<12 ng/ml), insufficiency (12-20 ng/ml), and sufficiency (> 20 ng/ml).

Results:

Serum 25 (OH) vitamin D levels of diabetic patients were significantly lower than in healthy individuals (p=0.024). However, when diabetic adults were separated into three groups according to 25(OH) vitamin D levels, there was no significant difference regarding HbA1c levels (p=0.905).

Conclusion:

Although preclinical data support the role of low serum vitamin D levels in the etiopathogenesis of type 1 diabetes mellitus, studies examining the connection between low serum vitamin D levels and the prevalence of type 1 diabetes or glycemic control are not sufficient to reach a clear conclusion, including our study.

Key Words:

Type 1 diabetes mellitus, Vitamin D, Glycemic control

ÖZ

Amaç:

Tip 1 diabetes mellituslu erişkinler ile sağlıklı kontrol grubu arasında D vitamini düzeylerini karşılaştırmak ve diyabetik grupta HbA1c ile D vitamini düzeyleri arasındaki ilişkiyi değerlendirmek amaçlanmıştır.

Gereç ve Yöntemler:

Kesitsel, tanımlayıcı tipteki çalışmamıza Endokrinoloji Polikliniği'ne başvuran 18 yaş üstü, 98 tip 1 diyabetli hasta ile yaş ve cinsiyet olarak eşleştirilen, kronik hastalığı olmayan 95 kişi dahil edildi. İleri derecede böbrek veya karaciğer hastalığı, primer hiperparatiroidizmi, metabolik kemik hastalığı olan veya vitamin D konsantrasyonlarını değiştirebilecek ilaç kullanan hastalar çalışma dışı bırakıldı. HbA1c ve 25(OH) Vitamin-D3 düzeyleri 9 aylık dönemde üç kez ölçüldü ve ölçümlerin ortalaması kullanıldı. Diyabetik hastalar ve kontrol grubu D vitamini düzeylerine göre; eksiklik (<12 ng/ml), yetersizlik (12-20 ng/ml) ve yeterlilik (>20 ng/ml) olmak üzere üç gruba ayrıldı.

Bulgular:

Diyabetik hastaların serum 25 (OH) D vitamini düzeyleri sağlıklı bireylerden anlamlı olarak daha düşüktü (p=0,024). Ancak, diyabetik erişkinler 25(OH) D vitamini düzeylerine göre üç gruba ayrıldığında HbA1c düzeyleri açısından anlamlı fark yoktu (p=0,905).

Sonuç:

Preklinik veriler, tip 1 diabetes mellitus etiyopatogenezinde düşük serum D vitamini düzeylerinin rolünü desteklese de, düşük serum D vitamini düzeyleri ile tip 1 diyabet prevalansı veya glisemik kontrol arasındaki bağlantıyı inceleyen çalışmalar, bizim çalışmamız da dahil olmak üzere, net bir sonuca ulaşmak için yeterli değildir.

Anahtar Kelimeler:

Tip 1 diabetes mellitus, D vitamini, Glisemik kontrol

INTRODUCTION

Type 1 diabetes mellitus (T1 DM) is a disease caused by autoimmune destruction of the pancreatic beta-cells. This destruction occurs with the triggering of environmental factors in genetically predisposed individuals (1). Vitamin D may be a possible trigger. Some studies have shown that vitamin D has direct effects on pancreatic beta cells with different mechanisms as well as positive immune-modulatory effects (2, 3). Besides, there are numerous studies showing an increased prevalence of vitamin D deficiency in patients with T1 DM (4, 5). Some studies examining the relationship between prenatal exposure to 25-hydroxyvitamin D [25(OH) D] and probability of developing T1 DM in later life have suggested that vitamin D deficiency may be a causative factor in the development of T1 DM (6, 7). Several studies have suggested that 25(OH)D deficiency in diabetic patients may be associated with poor metabolic control (8, 9). Contrary to these findings, some studies did not show any difference regarding vitamin D levels between individuals with T1 DM and healthy controls (10-12). Additionally, a prospective cohort follow-up study has not shown a relationship between prenatal vitamin D exposure and T1 DM risk (13). Besides, two studies found no association between serum vitamin D and HbA1c levels (14, 15). Additionally, that is not clearly established whether low 25(OH)D levels are a consequence of the disease or an environmental trigger of T1 DM (2). Previous studies on this subject have shown conflicting results. Additionally, it is known that vitamin D levels can vary internationally, regionally, and personally. Especially in Turkey, there are not many studies conducted on adult individuals regarding the relationship between type 1 diabetes and vitamin D. We thought that it would be important in terms of creating a national and international database on this subject. Furthermore, the definition of vitamin D deficiency has been made differently over the years, and different cut-off values have been specified. According to the negotiation results of the international conference in "Controversies in Vitamin D", held in Italy, in 2017, the cut-off value for the non-skeletal effects of vitamin D was accepted as 20 ng/ml. In our study, we made a classification based on these new vitamin D levels (16). In this context, our study aims to observe the serum vitamin D status in adults with T1 DM and in the healthy control group, and to determine the relationship between vitamin D levels and glycemic control in the diabetic group according to the newly proposed vitamin D classification.

MATERIAL and METHODS

This cross-sectional study was conducted at the Trakya University Faculty of Medicine. The data of the patients who applied to the Endocrinology and Metabolic Diseases Outpatient Clinic were used. The research was carried out by publication ethics and the Declaration of Helsinki. An informed consent form was obtained from the patients. The Ethics Committee of Trakya University Faculty of Medicine approval was granted before the study (TÜTF-BAEK 2021/205). Patients over 18 years of age with T1 DM were included. Gender, age, follow-up characteristics, and laboratory values of the patients were obtained from the hospital information systems and file records. People who applied to our clinic for any reason and had no chronic diseases were included in the control group. Ninety-eight T1 DM patients (47 males and 51 females) and 95 control individuals (44 males, 51 females) were included in our study. Age and gender were used as demographic data; serum 25(OH)D (chemiluminescence method in KOBAS E801, ROCH), HbA1c, phosphorus, creatinine, calcium levels were used as laboratory data (High-performance liquid chromatography method for HbA1c; spectrophotometry method for other laboratory parameters). The patients with advanced renal or liver disorders, primary hyperparathyroidism, metabolic bone disorders, or using medications that might change vitamin D concentrations were excluded from the study. Additionally, patients with conditions that could cause falsely high or low HbA1c levels, such as hemoglobinopathies, chronic liver disease, iron and B12 deficiency, or their treatment, were not

included in the study. Vitamin D classification was made according to the recommendations of the international conference on "Controversies in Vitamin D" held in Italy, in 2017; deficiency (<12 ng/ml), insufficiency (12-20 ng/ml), and sufficiency (> 20 ng/ml) (16). HbA1c and 25(OH) Vitamin-D3 levels were measured three times in a 9-month period and the average of the measurements was used. Mean Hba1c levels in each vitamin D group were used to assess the relationship between vitamin D levels and glycemic control.

Statistical Analysis

Continuous variables with normal distribution were expressed as mean ± standard deviation. Categorical variables were stated as number (n) and percentage (%). The Shapiro-Wilk test was used to assess distribution for all variables. The comparison between the study groups greater than two was evaluated using Oneway ANOVA test for quantitative data analysis with normal distribution. The comparison between study groups was evaluated using Mann-Whitney U test for quantitative data analysis without normal distribution. Pearson Chi-square analysis was used for the comparison between the groups for qualitative data analysis. P values of <0.05 were regarded statistically significant. Statistical analyses were carried out using SPSS 22.0 version (IBM Corporation, Armonk, NY, USA).

RESULTS

Ninety-eight patients with T1 DM and 95 healthy participants were included. There was a significant difference in serum 25(OH)D levels between diabetic patients and healthy controls (p=0.024) (Table I).

Table I. Demographic and biochemical features of the patients and healthy individuals

	Diabetic Patients **n=98**	**Healthy Individuals** **n=95**	**P**
Age, Median (IQR)	31.0 (19.0)	31.0 (19.0)	0.798
Gender (female/male)	51(52%) / 47(48%)	51(53.7%) / 44 (46.3%)	0.819[b]
25(OH)Vitamin-D, ng/ml, Median (IQR)	14.6 (7.0)	17.5 (7.0)	**0.024[a]**
Creatinine, mg/dl Median (IQR)	0.7 (0.2)	0.7 (0.3)	0.172[a]
Calcium, mg/dl Median (IQR)	9.4 (0.8)	9.6 (0.9)	0.174[a]
Phosphorus, mg/dl Median (IQR)	3.7 (1.0)	3.1 (0.9)	**0.001[a]**

P<0.005=significant, a= Mann-Whitney U test, b=Pearson Chi-Square, IQR: interquartile range, n= number of individuals

When vitamin D levels were divided into three groups as deficiency, insufficiency, and sufficiency, no significant difference was observed between the patient group and healthy participants (p=0.148). Besides, most of the individuals in both groups had vitamin D deficiency or insufficiency (Table II).

Table II. Comparison of the diabetic patients and healthy control group in terms of 25(OH)D levels

	25(OH)D level (ng/ml)			**P**
	<12	**12-20**	**>20**	
Diabetic Patients (n)	20 (20.4%)	59 (60.2%)	19 (19.4%)	0.148 [a]
Healthy Controls (n)	12 (12.6%)	55 (57.9%)	28 (29.5%)	

a=Pearson Chi-Square, n= number of individuals

Mean Hba1c levels in each vitamin D group were used to assess the relationship between vitamin D levels and glycemic control. HbA1c levels were similar between the groups (Table III).

Table III. Comparison of HbA1c levels between 25 (OH) D groups

	25(OH)Vitamin-D level (ng/ml)			**P**
	<12 **n:10**	**12-20** **n:56**	**>20** **n:32**	
HbA1c (%) Mean ± SD	8.60±1.96	8.84±2.09	8.70±1.63	0.905[a]

a= Oneway Anova, HbA1c= glycated hemoglobin A1c, SD= Standard Deviation, n: number of individuals

DISCUSSION

Vitamin D is thought to be actively involved in the arrangement of the immune system and also some metabolic pathways of diabetes mellitus (1). Calcitriol downregulates mechanisms related to adaptive immunity and has anti-inflammatory effects. It leads to the induction of immune tolerance and T cell anergy. These effects are thought to possibly reduce the risk of autoimmune diseases, including T1 DM (2). Additionally, vitamin D deficiency leads to impaired insulin secretion and glucose intolerance. The leading cause of this impairment may be the direct effect of vitamin D deficiency on the beta cells (3). Vitamin D has been the subject of many studies regarding its relationship with T1 DM because of its effects on immune system regulation and

pancreatic beta cells. Conflicting results have been obtained in these studies. A relationship was found between T1 DM and underlying genetic polymorphisms related to vitamin D deficiency in a case-control study (17). Some trials that determined the association between prenatal exposure to 25(OH)D and the T1 DM prevalence revealed the possibility that vitamin D deficiency could be a causative factor in the etiology of T1 DM (6,7). However, a meta-analysis of observational studies showed no effect of vitamin D supplementation during pregnancy on the incidence of T1 DM (18). In some observational trials, it was found that serum 25(OH)D levels in patients with T1 DM were lower than those in the control group (4, 5). Similarly, we observed a significant difference in serum 25(OH)D levels between diabetic patients and healthy participants. However, some other studies in the literature showed no difference between the patients with T1DM and the control groups (10-12). In a review of the interviews of the expert panels of an international conference on the " Controversies in Vitamin D " held in 2017, vitamin D levels were categorized as follows: deficiency (<12 ng / ml), insufficiency (12-20 ng/ml), and sufficiency (> 20 ng/ml) (16).

However, when we divided our patients and the control group into three groups in this way, there was a similarity between diabetic patients and healthy individuals regarding the number of patients in the vitamin D categories. Since the vitamin D cut-off levels in this category are determined according to the clinical effects of vitamin D on the body, it can be concluded that vitamin D levels between diabetic patients and healthy participants are not different enough to have a clinical effect. Moreover, the fact that vitamin D levels are below the adequate value of 20 ng/ml in both the patient and healthy groups can be attributed to a lack of exposure to appropriate and sufficient sunlight in Turkey. Additionally, conflicting results in the literature evaluating vitamin D levels between patients with T1 DM and healthy individuals may result from nutritional intake, geographical distribution, ethnic characteristics, genetic predisposition, and age differences of the subjects. Therefore, there is a need for extensive prospective studies that consider these variations. Conflicting results have also been obtained in studies examining the relationship between glycemic control and 25(OH)D levels. In two different studies, decreased blood 25(OH)D levels in individuals with T1 DM were shown to be associated with poor metabolic control (8, 9). On the other hand, no significant correlation was observed between serum 25(OH)D and HbA1c levels in some studies (14, 15). Similarly, our study showed no significant difference in HbA1c levels between the patient groups with vitamin D sufficiency, deficiency, and insufficiency.

Study Limitations

As it is known, T1 DM is associated with Celiac disease. Coexistence of Celiac Disease may affect vitamin D levels in patients. One of the limiting factors of the study is that the subjects' data regarding Celiac disease are insufficient. Since our study was conducted in a certain ethnic group with a limited number of participants and vitamin D polymorphisms depend on region and ethnicity, the study results are valid for this ethnicity, and it is difficult to generalize to other regions and ethnic groups.

CONCLUSION

Vitamin D levels were found to be lower in T1 DM patients; however, no relationship was found between vitamin D levels and glycemic control. In addition, no significant difference was found between the patient group and healthy participants in terms of vitamin D levels categorized as deficient, insufficient, or sufficient. Although the preclinical data support the possible link of serum vitamin D status in the etiopathogenesis of T1 DM, literature data, including our study, have revealed conflicting results between vitamin D deficiency and the prevalence of T1 DM or glycemic control.

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Ethics Committee Approval:
This research complies with all the relevant national regulations, institutional policies and, is in accordance with the tenets of the Helsinki Declaration, and has been approved by the Trakya University Faculty of Medicine Ethics Committee (TÜTF-BAEK 2021/205).

Informed Consent:
All the participants' rights were protected, and written informed consent was obtained before the procedures according to the Helsinki Declaration.

Author Contributions:
Concept - B.A., M.O.T., M.O., S.Y.C., B.E., M.C.; Design - B.A., B.Y.B., M.C; Supervision - B.Y.B., M.C.; Data Collection and/or Processing - B.A., M.O.T., B.E.; Analysis and/ or Interpretation - B.A, M.O., S.Y.C., B.Y.B, M.C.; Literature Search - B.A., B.Y.B., M.C.; Writing Manuscript - B.A., M.C; Critical Review - All authors.

Conflict of Interest:
The authors have no conflict of interest to declare.

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