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The relationship between serum Vitamin D level and type 2 diabetes mellitus

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ABSTRACT

Objective: Vitamin D (VD) could play a role in pathogenesis of Type 2 Diabetes Mellitus (T2DM) by affecting either insulin sensitivity or pancreatic β-cell function. This article is about the relationship between T2DM and VD levels.

Material and Methods: The 4678 individuals were included in the study. Of these, 1764 were T2DM patients and 2914 were healthy individuals. Correlation analysis was carried out between VD, age, Body Mass Index (BMI), Hemoglobin A1c (HbA1c), and duration of illness in the T2DM patients. Logistic regression analysis was used to determine the independent predictors.

Results: VD levels were significantly lower in the T2DM patients compared to the control group. The VD level of T2DM patients with HbA1c >7% was lower than those with HbA1c <7%. The VD level of T2DM patients using insulin was found to be significantly lower compared to those not using insulin. Among the T2DM patients, VD level was found to be the highest in those without complications and the lowest in those with nephropathy. The cut-off value for VD was calculated as 16.95 ng/mL. According to the logistic regression test, low serum VD levels were found to be an independent risk factor for the development of T2DM and its complications.

Conclusion: VD deficiency may be a risk factor for the development of T2DM. In our study, VD levels were significantly lower in the T2DM patients and those having complications of T2DM than the healthy individuals.

Keywords: Vitamin D, Type 2 Diabetes Mellitus, Nephropathy

INTRODUCTION

The role of vitamin D (VD) in maintaining body health is well known (1). VD level is evaluated by serum 25(OH)D levels. 25(OH)D indicates VD uptake and endogenous production. VD levels less than 20 ng/mL refer to a VD deficiency, those between 21 and 29 ng/mL to a VD insufficiency, those higher than 30 ng/mL to a normal VD level, and those higher than 150 ng/mL to a VD intoxication (2).

There are many risk factors for VD insufficiency or deficiency, including lack of sun exposure, inadequate dietary intake, darker skin color, age, obesity, and use of various medications (3). Low VD levels increase the risk for rickets and fractures and are also associated with hypertension, cancer, cardiovascular disease, Type 2 Diabetes Mellitus (T2DM), and chronic kidney disease (4).

In recent years, some studies have been carried out on the role of VD in the development of T2DM. VD could play a role in the pathogenesis of T2DM by affecting either insulin sensitivity or β-cell function, or both. 25(OH)D concentration has a positive relationship with insulin sensitivity. Low VD levels in elderly men were reported to be associated with glucose intolerance (5).

Observational studies and clinical trials show evidence that normal VD levels reduce the risk for T2DM. VD deficiency is related to insulin secretion, insulin resistance, and β-cell dysfunction in the pancreas (6). VD receptors (VDR) in pancreatic β-cells play an important role in the progression of T2DM (7).

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1alpha,25 Dihydroxyvitamin D3 (1,25(OH)2D3) binds to specific VDR and regulates hormone secretions, cell proliferation and differentiation. Detection of VDR in the pancreas and adipose tissue, skeletal muscles, and immune cells were reported to imply the antidiabetic role of VD by enhancing insulin synthesis and exocytosis, increasing the expression of the insulin receptor, and modulating immune cells function (**8**). VD can decrease the effects of systemic inflammation and protect against β-cell cytokine-induced apoptosis by directly modulating the expression and activity of cytokines, as shown in animal models (**9**). VD deficiency can affect the development of T2DM complications, insulin secretion, insulin sensitivity, inflammation, immunosuppression, microvascular and macrovascular events, and angiogenesis in several ways (**10**). Hyperglycemia is the main risk factor for diabetic microvascular complications, retinopathy, neuropathy, and nephropathy (**11**). In this study, we aimed to examine the relationship between VD levels and the development of T2DM and its complications.

MATERIAL AND METHODS

Participants

4678 people were included in the study. Of these individuals, 1764 were T2DM patients and 2914 were healthy individuals. The individuals were grouped according to age, gender, Body Mass Index (BMI), Hemoglobin A1c (HbA1c), T2DM complications, and diabetes drugs. VD levels were compared between these groups.

Socio-demographic and clinic data were obtained retrospectively from the hospital automation system. 30 ng/mL was accepted as the lower limit for normal VD.

The VD values were evaluated according to age, gender, BMI, HbA1c, T2DM complications, and diabetes drugs in the control group and the T2DM patients.

The T2DM patients and healthy individuals over 18 years old and those with VD test results were included in the study. Those with active infection or pregnancy, and those having a VD replacement therapy were excluded from the study (Figure 1).

Statistical analysis: Statistical analysis of the data was carried out using IBM SPSS (v.22.0). Chi-square test, one-sample t test, independent sample t-test, and ANOVA test were used to make comparison for parametric data, and Mann-Whitney U test for non-parametric data.

Correlation analysis was carried out between VD, age, BMI, HbA1c, and duration of illness in the T2DM patients.

Logistic regression analysis was carried out to determine the independent predictive factors for T2DM development. Statistical significance was set at $p< 0.05$.

Ethics committee approval: Approval was obtained for this study from the local clinical studies ethics committee (Decision Number: 2020/254).

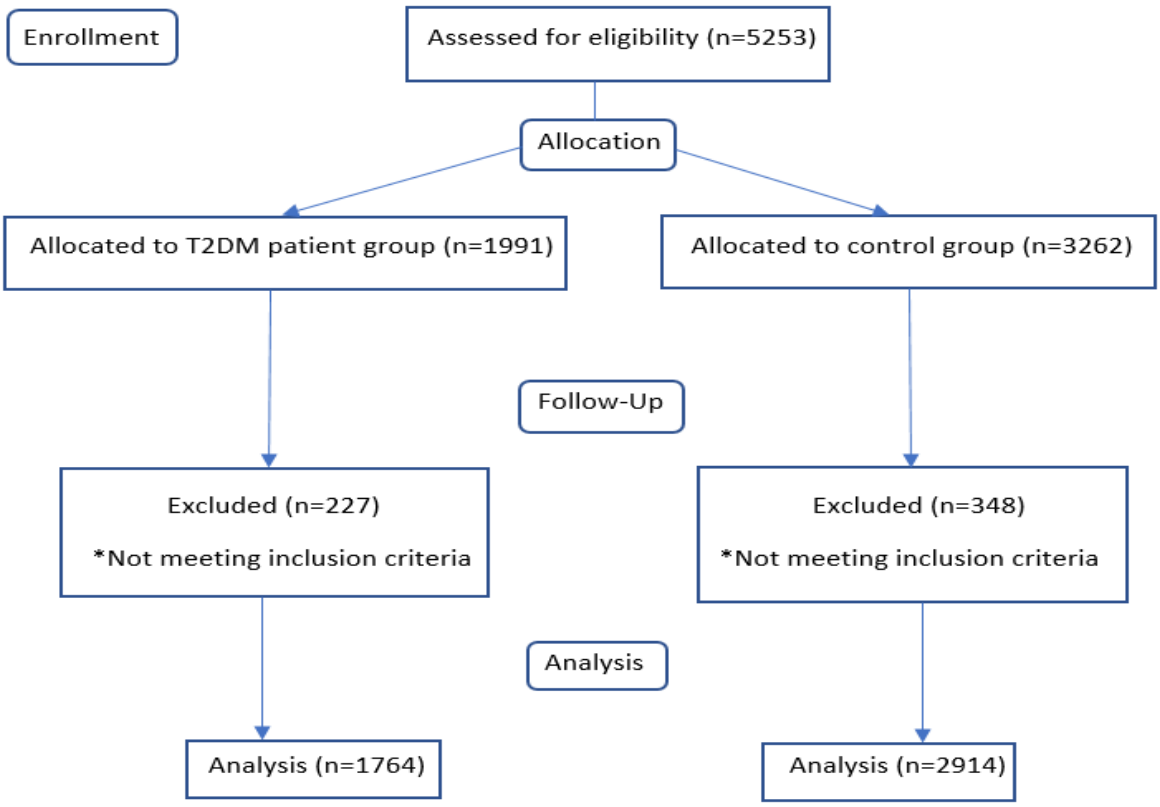

Figure 1. Flow diagram of the study. For our study, the data of 5253 individuals were retrospectively scanned. 1991 of these individuals were from the T2DM patient group and 3262 from the control group. 227 individuals from the T2DM group and 348 from the control group were excluded from the study because they did not meet the inclusion criteria. As a result, data of 1764 T2DM patients and 2914 control groups were analyzed.

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RESULTS

Of the 4678 individuals who participated in the study, 1764 (37.7 %) were T2DM patients and 2914 (62.3 %) were healthy individuals. The mean age (p=0.638) and gender characteristics (p=0.445) of the control group and diabetes mellitus patients were similar. In addition, there was no statistically significant difference between the control group and the group of T2DM patients in terms of profession, education, place of residence, smoking, and alcohol use (p > 0.05). The T2DM patients' mean BMI (28.7±6.5 kg/m2) was higher than the control group (p< 0.001). In the T2DM patients, the mean duration of illness was 7.2±9.4 years, and the mean HbA1c level was 8.3±1.7 % (Table 1). In our study, the mean serum VD level was found to be below the normal limit in both groups (< 30 ng/mL). The mean serum VD level in patients with T2DM was significantly lower than the control group (14.2±11.2 ng/mL versus 21.7±10.1 ng/mL, p< 0.001).

The T2DM patients over the age of 65 had a significantly lower mean serum VD level than the control group (12.1±10.9 ng/mL vs 20.4±10.2 ng/mL, p< 0.001). The mean serum VD level of the T2DM patients under 65 years of age was significantly lower than the control group (14.6±11.3 ng/mL vs 22.4±9.9 ng/mL, p< 0.001). The T2DM patients older than 65 years had lower VD levels than those younger than 65 years (14.6±11.3 ng/mL vs 12.1±10.9 ng/mL, p< 0.001). In the control group, those over 65 years of age had lower VD levels than those under 65 years of age (p< 0.001). The mean serum VD level in the female patients with T2DM was significantly lower than in the females in the control group (13.9±11.9 ng/mL vs 21.4±10.2 ng/mL, (p< 0.001). The mean serum VD level in the male patients with T2DM was significantly lower than in the males in the control group (14.6±10.1 ng/mL vs 21.9±9.8 ng/mL, p< 0.001). The T2DM patients' VD levels were found to decrease with increasing BMI (p< 0.001) (Table 2).

Table 1. Sociodemographic and clinical characteristics of all patients

Variables	Total (n = 4678)	T2DM patients (n = 1764)	Control group (n = 2914)	p
Gender, n (%)				
Female	2818 (60.2)	1055 (59.8)	1763 (60.5)	0.638*
Male	1860 (39.8)	709 (40.2)	1151 (39.5)	
Age (years), n (%), mean ± SD	60.0 ± 18.3	60.3 ± 13.0	59.9 ± 20.9	
< 65	2704 (57.8)	1066 (60.4)	1638 (56.2)	0.445**
> 65	1974 (42.2)	698 (39.6)	1276 (43.8)	0.075*
BMI (kg / m^2), n (%), mean ± SD	27.3 ± 8.5	28.7 ± 6.5	26.3 ± 6.8	
< 25	1672 (35.8)	558 (31.6)	1114 (38.2)	0.000**
25-30	1661 (35.5)	617 (35.1)	1044 (35.8)	0.000*
>30	1345 (28.7)	589 (33.3)	756 (26.0)	
Occupation, n (%)				
Not working	2412 (51.5)	899 (50.9)	1513 (51.9)	0.415*
Working	2266 (48.5)	865 (49.1)	1401 (48.1)	
Education, n (%)				
Primary school	2447 (52.3)	915 (51.8)	1562 (53.6)	0.093*
High school	2231 (47.7)	849 (48.2)	1352 (46.4)	
Residence, n (%)				
Town	1770 (37.8)	712 (40.3)	1058 (36.3)	0.069*
City center	2908 (62.2)	1052 (59.7)	1856 (63.7)	
Smoking, n (%)				
Yes	1836 (39.2)	698 (39.5)	1138 (39.0)	0.723*
No	2842 (60.8)	1066 (60.5)	1776 (61.0)	
Alcohol Use, n (%)				
Yes	253 (5.5)	91 (5.4)	162 (5.6)	0.663*
No	4425 (94.5)	1673 (94.6)	1752 (94.4)	
Duration of T2DM (years), mean ± SD	-	7.2 ± 9.4	-	-
HbA1c (%), mean ± SD	-	8.3 ± 1.7	-	-

p*, Chi square test; p**, Independent samples test; n, number; SD, Standard deviation; T2DM, Type 2 Diabetes Mellitus; VD, Vitamin D; BMI, Body Mass Index; HbA1c, Hemoglobin A1c.

Table 2. The comparisons of VD levels of all patients

Variable	VD (ng / mL) mean ± SD			
	Total (n = 4678)	T2DM patients (n = 1764)	Control group (n = 2914)	p
Gender				
Female	18.8 ± 10.5	13.9 ± 11.9	21.4 ± 10.2	0.000
Male	18.9 ± 11.5	14.6 ± 10.1	21.9 ± 9.8	0.000
p	0.816	0.184	0.202	-
Age (years)				
< 65	19.0 ± 11.2	14.6 ± 11.3	22.4 ± 9.9	0.000
> 65	16.9 ± 10.8	12.1 ± 10.9	20.4 ± 10.2	0.000
p	0.000	0.000	0.000	-
BMI (kg / m^2)				0.000
< 25	19.0 ± 11.2	15.6 ± 9.4	22.6 ± 10.1	
25-30	18. 6 ± 9.9	12.3 ± 7.9	21.8 ± 8.4	
> 30	16.9 ± 10.8	9.3 ± 8.8	20.1 ± 9.3	
p	0.057	0.038	0.065	-
Total	18.9 ± 11.1	14.2 ± 11.2	21.7 ± 10.1	0.000

p value, Independent samples test; n, number; SD, Standard deviation; T2DM, Type 2 Diabetes Mellitus; VD, Vitamin D; BMI, Body Mass Index.

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It was found that 55.9 % of the T2DM patients had an HbA1c level of >7 %. The T2DM patients with HbA1c >7 % had lower VD levels than those with HbA1c< 7 % (10.5±6.8 ng/mL vs. 14.1±7.2 ng/mL, p< 0.001). 1372 (77.7 %) of the T2DM patients had no complications whereas 392 (22.3 %) of them had complications. Nephropathy was present in 57 (3.2 %) of the T2DM patients, peripheral vascular disease in 72 (4.0 %), polyneuropathy in 154 (8.7 %), and retinopathy in 109 (6.1 %).

When the T2DM patients were grouped according to their complications, the mean VD levels of all groups were found to be statistically significantly lower than that of the control group (DM patients without complications, 14.7±11.6 ng/mL; nephropathy, 9.7±6.9 ng/mL; peripheral vascular diseases, 12.1±8.1 ng/mL; polyneuropathy, 14.3±10.7 ng/mL; retinopathy, 10.2±9.5 ng/mL) (p< 0.001, all).

In the T2DM patients, the VD levels were found to be the highest in those without complications and the lowest in those with nephropathy. 5.3 % of the T2DM patients were using insulin and 41.7 % were using Oral Anti Diabetics (OAD) + insulin. The most common diabetes drug they used was OAD (53.0 %).

The mean serum VD level (8.4±6.7 ng/mL) of the T2DM patients using insulin was significantly lower than that of the other T2DM patients (p< 0.001) (Table 3). According to the correlation analysis results between VD, age, BMI, HbA1c, and duration of illness in T2DM patients, a statistically significant negative correlation was observed between VD and age (r: -0.008, 95 % Confidence Interval (CI): -0.026, 0.013, p=0.041), BMI (r: -0.010, 95 % CI: -0.038, 0.042, p=0.039), HbA1c (r: -0.012, 95 % CI: -0.029, -0.005, p=0.021), and duration of illness (r: -0.004, 95 % CI: -0.015, 0.033, p=0.047). There was a positive correlation between HbA1c and BMI (r: 0.809, 95 % CI: 0.689, 0.779, p< 0.001), age (r: 0.257, 95 % CI: 0.028, 0.499, p=0.029), and disease duration (r: 0.321, 95 % CI: 0.034, 0.150, p=0.026) (Table 4).

According to the logistic regression test, low serum VD levels were found to be an independent risk factor for the development of T2DM (Odds Ratio (OR): 1.085, 95 % Confidence Interval (CI): 1.078, 1.093, p< 0.001) and its complications (OR: 1.027, 95 % CI: 1.014, 1.040, p< 0.001). It was seen that every 1-unit decrease from the VD value of 16.95 ng/mL increased the risk for T2DM (OR: 1.079, 95 % CI: 1.071, 1.086, p< 0.001) (Table 5).

Table 3. The comparisons of VD levels of T2DM patients

Variables of T2DM patients	N (%)	VD (ng / mL) mean ± SD	p
HbA1c (%)			
< 7	778 (44.1)	14.1 ± 7.2	0.000
> 7	986 (55.9)	10.5 ± 6.8	
Complications of T2DM, n (%)			
Nephropathy	57 (3.2)	9.7 ± 6.9	
Retinopathy	109 (6.1)	10.2 ± 9.5	
Peripheral vessel disease	72 (4.0)	12.1 ± 8.1	0.000
Polyneuropathy	154 (8.7)	14.3 ± 10.7	
No complication	1372 (77.7)	14.7 ± 11.6	
Diabetes drugs, n (%)			
Insulin	94 (5.3)	8.4 ± 6.7	0.000
OAD + Insulin	735 (41.7)	13.1 ± 9.8	
OAD	935 (53.0)	15.0 ± 11.5	

p value, Independent samples test; n, number; SD, Standard deviation; T2DM, Type 2 Diabetes Mellitus; VD, Vitamin D; HbA1c, Hemoglobin A1c; OAD, Oral Anti Diabetics.

Table 4. Correlation analysis between VD, age, BMI, HbA1c and duration of illness in T2DM patients

Variables		VD	Age	BMI	HbA1c	Duration of illness
VD	**r**	-	-0.082	-0.110	-0.102	-0.044
	95 % CI	-	-0.261, 0.132	-0.384, 0.423	-0.295, -0.056	-0.153, 0.334
	p	-	0.041	0.039	0.021	0.047
Age	**r**	-0.082	-	0.181	0.257	0.874
	95 % CI	-0.261, 0.132	-	-0.100, 0.513	0.028, 0.499	0.880, 0.976
	p	0.041	-	0.166	0.029	0.000
BMI	**r**	-0.110	0.181	-	0.809	0.129
	95 % CI	-0.384, 0.423	-0.100, 0.513	-	0.689, 0.779	-0.131, 0.391
	p	0.039	0.166	-	0.000	0.281
HbA1c	**r**	-0.102	0.257	0.809	-	0.321
	95 % CI	-0.295, -0.056	0.028, 0.499	0.689, 0.779	-	0.034, 0.150
	p	0.021	0.029	0.000	-	0.026
Duration of illness	**r**	-0.044	0.874	0.129	0.321	-
	95 % CI	-0.153, 0.334	0.880, 0.976	-0.131, 0.391	0.034, 0.150	-
	p	0.047	0.000	0.281	0.026	-

p value, Pearson Partial Correlation Test; r, Correlation Coefficient; CI, Confidence Interval; VD, Vitamin D; BMI, Body Mass Index; HbA1c, Hemoglobin A1c

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Table 5. Logistic regression analysis for the independent predictive factors of T2DM

Variables of T2DM patients	OR	95 % CI	*p*
VD			
< 16.95	1.079	1.071, 1.086	0.000

DISCUSSION

In our study, the VD level was found to be below the threshold level of 30 ng/mL in all groups. The mean serum VD level was significantly lower in the T2DM patients compared to the control group. A study reported that 25(OH)D concentration was lower in patients with T2DM than in the nondiabetic control individuals (**12**). A meta-analysis, including twenty observational studies involving 16515 individuals, revealed that maternal VD deficiency was associated with an increased risk for gestational diabetes (**13**).

In our study, 77.7 % of the T2DM patients had no complications. Nephropathy was observed in 3.2 % of them, peripheral vascular disease in 4 %, polyneuropathy in 8.7 %, and retinopathy in 6.1 %. In a study involving 842 diabetic patients, VD deficiency was found to be associated with severe diabetic retinopathy (**10**). Previous studies indicate that VD deficiency is associated with a significantly increased risk for diabetic retinopathy in T2DM patients (**8**). A study carried out on 1633 diabetic patients reported that the prevalence of peripheral neuropathy was 9.5 %, and VD deficiency was a risk factor for diabetic retinopathy (**11**).

A meta-analysis of data on the relationship between VD deficiency and the development of diabetes-induced neuropathy also revealed a strong correlation. Recovery of insulin secretion, increasing insulin sensitivity of target tissues, and reducing the inflammatory response have been proposed as potential mechanisms for improving the clinical manifestations of diabetic neuropathy following VD supplementation (**8**). In a study, 600,000 IU VD replacement provided a significant reduction in symptoms in patients with painful diabetic neuropathy (**14**). In the literature, various lower extremity complications (diabetic foot ulcer and peripheral arterial disease) have been reported to be associated with low serum VD in T2DM patients (**15**).

Our study found that the mean serum VD level was significantly lower in the T2DM patients using insulin than those not using insulin. In their study involving 632 T2DM patients, Suzuki et al. showed that the patients with low VD levels had higher HbA1c levels, and those using insulin had lower VD levels than those using OAD or receiving diet therapy (**16**). It can be asserted that, in T2DM patients, the nephropathy which develops due to using insulin decreases endogenous VD synthesis. We observed that the VD level was the highest in the T2DM patients without complications, while it was the lowest in those with nephropathy. VD deficiency is common in patients with diabetic nephropathy, and its severity increases with the progression of diabetic nephropathy. The degree of kidney dysfunction may affect serum 25(OH)D levels, and studies have reported that low serum 25(OH)D levels occur in patients with chronic kidney disease (**17**).

It was reported in the literature that high VD intake was associated with lower incidence of diabetes nephropathy in patients with T2DM (**18**). Supplementation with VD or its active derivatives has been shown to improve endothelial cell damage, reduce proteinuria, alleviate kidney fibrosis, and consequently delay the progression of diabetic nephropathy (**19**).

Obesity, a metabolic disorder that frequently accompanies T2DM, is an important risk factor for the development of diabetes. Although T2DM does not develop in all obese patients, the majority of T2DM patients are obese (**20**). In our study, it was observed that T2DM patients' VD levels decreased as their BMIs increased ($p< 0.001$).

HbA1c is a routine marker showing the average 3-month glycemic level. It also predicts the risk for developing diabetic complications. A one-unit increase in HbA1c increases the risk for developing cardiovascular disease by about 18 % (**21**). In the study of Özdoğan et al. a direct proportion was found between HbA1c levels and age of diabetes (**20**). In our study, a positive correlation was found between HbA1c and BMI, age, and disease duration. Targher et al. found that, in patients with T2DM, HbA1c levels were high in those with 25(OH)D deficiency. This was explained by the effect of VD on the recovery of beta-cell function in T2DM (**22**). Studies have shown that insulin sensitivity can improve by as much as 60 % when the level of VD increase from 25 to 75 nmol/L (**23**). Tekin et al. found that the lower the VD level, the higher the HbA1c value in female patients with T2DM (**24**). Yıldırım et al. found that VD levels were significantly lower in those with HbA1c > 7 % than in those with HbA1c< 7 ($p< 0.001$) (**25**). In our study, the VD level of the T2DM patients with HbA1c > 7 % was lower than that of those with HbA1c< 7% (10.5±6.8 ng/mL vs 14.1±7.2 ng/mL, $p< 0.001$).

In our study, a statistically significant negative correlation was found between VD and age, BMI, HbA1c, and duration of illness in T2DM patients. Thus, we observed that low VD level was associated with increasing age, BMI, HbA1c, and duration of illness. According to the logistic regression test, the increase in the VD level reduced the risk for T2DM (OR: 1.085, 95 % CI: 1.078, 1.093, $p< 0.001$). The decrease in the VD level increased the risk for developing complications in T2DM patients (OR: 1.027, 95 % CI: 1.014, 1.040, $p< 0.001$). VD deficiency may be a risk factor for T2DM. Adequate VD levels can be achieved through UV rays, nutrients, and, if necessary, drug therapy. VD supplementation may have a role in modifying the metabolic and cardiovascular derangements that accompany T2DM, including hypertension and endothelial dysfunction (**26**).

In a meta-analysis involving a total of nine randomized controlled trials and 43,559 participants, it was reported that in patients with prediabetes, VD supplementation at moderate to high doses (> 1000 IU/day) significantly reduced the risk for T2DM compared to placebo (27). In another meta-analysis, short-term VD support was not found effective in a population with T2DM. However, VD normalization has a positive effect on fasting glucose in patients with poorly controlled T2DM (28). A study on patients with type 1 diabetes mellitus showed that HbA1c levels decreased significantly after 12 weeks of serum VD treatment (29). In a meta-analysis, it was reported that there was insufficient evidence of beneficial effect to recommend VD supplementation as a means of improving glycemia or insulin resistance in patients with diabetes, normal fasting glucose or impaired glucose tolerance (30).

Our study was conducted at 41.20 north latitude and 32.60 east longitude. In the literature, it has been suggested that sunlight is not sufficient for the production of VD in the skin between November and February on 42.20 north latitude (31). In our study, the reason for low VD levels in older age was thought to be sun avoidance due to high temperature. In a study that includes Mediterranean countries, similar results supporting ours were obtained (32). The critical role of sunlight exposure in VD synthesis is a very important factor for VD level.

One of the limitations of our study is that it is a retrospective single-center study. Also, the VD levels consisted of the results measured every month of the year. To obtain more accurate results, there is a need for prospective studies covering seasonal differences. Another limitation of our study is that the benefits of VD replacement for patients with prediabetes and diabetes could not be evaluated due to the study design. The significance of our study lies in that it compares the VD level according to the complications in T2DM patients.

CONCLUSION

VD deficiency may be a risk for the development of T2DM. In our study, the VD levels in the T2DM patients and those who developed T2DM-related retinopathy, nephropathy, neuropathy, and peripheral vascular disease were significantly lower than those of the healthy individuals. However, lower VD levels in insulin users may indicate that low VD levels play an important role in the etiopathogenesis of T2DM and its complications. Well-designed clinical trials are needed to further study the relationship between VD deficiency and clinical outcomes in patients with T2DM.

Author contributions: Hİ, Fİ; Literature search and study design, data collection and analyzes **Hİ;** Writing article and revisions

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Ethical issues: All authors declare originality of research.

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