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Original Article

The association between 25-hydroxy vitamin D deficiency and diabetic complications in patients with type 2 diabetes mellitus

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ABSTRACT

Aims: To evaluation the relationship between serum 25-hydroxy vitamin D [25-(OH)D] deficiency and diabetic complications in patients with type 2 diabetes (T2DM).
Methods: One hundred and sixty three patients with T2DM [DM + uncomplicated (n = 36), DM + nephropathy (n = 31), DM + neuropathy (n = 30), DM + retinopathy (n = 30), DM + cardiovascular disease (CAD) (n = 36)], 35 CAD and 40 healthy volunteers were included.
Results: Serum 25-(OH)D levels were found as significantly lower in all patients compared to the control group ($p < 0.05$). 25-(OH)D in patients with DM + retinopathy ($p < 0.006$), DM + nephropathy ($p < 0.001$) and DM + neuropathy ($p < 0.001$) was significantly lower than that of the control group. 25-(OH)D in patients with DM + nephropathy ($p < 0.001$), DM + neuropathy ($p < 0.01$) and DM + retinopathy ($p < 0.001$) was significantly lower than in the DM + uncomplicated group. 25-(OH)D levels were found as significantly lower in DM + CAD compared to the CAD group ($p < 0.01$). Serum 25-(OH)D and HbA1c and parathyroid hormone (PTH) were found to be negatively correlated with each other in DM + all complications.
Conclusions: Low serum 25-OHD levels were found to be associated with the development of diabetes and complications. Low serum 25-OHD levels may be a consequence of even worse metabolic control of diabetes.

1. Introduction

Type 2 diabetes mellitus (T2DM) is a complicated chronic metabolic disorder that has become a major healthcare problem. The World Health Organization (WHO) estimates that 2.2 million people died from high blood glucose in 2012, 1.6 million people died from diabetes in 2015, and diabetes will be the 7th cause of death in 2030 [1]. T2DM is characterized by pancreatic beta cell dysfunction, systemic inflammation, elevated blood glucose levels (hyperglycemia) due to insufficient insulin production, insulin action, or both.

Vitamin D is considered to be closely related with various diseases and conditions, such as diabetes, obesity, thyroid dysfunction, infections, autoimmune disorders, cancer, vascular diseases, and skeletal-muscle system diseases [2]. There are studies suggesting a relationship between vitamin D and T2DM, and there is evidence that vitamin D affects these mechanisms and contributes to the onset of diabetes [3,4]. The mechanism of potential relationship between risk of developing diabetes, diabetes complications, and cardiovascular disease and vitamin D deficiency is unclear.

The studies related to vitamin D levels and diabetic complications are contradictory [5–14]. There is a paucity of information in the literature that evaluated the relationship between 25-hydroxy vitamin D [25-(OH)D] and diabetic complications (both microvascular and macrovascular complications). Therefore, it was aimed to evaluate the relationship between serum 25-(OH)D levels and diabetic complications in patients with T2DM in this cross-sectional study.

2. Materials and methods

2.1. Subjects

The protocol was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Cerrahpasa Medical Faculty. All participants were informed about the survey and voluntarily signed the consent form. The overall study

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population consisted of 238 participants, ranging in age from 30 to 71 years. The medical histories and physical examination of all participants were obtained.

Studied group is classified as follows:

Control group (n = 40): According to the results of oral glucose tolerance test (OGTT), Turkish healthy subjects were chosen from Endocrinology Clinic. Healthy subjects who have no endocrine, vascular, cardiac, or inflammatory disease were accepted as control group. An oral questionnaire was applied to the subjects and none of our subjects declared evidence of family history of diabetes.

Uncomplicated Type 2 Diabetic group (DM)(n = 36): Turkish patients with newly diagnosed T2D were included in this study. For the diagnosis of DM, guidelines of the American Diabetes Association (ADA) were used [15]. Diabetic patients involved in our study were receiving no other medical therapy. The presence of microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular disease, peripheral arterial disease, diabetic foot, cerebrovascular disease) were evaluated. There are not patients with microvascular and macrovascular complications in this group.

DM + retinopathy group (n = 30): Clinical evaluation was performed by evaluating the fundus with indirect ophthalmoscopy in dilated pupils. Patients with microaneurysms, severe exudative vascular proliferation, hemorrhages, and macular edema were selected.

DM + nephropathy group (n = 31): According to the ADA criteria, patients with a urinary albumin excretion rate (UAE) of 30–300 mg/24 h were diagnosed as microalbuminuria. Patients with persistent microalbuminuria were included in the study. Other factors that may cause microalbuminuria, such as urinary tract infection, intense exercise, and high fever were considered and were excluded from the study.

DM + neuropathy group (n = 30): Patients diagnosed with neuropathy with clinical symptomatic, clinical examination, EMG quantitative sensory tests, and autonomic function tests were included in the study.

DM + CAD group (n = 36): All patients had under the therapy for diabetes with insulin (25%) and/or metformin (83%). 84% of diabetic patients in this group have hypertension and they were under the therapy with beta blockers (52%), thiazide (33%) and/or ACE inhibitors (17%). Dyslipidemic diabetic patients (75%) were used antihyperlipidemic drugs such as statins.

CAD group (n = 35): 57% of the patients have hypertension. They were under the therapy with beta blockers (62%), thiazide (36%) and/or ACE inhibitors (15%).

2.2. Sample collection and measurements

Fasting venous blood samples were obtained between 08:00 and 10:00, following an overnight fasting (10–12 h) into the anticoagulant-free tubes. The samples were centrifuged for 10 min at 4000 rpm at 4 °C for separation of serum. Biochemical tests were performed immediately. For the determination of other parameters, serum aliquots were frozen and stored at −80 °C immediately until further analysis.

Routine parameters were measured using original Cobas reagents (Roche Cobas İntegra 400, Roche Diagnostics Ltd. Germany). Insulin concentrations were measured by the electrochemiluminescence immunoassay (ECLIA) method on Roche-Hitachi E170 (Roche/Hitachi MODULAR Analytics Combination Systems, Roche Diagnostics, USA). The early glycation product, HbA1c, was based on high-performance liquid chromatography (HPLC, Variant Turbo II, Bio-Rad Laboratories, Inc. USA). Parathyroid hormone (PTH), thyroid-stimulating hormone (TSH), calcium and phosphorous levels were measured by standard methods by clinical automated analyzer (Roche COBAS Integra 800; Roche Diagnostics Corporation, Germany).

The concentration of serum 25-(OH)D3 was evaluated by HPLC method on a Roche Cobas E 601, Germany (range of 25-OHD3; deficiency: <9 ng/mL, insufficiency: 10–24 ng/mL, optimal/sufficiency: 25–70 ng/mL and toxicity: >100 ng/mL).

After urine chemistry analysis, the remaining urine samples were aliquoted in polypropylene tubes with stoppers and stored at −80 °C until analysis. Protein excretion was measured first morning urine albumin/creatinine ratio (ACR). Microalbuminuria was defined as a urine albumin-creatinine ratio of 30–300/mg at least two measurements. Urinary albumin and creatinine concentrations were measured on the same analyzer using original Cobas reagents.

2.3. Statistical analysis

Statistical analysis was performed using SPSS 21.0 version for Windows Statistical Program (SPSS, Chicago, IL, USA). All data were expressed as means ± standard deviation (SD). Descriptive statistics were obtained, and data were tested for normality using the Kolmogorov-Smirnov test for Gaussian distribution. For comparison of parameters with normal distribution, parametric tests were used, and for comparison of parameters with abnormal distribution, non-parametric tests were used. For this purpose, analysis of variance (ANOVA), unpaired Student's t-test, Mann-Whitney U and Wilcoxon signed ranks tests were used. Relationships between variables were assessed with Pearson's or Spearman's correlation coefficient. A p-value equal to or lower than 0.05 was considered as statistically significant.

3. Results

The overall characteristics of the groups are summerized in Table 1. Patients with uncomplicated DM, DM + nephropathy, DM + neuropathy, DM + all complications groups had significantly higher BMI than controls ($p < 0.05$ for all subgroups) (Table 2). All diabetic patients had significantly higher plasma fasting blood glucose levels than controls (for each $p < 0.001$), and also the highest plasma fasting blood glucose levels were obtained from the DM + retinopathy group. Similarly, HbA1c levels were found as significantly higher in all diabetics compared to control patients ($p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.001$, $p < 0.005$, respectively). Only uncomplicated DM and DM + retinopathy groups had higher HOMA-IR levels than controls (for each $p < 0.05$). The insulin levels were not found as significantly different amongst groups. There were no significant differences between the groups for calcium and phosphorus levels. ACR was found as significantly increased in patients with diabetes, especially in the DM + nephropathy group when compared to the other group ($p < 0.001$).

Serum 25-(OH)D3 concentration was found as significantly decreased in patients with diabetes, especially in the DM + neuropathy group when compared to the control group ($p < 0.001$). Our results indicate that 25-(OH)D3 concentrations decreased respectively: Control > DM + retinopathy > Uncomplicated DM > DM + neuropathy > DM + all complications > DM + nephropathy. Their levels of significance compared to control respectively were $p < 0.006$, $p < 0.05$, $p < 0.001$, $p < 0.0001$, and $p < 0.0001$. Also, when we compared diabetes groups among themselves, lower serum 25-OHD3 levels were found in the DM + nephropathy and DM + retinopathy groups than in the uncomplicated DM patients ($p < 0.05$ and $p < 0.01$). No statistically significant difference was found between serum 25-OHD3 levels in nephropathy, neuropathy, and uncomplicated T2D groups.

CAD + DM and CAD groups had higher systolic pressure and

Table 1
Clinical and biochemical parameters of controls and all patients with DM.

	Control (n = 40)	Uncomplicated DM (n = 36)	DM + all complications (n = 127)
Age (years)	55.17 ± 7.16	55.08 ± 9.08	56.69 ± 7.94
BMI (kg/m^2)	24.37 ± 1.43	33.07 ± 6.31^{a3}	31.95 ± 6.17^{a3}
Waist circumference (cm)	79.64 ± 5.22	108,03 ± 11,92^{a3}	105.52 ± 12.00^{a3}
Systolic pressure (mmHg)	115,86 ± 10,59	131,67 ± 10,21^{a3}	135.44 ± 14.81^{a3}
Diastolic pressure (mmHg)	72,29 ± 6,80	79,44 ± 7,80^{a1}	82.22 ± 8.81^{a3}
FBG (mg/dL)	92,54 ± 7,49	138.71 ± 50.13^{a1}	155.74 ± 68.35^{a3}
HbA1c (%)	5.59 ± 0.30	7.10 ± 1.60^{a3}	8.29 ± 7.93^{a3,b1}
Insulin (μIU/mL)	14,47 ± 7,39	16,08 ± 9,23	16.37 ± 15.90
Creatinin (mg/dL)	0,76 ± 0,17	0,78 ± 0,20	0.87 ± 0.34^{a1,b1}
Urea (mg/dL)	12,54 ± 4,46	14,35 ± 3,74^{a1}	17,44 ± 8,92^{a3,b1}
ACR (mg/g)	3.50 ± 2.01	5.69 ± 4.46^{a2}	77.29 ± 140.78^{a1,b1}
Uric acid (mg/dL)	5,25 ± 1,58	5,37 ± 1,39	5,52 ± 1,73
Ca (mg/dL)	9.15 ± 0.33	9,26 ± 0,27	9.16 ± 0.59
P (mg/dL)	3.39 ± 0.50	3,41 ± 0,71	3.67 ± 0.66^{a1,b1}
PTH (pg/mL)	57,71 ± 12,75	62,61 ± 15,71	71.52 ± 19.55^{a3,b1}
TSH (mU/mL)	1,90 ± 0,55	2,50 ± 0,92^{a3}	2.27 ± 1.67
25-OHD3 (ng/mL)	37.30 ± 14,80	17.60 ± 8.17^{a3}	12.82 ± 4.24^{a3,b3}

DM, diabetes mellitus; **FBG,** fasting blood glucose; **25-OHD3,** 25-hydroxy vitamin D; **Ca,** calcium; **P,** phosphorus.
$^1p < 0.05$, $^2p < 0.0001$, $^3p < 0.001$.
[a]Comparison with control group.
[b]Comparison with uncomplicated DM group.

Table 2
Clinical and biochemical parameters of patients with microangiopathy.

	Uncomplicated DM (n = 36)	DM + nephropathy (n = 31)	DM + neuropathy (n = 30)	DM + retinopathy (n = 30)
Age (years)	54.50 ± 9.72	57,81 ± 6.80	57.57 ± 7.90	57.50 ± 7.60
BMI (kg/m^2)	33.07 ± 6.31	32.05 ± 6.66	32.88 ± 5.62	30.94 ± 5.32
Waist circumference (cm)	108,03 ± 11,92	106.07 ± 13.32	105.77 ± 12.05	103.67 ± 12.22
Systolic pressure (mmHg)	126,67 ± 7,73	134.84 ± 15.52	139.33 ± 13.50^{a1}	134.00 ± 15.28
Diastolic pressure (mmHg)	79,44 ± 7,80	80.32 ± 9.48	81.67 ± 9.86	81.67 ± 7.92
FBG (mg/dL)	138.71 ± 50.13	153.82 ± 85.21	161.73 ± 78.85	179.22 ± 63.81^{a3}
HbA1c (%)	7.10 ± 1.60	7.43 ± 1.81	8.19 ± 2.17^{a1}	8.68 ± 2.13^{a3,b1}
Insulin (μIU/mL)	16.08 ± 9,23	18.21 ± 17.38	18.02 ± 25.28	13.88 ± 13.23
Creatinin (mg/dL)	0,78 ± 0.20	0,94 ± 0.53	0.89 ± 0.32	0.87 ± 0.33
Urea (mg/dL)	14.35 ± 3.74	19.14 ± 10.80^{a1}	17.19 ± 8.75^{a1}	16.99 ± 9.56
ACR (mg/g)	5.69 ± 4.46	193.91 ± 239.19^{a3,c3}	39.01 ± 44.08^{a3,b3}	56.44 ± 29.75^{a3,b3,c1}
Uric acid (mg/dL)	5.37 ± 1.39	6.00 ± 1.87	5.73 ± 2.10	4.79 ± 1.41^{a1,b3,c1}
Ca (mg/dL)	9.26 ± 0.27	9.17 ± 0.56	9.08 ± 0.65	9.18 ± 0.67
P (mg/dL)	3.41 ± 0.71	3.40 ± 0.60	3.87 ± 0.75^{a1,a3}	3.80 ± 0.66^{a2,b2}
PTH (pg/mL)	62.61 ± 15.71	80.71 ± 17.50^{a3}	60.17 ± 13.44^{b3}	63.80 ± 17.00^{b3}
TSH (mU/mL)	2.50 ± 0.92	2.40 ± 2.04	2.30 ± 2.05	2.13 ± 1.54
25-OHD3 (ng/mL)	17.60 ± 8.17	11.90 ± 4.20^{a3}	13.55 ± 3.58^{a2,b1}	13.22 ± 3.26^{a3}

DM, diabetes mellitus; **FBG,** fasting blood glucose; **ACR,** albumin-to-creatinine ratio; **Ca**, calcium; **P**, phosphorus; **PTH**, parathyroid hormone; **TSH**, thyroid-stimulating hormone; **25-OHD3,** 25-hydroxy vitamin D.
$^1p < 0.05$, $^2p < 0.01$, $^3p < 0.001$.
[a]Comparison with uncomplicated DM group.
[b]Comparison with DM + nephropathy group.
[c]Comparison with DM + neuropathy group.

diastolic pressure levels than uncomplicated DM group (Table 3). Patients with CAD + DM had significantly lower 25-OHD3 than CAD ($p < 0.05$) and uncomplicated DM ($p < 0.001$).

When we performed correlation analysis in DM + all complications, negative correlations were found between 25-(OH)D3 levels and HbA1c ($r = -0.463$, $p < 0.001$) and PTH ($r = -0.702$, $p < 0.001$). Significant positive correlation was found between HbA1c levels and PTH (r: 0.359, $p < 0.01$).

4. Discussion

Vitamin D helps to improve the sensitivity against insulin and to reduce the risk of insulin resistance, which can lead to T2DM [16]. In this study, it was found that the serum 25-(OH)D concentrations are significantly decreased in patients with diabetes, especially in the DM + nephropathy group compared to both the control and uncomplicated DM group. Furthermore, a negative correlation between 25-(OH)D levels with HbA1c and PTH in the DM + all complications was found in this study. Our results indicate that decreased serum 25-(OH)D levels might be an independent risk factor for T2DM, which may help form an estimate of complications of the disease. Hence, screening and timely intervention is recommended.

Many human trials have demonstrated that vitamin D level and predominant hyperglycemia are negatively correlated. In addition to the prevalence, T2DM incidence was found to be higher in patients with decreased vitamin D levels in a majority of longitudinal observational trials [17]. In a meta-analysis, Song et al. [18] found reverse association between 25-(OH)D3 levels and incidence of T2DM, and this association was not found to be affected by gender, size of the study, duration of follow-up, diagnostic criteria, or 25-(OH)D3 measurement methods.

Decreased 25-(OH)D3 levels are highly prevalent among T2DM. Accumulating evidence supports that vitamin D might contribute

Table 3
Clinical and biochemical parameters of patients with macroangiopathy.

	Uncomplicated DM (n = 36)	DM + CAD (n = 36)	CAD (n = 35)
Age (years)	54.50 ± 9.72	56.50 ± 6.87	56.46 ± 9.97
BMI (kg/m^2)	33.07 ± 6.31	30.83 ± 6.49	29.63 ± 4.40
Waist circumference (cm)	108.03 ± 11.92	103.89 ± 10.45	103.29 ± 12.43
Systolic pressure (mmHg)	131.67 ± 10.21	133.75 ± 14.69[a2]	134.00 ± 14.77[a2]
Diastolic pressure (mmHg)	79.44 ± 7.80	83.61 ± 6.30[a2]	83.71 ± 8.97[a1]
FBG (mg/dL)	138.71 ± 50.13	149.89 ± 57.91	101.67 ± 13.71[a3,b3]
HbA1c (%)	7.10 ± 1.60	7.34 ± 1.50	5.59 ± 0.32[a3,b3]
Insulin (μIU/mL)	16.08 ± 9.23	15.79 ± 11.58	14.73 ± 7.90
Creatinin (mg/dL)	0.78 ± 0.20	0.86 ± 0.26	0.96 ± 0.33[a3]
ACR (mg/g)	5.69 ± 4.46	23.85 ± 41.96[a2]	10.54 ± 11.27[a2,b1]
Uric acid (mg/dL)	5.37 ± 1.39	5.53 ± 1.31	6.41 ± 1.64[a3,b2]
Ca (mg/dL)	9.26 ± 0.27	9.20 ± 0.50	8.97 ± 0.47[a3,b1]
P (mg/dL)	3.41 ± 0.71	3.63 ± 0.56	3.58 ± 0.75
PTH (pg/mL)	62.61 ± 15.71	79.50 ± 20.51[a3]	73.80 ± 15.26[a3.]
TSH (mU/mL)	2.50 ± 0.92	2.25 ± 0.86	2.26 ± 1.79
25-OHD3 (ng/mL)	17.60 ± 8.17	12.66 ± 5.24[a3]	14.69 ± 4.06[a1,b1]

DM, diabetes mellitus; **CAD,** cardiovascular disease; **FBG,** fasting blood glucose; **Ca**, calcium; **P**, phosphorus; **PTH**, parathyroid hormone; **TSH**, thyroid-stimulating hormone; **25-OHD3,** 25-hydroxy vitamin D.
[1]$p < 0.05$, [2]$p < 0.01$, [3]$p < 0.001$.
[a]Comparison with uncomplicated DM group.
[b]Comparison with DM + CAD.

to prevent T2D [2–4,16,19]. The association between 25-(OH)D3 and T2D may be related with the effects of 25-(OH)D3 on the regulation of glucose associated with increased HbA1c levels. Because both 1-α-hydroxylase and vitamin D receptor are found in pancreatic beta cells, 25-(OH)D3 has important functions in both the synthesis and release of insulin [20]. Moreover, 25-(OH)D3 influences insulin sensitivity via control of calcium flux through the membrane in both β cells and peripheral tissues [21]. Based on the studies conducted on this topic, several epidemiological studies have suggested increased risks of diabetes or impaired glucose metabolism among persons with low 25-(OH)D3 status [22,23]. Our results indicated that the level of 25-(OH)D3 is negatively correlated with HbA1c and FBG in all subjects, but this relationship was not observed in diabetic groups with the exception of the DM + neuropathy group. Only HbA1c levels were found to be negatively correlated with 25-(OH)D3 in the DM + neuropathy group. HbA1c is the most accepted measure of indicating glycemic control in people with diabetes. The relationship between 25-(OH)D3 and glycemic control parameters in the literature has not yet been clarified. Al-Timimi et al. [24] indicated that 25-(OH)D3 deficiency was negatively correlated with glycemic control (HbA1c), whereas Olt [25] did not find any relationship between these parameters. Therefore, our results add to evidence that serum 25-(OH)D3 level is not related to the glycemic profile, especially in patients with DM. Further, in accordance with our results, recent studies have reported that vitamin D supplementation in T2D patients was ineffective for glycemic control [26,27]. Usluogullari et al. [28] studied the frequency of 25-(OH)D3 deficiency in T2D patients in Turkey as well as the relationship between 25-(OH)D3 deficiency and the prevalence of microvascular complications. No significant difference has been observed between diabetic and control groups in terms of serum 25-(OH)D3 concentrations while no correlation was observed between HbA1C and serum 25-OH vitamin D levels. Serum 25-OH vitamin D level was found to be lower in diabetic patients with nephropathy. These findings suggest that vitamin D deficiency is related to microvascular complications in diabetic patients. Ucak et al. [29] compared the microalbuminuria level between 25-(OH) vitamin D deficiency and 25-(OH)D insufficiency patients and it was reported that microalbuminuria was significantly higher in 25-(OH)D deficiency patients. Vitamin D levels were found to be lower in patients with severe microvascular complications [30–32]. Low vitamin D status is associated with advanced diabetic nephropathy, in general [33]. Since the vitamin D levels are low in diabetics, especially in those with peripheral neuropathy, it can be asserted that there is a neurotrophic effect of vitamin D [34]. In a study including 63 centers in Australia, New Zealand, and Finland, it was found that the risk of macrovascular and microvascular disease development is higher in case of low blood 25OH-D concentrations [13].

Epidemiological studies have shown the opposite association between vitamin D status and CAD [35–38]. Different mechanisms have been hypothesized, including vitamin D effects on endothelial function, chronic inflammation, renin-angiotensin aldosterone system regulation, and calcium homeostasis [39]. In the 5-year Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial [13], A 25(OH)D concentration <20 ng/mL had a higher cumulative incidence of macrovascular and microvascular events than those with levels ≥20 ng/mL in an observational study of patients. The association between vitamin D status and cardiometabolic outcomes is uncertain, especially as intervention trials have shown no clinically significant effect of vitamin D supplementation. However, short-term underpowered interventions with low doses of vitamin D may have produced limited benefits [13]. A potential association of hypovitaminosis D with long-term micro- and macrovascular diabetes complications has been hypothesized based on the established actions of vitamin D (antiproliferative, immunomodulatory, angiogenic, inhibition of the renin-angiotensin-aldosterone system, and neurotrophic factor expression), which likely interact with the pathogenesis of diabetes complications [40]. In current study, patients with CAD + DM had significantly lower 25-OHD3 than CAD and uncomplicated DM. A negative correlation between 25-(OH)D levels with HbA1c and PTH in DM + CAD was also found in this study. Vitamin D supplementation therapy may reduce these complications. However, prospective studies have failed to demonstrate any benefit from vitamin D supplementation in reducing the incidence of CVD events and diabetes macrovascular complications [41,42].

Vitamin D deficiency has been shown to be an important health problem in Turkey [29–31,43–47]. These results suggest that at least in a Turkish population with T2D, vitamin D levels are low and correlate with body mass index (BMI); however, when vitamin D levels are so low, as obesity worsens vitamin D levels do not reduce. The vitamin D status of patients with diabetes should be considered during their regular follow-up, and supplementation should be

provided to those at risk of deficiency.

This study has some limitations. Firstly, all patients with T2D were older participants than control subjects, and the low level of 25-(OH)D may be due to the age of patients with T2D. Secondly, although all blood samples were taken in the summer season, the parameters thought to affect the vitamin D levels, such as the data on sun exposure time, use of sunscreen, and dietary habits were not collected in our study.

Low blood 25-(OH)D concentrations are associated with an increased risk of microvascular and macrovascular disease e in patients with T2DM. However, a causal link remains to be demonstrated [13]. Vitamin D deficiency has been linked to the onset of diabetes. This suggests that there is a relationship between vitamin D deficiency and poor metabolic control; however, they do not allow a causal relationship because they are observational studies. In this study, especially in the patients with complications, a negative correlation between serum vitamin D and HbA1c and PTH, as well as low serum 25-OHD levels may be a consequence of even worse metabolic control of diabetes. In conclusion, the hypothesis was that serum vitamin D status may affect metabolic control in Turkish patients with complicated T2DM. Vitamin D replacement therapy may alleviate complications of diabetes. Larger studies are necessary to confirm the role of vitamin D deficiency in the pathogenesis and DM complications.

Conflicts of interest

The author declares no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.01.043.

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