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Research article

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The role of vitamin D deficiency and thyroid dysfunction on blood glucose regulation in patients with type 2 diabetes mellitus: A retrospective cohort study

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Ethics Committee Approval
The study was approved by Afyonkarahisar Health Sciences University Clinical Research Ethics Committee (Date: 4.3.2020, Decision No:2020/4-2011 KAEK-2) and carried out in accordance with the Helsinki Declaration. This study was produced from Bedriye Açıkgöz Yıldız's Medical Specialty Thesis.
All procedures in this study involving human participants were performed in accordance with the 1964 Helsinki Declaration and its later amendments.

Conflict of Interest
No conflict of interest was declared by the authors.

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Abstract

Background/Aim: In patients with diabetes mellitus (DM), complications due to hyperglycemia decrease the quality of life and increase mortality. Vitamin D deficiency and thyroid dysfunction negatively affect blood glucose regulation. We aimed to demonstrate effects of treatment of vitamin D deficiency and thyroid dysfunction on blood glucose regulation. This study aimed to reduce the complications that may develop due to hyperglycemia.

Methods: In this retrospective cohort study, Type 2 DM patients admitted to our clinic between 2015-2018 were reviewed from hospital registry. Patients who did not attend to their control visits for DM at the 0^{th}, 3^{rd} and 6^{th} months and those with the exclusion criteria were not included. Patients who regularly attended diabetes controls at the 0^{th}, 3^{rd} and 6^{th} months were determined. Among them, those with 25-hydroxy (OH) vitamin D, glycated hemoglobin (HbA1c), fasting blood glucose (FBG), postprandial blood glucose (PPG), free T4, free T3, thyroid stimulating hormone (TSH) values in the hospital registry were sought. Patients with vitamin D deficiencies and thyroid disorders who began treatment at the 0^{th} month were finally included in the study, and the effects of vitamin D replacement treatment and thyroid dysfunction treatment on blood glucose regulation parameters at the 3^{rd} and 6^{th} months were examined.

Results: HbA1c levels significantly decreased in Type 2 DM patients whose vitamin D levels were within normal limits at the 3^{rd} month after receiving vitamin D replacement therapy (P=0.023). Vitamin D and HbA1c levels at the 3^{rd} month controls were negatively correlated (r=-0.23, P=0.016, respectively). There were no significant differences in FBG and PPG levels at the 3^{rd} month (P=0.063, P=0.361, respectively). In type 2 DM patients with hypothyroidism at the 0^{th} month who were euthyroid at the 3^{rd} month, there were no statistically significant differences in HbA1c, FBG and PPG (P=0.202, P=0.14, P=0.40, respectively). Six type 2 DM patients became euthyroid at the 3^{rd} and 6^{th} months after beginning levothyroxine treatment at the 0^{th} month, and six patients became euthyroid at the 3^{rd} and 6^{th} months after hyperthyroidism treatment. Two patients had their FBG, and PPG values measured. Due to the insufficient sample size, statistical significance of differences in HbA1c, FBG and PPG levels could not be determined.

Conclusion: Vitamin D replacement treatment had positive effects on blood glucose regulation in DM patients with vitamin D deficiency. The effects of vitamin D on blood glucose regulation should be evaluated by HbA1c. Thyroid dysfunctions were not sufficiently questioned during the three-month follow-up of DM patients, so its effects on blood glucose regulation could not be evaluated. Thyroid dysfunction should be questioned in the 3-month follow-up of DM patients and thyroid function tests should be requested.

Keywords: 25 hydroxy Vitamin D, Thyroid dysfunction, Type 2 diabetes mellitus, Blood glucose regulation

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Introduction

Type 2 diabetes mellitus (DM) is a chronic disease characterized by hyperglycemia, insulin resistance, and impairment of insulin secretion [1]. It is thought that insulin resistance, involved in the pathogenesis of type 2 DM, is reduced by the anti-inflammatory and immunomodulatory activity of vitamin D. Also, vitamin D may predict the progression of insulin resistance to type 2 DM [2,3]. Vitamin D acts on insulin receptor gene regulation through calcium metabolism and vitamin D receptors. It has been shown that adequate levels of vitamin D are effective in the release of insulin from pancreatic beta cells [4]. The main form of circulating vitamin D is 25-hydroxy (OH) vitamin D. The most important parameter that shows the amount of vitamin D in our body is 25 OH vitamin D [5]. Type 2 DM patients often have low 25 OH vitamin D levels, which could be associated with high fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) levels [6].

Type 2 DM and thyroid dysfunction are two often concomitant endocrinopathies. Both hyperthyroidism and hypothyroidism are more common in type 2 DM patients compared to those without diabetes. Thyroid hormones affect the lipid and glucose metabolisms [7]. By effect of thyroid hormones, phosphoenolpyruvate carboxykinase enzyme, which increases gluconeogenesis in the liver, is activated. Increased gluconeogenesis causes peripheral insulin resistance by inducing hyperinsulinemia [8]. Hyperthyroidism, subclinical hyperthyroidism, and hypothyroidism impair glycemic control in type 2 DM patients [7]. In addition, antithyroid drugs may worsen glycemic control [8].

In this retrospective cohort study, vitamin D replacement treatments were given to patients with Type 2 DM and 25 OH vitamin D deficiency, and thyroid dysfunction treatments were administered in patients with Type 2 DM as necessary. We aimed to demonstrate the effects of both treatments on diabetes regulation.

Materials and methods

Research method and study population

In this retrospective cohort study, patients diagnosed with Type 2 DM who were admitted to the Internal Medicine Outpatient Clinic of Afyonkarahisar Health Sciences University Medical Faculty Hospital between 2015 and 2018 were scanned from the hospital file system. A total of 4488 files with a diagnosis of DM were accessed. The exclusion criteria were as follows: Patients with chronic renal failure (GFR<60 ml/min), short bowel syndrome, chronic diarrhea, inflammatory bowel disease, history of gastrectomy, history of chronic pancreatitis, celiac disease diagnosis, bone metabolism disorders (rickets, osteomalacia, osteogenesis imperfecta), malignancy, osteoporosis, receiving oral/ intravenous/subcutaneous osteoporosis treatment, primary hyperparathyroidism, and being pregnant. The inclusion criteria were as follows: Type 2 DM patients who attended the regular control visits at the 0^{th}, 3^{rd} and 6^{th} months and were tested for 25 OH vitamin D, HbA1c, FBG, postprandial blood glucose (PPG), free T4, free T3, thyroid stimulating hormone (TSH) levels. Among variables, FBG, PPG and HbA1c parameters, which are the most related to blood glucose regulation, were selected. Patients with type 2 DM who met the exclusion criteria (n=896) and did not attend regular control visits (n=3329) were excluded from the study. Patients with both vitamin D deficiency and thyroid dysfunctions were not included to find out which treatment affected blood glucose regulation parameters. A total of 263 patients with 25 OH vitamin D, HbA1c, FBG, PPG, free T4, free T3, TSH levels at the 0^{th} month were included. Among them, the number of patients with vitamin D deficiency and thyroid dysfunction at the 0^{th} month were 168 and 53, respectively.

According to Turkish Endocrinology and Metabolism Society (TEMS) guideline, serum 25 OH vitamin D levels >20 ng/ml were considered normal, serum 25 OH vitamin D levels between 10-20 ng/ml were considered deficient, and serum 25 OH vitamin D levels <10 ng/ml were considered severely deficient [9, 10].

Patients with vitamin D deficiency at 0^{th} month who received vitamin D replacement therapy, those with thyroid disorders who received relevant treatment and whose Hba1c, FBG, PPG levels were examined at the 3^{rd} and 6^{th} months were determined. The effects of vitamin D replacement and thyroid dysfunction treatment on blood glucose regulation parameters were examined.

Statistical analysis

When evaluating the findings obtained in the study, IBM SPSS Statistics 26 (SPSS IBM, Turkey) program was used. Pearson- Fisher Chi-Square test and Fisher Exact test were used for comparison of categorical data. Descriptive data were presented as frequencies and percentages. The compliance of continuous variables to normal distribution was checked with the Shapiro Wilk test. Study data were presented as mean (standard deviation). Paired Sample T test was used for pre-post comparison of normally distributed continuous variables and Friedman test was used for multiple repeat comparisons. The Wilcoxon test was used for the pre-post comparison of continuous variables that did not show normal distribution. All data were evaluated at 95% confidence interval and values of $P<0.05$ were considered statistically significant.

Results

Among these 263 patients, the number of patients with vitamin D deficiency at baseline was 168 (63.8%). 72.6% (n=122) of the patients with vitamin D deficiency were female and 27.4% (n=46) were male. Severe vitamin D deficiency was found in 65.6% (n=80) of the female and 54.3% (n=25) of the male patients, and vitamin D deficiency was found in 34.4% (n=42) of females and 45.7% (n=21) of males. Severe vitamin D deficiency was significantly more common in females compared to males ($P=0.002$) (Table 1).

Severe vitamin D deficiency and vitamin D deficiency occurred most frequently between the ages of 50-70 years in type 2 DM patients.

One hundred and six patients had vitamin D deficiency at admission, received replacement therapy and had their HbA1c levels along with their vitamin D levels tested at the 3^{rd} month. The vitamin D levels of these patients returned to normal, and the mean HbA1c levels decreased from 7.19 (1.90) % at the 0^{th} month to 6.97 (1.81) % at the 3^{rd} month ($P=0.023$). Vitamin D

and HbA1c levels at 3rd month were weakly negatively correlated (r=-0.23, *P*=0.016) (Table 2).

Table 1: Distribution of vitamin D levels and gender of patients with type 2 diabetes mellitus and vitamin D deficiency at first admission

	25 OH vitamin D		
	Deficiency (10-20 ng/mL)	Severe Deficiency (<10 ng/mL)	Total
Female	42	80	122 (% 72.6)
Male	21	25*	46 (%27.4)
Total	63	105	168

* Female and male were compared in terms of severe 25 OH vitamin D deficiency, it was statistically significant (*P*=0.002).

Table 2. Laboratory parameters of patients who received vitamin D replacement therapy at 0 months and had normal vitamin D levels at 3th month

		0th month			3rd month					
	n	mean (SD)	Median	Min-max	mean (SD)	Median	Min-max	*P*-value[1]	r^2	*P*-value[2]
HbA1c (%)	106	7.19 (1.90)	6.73	4.45-15.5	6.97 (1.81)	6.39	4.35-13.1	0.023*	-0.23	0.016*
FBG (mg/dl)	93	161.5 (100)	109.2	42-654	147.4 (75)	106.4	81.5-578	0.063	- 0.353	<0.001*
PPG (mg/dl)	27	217 (106.74)	204	77.9-576	198.54 (89.43)	200	52.4-441	0.361	-	-

[1] Comparison of 0th and 3rd month laboratory parameters, [2] Correlation between 3rd month vitamin D level and laboratory parameters, * It is statistically significant (*P*<0.05). HbA1c: glycated hemoglobin, FBG: fasting blood glucose, PPG: postprandial blood glucose

Thirty-one patients had vitamin D deficiency at admission, received replacement therapy and had their HbA1c levels along with their vitamin D levels tested at the 3rd and 6th months. The vitamin D levels of these patients returned to normal, and the mean HbA1c levels did not change significantly. There was no correlation between vitamin D and HbA1c levels at the 6th month (Table 3).

Table 3: Laboratory parameters of patients who received vitamin D replacement therapy at 0th month and had normal vitamin D levels at 3rd and 6th months

		0th month			3rd month			6th month					
	n	mean (SD)	Median	Min-max	mean (SD)	Median	Min-max	mean (SD)	Median	Min-max	*P*-value[1]	r^2	*P*-value[2]
HbA1c (%)	31	6.71 (1.02)	6.86	4.19-11.4	6.78 (1.29)	6.75	4.17-9.7	6.79 (1.36)	6.79	4.16-9.95	0.053	0.147	0.430
FBG (mg/dl)	27	163.9 (70.65)	131	82.2-573	142.8 (51.25)	129	74.8-306	152.5 (65.70)	137	78.7-335	0.496	- 0.157	0.408
PPG (mg/dl)	6	219.94 (106.74)	256	217-334	194.54 (89.4)	205	112-361	214.73 (101.21)	228	54-351	-	-	-

[1] Comparison of 0th, 3rd and 6th month laboratory parameters, [2] Correlation between 36th month vitamin D level and laboratory parameters, HbA1c: glycated hemoglobin, FBG: fasting blood glucose, PPG: postprandial blood glucose

Ninety-three patients had vitamin D deficiency at admission, received replacement therapy and had their FBG levels along with their vitamin D levels tested at the 3rd month. The vitamin D levels of these patients returned to normal, but FBG levels did not differ significantly within that time (*P*=0.063) (Table 2). A low but significantly negative correlation was found between the 3rd month vitamin D and FBG levels after vitamin D replacement treatment (r=-0.353, *P*<0.001).

The FBG levels of patients who were given vitamin D replacement treatment at admission and had their vitamin D levels return to normal at the 3rd and 6th months (n=27) are shown in Table 3. No statistically significant difference was found between FBG levels (*P*=0.496), (Table 3).

The PPG levels of patients who were given vitamin D replacement treatment at baseline and had their vitamin D levels return to normal at the 3rd month (n=27) are shown in Table 2. There was no statistically significant difference between PPG levels (*P*=0.361). No correlation was found between 3rd month PPG and vitamin D levels (Table 2). The mean PPG levels of 6 patients who received vitamin D replacement therapy and had their vitamin D levels return to normal at the 3rd and 6th months after vitamin D replacement treatment were examined, but statistical significance could not be determined due to the insufficient sample size.

In our study, 53 type 2 DM patients had thyroid dysfunction at admission. The number of patients with newly diagnosed thyrotoxicosis and over hypothyroidism at baseline were 1 and 1, respectively. These two patients were not included in the study because of the small sample size. The number of patients diagnosed with type 2 DM and hypothyroidism at baseline, who became euthyroid at the 3rd month after receiving levothyroxine replacement treatment was 40. The mean HbA1c level of these 40 patients at baseline was 6.61 (1.26) %, which increased to 6.91 (1.76)% at the 3rd month (*P*=0.202). FBG levels were examined at baseline and the 3rd months in 37 patients. The mean FBG levels at baseline and the 3rd month were 129.3 (33.7) mg/dl and 150 (64.6) mg/dl, respectively (*P*=0.14). PPG levels at baseline and at the 3rd month were examined in 17 patients, with mean PPG levels of 173 (50.3) mg/dl, and 182 (69.6) mg/dl, respectively (*P*=0.40).

The number of patients diagnosed with type 2 DM and hypothyroidism, who received levothyroxine replacement treatment and became euthyroid at 3rd month and were followed up as euthyroid at 6th month was 6. The statistical significance of differences among the HbA1c, FBG and PPG levels of these patients could not be determined due to the insufficient sample size.

The number of patients diagnosed with type 2 DM and hyperthyroidism who received treatment and had their HbA1c levels tested at the 3rd and 6th months were 6. Among hyperthyroidism patients, the number of patients who were tested for FBG and PPG levels at baseline, 3rd, and 6th months were 2. Statistical significance of differences could not be determined in terms of HbA1c, FBG and PPG levels in these patients due to insufficient sample size.

Discussion

Type 2 DM is one of the leading causes of early morbidity and mortality worldwide. Type 2 DM's micro- and macrovascular complications have negative effects on quality of life and increase health expenditures [11]. In addition to its effects on the musculoskeletal system, vitamin D has various other important roles, such as the secretion of insulin from pancreatic beta cells and decreasing insulin resistance in type 2 DM [3, 12].

In the National Health & Nutrition Examination Survey (NHANES) study conducted on 4495 adult participants, the vitamin D deficiency rate was 41.6% [13]. In a study of 2488 patients conducted in Turkey, vitamin D deficiency rate was 24% [14]. However, in these studies, patients were not divided into groups according to DM presence.

Bayani et al. [15] included 120 diabetic and 120 non-diabetic patients in their study and found vitamin D deficiency in 64.2% of diabetic patients and 36.6% of non-diabetic patients. Parallel to this study, vitamin D deficiency was 63.8% among diabetic patients in our study. This rate was similar to that reported in the literature. Holick et al. [16] determined that 25 OH vitamin D levels were below 15 ng/ml in 28% of 242 patients. In their study, the presence of diabetes and female gender constituted higher risk for vitamin D deficiency. Similar to the study of Holick, in our study, vitamin D deficiency was more common in women with DM.

In a meta-analysis of 11 prospective studies, 3612 type 2 DM and 55.713 healthy participants were examined, and a

negative correlation was found between 25 OH vitamin D levels and the presence of type 2 DM [17]. In the NHANES study conducted between 2003 and 2006, Kositsawat et al. [16] examined the relationship between 25 OH vitamin D and HbA1c levels in 9773 adults and found that they were negatively correlated among DM patients. In another meta-analysis conducted by Mirhosseni et al. [18], 24 clinical studies (n=1528) were evaluated and the effects of vitamin D replacement in type 2 DM patients were examined. Although the duration of vitamin D administration varies in studies, the average is three months. In 10 studies, significant decreases in HbA1c levels were detected with vitamin D replacement compared to placebo. However, no significant differences were found in FBG levels. In the meta-analysis conducted by Wu et al. [19], HbA1c levels were examined in 24 studies and FBG levels, in 18 studies. When vitamin D replacement was given to type 2 DM patients for more than three months, Hba1c levels were found to decrease significantly (P=0.001), but FBG levels remained similar. The review of Lee et al. [20] evaluated HbA1c levels in 19 studies and FBG levels in 16 studies and stated that vitamin D replacement decreased HbA1C, but no changes were seen in FBG levels.

Similar to these studies, in our study, we found that after vitamin D replacement treatment, HbA1c levels found to decrease at the 3rd month, which shows the positive effect of vitamin D on blood glucose regulation in patients with DM. In addition, negative correlations found between HbA1c and 25 OH vitamin D levels at the 3rd month supports our thesis.

After vitamin D replacement treatment for three months, there were no significant decreases in FBG and PPG levels. FBG and PPG levels may be affected by many factors such as increase or decrease in the patient's fasting time, waiting time in the outpatient clinic, white coat syndrome, and hospital stress. FBG and PPG levels show blood glucose levels obtained at the time, but HbA1c levels show the 3-month average glucose levels. Therefore, we think that it would be more accurate to evaluate the effect of vitamin D replacement treatment with HbA1c levels.

Krul-Poel et al. [21] included type 2 DM patients in a double-blind, randomized, placebo-controlled study. Of these DM patients, 129 received a monthly vitamin D replacement treatment while 132 received placebo. After 6 months, no differences were found in HbA1c levels. Like Krul-Poel, we found that vitamin D replacement treatment did not affect HbA1c levels at the 6th month. The reason why Vitamin D replacement treatments have no effect on HbA1c levels at the 6th month may be attributed to the fact that vitamin D levels change seasonally (summer-winter). We think that long-term studies should cover at least 1 year, so that factors that affect vitamin D levels such as the duration of sun exposure can be considered. Type 2 DM and thyroid dysfunction are two endocrinopathies that are frequently seen together. Many studies have compared diabetic patients with a control group and more thyroid dysfunctions were observed in diabetic patients [7]. Elgazar et al. [4] investigated thyroid dysfunctions in 200 diabetic patients and 200 healthy controls. They found hypothyroidism in 7%, subclinical hypothyroidism in 13%, hyperthyroidism in 3%, and subclinical hyperthyroidism in 6% of the diabetic patients. Thyroid dysfunctions were detected in 5% of the control group. They stated that thyroid dysfunctions, especially subclinical hypothyroidism, were more common in diabetic patients. In their study of 713 type 2 DM patients, Jali et al. [22] found that thyroid dysfunction was more common among females. Similar to these studies, we observed that thyroid dysfunctions are common in DM patients and most of the DM patients with thyroid dysfunction are females.

Some studies have shown worsening of glycemic control in diabetic patients with thyroid dysfunction. Hage et al. [23] stated that glycemic controls were worse in the population of patients with thyrotoxicosis. In the study conducted by Ogbonna et al. [24], 354 type 2 DM patients were examined, and HbA1c levels were higher in patients with thyroid dysfunction. Bilic-Komerica et al. [25] examined 100 patients with subclinical hypothyroidism, 38 of which were found to be diabetic. After 6 months of levothyroxine treatment, HbA1c and FBG levels of these patients decreased significantly.

In our study, HbA1c levels of the hypothyroid patients at the 3rd month whose levothyroxine doses were increased at admission were similar. This may be due to the small sample size. The reason for the small sample size is that diabetic patients are not questioned in detail in terms of thyroid dysfunction in outpatient settings. When we wanted to examine the relationship between DM and thyroid dysfunctions at 0, 3, and 6 months of follow-up, we found that the number of patients who were followed up regularly for DM at 3-month intervals and whose thyroid hormone parameters were examined was insufficient. Insufficient parameters show that DM patients are not sufficiently questioned in terms of thyroid dysfunctions during their control examinations. Another reason for this may be that HbA1c levels can be requested at 3-month periods, but there is no such restriction in thyroid function tests. In other words, it may be caused by the fact that DM patients were examined at different times for diabetes and thyroid functions. Therefore, we could not evaluate the relationship between DM and thyroid dysfunctions at the 6th month of follow-up. More comprehensive studies are needed in larger populations to reveal the relationship between the two.

Limitations

The results obtained from the study are limited mainly because of the retrospective nature of this study, and the lack of DM patients who attended their 3-month check-ups regularly. We were unable to access patient information before 2015 due to the change in the hospital file system. Also, the number of cases of hypothyroidism and hyperthyroidism were relatively low. Finally, FPG and PPG levels were not examined together in each follow-up visit of the patients with thyroid dysfunction.

Conclusion

Considering the increase in the number of patients diagnosed with DM, attention should be paid to vitamin D and thyroid dysfunction, which may affect blood glucose regulation. Vitamin D replacement treatment had positive effects on blood glucose regulation. The effect of vitamin D replacement treatment on blood glucose regulation should be evaluated by HbA1c. While evaluating the effects of vitamin D levels on blood glucose regulation in the long term, it should be noted that the normal ranges of vitamin D vary seasonally (summer-

winter). Therefore, we think that the studies should cover at least 1 year if the effects of vitamin D replacement treatment on blood glucose regulation were to be evaluated.

Although thyroid dysfunction frequently accompanies DM, we found that thyroid function tests were not examined in the 3-month follow-up of DM patients. In this context, the history of thyroid dysfunctions should be questioned in all DM patients and thyroid function tests should be obtained.

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