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ORIGINAL RESEARCH

Effect of Vitamin D Administration on Glycemic Control in Patients with Type II Diabetes Mellitus and Vitamin D Deficiency

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Abstract: Introduction: The prevalence of diabetes mellitus (DM) and its morbidity and mortality are prominent all over the world. Observational data suggest that vitamin D deficiency is associated with insulin resistance. In this study, we aimed to assess this association. Methods: This study was a clinical trial consisting of 42 patients with type 2 DM who had vitamin D deficiency. The patients underwent vitamin D replacement with vitamin D pearls (50,000 iu) weekly for 10 weeks. The level of low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol (Chol), triglycerides (TG), hemoglobin A1c (HbA1C), 2 hour post prandial (2HPP), fasting blood sugar (FBS), body mass index (BMI), blood pressure (BP), and 25oHVitD3 were measured before and after the treatment in all patients. Data were analyzed with paired t test. Results: 100% of patients reached acceptable vitamin D level (above 30 mg/dl). No toxicity was reported. Changes in FBS, 2Hpp, HbA1C, Chol, SBP were significant and there was no significant change in LDL, HDL, and DBP. Conclusion: Screening for vitamin D deficiency and its replacement may have a beneficial effect on type 2 DM management and its associated risk factors. More studies with larger sample size and use of placebo are recommended.

Keywords: Diabetes mellitus type 2; Vitamin D deficiency; Lipid profile; Blood pressure

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1. Introduction

According to the report of the International Diabetes Federation, in 2019, about 463 million people with diabetes mellitus (DM) lived in the world and it is estimated that this number will reach more than 700 million in 2045. Also "374 million people are at increased risk of developing type 2 DM" (1). Over the past two decades, the global prevalence of DM has increased significantly (2). In the management of DM, considering a good glycemic control is important to reduce the risk of complications. The optimal level of HbA1c in the management of patients with DM is <7% (3). Therefore, trying to control this chronic metabolic disease and prevent its widespread complications is one of the priorities of health care systems. In addition to using lifestyle modification and blood sugar control drugs, controlling risk factors associated with this disease is of considerable importance.

Vitamin D deficiency is significantly more prevalent among different age and sex groups in all communities, including Iran (4-6). In addition to its crucial role in bone health, other functions for vitamin D such as preventing cell proliferation in colorectal, prostate and breast malignancies as well as its role in autoimmune diseases have been identified (7). High levels of 25-hydroxyvitamin D (25[OH]2D) are associ-

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ated with a lower risk of developing DM (8, 9). Also, a significant association between 25(OH)2D and HbA1c level is detected and after adjustment for DM duration, type of medication, and complications, in addition to hypertension and education level, vitamin D deficiency may be an independent predictor for poor glycemic control (10). The effect of Vitamin D on DM is not exactly understood but it may potentially promote beta-cell survival by modulating immune response and decreasing systemic inflammation, enhance insulin sensitivity by inducing insulin receptor expression, and affect beta-cell function by changing the calcium flux (11).

Based on recent in vitro and in vivo articles on vitamin D and insulin sensitivity, it has been shown that vitamin D is effective in the onset and progression of type 2 DM (12). Decreased vitamin D leads to an increase in PTH, which in turn increases intracellular Ca 2+ ions. Increased intracellular calcium inhibits insulin receptors in target tissues and closes the Glut4 channel. On the other hand, insulin secretion from pancreatic beta cells depends on the concentration of intracellular calcium (13). Studies in mice have shown that vitamin D can directly stimulate insulin secretion (14). Some other studies have also revealed the presence of specific receptors for vitamin D and the α1 hydroxylase enzyme, which converts 25(OH)2D to 1,25(OH)2D3 in pancreatic beta cells (15). These findings suggest a possible effect of vitamin D on glucose homeostasis, pathophysiology, and the progression of type 2 DM (16-18). One study showed that insulin resistance (HOMAIR index) was higher in the group with type 2 DM and vitamin D deficiency than in individuals with type 2 DM without vitamin D deficiency (VitD>20ng/ml, P=0.037) and Pearson correlation coefficient for 25oHVitD and insulin in type 2 DM was negative (r=0.294). Moreover, vitamin D was negatively correlated with HOMAIR in the whole sample. Thus, due to the role of vitamin D in glucose metabolism, its deficiency can lead to insulin resistance and DM (19). Parildar and colleagues reviewed vitamin D therapy for glucose metabolism and found that vitamin D therapy improves insulin resistance in people with vitamin D deficiency and has a positive effect on glycemic parameters. It was suggested that vitamin D replacement be performed as an initial preventive intervention in insulin resistance syndrome (20).

A study on patients with type 2 DM and chronic kidney disease (CKD) showed that in patients with vitamin D deficiency, median HbA1c levels were significantly higher compared with those with normal vitamin D status and vitamin D replacement was associated with a significantly low level of HbA1c and may have potential benefits on glycemic control in type 2 DM management (21). In contrast, in a review about the association between micronutrients such as calcium and vitamins D with glucose metabolism, Martini and colleagues reported that there were no sufficient and strong evidence to prescribe supplements to prevent or control DM. Therefore, to prevent deficiencies and maintain health, people with DM should receive the necessary micronutrients naturally and from rich food sources. Also, more studies with higher statistical samples and longer follow-up are needed to assess the definite benefit of using supplements in people at higher risk of DM and its complications (22).

Despite a report on significant improvement in HbA1c following vitamin D replacement therapy (23), a study on patients with insulin-naïve type 2 DM showed that vitamin D supplementation in patients with vitamin D deficiency was associated with a significant reduction in fasting blood sugar (FBs), but reductions in HbA1c, fasting insulin and HOMA-IR were not significant (24). A meta-analysis showed that administration of oral vitamin D supplement reduces insulin resistance but does not appear to affect FBS, HbA1c and fasting insulin levels. But studies in which medication adjustment during the intervention period was allowed and the diversity of treatment used for the management of DM between studies may affect the results (25). However, the clinical application and treatment effect of vitamin D deficiency have received little attention, results have been limited, and contradictory results have been obtained in studies. Also vitamin D deficiency was not considered as the main inclusion criteria, therefore the samples were mostly supplemented without considering vitamin D deficiency.

On the other hand, DM is significantly associated with higher risk of coronary artery disease and cardiovascular mortality (26). Studies show that low vitamin D level is an independent risk factor for coronary artery disease; moreover, vitamin D deficiency and DM have synergistic effect on pathogenic mechanisms of formation and progression of coronary atheroma, such as endothelial dysfunction, vascular smooth muscle cell proliferation, increasing the production of pro-inflammatory cytokines, and immune cell migration and infiltration (27). Bonakdaran and colleagues also found that vitamin D replacement may have beneficial effects on reducing cardiovascular risk factors in patients with DM (28).

Therefore, given the high prevalence of DM in the community and the exorbitant costs imposed by its effects on the health care system and on the other hand the simplicity of screening and the possibility of treating vitamin D deficiency, we decided to investigate the effect of vitamin D deficiency treatment by assessing on controlling the course of type 2 DM and its associated risk factors (hypertension and hyperlipidemia) in order to better control DM, also taking steps to prevent its complications.

2. Materials and Methods

2.1. Study design

People with diagnosis of type 2 DM according to World Health Organization referred to the endocrine and internal medicine clinic of Imam Hossein Hospital were randomly selected. Patients were invited to participate in the project with sufficient explanations about the project and its results and benefits, and their participation in the project was optional. The study was approved by the Ethics Committee, informed consent was taken and people were assured that their data would remain confidential and that the results of the project would be used without mentioning their names and addresses.

Inclusion criteria were age under 85 years, BMI below 35, HbA1C level below 10%, and vitamin D deficiency (25OHVitD3 level less than 20ng/ml), were considered to match the statistical sample and prevent confounding factors. Exclusion criteria were kidney or liver disease, history of kidney stones, hypercalcemia, pregnancy, use of drugs that interfere with vitamin D and calcium metabolism, and severe hypertension. The sample size of the study was calculated based on the following formula: $N = (Z_{1-\alpha/2} + Z_{1-\beta})^2 (S_1^2 + S_2^2)/d^2$ at 42 patients.

At the beginning of the study, the level of low-density lipoprotein (LDL), high-density lipoprotein (HDL), cholesterol (Chol), triglycerides (TG), hemoglobin A1c (HbA1C), 2 hour post prandial (2HPP), FBS, BMI, blood pressure (BP), and 25oHVitD3 were measured in all patients. The serum 25(OH)2D, shows the sum of endogenous synthesis and dietary intake and is the most stable and reliable indicator of vitamin D status.

All tests were performed in the same laboratory. HbA1C factor was measured by Direct Enzymatic HbA1C Assay method and by DIAZYME kits and 25oHVitD3 by ELISA method using IMMUN DIOGNOSTIC kits. Also, BP of the patients was measured in sitting position from the right arm, by performing the standard protocol including after at least 5 minutes of rest. Then participants which all had vitamin D deficiency, were treated with 50,000 units of vitamin D3 oral pearls weekly for 10 weeks. During the follow-up period, the patients' daily activities and diet did not have any change compared to before beginning of study and DM medications were continued with the previous dose. Daily dairy consumption was also recommended to provide the calcium requirement. Participants were followed up by telephone at specified intervals for the above. Cases that for any reason had to change medications, diet or activity were excluded. After three months, the above clinical and paraclinical data were re-examined for each patient. Treatment of vitamin D deficiency was monitored by measuring 25oHVitD3 level. Calcium levels of blood and urine were also measured to detect cases of toxicity.

2.2. Statistical analysis

Results were presented as mean, standard deviation (SD), median, range, frequency and percentage. Paired t-test was used to compare the results before and after vitamin D administration and Pearson correlation to examine the relationship between BMI and Chol, TG, HbA1C, 2HPP, and FBS. All analyzes were performed by SPSS 22.0 statistical software. P values of 0.05 or less were considered statistically significant.

3. Results

In this study, 30 (71.4%) women and 12 (28.6%) men participated. Their age and BMI are mentioned in Table 1. The mean BMI of the participants was 28.8 (min: 27.76, max: 35), which did not change significantly at the end of the study.

The mean±SD level of 25oHVitD3 at the beginning of the study was 15±4.1 ng/ml, and at the end of the study, vitamin D deficiency of all participants was treated and 25oHVitD3 achieved the desired level of above 30ng/ml. The mean±SD level of vitamin D at the end of the study was 45.3±14.6 ng/ml. During the study, no toxicity with vitamin D and Ca was observed.

As shown in table 2, the level of FBS after taking vitamin D in patients with DM decreased by 17.9 mg/dL (P=0.001) and the levels of HbA1C and 2HPP decreased by 0.55% and 32.71 mg/dL respectively (P<0.001).

As shown in table 3, HDL levels decreased about 1 mg/dL after taking vitamin D, which was not statistically significant (P=0.408). LDL levels decreased more than HDL after taking vitamin D, although the amount of reduction was not statistically significant (P=0.065). While cholesterol levels decreased by about 21 mg/dL, and TG level decreased by about 14 mg/dL which are both statistically significant (P=0.003 and P=0.022, respectively).

Pearson correlation coefficient was used to examine the relationship between BMI and the other factors. There was a significant positive correlation between BMI and TG (P=0.007). There was also a positive correlation between BMI and 2Hpp, FBS and cholesterol, while the correlation with HbA 1C was negative, although none of these correlations were significant (table 3).

Systolic blood pressure decreased significantly after taking vitamin D (P<0.001), while diastolic blood pressure did not decrease significantly (P=0.653, table 4). Of course, this reduction in systolic blood pressure was not clinically very significant.

4. Discussion

Due to the high prevalence of DM and its complications (1, 2) trying to control this chronic metabolic disease, considering a good glycemic control and prevent its widespread complications is one of the priorities of health care systems. In addition to using lifestyle modification and blood sugar control drugs, controlling risk factors associated with this disease is of considerable importance. Many studies have reported that vitamin D is associated with insulin secretion and type 2 DM (29, 30). Also, within its effect on parathyroid hormone, calbindin and calcium concentration, as well as delta receptor production activated by peroxisome proliferator, vitamin D affects insulin sensitivity and also apoptosis induced by β-cells inflammation (27, 31-33). In addition to the he high prevalence of vitamin D deficiency in all communities (4, 5, 6), considering a place for screening vitamin D deficiency in patients with type 2 DM and treating it if necessary, if it can help control the course of DM, will certainly lead to reduced mortality, morbidity, and the exorbitant costs of DM and its complications, including hemodialysis, surgeries related to diabetic foot and antibiotics needed to control the infection, costs associated with the treatment of ocular and cardiac complications. In recent years, several cross-sectional studies have been conducted on the relationship between these two diseases, the results of which have not been conclusive. Although studies showed that Vitamin D deficiency was associated with higher risk of DM, higher HbA1c level and higher mortality in patients with type 2 DM (34-39), the results of prospective studies on vitamin D supplementation was controversial. In this study, by examining the effect of vitamin D deficiency treatment on the course of glycemic control, lipid profile, and blood pressure in patients with type 2DM, the results showed that the treatment of vitamin D deficiency with high dose of vitamin D3 (50,000 units weekly) for 10 doses, has positive results at the level of 2Hpp, FBS, and HbA1C. The results were consistent some of the studies and in contrast with some others. The discrepancy in the findings can be related to several factors. In our study, the most important inclusion criterion was vitamin D deficiency, but this has not been the case in recent studies, and on the other hand, positive results are probably associated with high doses of vitamin D.

Examination of blood pressure at the beginning and end of the study confirmed that treatment with vitamin D may have effect in reducing systolic blood pressure in patients with DM. This result was consistent with some studies (28, 40) but in contrast with others (41, 42). Considering the method of administration and the dose used, it seems that similar results have been obtained in studies that have used high doses of vitamin D.

Data analysis did not show the effect of vitamin D on HDL and LDL levels, but a clear and significant effect of vitamin D supplementation on Chol and TG levels which was consistent with the results of study of Toxqui L et al (40). The reasons for the discrepancy in the results may include differences in race, differences in the form of supplementation (oral or injectable), its dose, and duration of use. Considering the mechanism of vitamin D and its fatty soluble nature, BMI may have an impact on the clinical effects of vitamin D supplement (43). Therefore a study using placebo with larger sample size and considering metabolic conditions of the patients is needed. Long-term follow-up should also be considered for patients treated with vitamin D.

5. Conclusion

According to the findings of this study, it can be stated that screening for vitamin D deficiency and its treatment in the management of patients with type 2DM can play a role in better control of their disease. On the other hand, by controlling other risk factors such as TG and blood pressure, it is possible to help reduce the complications of the disease and metabolic syndrome. Considering the limitations of this study, a randomized control trial study with the use of placebo, larger sample size and considering metabolic conditions of the patients is needed. Long-term follow-up should also be considered for patients treated with vitamin D.

6. Appendix

6.1. Acknowledgment

None.

6.2. Conflict of interest

The authors declare that they have no competing interests.

6.3. Funding support

None.

6.4. Author's contributions

All the authors have the same contribution.

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Table 1: Statistical population in terms of age and BMI.

	Mean±SD	Median(Range)
Age	58.67±8.32	60(30-72)
BMI before	28.8±3.4	27.76(22.34-35)
BMI after	28.6±3.5	27.76(22.34-35)
25(OH)vitD before	15±4.1	
25(OH)vitD after	45.3±14.6	

Table 2: Blood sugar factors in patients before and after administration of Vitamin D.

	Mean±SD	Median(range)	T-value	P-value
HbA1C before	7.65±1.04 %	7.5(6 to 9.8) %		
HbA1C after	7.1±0.9 %	7(5.6 to 9) %		
HbA1C difference	0.55±0.65 %	0.5(-0.9 to 2.6) %	5.53	<0.001
FBS before	153.1±30.41 mg/dL	149(91 to 210) mg/dL		
FBS after	135.19±31.65 mg/dL	134.5(75 to 204) mg/dL		
FBS difference	17.9±33.85 mg/dL	21.5(-63 to 106) mg/dL	3.43	0.001
2HPP before	213.14±48.27 mg/dL	211.5(131 to 339) mg/dl		
2HPP after	180.43±35.55 mg/dL	174(116 to 247) mg/dL		
2HPP difference	32.71±44.52 mg/dL	33(-75 to 188) mg/dL	4.76	<0.001

Table 3: Correlation between BMI and evaluated parameters after vitamin D administration.

		Chol	TG	HbA1C	2HPP	FBS
BMI	Pearson Correlation	0.147	0.413	-0.124	0.261	0.175
	P value	0.358	0.007	0.438	0.099	0.274

Table 4: Blood pressure of the patients before and after the vitamin D administration.

	Mean±SD	Median(Range)	T-value	P-value
SBP1 before	125.48±12.44 mmHg	125(110-170) mmHg		
SBP after	120.83±8.83 mmHg	120(110-140) mmHg		
SBP difference	4.64±7.84 mmHg	0(-5-30) mmHg	3.838	<0.001
DBP2 before	73.1±6.71 mm Hg	70(60-80) mmHg		
DBP after	72.74±6.46 mmHg	70(60-80) mmHg		
DBP difference	0.36±5.11 mmHg	0(-10-10) mmHg	0.453	0.653

1SBP: systolic blood pressure, 2DBP: diastolic blood pressure.