https://doi.org/10.46389/rjd-2022-0972
www.rjdnmd.org

Rom J Diabetes Nutr Metab Dis
2022; volume 29, issue 4, pages 420-429

Original Article

Effect of vitamin D3 on serum lipid profile and HbA1c levels in type 2 diabetes mellitus: a randomized controlled study

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Received: 21 May 2021 / Accepted: 26 August 2022

Abstract

The purpose of this study was to review the effect of vitamin D3 (VD3) supplementation on glycemic control and lipid profile in patients with Type 2 Diabetes Mellitus (T2DM). A total of 68 T2DM patients with hemoglobin A1C (HbA1c)>6.5 and 25(OH) VD3<30 ng/ml were included in the study. They were randomly divided into two groups: placebo (n=34), and VD3 (n=34). Patients received weekly (VD3 (50,000 IU)/placebo) for 8 weeks. HbA1c levels, FBS and lipid profiles were assessed at baseline and after 8 weeks. A number of 62 people included VD3 (n=30) and placebo (n=32) completed the study, 25(OH) VD3 serum increased significantly after 8 weeks in the VD3 group compared to the placebo group (P<0.001). HbA1c levels, slightly higher, had decreased in the VD3 group compared to the placebo group (-0.35±1.2 *vs.* -0.13±1.50%, P=0.50). FBS levels slightly decreased in the VD3 group, compared to the placebo group (-6.93±39.57 *vs.* 5.53±42.21 mg/dl, P=0.07). In contrast to the slight decrease in total cholesterol (TC) and LDL levels in the VD3 group, was observed a slight increase in TC and LDL levels in the placebo group, and this increase was almost significant for TC (-1.26±36.72 *vs.* 14.65±41.56 mg/dl, P=0.05). The effect of VD3 may increase in improving hyperglycemia and lipid profile levels with increasing intervention time and sample size.

Keywords: diabetes, VD3 supplementation, HbA1c, lipid profile.

Introduction

Type 2 diabetes mellitus (T2DM) is a disease associated with impaired insulin secretion and insulin function. Obesity is a risk factor for T2DM. Obesity induces insulin resistance by various mechanisms, including changes in adipokine levels and inflammatory responses, resulting in decreased absorption of glucose from insulin-sensitive tissues and hyperglycemia [1]. In the pre-clinical stages of T2DM, glucose tolerance remains normal, as pancreas β-cells compensate for this problem by increasing insulin production, whereas the pancreatic islets are unable to continue producing insulin as the disease progresses, resulting in hyperglycemia and overt diabetes [2, 3]. T2DM has always placed a heavy burden on global health. Depending on the region's lifestyle and geography, the Middle East is expected to have the highest prevalence of diabetes by 2030 [4, 5]. In Iran as well, the prevalence of diabetes among adults aged 25 to 70 years is 11.9% in 2011, which shows a growth of 35% compared to 2005. It is assessed that in 2030 nearly 9.2 million Iranians will likely have diabetes [6]. It is therefore urgent to adopt innovative approaches to prevent its development. Recently, the

potential role of VD3 in improving the risk of diabetes has been addressed. Recent studies show a prominent role of VD3 by its receptor on β-cells pancreatic in insulin sensitivity and systemic inflammation. This suggests that VD3 function goes beyond its involvement in regulating bone homeostasis [7, 8]. A small amount of VD3 is supplied from food sources, but the prime source of VD3 in humans is the conversion of 7-dehydrocholesterol to UVB-induced cholecalciferol in sun-exposed skin. The 7 dehydrocholesterol, after twice hydroxylation in the liver and kidney, convert to the active form (1,25-dihydroxyvitamin D3), which binds to its receptor and plays its biological role [9]. The VD3 receptors express in many tissues, including pancreatic β cells and adipose tissue [10, 11]. 1,25-dihydroxy vitamin D3 (1,25(OH) 2 VD3), upon binding to its receptor, directly activates transcription of the human insulin receptor gene and the peroxisome proliferator-activated δ receptor gene (PPAR δ) [12, 13]. VD3 also can be effective in the treatment of T2DM by increasing insulin response, glucose uptake, and the storage of its excess and beta-oxidation of free fatty acids. The lack of sunlight, especially in winter, inadequate nutrition, age-related changes in the skin, and kidney dysfunction, especially in the elderly, may lead to vitamin D deficiency [14, 15]. The 25(OH) VD3 level (the measurement of VD3 status) at 21 to 29 ng/ml is insufficient, and less than 20 ng/ml is considered as vitamin D deficiency. Children and adults need at least 1,000 IU of VD3 daily to compensate for this deficiency [16]. Given the above, the lifestyle and geography of each region have significant effects on the prevalence of diabetes and vitamin D deficiency. Therefore, this study investigates the effect of VD3 on the level of biochemical and anthropometric parameters in patients with T2DM in Birjand.

Material and methods

This randomized, double-blind, placebo-controlled trial was performed on diabetic patients. A total of 68 patients with T2DM and age range of 50–65 years, who were diagnosed by diabetic physicians using WHO criteria, were recruited from clinics in South Khorasan, Birjand, from 23 October 2019 to 3 February 2020. Inclusion criteria were no change in the medications during the study period, HbA1c >6.5, and serum level of 25(OH) VD3 <30 ng/ml. Exclusion criteria included taking VD3 supplements, serum creatinine >200 μmol/l, corrected calcium <8.6 or 10.6 < mg/dl, liver disease, kidney disease, and malabsorption.

Ethics statements

This research was carried out in accordance with the principles of the Helsinki Declaration and was approved by the Committee on Medical Research Ethics and also registered on the IRCT website with the code IRCT20200616047795N1. Before the beginning of the study, written consent was obtained from each patient.

Study design

After determining VD3 levels, patients were randomly divided into two groups to receive (placebo/VD3). During the study period, participants were asked not to change their physical activity or diet intake and not to take medication other than the capsules given to them.

Intervention

Patients received VD3 (50000IU) or placebo each week for 8 weeks. The pills were similar in shape and number and manufactured by Zahravi (Tabriz, Iran).

Treatment adherence

During the study, participants were repeatedly reminded verbally or by message to use the capsules on time and follow the instructions.

Assessment of anthropometric measures

Participants' weight and height were measured using a standard scale at the beginning of the study. BMI was obtained by the formula of weight in kilograms divided by height in square meters. The patient's blood pressure was measured from their right arm with a hand-held sphygmomanometer (KJ-106; EQUIMED, Switzerland) after 15 minutes of rest.

Measurement of biochemical parameters

At each turn, blood samples from subjects were taken after fasting for 10–12h. In this study, measuring VD3 level is considered a primary consequence and measuring lipid profile and HbA1c as a secondary result. In the hospital's sampling unit, 10 ml of venous blood (morning blood sample) were taken from subjects at baseline and after 8 weeks. The samples were divided into CBC-specific vials (containing K2EDTA anticoagulant) and clot vials. Then, they were immediately transferred to the hospital laboratory for testing.

Assuming the need to repeat experiments, serum samples were stored at freezing temperature (-20°C), and the CBC vials at refrigerated temperature (2–6°C) until testing.

The level of 25(OH)VD3 was measured with the kit (Diasorin Co., USA) and device (Liaison, Germany) using the Chemiluminescence technique. Serum levels of urea, acid uric, triglyceride (TG), total cholesterol (TC), creatinine, albumin, and calcium and phosphorus levels were measured with a kit (Pars Azmun Co., Iran) and photometric method. Fasting blood glucose (FBS) was measured with enzymatic methods by glucose oxidase. Hemoglobin A1C (HbA1c) was measured with the kit (Pishtaz Teb Co., Iran) and by the HPLC method. HDL-C and LDL-C measurements were performed by the immune inhibition method and kit (Pars Azmoun Co., Iran). The eGFR (estimated glomerular filtration rate) was calculated by the abbreviated MDRD equation: 186 × (Creatinine/88.4)-1.154 × (17)-0.203 × (0.742 if female) × (1.210 if black).

Sample size

In this study, HbA1c is considered the main outcome. Then, the sample size is calculated based on the reference study and finally, the maximum number is selected as the optimal sample size. The default sample size based on the HbA1c variable would be as follows [1]: M=112.1, SD=31.5, α=0.05, 1-β=0.83, Attrition Rate=15%, effect size=0.2.

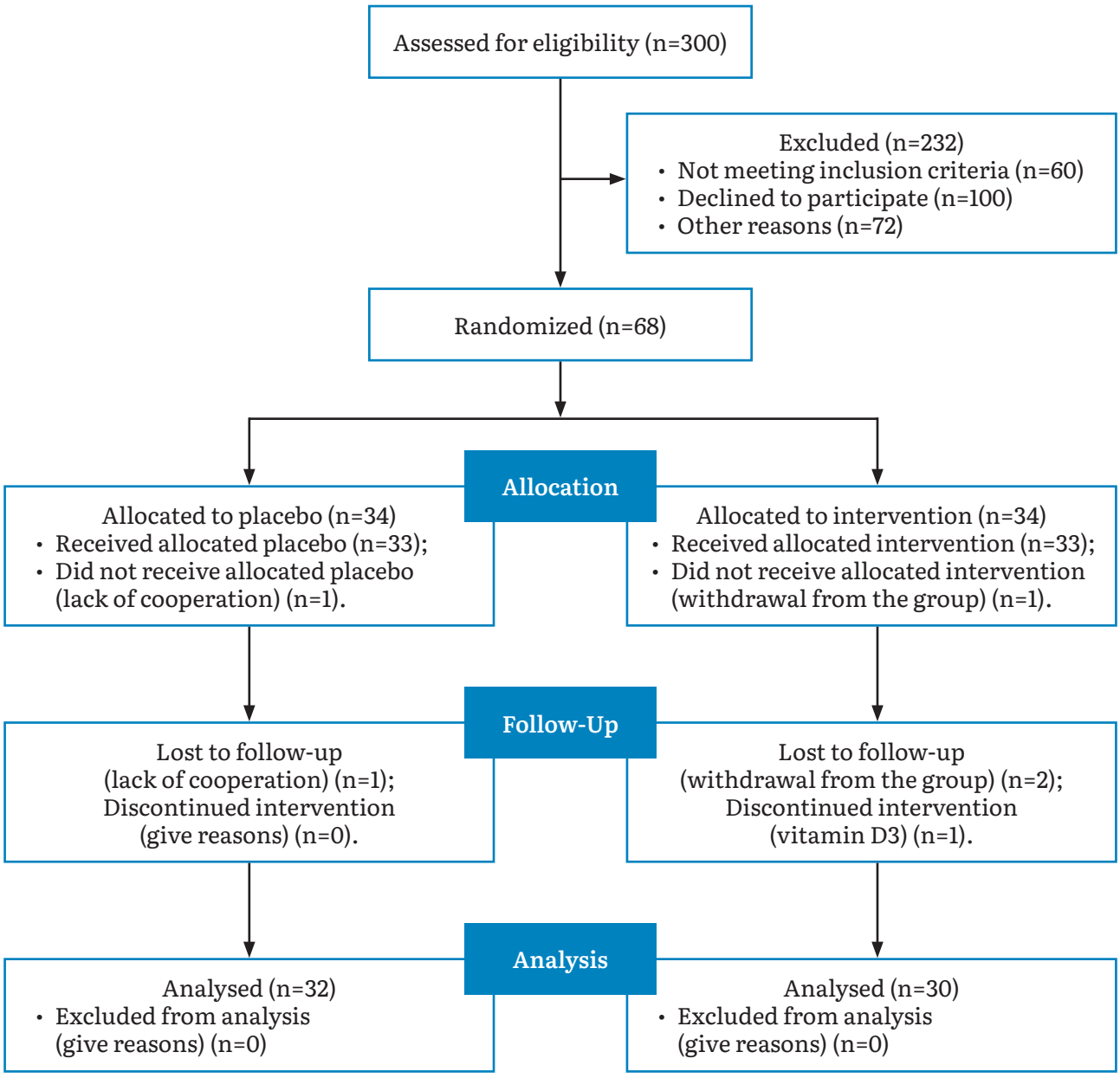

Figure 1: Flow chart for subject participation.

https://doi.org/10.46389/rjd-2022-0972

Table 1: Baseline characteristics of patients; age, sex and diabetes duration are mean (SD).

Variable	Vitamin D3 group (n=30)	Placebo group (n=32)	P-value (Difference between groups)
Age (years)	57.30±4.750	57.22±5.302	0.95 +
Male sex (%) **Female sex (%)**	60% (18/37) 40% (12/25)	59.4% (19/37) 40.6% (13/25)	0.96
Duration of diabetes (years)	9.27±3.25	8.88±3.44	0.65 +

Note: + – P-values obtained using the independent-samples t-test.

Randomization

A finite block randomization method was used to match age and sex. Four individuals were assigned to each block. Of these four, two received accidental VD3 and two others the placebo. Neither the data collectors nor the laboratory staff knew the participants' random group status. To ensure blindness, VD3/placebo capsules were uniformly packaged and coded by the manufacturer.

Statistical analysis

Data analyzed by SPSS software (version 22) and Values of P≤0.05 were considered significant. Results are expressed as mean±SD. The Shapiro-Wilk test investigated the normal distribution of data. Pearson Chi-Square test was used to analyze and compare the two groups in terms of gender. An independent T-test or its equivalent non-parametric test (Mann-Whitney test) was used to compare the two groups. Moreover,

Table 2: Comparison changes of characteristics anthropometric and biochemical between the vitamin D3 group and the placebo group.

Variable	Vitamin D3 group (n=30)	Placebo group (n=32)	P-value
Body mass index	-0.04±0.34	-0.12±0.47	0.72 +
Blood pressure			
Systolic BP (mmHg)	-0.3±16.26	-3.1±14.17	0.48 +
Diastolic BP (mmHg)	-1.86±11.28	-0.78±8.38	0.54 +
Triglycerides (mg/dl)	1.23±64.01	3.18±43.72	0.60 ‡
Cholesterol (mg/dl)	-1.26±36.72	14.65±41.56	0.16 +
HDL-cholesterol (mg/dl)	0.03±6.24	-0.46±4.37	0.50 ‡
LDL-cholesterol (mg/dl)	-0.6±31.35	8.90±30.55	0.29 +
25(OH)VD3 (ng/ml)	21.91±9.81	1.18±7.41	<0.001 +
serum uric acid (mg/dl)	0.39±1.51	-0.08±.1.21	0.18 +
HbA1c (%)	-0.35±1.2	-0.13±1.50	0.50 +
FBS (mg/dl)	-6.93±39.57	5.53±42.21	0.07 +
Calcium (mg/dl)	0.13±0.83	0.07±0.44	0.17 ‡
Phosphorus (mg%)	0.09±0.78	0.14±0.70	0.75 ‡
Serum creatinine (mg/dl)	0.02±0.19	0.03±0.22	0.80 ‡
Serum urea (mg/dl)	1.20±6.38	0.78±10.88	0.90 ‡
Serum Albumin (g/dl)	0.06±0.26	0.01±0.23	0.39 ‡
eGFR (cc/min)	-1.42±17.32	-0.56±16.27	0.92 ‡

Note: + – P-values obtained using the independent-samples t-test. ‡ P-values obtained using the Mann-Whitney test.

the pair T-Test or its equivalent non-parametric (Wilcoxon test) was used to compare intragroup (before and after). Also, descriptive methods [statistical tables (quarters) and central indicator (median)] were used to analyze the information of non-parametric variables.

Results

Three hundred subjects were screened, of whom 68 (23%) had 25(OH) VD3 levels <30 ng/ml. Of the 68 patients with subnormal 25(OH) VD3 levels, two patients withdrew, and four (two in each group) had their medications changed by their usual physician during the study period (Figure 1). Baseline details of the patients who completed the study are presented in Table 1. At baseline, there was no significant difference in 25(OH) VD3 levels, calcium, phosphate, HbA1c, FBS, albumin, uric acid, urea, lipid profile, blood pressure, and BMI between groups. Then, they were randomly allocated to two groups (placebo or VD3 supplement). After eight weeks of intervention, the findings were as follows:

25(OH) VD3 levels

Comparing the changes between the two groups, the serum level of 25(OH) VD3 in the VD3 group was significantly higher than in the placebo group. (21.91±9.81 *vs*. 1.18±7.41, P<0.001) (Table 2). Moreover, in the comparison of the within-group changes (before and after), 25(OH) VD3 levels in the VD3 group (P<0.001) compared to the placebo group (P=0.38) were significant (Table3).

HbA1c and FBS levels

Comparing the changes between the two groups, the serum level of HbA1c decreased slightly in both groups, and this decrease was slightly greater in the VD3 group than in the placebo group (-0.35±1.2 *vs*. -0.13±1.5, P=0.50) (Table2).

Besides, the FBS levels decreased slightly in the VD3 group compared to the placebo group (-6.93±39.57 *vs*. 5.53±42.21, P=0.07) (Table 2).

Lipid profile levels

Triglycerides (TG)

Compared to changes between the two groups, the serum level of TG increased slightly in both groups. In addition, this increase was slightly greater in the placebo group (1.23±64.01 *vs*. 3.18±43.72, P=0.60) (Table 2).

Total cholesterol (TC) in front of

Based on the results, the serum level of TC decreased slightly in the VD3 group than in the placebo group (-1.26±36.72 *vs*. 14.65±41.56, P=0.16) (Table 2). While TC levels most significantly increased in the placebo group (p=0.05) after 8 weeks (Table 3).

High-Density Lipoprotein (HDL-C)

The changes in serum HDL-C levels in the VD3 group were almost constant (P=0.56). In contrast, there was a small decrease in the placebo group after 8 weeks (0.03±6.24 *vs*. -0.46±4.37, P=0.50) (Table 2).

Low-Density Lipoprotein (LDL-C)

In addition, when examining the variations between the two groups, we found a small decrease in LDL-C levels in the VD3 group *versus* the serum levels of LDL-C that increased slightly in the placebo group (-0.6±31.35 *vs*. 8.90±30.55, P=0.29) (Table 2).

Also, there were no significant changes in serum levels of uric acid (Table 3), phosphate, calcium, and albumin in both between and within-group comparisons. Also, in comparison between and within the groups, there were no significant changes in serum levels of parameters of kidney function evaluation, including creatinine, urea, and estimated glomerular filtration (eGFR), and all were in the reference range (Table 4).

Discussion

T2DM is the most common metabolic disease around the world [18]. Vitamin D deficiency or insufficiency also is highly prevalent and this observation is more profound in patients with T2DM [19, 20]. Recent convincing evidence indicates a role of vitamin D deficiency in the pathogenesis of insulin resistance and insulin secretion disorders. In this area, epidemiologic studies suggest that VD3 status plays a role in glycemic control in patients with T2DM. In the present study, oral administration of VD3 at a dose of 50000 IU/week for 8 weeks caused a significant increase in 25-hydroxyvitamin D3 levels in the intervention group compared to the placebo group.

Moreover, the levels of FBS and HbA1c insignificantly decreased in the VD3 group. Nonetheless, findings of a systematic review and meta-analysis show no effect of VD3 supplementation on the parameters of glycemic control, including HbA1c and FBS, in patients with T2DM [21]. In a study by Davidson *et al*., the VD3

https://doi.org/10.46389/rjd-2022-0972

Table 3: Characteristics anthropometric and biochemical measures; comparison changes of parameters in the Vitamin D3 and placebo groups at 8 weeks mean (SD).

Variable α	Baseline		Endpoint		P-value + (Difference within vitamin group)	P-value + (Difference within placebo group)	P-value ‡ (Difference between groups)
	Vitamin D3 group (n=30)	Placebo group (n=32)	Vitamin D3 group (n=30)	Placebo group (n=32)			
Body mass index	25.64±3.13	25.35±3.02	25.60±3.07	25.22±2.86	0.52	0.14	0.62
Blood pressure							
Systolic BP (mmHg)	134.73±17.57	133.56±18.58	134.43±17.76	130.47±15.05	0.92	0.23	0.51
Diastolic BP (mmHg)	73.30±9.63	72.88±8.71	71.43±7.46	72.09±7.91	0.37	0.60	0.74
Cholesterol (mg/dl)	157.17±37.69	143.31±30.65	155.90±29.54	157.97±32.37	0.85	0.05	0.84
LDL-cholesterol (mg/dl)	83.50±29.47	79.44±28.26	82.90±22.70	88.34±30.60	0.92	0.12	0.43
25(OH) VD3 (ng/ml)	18.14±6.28	18.89±6.56	40.05±9.69	20.07±6.79	<0.001	0.38	<0.001
Serum uric acid (mg/dl)	3.89±0.95	4.17±1.02	4.28±1.33	4.09±1.03	0.12	0.88	0.87
HbA1c (%)	8.29±1.66	7.91±1.93	7.94±1.48	7.79±1.52	0.12	0.65	0.70
FBS (mg/dl)	166.03±43.72	146.81±31.72	159.1±45.12	152.34±35.32	0.35	0.46	0.51

Note: LDL-C – low-density lipoprotein cholesterol; 25(OH) VD3 – 25-hydroxy vitamin D3; HbA1c – glycosylated hemoglobin; FBS – fasting blood sugar. α; parametric. + – P-value for comparing baseline with endpoint values within each group; Paired sample t-tests were used. ‡ – P value for the comparison between study groups in endpoint; independent-samples t-test were used for variables parametric.

Table 4: Changes from baseline to endpoint measures of outcomes within vitamin D3 and placebo groups and between groups (Median values and 25th, 75th percentiles).

Variable β	Placebo			Vitamin D3			P-value ‡
	Median	25th, 75th percentiles	P-value +	Median	25th, 75th percentiles	P-value +	
Triglycerides (mg/dl)							
Baseline	121.00	96.50, 142.75	0.84	133.50	94.50, 186.25	0.60	0.54
Endpoint	125.00	99.25, 148.75		146.00	78.75, 180.50		
HDL-C (mg/dl)							
Baseline	42.00	41.00, 43.75	0.28	42.00	40.0, 45.00	0.88	0.56
Endpoint	42.00	41.00, 43.00		42.00	42.00, 43.00		
Calcium (mg/dl)							
Baseline	9.30	9.02, 9.60	0.24	9.30	9.05, 9.60	0.07	0.14
Endpoint	9.30	9.22, 9.60		9.55	9.30, 9.70		
Phosphorus (mg%)							
Baseline	3.70	3.50, 4.10	0.28	4.00	3.50, 4.22	0.52	0.79
Endpoint	4.00	3.50, 4.47		4.10	3.50, 4.50		
Serum creatinine (mg/dl)							
Baseline	1.10	1.00, 1.20	0.26	1.10	0.90, 1.20	0.64	0.34
Endpoint	1.20	1.00, 1.20		1.00	0.97, 1.20		
Serum urea (mg/dl)							
Baseline	27	24.00, 33.50	0.29	25.00	20.75, 30.50	0.22	0.23
Endpoint	28.50	22.00, 35.75		25.50	23.00, 29.00		
Serum Albumin (g/dl)							
Baseline	3.70	3.62, 3.90	0.32	3.70	3.60, 3.90	0.13	0.43
Endpoint	3.80	3.70, 3.84		3.80	3.70, 3.93		
eGFR (cc/min)							
Baseline	65.15	57.68, 79.23	0.85	67.75	60.90, 82.02	0.66	0.57
Endpoint	63.01	52.56, 80.07		69.40	61.05, 77.72		

Note: HDL-C – high-density lipoprotein cholesterol; β; Nonparametric.+ – P-value for comparing baseline to endpoint values within each group; Wilcoxon test was used. ‡ – P-value for the comparison between study groups; Mann-Whitney test were used for variables for nonparametric.

intake (88,865 IU/Week, 12 months) had no significant effect on FBS and 2-hr glucose in a relatively large population of pre-diabetes and hypovitaminosis D, while HbA1c became less than 0.2% significant in the VD3 group [10]. Interestingly, the administration of VD3 (50,000 IU/Week, for 12 weeks) to type 2 diabetic patients without vitamin D deficiency showed significant changes in HbA1c levels in men [13]. Numerous studies have reported the role of VD3 in controlling diabetes through two mechanisms: its direct effect on the stimulation of insulin receptors and its indirect effect on regulating extracellular calcium and calcium flow. Calcium is needed for intracellular processes in insulin-responsive tissues such as skeletal muscle and adipose tissue, so VD3 facilitates pancreatic β-cell function and improves insulin resistance [3]. Our study showed that VD3 supplementation decreased LDL-C and TC levels in the VD3 group compared to the placebo group, although the differences were not statistically significant. It is possible that using higher VD3 doses or longer intervention times can lead to more effective results. In this field, a systematic review and meta-analysis were performed to check the effect of VD3 supplementation on serum lipid profile. The results were associated with a

https://doi.org/10.46389/rjd-2022-0972

beneficial effect on lowering TC, LDL-C, and TG serum levels but not HDL-C levels [22]. A meta-analysis study of 17 articles on participants with T2DM detected that VD3 supplementation decreased TC and LDL-C but had no beneficial effect on TG and HDL-C [23]. Another meta-analysis in 2017 among women with gestational diabetes observed that VD3 supplementation had a beneficial effect on serum LDL-C but had no positive effect on TC, HDL-C, and TG [24].

Several studies have inferred that the connection between low levels of 25(OH) VD3 and metabolic syndrome was more in overweight and obese people than in normal-weight individuals; because fat mass acts as a reservoir of 25(OH) VD3 and its metabolites. Also, obese people have less exposure to sunlight because of less exercise and less mobility [25]. In our study, people were, on average, overweight, which could be a possible cause of vitamin deficiency in these patients. However, it is not clear whether VD3 has a reciprocal effect on reducing BMI. The meta-analysis performed in this regard did not show any evidence of a direct effect of VD3 on BMI [17]. Similarly, no positive effect was observed in our results.

Recent observations have indicated that chronic kidney disease seems to be associated with a high incidence of nutritional vitamin D insufficiency or deficiency as manifested by decreased levels of 25(OH) VD3 [26]. Serum urea, creatinine, and eGFR are the most widely accepted parameters for assessing renal impairment [27]. As GFR declines, urinary excretion of urea and creatinine also declines, and blood concentration increases [28]. Some studies have also linked BMI to renal impairment, but our findings did not show a significant association in parameters related to renal function, including creatinine, urea, and eGFR. There was no sign of kidney failure in the patient's study. A meta-analysis in this area also shows that higher BMI is significantly associated with renal dysfunction [29]. Also, in a meta-analysis study that was restricted to RCTs, no beneficial effect was noted with VD3 supplementation in the chronic kidney disease (CKD) population [30]. While in the present study, taking supplements was associated with positive effects on serum lipid profile and HbA1c levels.

Strength and limit

Our study contains several strengths; first, the current study is a double-blind randomized controlled study that is proposed as a valid study. In addition, patients were matched according to gender and age in the reference scenario. Also, we undertreated patients in winter to eliminate the effect of sunlight on VD3 levels. This study also included limitations; we did not know about the patients' diet, but we gave them training in this regard and asked them not to change their diet during the study. Individuals used different anti-diabetic drugs, which caused heterogeneity in groups. To avoid drug interactions, we had to shorten the study time. Because patients were clinically checked every three months and dose changes were probable. According to the results, it seems that increasing the intervention period and measuring the level of parameters at different time intervals may be more effective in evaluating the effectiveness of VD3.

Conclusion

This study demonstrated that VD3 decreased TC, LDL-C, HbA1c, and FBS serum levels in patients with T2D, but changes between groups were insignificant. It is possible that the effect of VD3 on improving hyperglycemia and lowering the lipid profile levels increases with increasing intervention time and increasing sample size.

Acknowledgments

We are extremely grateful for the cooperation and assistance of the staff and doctors of the Central Diabetes Clinic located in Birjand.

Conflicts of interest

The author declares no conflict of interest.

Ethical approval

This study was approved by the Ethics Committee of Birjand University of Medical Sciences and registered on the IRCT website with the code IRCT20200616047795N1.

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