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Original Article

Effects of vitamin D supplementation on depressive symptoms in type 2 diabetes mellitus patients: Randomized placebo-controlled double-blind clinical trial

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ABSTRACT

Aim: Diabetes increases the odds of depression and depression is often associated with poor glycemic control and complications of diabetes. Vitamin D is also believed to improve glycemic control and ameliorate depressive symptoms. Therefore, we examined effects of vitamin D monotherapy (without antidepressant drugs) on depressive symptoms in Type 2 diabetic patients with mild to moderate depressive symptoms.

Methods: We conducted 12 weeks, placebo-controlled, double-blind, randomized trial on 68 subjects with T2DM and mild to moderate depressive symptoms. Subjects received 100 μg (4000 IU) vitamin D (n = 32) or placebo (n = 34) daily. Beck Depression Inventory-II (BDI–II–PERSIAN) was applied for assessment of the severity of depression. Depression scores and metabolic profiles were measured at the beginning and end of trail.

Results: after 3 months of vitamin D supplementation, mean values of 25(OH) D increased from 15.5 ± 8.8 to 32.2 ± 8.9 ng/ml (p-value <0.001) in the vitamin D group. Moreover, BDI-II scores decreased from 15.2 ± 9.6 to 9.8 ± 7.2 (p-value <0.001) in the vitamin D group and 15.5 ± 11.2 to 13.7 ± 11.5 (p-value = 0.03) in placebo group. This decrease in BDI-II scores were significant (27.6% vs 10.8%) compared with placebo (p-value = 0.02). In term of metabolic profiles, mean change in level of Hemoglobin A1c (HbA1c), insulin and triglycerides (TG) were significantly higher in response to the treatment with vitamin D compared to placebo (p-value <0.02).

Conclusions: In conclusion, supplementation of vitamin D in T2DM patients may protect these patients against the onset of major depressive disorder (MDD), with noticeable favorable effects on measures of metabolic profiles.

Trial registration: NCT03008057

1. Introduction

The diabetes mellitus has reached worldwide epidemic. The overall prevalence of diabetes was reported 6.6% in 2010 and it is estimated to reach 7.8% by 2030 [1]. Micro-vascular and macro-vascular complications are more common among diabetic patients. Vascular complications can lead to premature death in diabetic patients [2,3]. It seems that body weight and blood pressure control and adhering from a healthy life style, along with medical management are effective factors in reducing vascular complications of diabetes [4]. But, the compliance of diabetic patients from these recommendations are not satisfying [5]. Emerging evidence indicated that comorbid depression in diabetic patients may be one of the main cause of being non-compliance [6]. Earlier studies have shown that chronic hyperglycemia increase the incidence of

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depression and cognitive impairment in diabetic patients [7–9]. In addition, some studies have demonstrated that comorbid depression in diabetic patients play an important role in increasing diabetic complications [8].

Depressed diabetic patients have poor adherence to dietary recommendations or self-monitoring plans [10].

Antidepressant drugs have been shown to improve the depressive symptoms in these patients. However, these medications have adverse effects on weight and some glycemic indices [11,12]. Therefore, it is crucial to provide an adjunctive therapy for prevention of major depressive disorder (MDD) initiation in diabetic patients.

Previous evidence has reported that vitamin D has few side effects and reduces the development of T2DM as well as its complication [13,14]. Moreover, accumulating data has indicated that vitamin D has antidepressant effects in patients with various types of depressive disorders [15,16].

The function of vitamin D in the brain is not completely understood but there are hypotheses that vitamin D receptors exist in different regions of the brain which can regulate serotonin production. Serotonin is one of the most important neurotransmitters involved in mood regulation [17,18]. Although vitamin D has beneficial effects on diabetes and depression, but there is still a lack of evidence of these two conditions comorbid. Thus, we aimed to examine effects of vitamin D in T2DM patients with mild to moderate depressive symptoms and assess glycemic indices, lipid profile, and blood pressure as secondary outcomes.

2. Subjects

68 patients with T2DM were included for this randomized, double-blind placebo controlled clinical trial from the Iranian Diabetes Society during October 2017 to May 2018. Diabetes Type 2 was diagnosed by an endocrinologist in accordance with of the American Diabetes Association criteria with fasting blood sugar (FBS) concentrations higher than 126 mg/dl (confirmed by testing twice without using antiglycemic medications). Inclusion criteria were: willingness to participate, aged 30–60 years old, body mass index (BMI) from 20 to 30 kg/m^2, receiving no herbal products or dietary supplements at least 3 months before and throughout the intervention, willingness to maintain their current diet, physical activity and life style during 3 months of trial. These patients were not included: patients consuming vitamin D supplements within past 3 months, patients with major depressive disorder (MDD) and taking antidepressants, having chronic kidney diseases, hepatobiliary diseases, gastrointestinal (GI) diseases, consuming drugs that interact with vitamin D such as anti–consultants drugs (Phenytoin and Phenobarbital), Using insulin or thiazolidinediones or anti-obesity drugs, pregnancy and lactation. The exclusion criteria were: Any changes in the type or dosage of medications during the study, and lack of adherence to the trial based on refusing to consume at least 90% of recommended treatments.

All patients signed written informed consent. The study was approved by the local Ethical Committee of Tehran University of Medical Sciences (Reference number 32615). Furthermore, this trial was registered at ClinicalTrials.gov (Identifier: NCT03008057). The specialists, staffs and patients were blinded during trial. We called patients weekly to check their adherence to treatment.

3. Materials and methods

3.1. Randomization and intervention

Sixty-eight patients enrolled in this study. We used stratified randomization based on sex (male/female) and BMI (normal/overweight). Participants of this study allocated into two groups (vitamin D and placebo) by random permuted block method. An assistant performed block randomization base on computer-generated random sequences and the intervention was blinded for both researchers and patients.

Vitamin D and placebo tablets were prepared by the Pars Minoo Pharmaceutical, Cosmetic and Hygienic Company (Iran). Each tablet of vitamin D contains 100 μg or 4000 IU of vitamin D [19, 20]. Each tablet of placebo contains gelatin starch, lactose powder, magnesium stearate, and citic acid. The percentage of lactose powder has decreased in vitamin D supplements and vitamin D added instead. Placebo and vitamin D tablets were similar in the shape, size, and the color. The type of supplements was blinded as A and B packages for investigators and patients. Simultaneously, participants of the both groups received their own anti-diabetic medications and were recommended to sustain their usual diets and physical activity.

3.2. Outcomes and measurements

Primary outcome was defined as improved depression scores. We used Persian version of Beck Depression Inventory-II (BDI–II–PERSIAN) for assessment of depression. BDI-II is a questionnaire with 21 items with a 4-point scale which identifies the severity of depression. The overall score of this questionnaire ranges from 0 to 63.

The validation and reliability of Persian version of BDI-II was studied by Ghasemzadeh et al. [21].

Secondary outcomes were anthropometric parameters, blood pressures, fasting blood sugar (FBS), hemoglobin A1c (HbA1c), serum insulin, triglyceride (TG), High-density lipoproteins (HDL), Low-density lipoprotein (LDL). At the beginning and the end of the study, venous blood samples were taken from patients after 12–14 h fasting. The anthropometric parameters were measured before the intervention according to standard protocols. Body mass index (BMI) was calculated.

FBS levels were measured using enzymatic method by auto-analyzer instrument. HbA1c percentages were measured in whole blood by immunoturbidometruc method. Serum insulin was measured by human insulin ELISA kit (Diametra, Italy). For measuring serum vitamin D, we used chemiluminecense method (Cobas E411 system) with Roche kit. Lipid profile was determined by autoanalyzer (BT system 1500). Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured using a manual sphygmomanometer, while patients sitting. Physical activity of participants were assessed by validated Persian, last 7-day long form of International Physical Activity Questionnaire (IPAQ) [22].

3.3. Statistical analyses

The Kolmogorov-Smirnov test was performed for determining the normality of the parameters. The initial anthropometric, clinical and biochemical variables were compared between the two groups by *t*-test for quantitative and χ^2 test for categorical data. Changes in clinical and biochemical variables are reported as mean ± SD and compared between the groups using the *t*-test. In all analysis, p-value <0.05 was considered statistically significant.

4. Results

4.1. Trial profile

From October 2017 to May 2018, 359 T2DM patients were volunteered to participate, 291 patients were not eligible following the baseline visit for the following reasons: consuming vitamin D supplements or any supplements contain vitamin D, having kidney

or liver diseases, using insulin, having depression requiring additional care and treatment. Finally, 68 subjects who were eligible and willing to participate in the study were included. During the study, 2 subjects (1 woman and 1 man) of the vitamin D group withdrew from the study due to personal reasons, resulting in 64 subjects included (32 in vitamin D group and 34 patients in placebo group) and completed the study in accordance with the study program (see Fig. 1).

4.2. Baseline

The demographic data and baseline characteristics of participant randomized to the study are indicated in Table 1. The groups were homogenous in terms of general, anthropometric and laboratory parameters (p-value >0.05). The mean age was 49.7 ± 6.5 year and 51.3 ± 5.9 year, with BMI of 27.3 ± 2.3 kg/m^2 and 27.5 ± 1.6 kg/m^2 in vitamin D and control group, respectively. The estimated mean FBS and total cholesterol was higher in control group, but with no difference between two groups (p-value >0.05). Mean 25(OH) serum D concentrations showed vitamin D deficiency in both groups (serum 25(OH) D < 20 ng/ml).

4.3. Post-intervention

Fig. 2 shows changes of BDI-II scores of patients before and after interventions.

BDI-II scores decreased 27.6% (5.4) in intervention and 10.8% (1.8) in placebo group, which was significant between the two group (p-value = 0.02).

Table 2 shows the comparison of mean change in laboratory parameters at the beginning and end of trial. There was significant difference in mean change of 25(OH) D serum level after 3 months between two groups (16.9 ± 5.9 ng/ml vs. 0.8 ± 4.3, p-value <0.001). Vitamin D group had a larger decrease of HbA1c and serum insulin levels compared with placebo group (p-value <0.02). These findings were similar for TG level as the mean change was significantly higher in vitamin D group compared with placebo (p-value = 0.003). There was marginal difference in mean change of DBP between two groups (p-value = 0.056), and no significant difference in mean change of FBS, HDL, LDL, and total cholesterol level between vitamin D group and control group (p-value >0.05).

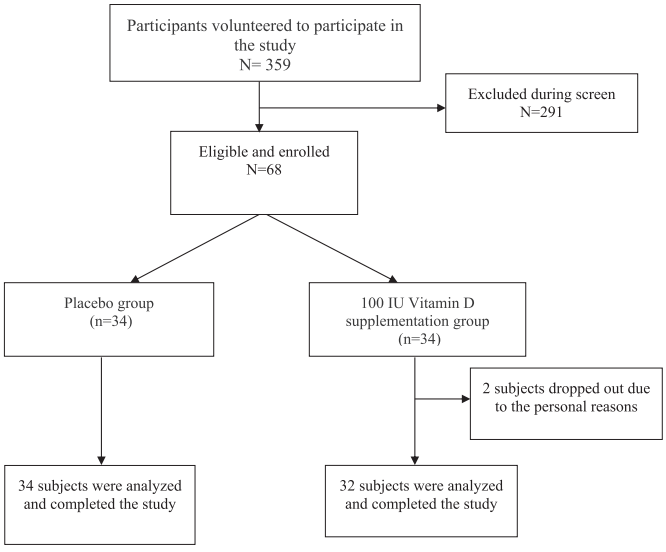

Fig. 1. Trial profile.

Table 1
Baseline characteristics of participants.

	Vitamin D2 (n = 32)	Placebo (n = 34)	P-value[a]
Sex, n (%)			
Male	19 (35.8)	20 (36.4)	0.9
Female	13 (24.5)	14 (25.5)	
Age, (year)	49.7 ± 6.5	51.3 ± 5.9	0.2
Educational level, n (%)			
Not-educated/Primary-secondary	0 (0.0)	3 (4.5)	0.3
	8 (12.1)	7 (10.6)	
University/college	24 (36.4)	24 (36.4)	
Employed, n (%)			
Yes	19 (28.8)	21 (31.8)	0.8
No	13 (19.7)	13 (19.7)	
Marital status, n (%)			
Single	2 (3)	3 (4.5)	0.9
Married	27 (40.9)	28 (42.4)	
Divorced/widow	3 (4.5)	3 (4.5)	
Smoking habit, n (%)			
Never	28 (24.4)	28 (24.4)	0.9
Current	4 (6.1)	5 (7.6)	
Ever	0 (0)	1 (1.5)	
Height (cm)	169.0 ± 10.9	166.0 ± 7.7	0.2
Body weight (kg)	78.7 ± 14.1	76.3 ± 9.4	0.4
BMI (kg/m^2)	27.3 ± 2.3	27.5 ± 1.6	0.6
WHR	0.9 ± 0.05	0.9 ± 0.06	0.3
Metformin use, n (%)			
Yes	17 (32.1)	21 (23.6)	0.4
No	15 (28.3)	13 (28.3)	
PA (MET/mint/week)	16.9 ± 13.2	16.8 ± 10.8	0.9
SBP (mmHg)	126.7 ± 9.5	129.8 ± 14.3	0.3
DBP(mmHg)	81.8 ± 8.1	85.1 ± 10.8	0.1
FBS(mg/dl)	177.6 ± 43.6	186.1 ± 53.4	0.4
HbA1c (%)	7.6 ± 1.1	7.9 ± 1.1	0.3
Serum insulin (mU/L)	11.4 ± 5.5	11.7 ± 4.3	0.8
TG (mg/dl)	182.5 ± 69.8	179.6 ± 83.5	0.8
HDL (mg/dl)	43.1 ± 12.2	45.5 ± 10.8	0.3
LDL (mg/dl)	98.1 ± 35.3	93.6 ± 34.6	0.6
Total cholesterol (mg/dl)	189.4 ± 48.4	205.4 ± 49.4	0.1
Serum 25(OH)D (ng/ml)	15.5 ± 8.8	14.6 ± 11.4	0.8

BMI: Body Mass Index, WHR: Waist to Hip Ratio, PA: Physical Activity.
SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, FBS: Fasting Blood Sugar; HbA1C: Hemoglobin A1c, TG: triglycerides, HDL: High-density lipoproteins, LDL: Low-density lipoprotein.
Quantitative variables are presented as mean ± SD, and categorical variables are expressed by frequencies (percent).
[a] Independent *t*-test was applied for mean differences, chi-square and Fisher exact tests were performed for categorical variables.

Dietary intake of participants showed there was no significant difference between the energy intake, macro nutrients and vitamin D at the baseline and end of trial (data not shown).

5. Discussion

The results of this study showed that vitamin D supplementation is effective to ameliorate depressive symptoms of Type 2 diabetic patients with mild to moderate depressive symptoms. Not only treatment with vitamin D supplements significantly improved depressive symptoms, but also significantly decreased HbA1c, insulin and TG levels in diabetic patients with vitamin D deficiency. Our findings are in line with other's results.

In the clinical trial conducted by Mozaffari-Khosravi et al. [15], after three months of intervention, there was a significant improvement in depression mood of those who were received injected vitamin D. Other clinical trial was carried out by Penckofer et al. [23] reported that vitamin D supplementation in depressed diabetic women significantly improved depression state. In addition, compelling evidence indicated that vitamin D supplementation is effective for treating depression in patients with major depressive disorder as an adjunctive therapy to antidepressant

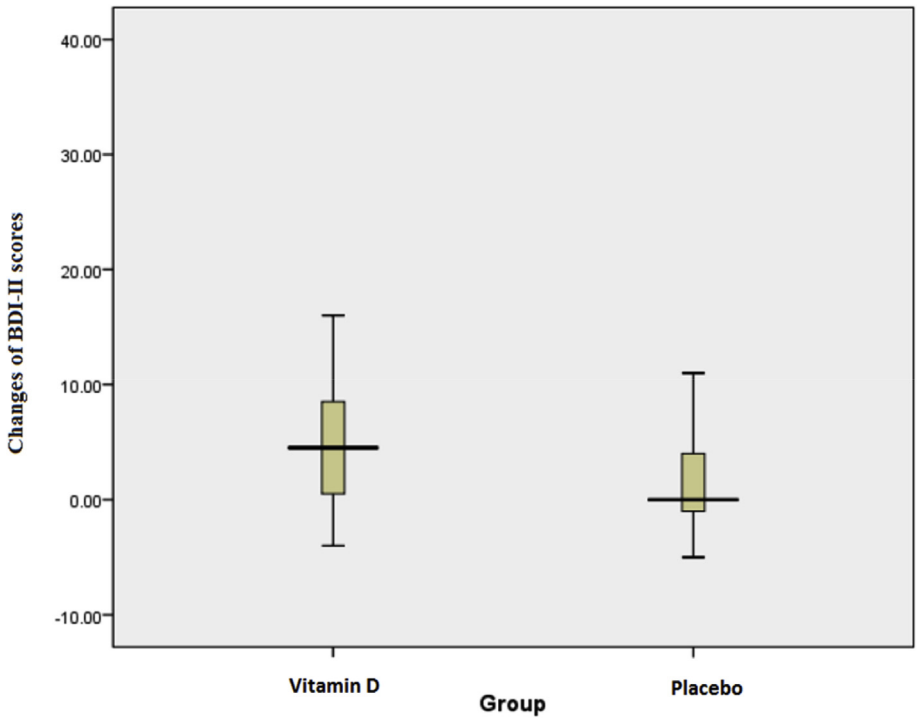

Fig. 2. Boxplot summarizing changes of depression score assessed by Beck Depression Inventory-II (BDI-II) score in type-2 diabetes mellitus patients treated with vitamin D and placebo. Data are reported as mean and standard deviation. P- value is according to results of an independent *t*-test. (P-value = 0.02).

Table 2
Between-group comparison of mean change in each laboratory outcomes between vitamin D supplementation and placebo groups after 3 months of supplementation*.

	Vitamin D group (n = 32)	Placebo group (n = 34)	p-value
	Mean change ± standard deviation	Mean change ± standard deviation	
Serum 25(OH)D (ng/ml)	16.9 ± 5.9	0.8 ± 4.3	<0.001
SBP(mmHg)	−1.3 ± 4.7	−0.1 ± 7.0	0.4
DBP(mmHg)	−1.4 ± 5.2	1.4 ± 6.4	0.056
FBS(mg/dl)	−22.9 ± 33.3	−6.6 ± 43.1	0.09
HbA1c (%)	−0.5 ± 0.5	−0.07 ± 0.9	0.01
Serum insulin (mU/L)	−0.7 ± 1.4	0.1 ± 1.1	0.007
TG (mg/dl)	−34.0 ± 61.4	7.4 ± 49.3	0.003
HDL (mg/dl)	−2.1 ± 6.6	−2.1 ± 5.6	0.9
LDL (mg/dl)	−0.5 ± 33.3	−0.4 ± 27.3	0.9
Total cholesterol (mg/dl)	−5.3 ± 51.5	−13.2 ± 37.8	0.4

SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure, FBS: Fasting Blood Sugar; HbA1c: Hemoglobin A1c, TG: triglycerides, HDL: High-density lipoproteins, LDL: Low-density lipoprotein.
*Student's t-test comparing mean change between groups.

drugs [24]. Several cross-sectional studies have reported the relationship between low serum levels of 25-hydroxyvitamin D and depressive symptoms [25,26], whereas no such associations were observed by other studies [27,28].

Antidepressant drugs can effectively improve depression mood and its related symptoms in diabetic patients [29], but antidepressants such as tricyclics and paroxetine may cause weight gain and insulin resistance [30,31], thereby, leading to further metabolic disturbance.

Mechanisms involved in mood regulation of vitamin D are not completely understood but there are several hypotheses. Vitamin D receptors exist in different regions of the brain and vitamin D enables to pass through blood brain barrier [17,18,32]. It is known that vitamin D can regulate production of serotonin. Serotonin is one of the key neurotransmitters involved in mood regulation [33]. Moreover, depression is caused by the imbalance between the GABAergic inhibitory and excitatory neurons and the change in neuronal activity. In people with depression, there is a deficit in the function and number of GABAergic neurons which have an important role in mood regulation. Activation of glutamatergic pathway in depression state can lead to diminished GABAergic neurons. High level of glutamate can increase the neuronal level of Ca^{2+} through activation of the inositol trisphosphate cellular pathway (InsP3). This increase in Ca^{2+} neuronal levels may contribute to the development of depressive symptoms [34–37]. Vitamin D may regulate the expression of Ca^{2+} pumps and buffers which can lead to decline Ca^{2+} neuronal levels [38,39].

In the current study, vitamin D significantly decreased HbA1c, and insulin levels in diabetic patients. It agrees with several studies that reported consumption of vitamin D could decrease HbA1c and insulin levels in diabetic patients [40,41].

One suggested mechanism for this effect is related to beneficial

effects of vitamin D on insulin secretion. Vitamin D facilitates the release of insulin from beta cells [42].

It is noticeable that in this study, we included type 2 diabetic patients without filling MDD criteria and without using antidepressant drugs. Also our results are only generalizable to T2DM patients with mild to moderate depressive symptoms and vitamin d deficiency levels.

The Strengths of our study include the homogeneity of population, the small number of missing, the double-blind randomized placebo-controlled design, and using a reliable and valid method to measure depression (BDI–II–PERSIAN). Our limitation was short follow up period.

This placebo-controlled double-blind randomized trial showed that vitamin D supplementation can attenuate depressive symptoms in diabetic patients, along with exerting metabolic improvements. Depression is more common in diabetic patients and is associated with an increase in incidence of diabetes complications. Vitamin D supplementation may prevent the onset of MDD in depressed diabetic patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.dsx.2019.06.011.

Conflicts of interest

The authors have no other conflicts to disclose.

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