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The Effect of Vitamin D Supplementation in Overweight or Obese Type 2 Diabetic Patients with Vitamin D Deficiency and Dyslipidemia

Sahar Shahriari[1], Mohammad Hassan Eftekhari[2*], Marjan Jeddi[3]

1. Student Research Committee, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
2. Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
3. Internal Medicine Department, Shiraz University of Medical Sciences, Shiraz, Iran

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**Corresponding author:*
Mohammad Hassan Eftekhari, Nutrition Research Center, Department of Clinical Nutrition, School of Nutrition and Food Sciences, Shiraz University of Medical Sciences, Shiraz, Iran
Tel: +98-71-37251001
Email: h_eftekhari@yahoo.com
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ABSTRACT

Background: Vitamin D supplementation was shown to reduce obesity-related oxidative stress and inflammation among overweight or obese people as well as improving glycemic control and lipid profile in type 2 diabetic (T2D) patients. This study was conducted to determine the effect of vitamin D supplementation on metabolic biomarkers, oxidative stress and systemic inflammation in overweight or obese T2D patients with vitamin D deficiency and dyslipidemia.

Methods: In this randomized, double-blind placebo-controlled clinical trial, 60 individuals with T2D, vitamin D deficiency and BMI greater than 25 kg/m^2 were randomly divided in two groups to receive either vitamin D (50000 IU, once a week) or placebo (1000 mg corn oil, once a week) for eight weeks. At the entry and end of study, blood samples were collected to evaluate serum high sensitive C-reactive protein (hs-CRP), fasting blood sugar (FBS), glycated hemoglobin (HbA1c) malondialdehyde (MDA), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG).

Results: At the end of the study, serum FBS (p=0.04), TG (p=0.02) and hs-CRP (p=0.02) levels significantly decreased in the vitamin D supplemented group in comparison to the control group. Supplementation with vitamin D was associated with significant improvements in serum 25 –OH vitamin D levels when compared to the control group.

Conclusion: This study indicates that eight weeks supplementation of vitamin D may improve lipid, glycemic and inflammatory indices in overweight or obese T2D patients with vitamin D deficiency and dyslipidemia.

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Introduction

As the number of overweight or obese people raised all over the world in recent decades, obesity related problems such as diabetes and lipid profile disorders are also increasing. In fact, obesity is characterized by a gain in fat mass. Increased fat mass can develop

oxidative stress and inflammation, which leads to beta cells dysfunction and insulin resistance in the body tissues. Type 2 diabetic (T2D) is a progressive disease with various metabolic complications, which affects the function of body organs. The prevalence of T2D has significantly risen during the last decades. In 2015, there were about 382 million adults with diabetes and it is estimated that in 2030, this figure will reach 439 million worldwide due to inactivity, high-calorie diets, obesity, and increased life expectancy (1-4).

The most common finding in overweight or obese people with T2D is vitamin D deficiency. Based on results of the previous studies, 39% of T2D patients suffered from vitamin D deficiency. Increased fat mass presents in overweight or obese people with T2D causes vitamin D retention within adipose tissues and consequently reduces its circulating levels. Serum 25-OH D levels can be valuable in predicting long-term complications of diabetes (5-7).

Vitamin D deficiency leads to an increase in the level of several inflammatory mediators such as hs-CRP via effect on the transcription of inflammatory genes and exacerbate insulin resistance in turn. As an important risk factor, dyslipidemia, which has been reported in the 64% of diabetic patients, it can be partly explained by vitamin D deficiency. Vitamin D deficiency through various cellular and genomic mechanisms disrupt normal blood lipoproteins metabolism. In addition, inflammation and insulin resistance in people with T2D can play an important role in dyslipidemia presenting in these patients (1, 3, 8-10).

Therefore, it was hypothesized that improvement of vitamin D deficiency in diabetic patients might affect several serum parameters in these patients. Hence, some studies showed that vitamin D did not have any correlation with total diet quality, adequacy, variety, moderation, and overall balanced subscale scores (11). So we aimed to investigate the effect of vitamin D supplementation on metabolic biomarkers, oxidative stress and systemic inflammation in overweight or obese type 2 diabetic patients with vitamin D deficiency and dyslipidemia.

Materials and Methods

This randomized double-blind placebo-controlled clinical trial was performed on 60 qualified patients (26 men and 34 women) with an established diagnosis of T2D (with serum glucose levels and medication doses that had been stable for at least 6 months). Overweight or obese people (BMI greater than 25 kg/m^2) were enrolled in the study from Shahid Motahhari and Shahid Faghihi hospitals affiliated to Shiraz University of Medical Sciences, Shiraz, Iran.

Inclusion criteria were ability to give informed consent, diabetes' duration at least for 2 years that was diagnosed by a co-advisor endocrinologist, vitamin D deficiency (defined as 20 ng/mL>serum 25-Hydroxyvitamin D), (12) being overweight or obese (BMI greater than 25 kg/m^2), not using any dietary or food supplement, and avoid using orlistat. Eligible participants were non-smokers and did not have any cardiac, hepatic or renal function disorders. The exclusion criteria were pregnancy and lactation conditions, and also not using prescribed supplements in the context of present study.

Sample size was determined according to the study in obese subjects with T2D (13). The number of participants was estimated for each group to be 30 at 80% power and α of 0.05 to detect a difference of 14.8 mg/dL in TG concentrations between groups with an SD of 25. To allow for drop outs, it was decided to recruit 30 participants for each group. Study protocol was explained to all participants who met the study criteria, and then a written consent form was obtained from each participant.

The procedure of this clinical trial was approved by the Ethics Committee on Human Experimentation of Shiraz University of Medical Sciences (No. IR. SUMS. REC. 1396. 22). It was also registered at Iranian Registry of Clinical Trials (IRCT) (ID number: IRCT 201707252480N8). All the study steps were performed in accordance with the Helsinki Declaration. Eligible participants were assigned to two groups by block randomization.

Intervention Group who received one vitamin D capsule, 50000 IU, weekly for eight weeks (based on protocol of vitamin D deficiency treatment (14) and the control Group who received the placebo with the same appearance as the intervention group weekly for eight weeks.

Vitamin D and placebo capsules were prepared by Zahravi Pharmaceutical Company, Tabriz, Iran. The placebo capsules were with the same size, shape, and color in comparison to capsules containing vitamin D. The participants were asked to avoid any changes in their physical activity during the study phase. On the other hand, both group were advised to have exposure to sunlight (with no cover or sunscreen usage; head, neck, and arms) for 30 minutes on regular daily basis and also consume more vitamin D-rich foods including egg yolks and fish.

Measurements were performed at entry and after 8 weeks of intervention. All data were collected by trained researchers and all participants were given clear instructions. Additional information about age, medical history, current use of medications, and cigarette smoking were obtained via face to

face interview. Height was measured to the nearest 0.5 cm, and weight to the nearest 0.1 kg in light clothes and no shoes. Body Mass Index (BMI) was calculated as weight (kg) divided by the square of height (m^2). Waist Circumference (WC) was measured at the level of the iliac crest at the end of normal expiration to the nearest 0.5 cm.

After 10-12 hours fasting, 5 mL venous blood sample was taken from each participant at entry and at the end of the study. Blood samples were distributed among tubes containing K2EDTA. The samples were then centrifuged to obtain serum. All serum samples were stored at -72°C for further biochemical analysis. serum high sensitive C-reactive protein (hs-CRP), fasting blood sugar (FBS), malondialdehyde (MDA), total cholesterol (TC), low-density lipoprotein (LDL), high-density lipoprotein (HDL) and triglycerides (TG) concentrations were assayed using standard kits (Pars Azmoon Inc., Tehran, Iran) with the colorimetric analysis method via autoanalyzer machine (BT-1500, Italy).

MDA was quantified colorimetrically (optical density at 532 nm). Glycated hemoglobin (HbA1c) percentage was quantitatively estimated in vitro using a Dimension® system (Dade Behring Inc., Milton Keynes, UK). The serum concentration of vitamin D was quantitatively analyzed *in vitro* using standard ELISA method (Immune Diagnostic Systems, UK). All the laboratory measurements were performed in the lab of Nutrition and Food Science School under the supervision of qualified experts and carried out in standard laboratory conditions. Serum hs-CRP concentration was measured by a high sensitivity latex-enhanced immunonephelometric assay on a BN II analyzer (Dade Behring; intra assay CV: 3.8%). Dietary intakes were monitored by 3-day 24 hour food recall, including 2 week day and 1 weekend day, at entry and end of the study, and the daily nutrient intakes were determined using nutritionist IV software (N-squared Computing, San Bruno, CA) (15).

Statistical analyses were performed by SPSS software (version 15, SPSS Inc., Chicago, IL, USA). The one sample Kolmogorov-Smirnov was used to check data normality. Qualitative variables were compared using the Chi Square test. Data for continuous variables were presented as mean±SD. Normally distributed data within groups were compared using paired-samples t-test and between groups by independent-samples t-test. Comparison of non-normally distributed data was conducted using Wilcoxon signed ranks and the Mann-Whitney U-test, respectively. A two-tailed p-value≤0.05 was considered statistically significant.

Results

Three patients, 2 in the intervention group and 1 in the control group were withdrawn from the study due to unwillingness to participate until the end the study (Figure 1). No adverse events were reported during the study. To monitor adherence to intervention, we contacted all participants by telephone, weekly. Compliance, assessed by measuring the remaining volume of capsules in

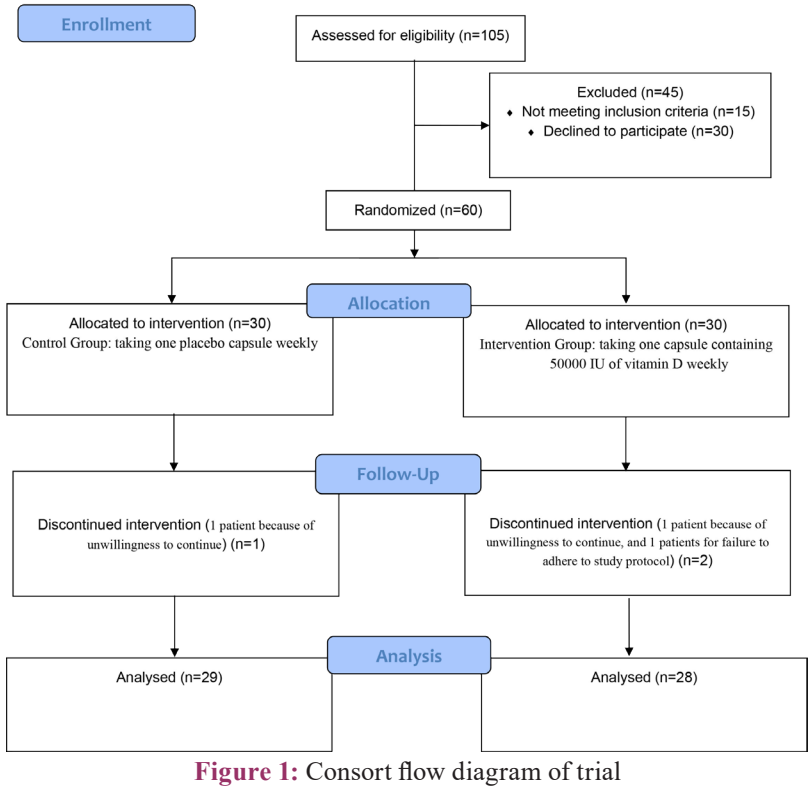

Figure 1: Consort flow diagram of trial

the returned bottles, was more than 90%. Baseline characteristics of the 57 participants who completed the study were shown in Table 1. There were no significant differences between groups regarding age, sex, weight, waist circumference, disease duration. Likewise, no significant differences were observed for dietary intake and biochemical variables between the groups at the baseline.

Effects of vitamin D supplementation on dietary intake, anthropometric indices, glycemic control, lipid profile, oxidative stress and systemic inflammation were presented in Table 2. Dietary intake of energy, carbohydrate, protein, fat, dietary fiber, cholesterol and vitamin D intake as determined by the 3-day food recall were not significantly different between and within the groups after the intervention. Moreover, at the end of study, in the anthropometric indices, weight, waist circumference and BMI, we observed no significant difference between and within the groups (Table 2).

At the end of the study, in comparison to the baseline, in the placebo group, there were no significant changes in biochemical parameters at the end of the study ($p>0.05$). However, vitamin D administration caused a significant reduction in FBS ($p=0.04$), TG ($p=0.02$), and hs-CRP ($p=0.02$) levels and a significant increase in serum 25–OH, D level ($p<0.001$), when compared to the baseline. Furthermore, at the end of the study, in comparison to the placebo group, the FBS, TG and hs-CRP concentrations were significantly lower ($p=0.008$, $p<0.001$, $p=0.01$, respectively) and the serum 25–OH, D level concentration was significantly higher ($p<0.001$) in Vitamin D supplemented group. No significant different was observed regarding MDA, TC, LDL and HDL concentrations.

Discussion

The present study showed that administration of 50000 IU vitamin D, weekly for 8 weeks caused an improvement in serum 25-OH D, FBS, TG, and hs-CRP levels, which the serum 25-OH D changed from deficiency to adequacy range. This significant improvement was only related to supplemental efficacy because, as stated in the results, dietary vitamin D intake did not change significantly during the study in both groups, so this significant change could be as a result of supplementation.

Table 1: The patients' baseline characteristics and biochemical profiles.

Parameters	Groups		*p* value
	Vitamin D (n=28)	Placebo (n=29)	
No. (female/male)	28 (18/10)	29 (17/12)	0.66
Age (years)	57.1±9.2	56.6±6.2	0.32
Duration of diabetes (years)	6.9±4.2	7.1±6.2	0.68
Weight (kg)	76.1±13.1	75.6±14.2	0.71
Waist circumference (cm)	92.1±6.6	91.2±8.6	0.57
Body mass index (kg/m^2)	27.6±3.3	28.4±3.8	0.21
Energy (Kcal/day)	2317±842.7	2152.6±548.4	0.55
Protein (g/day)	81.1±28	88.8±39.2	0.63
Carbohydrate (g/day)	287.8±113	261.2±141	0.69
Fat (g/day)	72±24.6	91.7±35	0.82
Dietary fiber (g/day)	17.9±18	18.1±19.1	0.74
Dietary Chol (mg/day)	300.6±134	334±192	0.91
Dietary vitamin D intake (µg/day)	7.2±1.9	6.9±2.2	0.77
FBS (mg/dL)	136.14±23.6	138.8±31.2	0.23
HbA1c (%)	6.4±0.8	6.6±0.8	0.16
TG (mg/dL)	278.3±56.1	262.2±69.1	0.53
TC (mg/dL)	320.2±43.1	314.1±23.9	0.21
LDL (mg/dL)	145.4±39.1	148.2±30.1	0.62
HDL (mg/dL)	29.6±20.4	30.4±7.3	0.43
Serum 25-OH D (ng/L)	16.8±4.6	15.2±6.2	0.7
MDA (µmol/L)	4.5±1.4	4.4±1.3	0.41
hs-CRP (µg/mL)	3.2±1.5	3.5±1.2	0.31

*Data were expressed as Mean±SD, except for No. (number of participants). Dietary Chol=dietary cholesterol; FBS=fasting blood sugar; HbA1c=glycated hemoglobin; TG=triglyceride; TC=total cholesterol; LDL=low density lipoprotein; HDL=high density lipoprotein; MDA=Malondialdehyde; hs-CRP=High-sensitivity C-reactive protein. $p<0.05$ considered as statistically significant. P values refer to comparisons between groups (independent t-test or Mann-Whitney as appropriate).

Table 2: The patients' parameters scores before and after the intervention.

Parameter	Vitamin D (n=28)			Placebo (n=29)			p_2
	Before	After	*p* value	Before	After	p_1	*p* value
Energy (Kcal/day)	2317±842.7	2298±836.8	0.67	2152.6±548.4	2122.1±537.3	0.51	0.53
Protein (g/day)	81.1±28	80.3±15	0.45	88.8±39.2	89±38.8	0.61	0.2
Carbohydrate (g/day)	287.8±113	288.6±121	0.82	261.2±141	259.3±136	0.77	0.92
Fat (g/day)	72±24.6	70±23.3	0.61	91.7±35	92.9±61	0.59	0.87
Dietary fiber (g/day)	17.9±18	19.3±22.1	0.41	18.1±19.1	18.6±41.2	0.85	0.31
Dietary Chol (mg/day)	300.6±134	311.6±153	0.68	334±192	303±134	0.72	0.74
Dietary vitamin D intake (µg/day)	7.2±1.9	7.8±2.6	0.19	6.9±2.2	7.1±3.1	0.44	0.79
Weight (kg)	76.1±13.1	75.9±14.2	0.49	75.6±14.2	76.1±13.1	0.42	0.68
Waist circumference (cm)	92.1±6.6	92.5±6.7	0.86	91.2±8.6	90.9±7.7	0.11	0.54
BMI (kg/m^2)	27.6±3.3	27.3±3.8	0.71	28.4±3.8	28.7±3.1	0.32	0.28
FBS (mg/dL)	136.14±23.6	122.6±41.7	0.04	138.8±31.2	135.2±32.6	0.48	0.008*
HbA1c (%)	6.4±0.8	6.3±0.9	0.54	6.6±0.8	6.6±1.1	0.64	0.38
Triglycerides (mg/dL)	278.3±56.1	148.1±32.3	0.02	262.2±69.1	258.1±4.2	0.24	0.001*
Total cholesterol (mg/dL)	320.2±43.1	299.2±43.9	0.09	314.1±23.9	298.5±44.2	0.51	0.19
LDL cholesterol (mg/dL)	145.4±39.1	142.7±33.2	0.43	148.2±30.1	146.7±40.1	0.61	0.69
HDL cholesterol (mg/dL)	29.6±20.4	31.7±12.3	0.28	30.4±7.3	32.8±14.2	0.33	0.28
Serum 25(OH)D (ng/L)	16.8±4.6	59.3±33.4	≤0.001	15.2±6.2	19.1±30.8	0.09	≤0.001*
MDA (µmol/L)	4.5±1.4	4.7±3.74	0.55	4.4±1.3	6.6±4.2	0.18	0.41
hs-CRP (µg/mL)	3.2±1.5	2.1±1.6	0.02	3.5±1.2	3.6±1.4	0.82	0.01*

*Data were expressed as Mean±SD. Dietary Chol=dietary cholesterol; FBS=fasting blood sugar; HbA1c=glycated hemoglobin; TG=triglyceride; TC=total cholesterol; LDL=low density lipoprotein; HDL=high density lipoprotein; MDA=Malondialdehyde; hs-CRP=High-sensitivity C-reactive protein. $p<0.05$ considered as statistically significant. p_1-values refer to comparisons between week 0 and week 8 within groups (Paired t-test or Wilcoxon as appropriate). p_2-values refer to comparisons between groups (independent t-test or Mann-Whitney as appropriate).

In the present study, vitamin D supplementation improved FBS, but had no effect on HbA1c. In consistent with the result of present study, Harris et al. (16), reported that Vitamin D supplementation (4000 IU per day) improved insulin resistance and increased insulin secretion in overweight and obese subjects. In a study published by Baziar *et al*. (17), eight weeks of vitamin D supplementation (50000 IU per week) reduced insulin resistance and improved glycemic indices in patients with T2D with insufficient levels of vitamin D. Of note, population study and research design was very similar to the present study, which gives further validation to present finding.

Several mechanisms have been proposed which are pointed toward that vitamin D can affect diabetes directly through binding to vitamin D receptors in beta cells. The presence of vitamin D receptors in the promoter of insulin-producing genes in humans affects the expression of the gene and the transcription of insulin genes which are related to the production and secretion of insulin. The indirect effect of vitamin D on beta cells may be due to the effect on calcium. Insulin secretion is followed by calcium-dependent process. In addition, the active form of vitamin D can increase the synthesis of these receptors by binding to the nuclear receptor on the gene synthesizing the insulin membrane receptors, resulting in the presence of more glucose transferase in the cell membrane (18).

Vitamin D also increases the expression of the PPAR-γ gene, which improves the metabolism of fatty acids and increases insulin sensitivity. It has also been reported that vitamin D modifies the function of the renin-angiotensinogen system by reducing the renin gene expression and also inhibiting angiotensin receptors. Increasing the activity of this system plays an important role in insulin resistance and inflammation (16, 19). The present study attempted to measure the level of glycosylated hemoglobin before and after 8 weeks of intervention. The results of this study did not show any significant changes in this glycemic control index.

In consist with the present study, Jorde *et al*. (19) reported that 6 months of supplementation with 40,000 units of vitamin D on 32 patients with T2D had a significant effect on glycosylated hemoglobin level. It is likely that due to the duration of present study, eight weeks is insufficient to influence such a long-term glycemic control index. We showed that supplementation with vitamin D significantly reduced TG levels. In line with the present study, Zittermann *et al*. (20) reported that vitamin D supplementation for one year (3332 IU per day) significantly improved TG. Of note, in this study the participants were healthy and without vitamin

D deficiency. The possible effect of vitamin D supplementation on TG level is due to the effect of this vitamin on PPARs, as discussed earlier.

In the present study, hs-CRP decreased significantly in vitamin D group. Similarly, one clinical trial studied on 54 vitamin D deficient patients reported that supplementing Vitamin D (50000 IU per three months) for one year, caused significant reduction in hs-CRP (21). Vitamin D has an effect on the promoter region in cytokines producing genes and changes in the production and activity of cytokines. In addition, vitamin D can activate the KB factor, which is an important factor in regulating the genes associated with pro-inflammatory cytokines and insulin resistance (22).

The main limitations of the present study were the duration of the intervention to be insufficient to observe changes in various indices such as anthropometric indices. In addition, due to the small sample size, the possibility of grouping subjects according to the severity of vitamin D deficiency was not possible. One of the strengths of the present study was measuring serum 25-(OH)-D level in order to determine the adherence to vitamin D supplementation, which showed good compliance with prescribed supplements. The aim of this study was to neutralize the effects of other dietary factors such as energy, macronutrients and fiber intake on metabolic and anthropometric indices whether at baseline or during the study period. It was advised to participants not to change the amount energy and macronutrient intake, which, according to the results, did not change during the study and all the reported positive changes, could be attributed to the prescribed intervention.

Conclusion

The findings of the present study indicated that eight weeks supplementation with vitamin D might be helpful in improving several serum parameters such as vitamin D, FBS, TG and hs-CRP levels in overweight or obese T2D patients with vitamin D deficiency and dyslipidemia. Yet, further studies are needed to determine additional molecular mechanisms underlying vitamin D therapy in general health of individuals similar with our study subjects.

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Conflict of Interest

None declared.

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