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Original Article

The effects of vitamin D supplementation on lipid profiles and oxidative indices among diabetic nephropathy patients with marginal vitamin D status

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ABSTRACT

Aims: Diabetic nephropathy is one of the major microvascular complications of type 2 diabetes which insufficient vitamin D might -have a role in it's incidence. This study evaluated the effects of vitamin D supplementation on lipid profiles and oxidative/anti-oxidative indices in marginal vitamin D status patients with diabetic nephropathy.
Methods: For the current paralleled, randomized, double-blinded, placebo-controlled clinical trial, 50 diabetic nephropathy patients with marginal serum vitamin D were selected. Intervention group received 1,25-dihydroxycholecalciferol (50000 IU/week, n = 25), and placebo group (n = 25) received an identical placebo, for 8 weeks. Lipid profiles (LDL, HDL, TG and TC) and oxidative/anti-oxidative markers (TAC, SOD, CAT, GPX and MDA) were measured.
Results: Vitamin D supplementation significantly increased vitamin D status in the intervention group, compared to the control group (P = 0.001). The reductions in the serum levels of TG, LDL and TC were significant (P = 0.04, P = 0.006 and P = 0.02, respectively) in the intervention group. The changes in oxidative/anti-oxidative markers and HDL levels were not significant after intervention.
Conclusion: In conclusion, vitamin D supplementation for 8 weeks among diabetic nephropathy patients has beneficial effects on serum vitamin D status and dyslipidemia.

1. Introduction

Diabetes mellitus is one of the most prevalent chronic metabolic disorders globally [1]. There were approximately 382 million people with diabetes worldwide in 2013, and this number is expected to rise to 592 million by 2035 [2]. Diabetic nephropathy is one of the major microvascular complications of type 2 diabetes, which is characterized by morphological changes in the kidney and loss of the charge barrier on the glomerular basement membrane [3,4].

In order to prevent the progression of microvascular complications in diabetic patients, it has been recommended to emphasize the management of both metabolic and cardiovascular disease (CVD) risk factors [5]. Several factors are associated with increased risk of CVD in diabetic patients, including hyperglycemia, hypertension and dyslipidemia [6]. The most common pattern of dyslipidemia in diabetic nephropathy is elevated triglycerides (TG), total cholesterol, and low-density lipoprotein (LDL) levels, and decreased high-density lipoprotein (HDL) levels [7]. Lipid reduction strategies have beneficial effects in diabetic patients, such as preserving glomerular filtration rate (GFR) and decreasing proteinuria [4].

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There is growing number of studies showing that oxidative stress plays a crucial role in the pathogenesis of diabetes and its complications [3]. Diabetes is accompanied by increased reactive oxygen species (ROS) production and impaired antioxidant defenses and there is a close link between oxidative stress and hyperglycemia in diabetic patients [3]. On the other hand, hyperglycemia could induce oxidative stress through the activation of stress pathways and mitochondrial dysfunction [8].

It has been suggested that there is a relationship between vitamin D deficiency and non-skeletal diseases such as type 2 diabetes, CVD and metabolic syndrome disorders [9]. Studies have shown that patients with type 2 diabetes, compared to healthy controls, have significantly lower vitamin D levels, which are associated with worse glycemic control, higher serum lipid levels and a higher prevalence of CVD [10]. In addition, the relationship of vitamin D status and lipid profiles has been shown in several studies [9,11]. Furthermore, the antioxidative effects of vitamin D have been shown in animal models of diabetes and in human studies [12], but the studies regarding the effects of vitamin D supplementation on oxidative stress markers are limited. Due to the increased prevalence of dyslipidemia and oxidative stress in patients with diabetic nephropathy, and with respect to the role of vitamin D in the attenuation of dyslipidemia and oxidative stress, this study was performed to test the effects of vitamin D supplementation on serum markers of lipid profiles (LDL, HDL, TG and total cholesterol) and oxidative stress markers (total antioxidant capacity (TAC), SOD, CAT, GPX and MDA) in diabetic nephropathy patients with marginal vitamin D status.

2. Materials and methods

2.1. Study population

This was an 8-week, double-blind, randomized, placebo-controlled clinical trial. The study protocol was approved by the ethics committee of Tabriz University of Medical Sciences (IRCT201511173140N15). Key eligibility criteria were an age of 20–50, a diagnosis of type 2 diabetes and nephropathy with GFR <60 ml/min and albuminuria >30 mg/day, controlled fasting glucose level of <140 mg/dl, marginal serum vitamin D deficiency (defined as serum levels of vitamin D between 15 and 30 ng/ml) [13] and body mass index (BMI) of 20–35 kg/m^2. Subjects were excluded from the study by the following criteria: a known history or presence of glomerulonephritis, active malignancies and uncontrolled hypertension; those who were on habitual vitamin D, calcium or other antioxidant supplementation; those who were currently taking lipid-lowering drugs, magnesium antacids and tiasidic diuretics. Patients with serum phosphorus levels > 4.5 mg/dl and serum calcium levels >10 mg/dl were also excluded. Patients were permitted to continue using other disease modifying therapies for diabetes and nephropathy not affecting vitamin D metabolism, without changing the dosage. All participants provided written informed consent before participation.

The sample size was determined on the basis of a change in TNF-α level, which was obtained from a previous study [14]. Twenty five patients per each group were computed as necessary.

2.2. Study design

Fifty eligible subjects were randomly assigned to one of two groups using random allocation software. The intervention group received 1,25-dihydroxycholecalciferol (50000 IU once a week, n = 25) and the control group received a placebo with similar appearance (once a week, n = 25) for 8 weeks (Daana Pharmaceutical Company, Tabriz, Iran). The allocation and coding of supplements were performed by a pharmacist with no clinical involvement in the study and all physicians and technician remained blinded until the end of the analysis. Compliance was monitored through weekly phone call. Patients were asked to continue with their usual physical activity level and dietary intake throughout the study. At the beginning and end of the trial, anthropometric indices were measured. Body weight was measured in an overnight fasting status with subjects standing without shoes and wearing light clothing, to the nearest 0.1 kg, using Seca Electronic Weighting Scale (Seca, Hamburg, Germany). Height was recorded by the use of a non-stretch tape measure (Seca, Hamburg, Germany) in a standing position without shoes, to the nearest 0.1 cm accuracy. BMI was calculated by dividing weight (kg) by height squared (m^2). GFR was estimated from serum creatinine concentrations. Nutrient intake was estimated by using 3-day dietary records (two for weekdays and one for the weekend), at the baseline and endpoint of the trial. Dietary intake data were analyzed using Nutritionist 4 software (First Databank Inc., San Bruno, CA, USA), modified for Iranian foods. Sun exposure was assessed by asking the subjects to determine their usual period of time exposed to sunlight per day, with or without sunscreen use. Information was collected about patients' physical activity using the International Physical Activity Questionnaire (IPAQ) at the baseline and endpoint of the study and the activity was classified as being at a light, average or heavy level [15].

2.3. Blood sampling and biochemical measurements

Seven milliliter (7 ml) fasting blood samples were collected from all patients at the baseline and endpoint of the study, put into serum separation vacutainers, and allowed to clot for 10 min. Serum samples were collected using centrifugation at 3000 rpm for 10 min at room temperature, then were quickly frozen and stored at −80 °C until analyzed. Total cholesterol, HDL and TG were measured via the enzymatic method with the use of commercial kits (Farzan-Teb, Tabriz, Iran) according to the manufacturer's instructions. LDL was calculated using the Friedewald equation [16]. The measurements of TAC in serum, and antioxidant enzymes activity including SOD and GPX, were performed using spectrophotometric methods with commercial kits (TAC, RANDOX kits, SOD, RANSOD kits GPX, RANSEL kits; RANDOX laboratory, Crumlin, UK). Catalase activity was determined by the method described by Aebi [17]. Serum MDA was determined through a reaction with thiobarbituric acid (TBA) in order to produce a pink-colored complex. Then, its fluorescence intensity was measured at 547 nm with excitation at 525 nm by a spectrofluorimeter (Kontron, model SFM 25A, Milan, Italy). Serum vitamin D was determined using the commercial ELISA kit (Euroimmun kit, Germany).

2.4. Statistical analyses

Data were analyzed with SPSS software version 17.0 (SPSS Inc., Chicago, IL, USA) and results are expressed as mean (±SD). The normality of the distribution of data was assessed by a one-sample Kolmogorov-Smirnov test. Baseline variables in the two groups were compared by the use of an independent sample *t*-test for quantitative variables and a chi-square test for qualitative variables. Within-group differences were analyzed using a paired sample *t*-test. In order to identify any differences between the two groups after intervention, an analysis of covariance (ANCOVA) was used. Results were considered statistically significant at $P < 0.05$.

3. Results

All 50 patients with diabetic nephropathy completed the 8-

Table 1
Basic characteristics of study subjects.

Variable	Vitamin D group (n = 25)	Placebo group (n = 25)
Mean age (years)	39.7 ± 7.3	43.7 ± 6.1
Sun exposure per day (*n*)		
10 min to 1 h	10 (40%) *	8 (32%) *
1–2 h	12 (48%) *	11 (52%)*
2 h and more	3 (12%)*	6 (24%) *
Physical activity (*n*)		
Light	14 (56%) *	7 (28%)*
mean	8 (32%) *	13 (52%) *
heavy	3 (12%) *	5 (20%) *
Weight (kg)	74.91 ± 11.1	72.1 ± 11.6
Height (cm)	167.1 ± 8.2	167.3 ± 8.0
BMI (kg/m^2)	26.8 ± 3.9	25.8 ± 4.5
GFR (ml/min)	45.87 ± 17.39	46.97 ± 12.26

BMI, body mass index; GFR, glomerular filtration rate; Values are means ± standard deviation. * Values are number and percent.

week clinical trial. The vitamin D and placebo capsules were well tolerated and there were no adverse effects or symptoms reported by patients. Table 1 shows the basic characteristics of the study subjects in the two groups. There were no significant differences among the groups in mean age, body weight and BMI values at baseline. Mean physical activity, sun exposure per day, daily energy and dietary nutrient intakes showed no significant differences between the two groups (Table 1).

Energy adjusted dietary intake of study patient at baseline and endpoint is demonstrated in Table 2. There is no significant different for intake of macro and micronutrients in baseline and endpoint of study in both placebo and vitamin D groups.

Within-group differences were also not significant, which indicates that dietary intakes were not confounding factors with respect to oxidative stress markers and lipid profile levels (data not shown).

After 8 weeks, the supplementation of patients with vitamin D led to a significant increase in serum vitamin D levels (84.58%, P = 0.001) and HDL levels (15.3%, P = 0.001), and a significant decrease in total cholesterol (21.8%, P = 0.02) and LDL levels (30.3%, P = 0.03). Within-group differences in the control group revealed a significant increase in serum levels of vitamin D (P = 0.08), HDL (P = 0.001), MDA (P = 0.02) and TG (P = 0.02) (Table 3). The reductions in the serum levels of TG, LDL and total cholesterol were significant (24.6%, 30.35% and 21.8%, respectively) in the intervention group, compared to the control group. After adjusting for baseline values, there was a significant increase in vitamin D levels (P = 0.001) and a significant decrease in TG (P = 0.007), LDL (P = 0.005) and total cholesterol (P = 0.001) levels in the intervention group, compared to the control group. No significant increase was observed in TAC (0.26 ± 0.94 mmol/L) in the intervention group as compared with the control group (P = 0.34, adjusted for baseline values). The increase in SOD, GPX and CAT activities were not significant in the intervention group (P > 0.05). Table 3.

A comparison of the mean blood and urine parameters between two groups of the study is shown in Table 4. As shown, there were no significant differences of creatinine, calcium, albumin and GFR between the intervention and placebo groups (P > 0.05). On the other hand, the phosphorous and protein percentage changes in urine were lower (P = 0.07) and higher (P = 0.003) among both groups, respectively. After adjustment for physical activity, only the protein level remained significant. The analysis showed lower levels of urinary protein (P = 0.001) only in the intervention group.

4. Discussion

The main purpose of this study was to investigate the effects of vitamin D supplementation on lipid profiles and oxidative stress markers in diabetic nephropathy patients with marginal vitamin D status. It was found that vitamin D supplementation for 8 weeks resulted in a significant increase in concentrations of serum vitamin D levels and a significant decrease in TG, LDL and total cholesterol levels, compared with a placebo. No significant effects were found of vitamin D supplementation on serum TAC, levels, antioxidant enzymes activity (SOD, GPX and CAT) and MDA concentrations.

Low concentrations of serum vitamin D are highly prevalent in patients with diabetes, and studies have shown that vitamin D deficiency and vitamin D insufficiency is associated with nephropathy in subjects with diabetes [10]. Further, low vitamin D levels are associated with worse glycemic control, lipid profiles and cardiovascular outcomes in diabetic patients [10]. Vitamin D is thought to have a renoprotective role in diabetic nephropathy due to its actions in attenuating the development of glomerusclerosis and the progression of proteinuria, and by maintaining podocyte health, decreasing podocyte loss and podocyte hypertrophy and preventing epithelial-to-mesenchymal transformation [18]. 1,25-dihydroxyvitamin D_3, the active metabolite of vitamin D, down-regulates renin-angiotensin system (RAS) by suppressing renin gene transcription which is important in renal and cardiovascular health [19]. Several studies have investigated the relationship between serum levels of vitamin D with lipid parameters in diabetic patients. The proposed putative mechanisms by which lipids could induce renal injury are: stimulation of transforming growth factor (TGF)-β, induction of ROS production, activation of monocytes, degradation of glycocalyx, and increasing permeability of the glomerular filtration barrier [20]. Saedisomeolia et al. found an

Table 2
Dietary intake of study patients at baseline and endpoint of the study.

	Vitamin D group (n = 25)			Placebo group (n = 25)		
	baseline	endpoint	P	baseline	endpoint	P
Energy (kcal/d)	1560 ± 550	1607 ± 532	0.42	1594 ± 567	1628 ± 546	0.53
Carbohydrate (g/d)	188.7 ± 81	192.3 ± 83	0.91	201.4 ± 97	204.5 ± 78	0.68
Protein (g/d)	57.8 ± 12.7	60.7 ± 14.4	0.46	59.6 ± 12.9	62.6 ± 11.1	0.49
Total fat (g/d)	57.9 ± 15	59.5 ± 16.2	0.57	62.6 ± 14.7	63.0 ± 15.3	0.61
Fiber (g/d)	16.4 ± 7.4	17.6 ± 3.6	0.32	15.5 ± 6.3	16.6 ± 5.4	0.63
Vitamin D (μg/d)	2.2 ± 0.7	2.1 ± 0.4	0.61	2.3 ± 0.3	2.2 ± 0.8	0.57
Vitamin E (mg/d)	21.6 ± 5.8	19.3 ± 5.6	0.53	20.32 ± 6.1	19.73 ± 5.3	0.67
Vitamin C (mg/d)	155.4 ± 98.2	140.3 ± 101.2	0.43	127.6 ± 92.3	112.1 ± 76.2	0.52
Calcium (g/d)	1.13 ± 0.13	1.21 ± 0.21	0.43	1.24 ± 0.25	1.19 ± 0.17	0.48
Zinc (mg/d)	12.5 ± 5.2	13.8 ± 6.6	0.72	13.2 ± 6.2	12.9 ± 6.7	0.64
Iron (mg/d)	18.3 ± 4	19.6 ± 6	0.31	17.7 ± 7.2	16.3 ± 5.4	0.42
Phosphorus (g/d)	1.17 ± 0.18	1.20 ± 0.15	0.59	1.15 ± 0.19	1.21 ± 0.19	0.73

Values are means ± standard deviation. P value is reported based on the analysis of paired sample *t*-test.

Table 3
Serum oxidative stress parameters and lipid profile levels of the subjects at the baseline and at the end of intervention.

	Vitamin D group (n = 25)			Placebo group (n = 25)		
	baseline	endpoint	P	baseline	endpoint	P
TAC (mmol/L)	1.4 ± 0.46	1.6 ± 0.75	0.15*	1.5 ± 0.44	1.5 ± 0.43	0.86*
SOD (U/g Hb)	1318.5 ± 228	1356 ± 189	0.62†	1322.4 ± 197	1327.5 ± 178	0.44†
GPX (U/g Hb)	36.8 ± 8.7	37.7 ± 9.4	0.77*	31.63 ± 6.9	30.6 ± 6.1	0.22*
CAT (units/mg of protein)	68.9 ± 15	73.5 ± 15	0.12*	68.6 ± 15	68.0 ± 15	0.36*
MDA (mmol/L)	1.4 ± 0.4	1.6 ± 0.6	0.18†	1.5 ± 0.3	1.6 ± 0.4	0.02†
HDL (mg/dl)	37 ± 7.3	41.1 ± 12.4	0.001†	35.3 ± 7.3	35.6 ± 7.7	0.001†
LDL (mg/dl)	92.3 ± 38	70.9 ± 36	0.03*	93.3 ± 25	101.8 ± 37	0.31*
TG (mg/dl)	171.7 ± 89	152.2 ± 61	0.29*	175.5 ± 76	202.2 ± 76	0.02*
Total cholesterol (mg/dl)	163.5 ± 47	139.1 ± 29	0.02†	163.7 ± 34	177.9 ± 39	0.12†
Serum vitamin D (ng/ml)	21.67 ± 5.62	37.63 ± 7.73	0.001†	22.36 ± 5.7	24.11 ± 7.62	0.001†

TAC: total antioxidant capacity; SOD: superoxide dismutase; GPX: glutathione peroxidase; CAT: catalase; MDA: malondialdehyde; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TG: triglyceride. Values are means ± standard deviation. *P value is reported based on the analysis of paired sample *t*-test. †P value is reported based on the analysis of Wilcoxon test.

Table 4
Blood and urine parameters of the subjects at the baseline and at the end of intervention.

		Groups				P value*	P value**
		Vitamin D (n = 25)		Placebo (n = 25)			
		Mean ± SD	PC	Mean ± SD	PC		
Cr (μg/ml)	Before	1.31 ± 0.33	15.41	1.15 ± 0.36	46.34	0.25	0.59
	After	1.13 ± 0.66		1.31 ± 0.53			
	P-Value	0.95		0.35			
Ca (mg/dl)	Before	8.29 ± 1.05	5.22	7.99 ± 1.08	7.67	0.14	0.62
	After	8.56 ± 1.16		8.50 ± 1.14			
	P-Value	0.40		0.1			
P (mg/dl)	Before	3.06 ± 0.7	22.47	2.88 ± 0.74	12.07	0.07	0.11
	After	3.56 ± 1.27		3.08 ± 0.47			
	P-Value	0.09		0.26			
Alb (g/l)	Before	46.70 ± 17.10	8.33	49.35 ± 15.61	1.44	0.82	0.70
	After	47.86 ± 17.59		48.48 ± 12.93			
	P-Value	0.72		0.71			
Pr (urine)	Before	333.80 ± 112.96	−23.70	325.38 ± 110.75	1.47	0.03	0.006
(mg/dl)	After	233.96 ± 118.75		319.91101.91			
	P-Value	0.001		0.72			
GFR (ml/min/1.73^2)	Before	45.87 ± 17.39	0.92	46.97 ± 12.26	1.13	0.96	0.81
	After	46.96 ± 12.17		46.46 ± 13.64			
	P-Value	0.58		0.89			

P-value reported based on Paired Sample T test. * P-value reported based on ANCOVA after baseline value adjustment. ** P-value reported based on ANCOVA after adjustment of baseline values and physical activity. PC: percent change.

inverse association between serum levels of vitamin D with TG and total cholesterol and a positive correlation with HDL and LDL in diabetes [9]. In another cross-sectional study on 909 men with diabetes, Karhapää et al. showed an association between low levels of active vitamin D and low HDL levels, and also between low levels of the storage form of vitamin D and high levels of TG, LDL and total cholesterol [21]. However, there are limited studies regarding vitamin D supplementation on cardiovascular biomarkers such as blood lipid profiles and oxidative stress markers in diabetic patients with nephropathy, and have produced conflicting results, especially in subjects with marginal vitamin D status.

The current study's results, with regard to the increase in serum levels of vitamin D, are similar to those of Talaei and colleagues, who showed that 50000 units of vitamin D taken orally per week for eight weeks in 100 patients with type 2 diabetes caused a significant increase in serum vitamin D levels [22].

The current study's finding of decreased TG following vitamin D supplementation was in accord with the results of Bonakdaran et al. whose supplementation of diabetic patients on hemodialysis with 0.5 μg vitamin D daily for eight weeks led to a significant decrease in TG and total cholesterol levels [23]. In line with the present study, supplementation with 2000 IU vitamin D daily for 18 months had a significant effect on 25-hydroxyvitamin D levels. The study further showed that vitamin D significantly reduced LDL and total cholesterol levels in type 2 diabetes patients. They demonstrated that the beneficial effects of vitamin D may be due to its role in elevating serum apolipoprotein A1 concentrations and to the independent involvement of vitamin D in improving cardiometabolic risk factors, including blood pressure, insulin resistance and aortic media fragmentation [24]. Another mechanism by which vitamin D reduces TG levels is by increasing intestinal calcium absorption and serum calcium levels, which in turn results in reducing hepatic TG formation and secretion. Lastly, vitamin D has a suppressive effect on serum parathyroid hormone concentrations, which reduces serum TG via increasing peripheral removal [12].

Another outcome of vitamin D supplementation in patients with diabetic nephropathy was a reduction in LDL and total cholesterol levels. In line with this finding, some investigators have found a significant effect of vitamin D on serum LDL and total cholesterol concentrations [23,24]. Shab-Bidar and colleagues observed that supplementation of patients with type 2 diabetes with a vitamin D-fortified yogurt drink (containing 170 mg calcium and 200 IU/250 ml vitamin D twice a day) for 12 weeks reduced serum concentrations of LDL and total cholesterol [25]. Consistent with the

current study's findings, another study showed that calcium/vitamin D supplementation in otherwise healthy obese or overweight women during a weight-loss intervention for 15 weeks resulted in significant reductions of serum TG, LDL, the ratio of the total cholesterol to LDL, and the ratio of LDL to HDL [26]. In contrast, others did not find a significant effect of vitamin D on LDL and total cholesterol levels [12,27]. The same results were also obtained with supplementation of vitamin D (in two phases with 3 months period, 6000 IU and 3000 IU per day in each phase) in obese type 2 diabetes patients [28]. Some of these discrepancies in findings might be related to the baseline blood lipids and vitamin D levels of study participants, different dosages of vitamin D, and differences in study design and duration. The beneficial effects of vitamin D on improved serum LDL and total cholesterol may be explained by its effects on the up-regulation of adiponectin [29]. The association between vitamin D and adiponectin may also be mediated through the down-regulation of the tumor necrosis factor-α gene (which has inhibitory effects on adiponectin synthesis) [29]. Subsequently, adiponectin could increase HDL levels and decrease LDL and VLDL levels [30]. The effects of vitamin D supplementation in improving LDL and total cholesterol may also be secondary to its ameliorating effects on glycemic status [26]. The effects of vitamin D on blood lipids and lipoproteins in diabetic patients need to be elucidated by further investigations.

There are limited studies regarding the antioxidant effects of vitamin D supplementation in diabetic patients. Mechanisms by which oxidative stress is involved in diabetes include: 1) hexosamine pathways; 2) advanced glycation end-products (AGEs) production; 3) protein kinase C activation; and 4) transcription factors activation [31]. Findings from the current study showed that vitamin D supplementation did not significantly affect TAC, antioxidant enzymes activity (including SOD, GPX and CAT) and MDA in diabetic nephropathy patients. In agreement with these findings, supplementation with 0.25 μg/d vitamin D had no significant effect on serum MDA levels in patients with diabetes after 12 weeks [12]. The same has been found after 6 weeks' twice-daily consumption of vitamin D capsules containing 50000 IU vitamin D_3 during a study on women with gestational diabetes mellitus [32]. In contrast to the present study's finding, a significant increase in plasma TAC and total glutathione concentrations was seen in healthy pregnant women after supplementation with 400 IU/d vitamin D [33]. Deng et al. demonstrated that vitamin D combined with irbesartan (an angiotensin II type 1 receptor blocker) improved diabetic nephropathy and renal pathophysiological changes by inhibiting renin, reducing oxidative stress and increasing renal antioxidant capacity [18]. Although observational studies have shown associations between vitamin D and improvements in oxidative stress biomarkers, the exact mechanisms by which vitamin D affects these biomarkers are unknown. It has been proposed that vitamin D exerts its antioxidant action through reducing lipid peroxidation and modulating the expression of radical generating and scavenging enzymes [33]. However, in the current study, vitamin D supplementation for 8 weeks did not affect lipid peroxidation and antioxidant enzymes activity. These conflicting results might be due to variations in study designs, varying dose, type and duration of vitamin D supplementation, basal levels of oxidative stress indices, as well as the dietary intake of subjects.

The relatively small sample size and short intervention period were limitations in the current study. In conclusion, the results of this trial showed that vitamin D supplementation improved serum vitamin D status and reduced serum TG, LDL and total cholesterol levels in patients with diabetic nephropathy and marginal vitamin D status; however, it did not affect antioxidant status, antioxidant enzymes activity and lipid peroxidation. Further studies with a larger sample size and longer intervention period are needed to confirm the beneficial effects of vitamin D in the management of diabetes complications.

Conflicts of interest

The authors declared that they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.dsx.2018.11.008.

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