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Original Article

Effects of vitamin D supplementation on circulatory YKL-40 and MCP-1 biomarkers associated with vascular diabetic complications: A randomized, placebo-controlled, double-blind clinical trial

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ABSTRACT

Aim: Diabetic patients predispose to vascular diseases such as nephropathy, and retinopathy. Poor adherence to medical treatment and dietary recommendations in uncontrolled diabetes leads to vascular damages. Vitamin D has been extensively studied and found to be protective against diabetes mellitus. YKL-40 and Monocyte chemoattractant protein-1 (MCP-1) are considered to exert crucial role in diabetes and its complications. Therefore, this study was designed to investigate effects of vitamin D supplementation on serum levels of YKL-40 and MCP-1 involved in the development of diabetic complications.
Methods: For 12 weeks, 48 type 2 diabetic patients enrolled in the trial and randomly were divided into two groups (n = 24 per group), receiving one of the following: 100 μg (4000 IU) vitamin D or placebo. Before and after intervention, serumYKL-40, MCP-1, insulin, IL-6, TNF-α, 25- (OH) vitamin D and HbA1c were measured.
Results: Our results revealed that serum levels of 25 (OH) vitamin D significantly increased in vitamin D group ($p < 0.001$). Vitamin D supplementation also significantly reduced serum YKL-40 levels (−22.7 vs. −2.4 ng/ml; (p-value = 0.003)). There was a significant decline in MCP-1 concentration in intervention group at the end of the study (−45.7 vs. −0.9 pg/ml; ($p = 0.001$)). Furthermore, there was a significant decrease in IL-6, fasting insulin and HOMA-IR in intervention group after 3 months supplementation.
Conclusions: Daily vitamin D supplementation effectively reduced circulatory YKL-40 and MCP-1 levels in patients with type-2 diabetes and vitamin D deficiency. Vitamin D might contribute in reducing diabetic complications via modulating YKL-40 and MCP-1 signaling pathways.

1. Introduction

Diabetes is defined as a group of metabolic disorders which are common in hyperglycemia state [1].

Chronic hyperglycemia induces activation of various cellular pathways and a wide range of cellular damages leading to diabetic complications [2].

The pathogenesis of vascular diabetic complications is multifactorial and various metabolic and hemodynamic changes play roles in these complications. Moreover, recent evidence has provided insight into the cellular and molecular level of diabetic complications. Low-grade chronic inflammation and endothelial dysfunction were reported to be key processes in the occurrence and progression of vascular diabetic complications [3,4].

YKL-40 or chitinase-3-like-1 protein (CHI3L1) is an inflammatory marker which is facilitating endothelial abnormalities and vascular damages. The name YKL-40 originates from three N-terminal amino acids: tyrosine (Y), lysine (K) and leucine (L). This factor is secreted by different immune cells, vascular smooth

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muscle cells and endothelial cells [5,6].

Serum levels of YKL-40 are elevated in type 2 diabetic patients and these enhanced levels are positively associated with the progression of diabetes and its complication [7,8].

YKL-40 induces macrophage activation, vessels remodeling and plaque destabilization [9]. Previous data reported that there is a positively correlation between circulatory YKL-40 levels and urinary albumin in diabetic patients. So, it could be hypothesized that circulatory YKL-40 levels might become a non-invasive and clinical biomarker for diagnose of diabetic nephropathy [10].Recent evidence also suggests that YKL-40 levels are increased in patients with diabetic retinopathy and have significant difference between two groups of patients with type 2 diabetes and different forms of diabetic retinopathy [11,12]. In patients with proliferative diabetic retinopathy (PDR), methylation of YKL-40 gene is decreased which may cause up-regulation of this gene [13]. In addition, YKL-40 levels in all zones and in both eyes are associated with outer diameter of retinal blood vessels [12].

MCP-1 is another promoter of inflammatory pathways involved in the progression of diabetic complications. It was showed that MCP-1 contributes to renal injury and the development of atherosclerosis plaque. MCP-1 may become a therapeutic target for improving diabetic complications [14,15].

Involvement of vitamin D in the pathogenesis of diabetes and its complications has been assessed in various studies [16–18]. We designed this trial regarding to the crucial roles of YKL-40 and MCP-1 in the pathogenesis of diabetes and its complications and lack of study investigating effects of vitamin D supplementation on these inflammatory biomarkers in type 2 diabetic Patients.

2. Material and methods

2.1. Participants and study design

This parallel randomized double-blind placebo-controlled clinical trial (RCT) was conducted on 48 patients with T2DM. During October 2017 to May 2018, 116 patients with type 2 diabetes were referred from the Iranian Diabetes association (IDA) in Tehran. We screened these patients based on defined inclusion criteria and excluded 68 patients due to lack of eligibility or refused to participate to trial. Overall, 48 patients enrolled in this trial.

Inclusion criteria were as following: Patients with type 2 diabetes based on the American Diabetes Association criteria, aged 30–60 years old, history of taking a stabilized dose of oral antidiabetic drugs, willing to participate in this trial, willing to maintain their current diet, physical activity throughout the trial and no history of taking vitamin D supplements within 3 months. These patients were not included: having complication of diabetes based on medical history, being on medical treatment with insulin or thiazolidindions or anti-obesity drugs, pregnancy or lactation, having a history of clinical diseases such as gastrointestinal diseases, type 1 diabetes, pancreatitis, liver damage, inflammatory diseases, asthma, chronic obstructive pulmonary disease (COPD), malignancy, consuming drugs that interact with vitamin D such as anti–consultants drugs (Phenytoin and Phenobarbital), body mass index (BMI) ˃30 kg/m. The exclusion criteria were: Any changes in medical treatments during trial, and lack of compliance based on taking less than 90% of supplementations.

We checked compliance of participants by weekly phone calls.

We explained for all participants about the purpose of trial and asked them to sign written consent form approving by local Ethical Committee of Tehran University of Medical Sciences (reference number: 32615).

We registered this trial at ClinicalTrials.gov (Identifier: NCT03008057).

2.2. Randomization and intervention

48 patients included in this study after screening procedure. We used permutated-block randomization method to allocate patients into two groups (vitamin D or placebo). For matching patients, we used stratified randomization based on sex (male/female) and BMI (normal/overweight).

An assistant performed the randomization procedure and the intervention allocation was blinded for both investigators and patients. The supplement group (24 patients) received one tablet of vitamin D (each tablet contained 100 μg or 4000IU of vitamin D) [19,20]daily and the placebo group (24 patients) also received one tablet with the same appearance (each tablet contained gelatin starch, lactose powder, magnesium stearate, and citic acid) daily for 3 months. Pars Minoo Pharmaceutical, Cosmetic and Hygienic Company (Iran) prepared both vitamin D and placebo tablets. The percentage of lactose powder has decreased in vitamin D supplements and vitamin D added instead. An assistant performed Blinding procedure and prepared supplements as A and B packages. We asked participants of both groups to sustain their usual diets and physical activity.

2.3. Serum sample collection

At the beginning and the end of the study, we drawn10 ml of venous blood from patients after 12 h fasting, transferred in gelatinous tubes for serum separation. We separated serum samples after centrifuging at 3000 RPM for 20 min and kept them at −80 °C.

2.4. Outcomes and measurements

We completed general information questionnaire, 24-h food recall, and short-form International Physical Activity questionnaires (IPAQ) [21]for all participants before and after intervention.

We used ELIZA Kits for measuring circulatory YKL-40 (Bioassay Technology Laboratory, China), serum insulin (Diametra, Italy) and serum MCP-1 (Diaclone, France), serum IL-6 and TNF-α (Shanghai Crystal Day Biotech Co., Ltd, China).

Also, we tested serum 25(OH) vitamin D levels by chemiluminecense method (Cobas E411 system). For measuring HbA1c percentages in whole blood, we used immunoturbidometruc method. We also calculated HOMA-IR according to fasting insulin (microU/L) x fasting glucose (nmol/L)/22.5 formula.

2.5. Statistical analysis

The normality of data distribution was assessed by using the Kolmogorov-Smirnov test and logarithmic transformation was applied to skewed variables.

To determine the mean differences between groups, independent sample *t*-test and chi-square test was used for quantitative and categorical variables, respectively. Between-group analysis was conducted by using analysis of covariance (ANCOVA) with the metformin dose values as covariates.

Besides, independent sample *t*-test was employed to assess mean change differences between groups. All statistical analysis was done using the statistical package for social sciences (SPSS ver. 16). $P < 0.05$ was considered significant.

3. Results

From a total of 116 subjects who volunteered for study, 48 were found eligible to enter the study. During the 12 weeks follow-up, 2 patients (1 from intervention and 1 from placebo groups) were

excluded (Fig. 1). In total, 50% of study subjects were males and 50% were female. Baseline characteristics of the study participants have been described. In brief, there were no significant differences between general characteristic, anthropometric values, blood pressure and metabolic indices between study groups at baseline ($p > 0.05$). However, HbA1c concentration was marginally different (p-value = 0.06). In addition, There was a significant difference between the metformin doses between the groups (p-value = 0.01) Table 1.

No adverse effects due to the high dose of vitamin D consumption were reported. The mean value of 25(OH) D values increased from 14.70 to 30.2 ng/ml after 12 weeks intervention in vitamin D group ($p < 0.001$). In the placebo group, there was no significant change in the vitamin D status 14.8 vs. 16.8 ng/ml) ($p > 0.05$) (data not shown in table).

The result of ANCOVA test showed there was a statistical significant difference between the biochemical factors at the end of the intervention. As shown in Table 2, in between-group analysis, the YKL-40 level was significantly lower in vitamin D group than placebo after supplementation (70.3 vs. 95.9 ng/ml, p-value = 0.003). A significant difference was observed for MCP-1 levels at the end of the study, with lower level for the intervention group (179.0 vs. 241.2 pg/ml, p-value = 0.02). Similarly, compared with placebo group, decreased level of IL-6 and HOMA-IR was observed in intervention group (p-value <0.03). No difference was found between the groups at the end of the study for the fasting insulin level (p-value = 0.1).

Compared with placebo group, the mean of YKL-40 level significantly decreased in intervention group (−22.7 vs. −2.4 ng/ml; p-value = 0.003). There was a significant decline in MCP-1 concentration in intervention group at the end of the study (−45.7 vs. −0.9 pg/ml; p = 0.001). Furthermore, there was a significant decrease in inflammatory biomarker and metabolic factors, IL-6, fasting insulin and HOMA-IR in intervention group after 3 months supplementation (p-value < 0.04) (Table 3).

4. Discussion

Our study indicated that vitamin D treatment could significantly decrease circulatory YKL-40 and MCP-1 levels in patients with type-2 diabetes and vitamin D deficiency. A substantial body of evidence reported that chronic hyperglycemia activates various inflammatory cellular pathways. So, it is widely reported that there is a chronic low-grade inflammatory state in diabetic patients [22].

Chronic low-grade inflammation may contribute to the development of renal injury, atherosclerotic plaque formation and diabetic retinopathy in these patients [23]. YKL-40 is a biomarker regulating cell activation, proliferation and migration. Moreover, YKL-40 appears to be a major factor in inducing of inflammatory factors such as CXCL2, MMP-9 [24–26]. It is known that YKL-40 exerts anti-apoptotic and angiogenic properties through activation of the protein kinase B (AKT) and phosphoinositide-3 kinase (PI3K) signaling pathways [27,28]. The expression of YKL-40 is elevated in diabetic patients [7]. YKL-40 precedes the progression of atherosclerosis by mediating differentiation of monocytes to foam cells [9]. Moreover, YKL-40 contributes to atherosclerotic plaque formation via vascular smooth muscle cell migration and attachment [29].

Based on previous evidence, circulatory YKL-40 levels correlated with albuminuria which was proposed as a risk factor for cardiovascular disease in diabetic patients [30]. Overall, Diabetic patients are more prone to development of cardiovascular disease compared to non-diabetic patients [31]. Notably, circulatory YKL-40 levels are related to urinary albumin/creatinine ratio and may become a useful marker for detecting early renal injury in diabetic patients [30] MCP-1 is another inflammatory cytokine involved in aggregation of monocytes while monocytes contribute in different phases of cardiovascular diseases. Elevated levels of MCP-1 and YKL-40 are prognostic factors for all-cause mortality and cardiovascular mortality [32,33].

A large number of studies assessed the link between diabetes and vitamin D. Involvement of vitamin D in the pathophysiology of

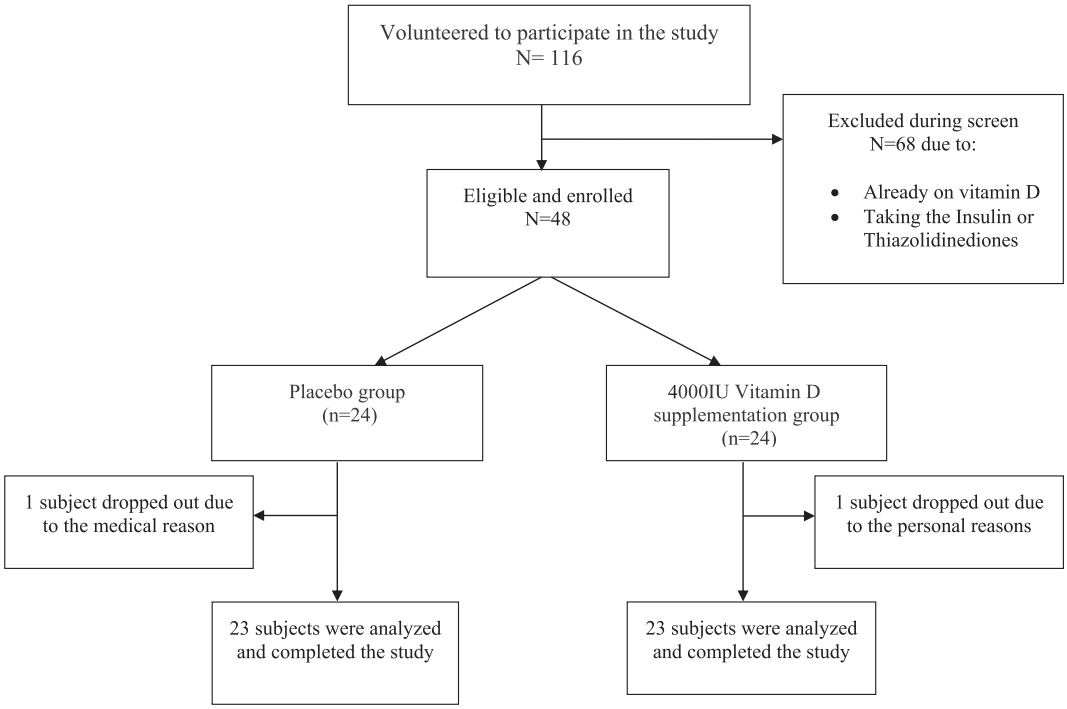

Fig. 1. Trial profile.

Table 1
Baseline characteristics of study group.

Study variable	Vitamin D2 (n = 23)	Placebo (n = 23)	P-value
Sex, n (%)			
Male	11 (23.9)	12 (26.1)	0.7[b]
Female	12(26.1)	11(23.9)	
Age, (year)	51.3 ± 4.7	52.4 ± 5.7	0.4[a]
Educational level, n (%)			
Primary	6 (13.0)	4(8.7)	0.5[b]
Diploma	10(21.7)	6(13.0)	
Bachelor or master degree	7(15.2)	13(28.8)	
Employed, n (%)			
Yes	14(30.4)	15(26.3)	0.7[b]
No	9(19.7)	8(17.4)	
Aspirin use, n (%)			
Yes	10(21.7)	11(23.9)	0.7[b]
No	13 (28.3)	12 (26.1)	
Diabetes duration (year)	5.8 ± 2.6	6.7 ± 3.0	0.3[a]
WC (cm)	96.6 ± 7.4	97.2 ± 8.5	0.8[a]
BMI (kg/m^2)	26.8 ± 1.4	27.5 ± 1.6	0.6[a]
Physical activity, n(%)			
Mild	12 (26.1)	17 (37)	0.2[b]
Moderate	10 (21.7)	6 (13)	
High	1 (2.2)	0 (0)	
FBS (mg/dl)	169.5 ± 35.5	186.5 ± 52.8	0.2[a]
HbA1c (%)	7.4 ± 0.8	7.9 ± 1.1	0.06[a]
TNF- α (ng/L)	247.1 ± 71.4	279.3 ± 97.0	0.2[a]
Serum 25(OH)D (ng/ml)	14.7 ± 9.9	14.8 ± 13.1	0.7[a]
Metformin dose (mg/d)	1065.2 ± 274	1282.6 ± 253.4	0.01[a]
Fasting insulin (μIU/dl)	11.6 ± 5.1	12.0 ± 4.5	0.7[a]
HOMA-IR	4.8 ± 2.5	5.5 ± 2.6	0.3[a]
YKL-40 (ng/ml)	90.9 ± 33.2	100.4 ± 30.6	0.3[a]
MCP-1(pg/ml)	240.2 ± 27.6	242.9 ± 62.9	0.8[a]
IL-6 (ng/L)	138.6 ± 43.1	147.6 ± 39.9	0.4[a]

WC: waist circumference, BMI: Body Mass Index, FBS: fasting blood sugar, HbA1c: Hemoglobin A1c, TNF- α: tumor necrosis factor-alpha, HOMA-IR: Homeostasis model assessment of insulin resistance, MCP-1: Monocyte chemoattractant protein-1, IL-6: interleukin-6.
Quantitative variables are presented as mean ± SD, and categorical variables are expressed by frequencies (%).
[a] Student t-test was applied for variable with normal distribution.
[b] Chi-square and Fisher exact tests were performed for categorical variables.

Table 2
Between-group comparison of adjusted mean of biochemical variable between intervention and placebo groups after 3 months of vitamin D supplementation[a].

	Vitamin D (n = 23)	Placebo (n = 23)	P-value[a]
	Mean (SE)	Mean (SE)	
YKL40 (ng/ml)	70.3 (6.2)	95.9 (6.2)	0.008
Fasting insulin (μIU/dl)	10.1(1.06)	12.4(1.06)	0.1
IL-6 (ng/L)	79.3 (7.8)	121.6(7.8)	0.001
HOMA-IR	3.7(0.51)	5.4 (0.51)	0.02
MCP-1(pg/ml)	197.0(12.7)	241.2(12.7)	0.02

[a] ANCOVA test; adjusted for metformin dose.

Table 3
Between-group comparison of mean change in biochemical variable between vitamin D supplementation and placebo groups after 3 months of supplementation[a].

	Vitamin D (n = 23)	Placebo (n = 23)	P-value[a]
	Mean change ± SD	Mean change ± SD	
YKL-40 (ng/ml)	−22.7 ± 24.6	−2.4 ± 19.3	0.003
Fasting insulin (μIU/dl)	−1.5 ± 2.5	0.4 ± 1.1	0.001
IL-6 (ng/L)	−62.4 ± 34.5	23.6 ± 38.0-	0.001
HOMA-IR	1.2 ± 1.5-	0.01 ± 1.2	0.03
MCP-1(pg/ml)	−45.7 ± 58.2	0.9 ± 21.9	0.001

[a] Student's t-test.

diabetes may be mediated by regulating insulin signaling pathway, glucose homeostasis and inflammatory pathways [16–18]. We designed this study Because of the elevated levels of YKL-40 and MCP-1 in diabetic patients and crucial role of these factors in the progression of diabetes and its complications.

In our study, vitamin D could significantly decrease serum levels of YKL-40. It is known that other inflammatory cytokines such as TNF-αinduces expression of YKL-40 [34]. Data from our study and a systematic review and meta-analysis has shown that vitamin D supplementation can significantly decrease circulatory TNF-α levels in patients with type 2 diabetes [35]. So, protective effects of vitamin D in lowering YKL-40 may be mediated by targeting TNF-α. To date, no study examined effects of vitamin D on YKL-40 levels.

Our results also revealed that MCP-1 levels significantly decreased after vitamin D treatment. A number of studies have investigated the effect of vitamin D on MCP-1 marker, with inconsistent results in different diseases and tissues.

Zhang Z et al. reported that vitamin D could decrease MCP-1 expression through suppressing NF-κB signaling pathway in mesangial cells [36]. Other in vitro study also showed that vitamin D could reduce secretion of MCP-1 from preadipocytes and limit infiltration of adhesion cells [37]. On the contrary, one clinical trial reported that treatment with paricalcitol orally for 3 months did not improve inflammatory cytokine levels including MCP-1 and TNF-α in patients with type 2 diabetes and advanced diabetic nephropathy. Patients in this study had advanced chronic kidney diseases (CKD) and this fact may lead to lack of significant changes in inflammatory markers [38].

Our study has several Strengths. First, our study had double-blind randomized placebo-controlled design. Second, participants of both groups had not significant difference in age, BMI, glycemic indices, other inflammatory factors (TNF-α and IL-6), lipid profile, diabetic duration, and physical activity at the start of study. Third, only two patients missed through trial.

Limitations of our study were as follows: We didn't measure and report urinary YKl-40, MCP-1, albumin and urinary albumin/creatinine ratio. Furthermore, we didn't assess clinical outcomes following vitamin D treatment. It is necessary to establish other clinical trials to examine whether reduced YKL-40 and MCP-1 levels can lead to ameliorated clinical outcomes in patients with type 2 diabetes. Finally, sample size of our study was small.

Our study revealed that Daily vitamin D supplementation could significantly decrease YKL-40 and MCP-1 levels in patients with type 2 diabetes and vitamin D deficiency. YKL-40 and MCP-1 are considered to be powerful predictors of all-cause mortality and cardiovascular mortality. It can be concluded that vitamin D might contribute in reducing diabetic complications via modulating YKL-40 and MCP-1 pathways. It is needed to establish other clinical trials to assess whether vitamin D supplementation can result in improved clinical outcomes in patients with type 2 diabetes.

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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.2019.07.047.

Conflicts of interest

The authors have no other conflicts to disclose.

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