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## The effects of calcitriol on microalbuminuria in patients with type 2 diabetes mellitus; a double-blind randomized clinical trial

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### ABSTRACT

**Introduction:** Diabetes mellitus (DM) is a metabolic disorder appearing as a main public health problem nowadays.

**Objectives:** This study aimed to evaluate the effect of calcitriol on microalbuminuria in patients with type 2 DM (T2DM).

**Patients and Methods:** This double-blind randomized clinical trial was performed on 38 patients with T2DM who had micro-albuminuria. These patients were randomly classified into two groups of treatment and control. The treatment group received calcitriol 0.25 µg daily since the control group received a placebo. Duration of treatment was three months. In baseline, serum creatinine (Cr), fasting blood sugar (FBS), glycosylated hemoglobin (HbA1c), cholesterol (Chol), triglyceride (TG), low-density lipoprotein (LDL-c), high-density lipoprotein (HDL-c), and micro-albuminuria were measured. Patients were followed up for three months.  $P < 0.05$  was set as a significant level.

**Results:** In baseline, two groups did not differ significantly in terms of serum Cr, FBS, HbA1c, Chol, TG, HDL-c, LDL-c, and micro-albuminuria ( $P > 0.05$ ). After the intervention, there was no significant difference between the two groups regarding the median of serum Cr, FBS, HbA1c, Chol, TG, LDL-c, HDL-c, and microalbuminuria. The median of microalbuminuria in the treatment and control groups was decreased at 46 mg/g and 11 mg/g, respectively. The difference in median of micro-albuminuria was not statically significant between the two groups; however, a significant difference was detected in the treatment group before and after the intervention ( $P = 0.03$ ).

**Conclusion:** Administration of calcitriol could reduce micro-albuminuria after three months. Therefore, the addition of calcitriol to angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients with T2DM and micro-albuminuria may have a beneficial effect on reducing their proteinuria.

**Trial Registration:** The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT2016091429812N; <https://en.irct.ir/trial/23865>, ethical code; IR.SSU.Rec.65415).

### Implication for health policy/practice/research/medical education:

This trial was conducted on 32 patients with type 2 diabetes mellitus who had microalbuminuria. The difference in median of microalbuminuria was not statically significant between the two groups; however, a significant difference was detected in the treatment group before and after the intervention. Administration of calcitriol could reduce microalbuminuria after three months.

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## Introduction

Type 2 diabetes mellitus (T2DM) accounted for 85.5% of cases with DM during 2015–2016 (1). According to non-communicable diseases project, the prevalence of DM was 11.4% in adult in 2011 (2). End-stage renal disease is the most common kidney complication associated with diabetic kidney disease and high mortality. DM causes a variety of metabolic, chemical, and hemodynamic changes in the kidney (3). In DM, the expression of inflammatory factors increases, resulting in a chronically activated innate immune system and low-grade inflammatory state (3). Nuclear receptors are the negative regulators of inflammation, oxidative stress, and fibrosis, and vitamin D receptor is one of these nuclear receptors involved in inflammatory pathways (4).

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) are drugs used for the management of elevated blood pressure reducing proteinuria and glomerular filtration rate (5). Although these drugs slow the progression of kidney and heart disease by reducing proteinuria (6), end-stage renal disease and cardiac complications are not completely prevented in many patients with chronic renal failure (7). Therefore, patients who have micro-albuminuria despite taking the above medications should be managed.

## Objectives

Calcitriol (1,25-dihydroxycholecalciferol) is the active form of vitamin D and can reduce proteinuria in patients with type 1 DM (8). Therefore, we aimed to evaluate the effects of calcitriol on micro-albuminuria in patients with T2DM.

## Patients and Methods

### Study design

This study was performed between 2017 and 2019 in Yazd, Iran. Among 200 patients who referred to the nephrology clinic in Diabetes Research Center, 38 met the inclusion criteria.

Inclusion criteria were as follows; suffering from T2DM, being under treatment with ARBs or ACEs for at least one year, and having micro-albuminuria (excretion of 30–300 mg of albumin after 8–12 hours of fasting).

Exclusion criteria were defined as having type 1 diabetes mellitus, systolic blood pressure (SBP) above 140 mm Hg or diastolic blood pressure (DBP) above 90 mm Hg, HbA1c more than 9%, micro-albuminuria greater than 300 mg/g, parathyroid hormone greater than 75 pg/mL, kidney stone disease or hypercalcemia (calcium more than 10.3 mg/dL), and acute liver disease and taking calcitriol or derivatives of vitamin D.

This study was a double-blind randomized clinical trial. Participants included 38 patients (19: treatment group

and 19 placebo group) with T2DM aged 30–75 years old and referred to nephrology clinic in Yazd diabetes research center.

Block randomization method was used to prevent the selection bias and ensure against the accidental bias. A block size of six was considered. Patients were randomly assigned in two groups of treatment and control. The treatment group received calcitriol 0.25 microgram daily, since the control group received a placebo. Duration of treatment was three months. Calcitriol and placebo were obtained from Zahravi Pharmaceutical Company (Tabriz, Iran). Calcitriol and placebo were similar in shape, size, and color. By coding the patients, the researcher was not aware of treatment and control groups. In fact, neither physician nor patients was informed of group classification or the used medicine.

A nurse measured patients' blood pressure by a standard mercury manometer. Biochemical tests, such as serum creatinine (Cr), fasting blood sugar (FBS), glycated hemoglobin (HbA1c), cholesterol (Chol), triglyceride (TG), low-density lipoprotein (LDL-c), and high density protein (HDL-c), were checked in the central laboratory. Serum Cr was evaluated by enzymatic colorimetric assay. Serum glucose was measured by glucose oxidase kit (Pars Azmoon, Iran) and HbA1c was determined by high-performance liquid chromatography. Serum Chol, TG, and HDL-c were measured by glycerol phosphate oxidase (GPO) -PAP method (Pars Azmoon kit). The LDL-c was calculated according to the Friedewald formula in patients with TG level less than 300 mg/dL [ $LDL = Chol - (HDL + TG/5)$ ]. The level was assessed by column chromatography (Biosource kit, Barcelona, Spain). Micro-albuminuria was measured in a morning urine sample by immunoturbidimetric assay (Pars Azmoon) in the central laboratory. Micro-albuminuria was evaluated by obtaining urine albumin to creatinine ratio. Micro-albuminuria was defined as fasting urinary albumin–creatinine ratio of 30–300 mg/g. After three months, serum Cr, FBS, HbA1c, Chol, TG, LDL-c, HDL-c, and microalbuminuria were measured in the central laboratory and compared in two groups (Figure 1).

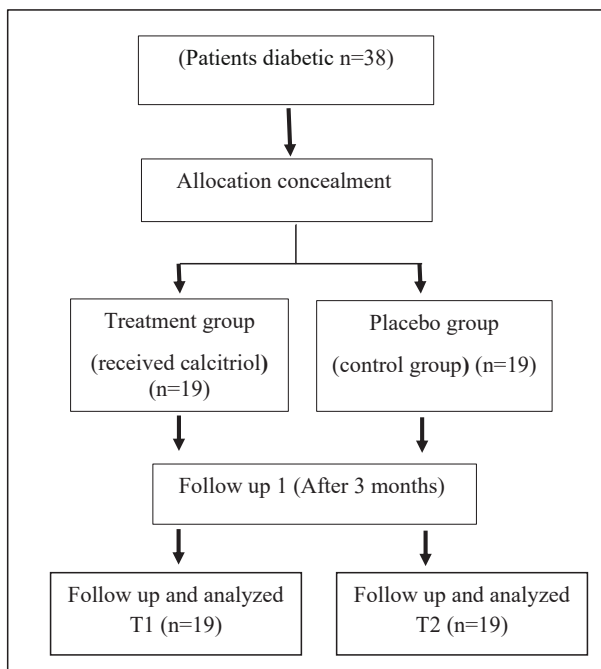
### Statistical analysis

SPSS (version 22) was used to analyze the data. Given that the data did not have a normal distribution, non-parametric statistics (chi-square test and Mann-Whitney U test) were used for data analysis.  $P < 0.05$  was set as significant level.

## Results

### Baseline characteristics

In this trial, we recruited 38 patients with T2DM. In terms of gender, there were 16 (42.1%) males and 22



**Figure 1.** The consort flow diagram of the trial.

(57.9%) females in this study. The median  $\pm$  range of age in patients was  $57 \pm 40$  years old and  $59 \pm 28$  years old in the treatment and control groups, indicating no significant difference between two groups in this regard ( $P=0.84$ ). In terms of family history of DM, diabetic kidney disease, hypertension, and ischemic heart disease, two groups did not differ significantly ( $P>0.05$ ; Table 1). At baseline, there was not any significant difference between median of variables in treatment and control groups. Before intervention, median of micro-albuminuria in the treatment group and control group were  $133 \pm 269$  mg/g and  $60 \pm 269$  mg/g, respectively ( $P=0.08$ ; Table 2).

#### After intervention

After intervention, there was no significant difference between the median of variables in the two groups. The medians of microalbuminuria in both groups were decreased after the intervention (in the treatment group was 46 mg/g and in the control group was 11 mg/g), though it was significant only in the treatment group ( $P=0.03$ ; Table 3). The patients were interviewed for detecting the side effects of the drug such as weakness, headache, nausea, constipation, dry mouth, anorexia and abdominal pain.

#### Discussion

In DM, hyperglycemia leads to activate cellular pathways like diacylglycerol protein-kinase C pathway, advanced glycation end-products, oxidative stress through active oxygen species, and glomerular hyperfiltration

and hypertension (3). Hyperglycemia stimulates the production of angiotensin 2, which leads to hemodynamic, inflammatory, and profibrogenic changes in renal cells (10).

Due to important role of renin-angiotensin system (RAS) in diabetic nephropathy, ACEIs and ARBs have critical role in treatment of these patients. Albuminuria did not improve completely in the majority of patients with T2DM who received ACEIs and ARBs, and these patients progress to end-stage renal disease. Therefore, using other medications to improve residual proteinuria is necessary. Calcitriol is the active form of vitamin D with modulatory effects on RAS, and immune system decreasing proteinuria in animal models. The activators of vitamin D receptor could reduce proteinuria with mechanisms, such as inhibition of synthesis and activity of monocyte chemoattractant protein 1, regulation of transforming growth factor  $\beta$ , expression of angiotensinogen, antiproliferative effects, antifibrotic effects, or combination of them (11-14).

In baseline data, there was no significant difference between the two groups. After intervention, the results of the study did not show a statistically significant difference between groups. It was also found that the median of micro-albuminuria was decreased after the intervention in the treatment group (46 mg/g) and in the control group (11 mg/g); however, changes in median of micro-albuminuria were significant only in the treatment group.

Another important point was related to consideration of strict inclusion criteria in our study to minimize the confounding effects of other factors, including hyperglycemia, hyperlipidemia and systolic and diastolic blood pressure (15,16), which did not significantly differ between two groups, indicating the correct randomization of sampling.

Krairitichai et al investigated patients with T2DM with urinary protein to creatinine ratio of more than 1 g/g. After four months, a significant decrease in proteinuria was observed in the calcitriol group, since no significant change was observed in other variables, including systolic and diastolic blood pressure, serum creatinine, Chol, and HbA<sub>1c</sub>, which is in line with the findings of current study. However in aforementioned study, patients' creatinine level was higher than that of the present study. In other words, patients with more advanced degrees of kidney failure were included in their study. The dose of calcitriol was also lower than that of our study (17).

The study of Liyanage et al was performed as a double-blind, randomized, placebo-controlled study on 85 patients. The researchers concluded that administration of vitamin D (50 000 IU) for six months reduced urinary albumin levels in patients with diabetic nephropathy. (18). However, in our study, there was no difference between

**Table 1.** Baseline categorical characteristics in patients of two groups

Characteristics	Treatment group, No. (%)	Control group, No. (%)	P value*
Positive family history of diabetes mellitus	13 (76.5)	12 (63.2)	0.30
Positive family history of diabetic kidney disease	5 (27.8)	6 (31.6)	0.54
Positive family history of hypertension	16 (94.1)	13 (72.2)	0.10
Positive family history of ischemic heart disease	4 (30.8)	2 (10.5)	0.16

\* Chi-square test.

**Table 2.** Baseline characteristics in total participant (N=28)

Characteristics	Treatment (Median ± Range)	Placebo (Median ± Range)	P value*
Micro-albuminuria (mg/g)	133 ± 269	60 ± 269	0.08
Serum creatinine (mg/dL)	1.2 ± 2.8	0.91 ± 1.9	0.08
HbA1c (%)	7.7 ± 5.1	7.85 ± 4	0.96
SBP (mm Hg)	137.5 ± 60	140 ± 50	0.56
DBP (mm Hg)	80 ± 30	75 ± 30	0.29
FBS (mg/dL)	127 ± 141	137 ± 129	0.38
OGTT	201 ± 244	236.5 ± 330	0.37
HDL-c (mg/dL)	43 ± 51	39.5 ± 29	0.50
LDL-c (mg/dL)	91 ± 90	81.9 ± 99.20	0.60
Cholesterol (mg/dL)	159 ± 167	152 ± 103	0.50
TG (mg/dL)	157 ± 385	175 ± 237	0.84

HbA1c: Glycated hemoglobin; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; OGTT: Oral glucose tolerance test; FBS: Fasting blood sugar; TG: Triglyceride; LDL-c: Low-density lipoprotein; HDL-c: High density lipoprotein.

\*Mann-Whitney U test.

two groups after three months of intervention regarding systolic and diastolic blood pressure, serum creatinine, FBS, HbA1c, TG, Chol, HDL-c, and LDL-c. This contrast between the results of aforementioned study and those of us can be attributed to difference in study design and omission of confounding factors in the present study. These confounding factors were SBP, DBP, FBS, HbA1c, TG, Chol, and LDL-c. In the current study, changes in the median of micro-albuminuria were significant in the treatment group.

Recent studies also showed that patients with diabetes with vitamin D deficiency have a higher risk of developing nephropathy (19,20).

The patients included in the present study did not report any side effect due to calcitriol use. After three months, there was no significant difference between two groups in any of the variables. However, in the treatment group, a significant decrease in micro-albuminuria level was observed after three months. Before intervention, the median of micro-albuminuria in the treatment and control groups was 133 ± 269 mg/g and 69 ± 269 mg/g, respectively, indicating no statistically significant (which can be clinically notable). In other words, in the treatment group, patients with higher micro-albuminuria, calcitriol significantly decreased micro- albuminuria after three months, suggesting the efficacy of calcitriol on reducing

micro-albuminuria level in patients with T2DM

## Conclusion

The results of our study showed that calcitriol could reduce median of micro-albuminuria after three months. Therefore, calcitriol to ACEs and ARBs in patients with T2DM and micro-albuminuria may have beneficial effects on reducing their residual proteinuria.

## Limitations of the study

One of the strengths of this study is its design, which was conducted as a double-blind clinical trial. Inclusion and exclusion criteria in the present study were both strengths and limitations. On the other hand, at the beginning of the study, patients became very special, and taking this drug will affect these unique patients. On the other hand, it has reduced its generalizability to a wide range of diabetic patients. It was also tough to find patients with these characteristics and

## Authors' contribution

**Conceptualization:** Maryam Askari, Roya Hemayati, Shadab Kharazmi, Akram Ghadiri-Anari

**Data curation:** Maryam Askari, Roya Hemayati

**Formal analysis:** Asma Jaafarinaia, Maryam Askari, Roya Hemayati, Akram Ghadiri-Anari

**Table 3.** Comparison of variables in two groups before and after the study

		Treatment group (Median ± Range)	P value*	Control group (Median ± Range)	P value*
Micro-albuminuria (mg/g)	Before	133 ± 269	0.03	60 ± 269	0.10
	After	87 ± 368		49 ± 219	
Cr (mg/dL)	Before	1.2 ± 2.8	0.53	0.91 ± 1.9	0.96
	After	1.2 ± 1.9		1 ± 1.5	
HbA1c (%)	Before	7.7 ± 5.1	0.60	7.85 ± 4	0.17
	After	7.75 ± 5		7.50 ± 3	
SBP (mm Hg)	Before	137.5 ± 60	0.87	140 ± 50	0.85
	After	130 ± 80		140 ± 60	
DBP (mm Hg)	Before	80 ± 30	0.64	75 ± 30	0.40
	After	80 ± 40		85 ± 30	
FBS (mg/dL)	Before	127 ± 141	0.63	137 ± 129	0.98
	After	124 ± 162		139 ± 173	
HDL-c (mg/dL)	Before	43 ± 51	0.10	39.5 ± 29	0.58
	After	36 ± 37		37.5 ± 25	
LDL-c (mg/dL)	Before	91 ± 90	0.92	81.9 ± 99.20	0.73
	After	86 ± 291		75.9 ± 135.10	
Chol (mg/dL)	Before	159 ± 167	0.45	152 ± 103	0.67
	After	146 ± 199		144 ± 140	
TG (mg/dL)	Before	157 ± 385	0.12	175 ± 237	0.82
	After	180 ± 448		185 ± 243	

Cr, creatinine; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; TG, triglyceride; LDL-c, low-density lipoprotein, HDL-c, high density lipoprotein.

\*Mann-Whitney U test.

**Investigation:** Maryam Askari, Roya Hemayati, Shadab Kharazmi, Akram Ghadiri-Anari.

**Methodology:** All authors.

**Project administration:** Roya Hemayati.

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**Supervision:** Maryam Askari, Roya Hemayati.

**Validation:** Shadab Kharazmi, Akram Ghadiri-Anari, Asma Jaafarinia.

**Visualization:** Maryam Askari, Roya Hemayati.

**Writing—original draft:** Maryam Askari, Roya Hemayati.

**Writing—review & editing:** Shadab Kharazmi, Akram Ghadiri-Anari, Asma Jaafarinia.

### Conflicts of interest

The authors declare that they have no competing interests.

### Ethical issues

The research followed the principles outlined in the Declaration of Helsinki. The institutional ethical committee at Shahid Sadoughi University of Medical Sciences approved all study protocols (IR.SSU. Rec.65415). Accordingly, written informed consent was obtained from all participants before any intervention. The trial protocol was approved by the Iranian Registry

of Clinical Trials (#IRCT2016091429812N; <https://en.irct.ir/trial/23865>). Moreover, ethical issues (including plagiarism, data fabrication and double publication) were also completely observed by the authors.

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