ORIGINAL ARTICLE

Curcumin as a major active component of turmeric attenuates proteinuria in patients with overt diabetic nephropathy

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Background: Diabetic nephropathy (DN) is a common cause of end-stage renal disease (ESRD). The benefits and effects of renin–angiotensin system blocker drugs are obvious in decreasing albuminuria, but there is a need to find other drugs that can decrease albuminuria. The aim of our study is to evaluate the effect of short-term administration of curcumin on overt albuminuria in patients with type 2 diabetes mellitus (T2DM). **Materials and Methods:** A randomized, double-blind clinical trial was performed on 46 patients with T2DM, overt albuminuria ≥300 mg/24 h, and estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m^2. After the random allocation of the patients, they were divided into two groups. In the curcumin group, the patients received 500 mg (one capsule) of curcumin with each meal (three times/day after meal) for 16 weeks. Other variables including blood urea nitrogen (BUN), creatinine (Cr), fasting blood sugar (FBS), 2-h postprandial blood sugar (2-h pp BS), lipid profile, 24-h urine analysis for albuminuria, serum albumin, and hemoglobin A1C (HbA1C) were checked at baseline and bimonthly too. **Results:** two groups at baseline were comparable in terms of basic characteristics ($P > 0.05$). Albuminuria decreased significantly from 900.42 ± 621.91 at the baseline to 539.68 ± 375.16 at the end of the study in the curcumin group ($P_{Time} = 0.002$); however, no statistically significant changes were observed in the placebo group (519.94 ± 214.33 at the baseline vs. 444.00 ± 219.10 at the end of the trial; $P_{Time} = 0.43$), and the decrease was significantly higher in the curcumin group than that of the placebo group ($P_{Intervention} = 0.01$). No significant differences were observed between the placebo and curcumin in terms of changes in serum BUN, Cr, FBS, 2-h pp BS, HbA1C, lipid profile, and albumin. **Conclusion:** Our study showed that curcumin as an active turmeric metabolite was an effective adjuvant therapy for ameliorating macroscopic proteinuria in type 2 diabetic patients. Its effect may appear after 2 months of therapy and even in patients with a mild decrease in GFR. Further studies with larger sample size and longer duration are recommended.

Key words: Albuminuria, curcumin, diabetic nephropathy, end-stage renal disease, proteinuria, turmeric (curcuma)

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INTRODUCTION

Diabetic nephropathy (DN) is the leading cause (45%) of end-stage renal disease (ESRD) cases in European, Japanese, and American people, as well as in 20%–48% of the cases in the Middle East.[1] One characteristic of DN is that the persistent albuminuria is more than ≥300 mg/24 h.[2] Although renin–angiotensin system blocker drugs are beneficial and effective in reducing albuminuria, they can cause few adverse effects among cough (up to 20%) and angioedema.[3] Therefore, there is a need to find alternative drugs that can decrease albuminuria.

Cytokines such as interleukin (IL)-8 and transforming growth factor-beta (TGF-β), which have a cardinal role

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in the inflammatory cascade, result in functional damage of the renal cells. They also have a key role in cell proliferation and interstitial fibrosis. Turmeric is a wild plant from the ginger family that grows in South Asia. Curcumin is known to be a more active and nontoxic component of turmeric. Experimental studies have shown that turmeric blocks cytokines, including IL-8 and TGF-β signaling cascade in renal cells. Also it is delaying apoptosis by decreasing the mRNA expression of tumor necrosis factor-alpha (TNF-α). It has immunomodulator, immune stimulator, and antioxidant effects. So, curcumin can be effective in protecting renal cells from proliferation and fibrosis.[4-9] Therefore, it prevents glomerular hypertension, which is the main mechanism in the pathogenesis of DN.[10-14] Curcumin, as an antioxidant (same as allopurinol and N-acetylcysteine), reduces renal inflammation and fibrosis due to hyperglycemia-induced oxidative stress in diabetic patients.

Three studies have been conducted in Shiraz University of Medical Sciences on the effects of curcumin on different kinds of renal damage. All these studies have shown that curcumin can be administrated as a safe alternative drug for treatment.[9,15,16]

Owing to the high prevalence of type 2 diabetes mellitus (T2DM) and CKD caused by proteinuria and other known and unknown mechanisms related to DM, it is necessary to find new and effective drugs for the preservation of the kidney by decreasing proteinuria. Hence, the administration of curcumin can be considered due to its capability to decrease proteinuria.[17]

Curcumin is safe in usual doses; however, as found in the reports, peptic ulcer, gastrointestinal upset (GI), and a tendency to cause bleeding in the concurrent anticoagulant use were reported for only long-term consumers.[4]

As the number of studies conducted in Iran on the effects of curcumin on diabetic patients is very limited and the duration of these studies is 2 months, the aim of our study was to examine the effects of curcumin on diabetic patients for the first time in our center to find if it can reduce albuminuria in patients with DN.

MATERIALS AND METHODS

Study design and participants

This was a randomized, double-blind controlled trial conducted in Diabetes Clinic of Isfahan Endocrine and Metabolism Research Center, Isfahan, Iran, from June 10, 2015, to July 28, 2016. Sixty patients were selected at the beginning of the study but eventually the study ended with 46 T2DM patients on oral antidiabetic drugs or insulin. The inclusion criteria were as follows: age ≥18 years, overt proteinuria (≥500 mg protein or ≥300 mg/24 h albumin), estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 m2, and controlled HTN (systolic blood pressure [BP] <140 and diastolic BP <90).

The exclusion criteria were patients with other causes of proteinuria (recurrent urinary tract infection, bacteremia, pyuria, or hematuria), eGFR <30 mL/min/1.73 m^2, history of gallstone, biliary obstruction (due to the adverse effect of curcumin on these problems), intolerance to the drug, or if the patient was noncooperative. The Bioethics Committee of Isfahan University of Medical Sciences approved the study protocol (study project number: 293354), and after explaining the study objectives for patients, written informed consent was obtained from all participants before the recruitment.

Procedures and assessment of variables

Patients were randomized into two groups (curcumin and placebo) using permuted block randomization method with block size 4. The complete clinical history was obtained by the researcher, and the eGFR was calculated according to the Modification of Diet in Renal Disease (MDRD) formula: $175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female).[18] In the curcumin group, the patients received 500 mg of curcumin capsule (Aburaihan Co., Tehran, Iran) three times/day after meal. In the placebo group, the patients received a placebo capsule with a similar packing. During the trial (4 months), all patients received the same dietary protocol during the trial (4 months), and were routinely evaluated for compliance. Patients were referred for 4 months each month for blood pressure control and data on drug use or side effects. In each visit, the questionnaires were completed by the nurse who was as the communicator between the patient and the researcher. The baseline and bimonthly tests were as follows: 24-h urinary test for albumin, Cr, volume, urinalysis, serum blood urea nitrogen (BUN), creatinine (Cr), fasting blood sugar (FBS), 2-h postprandial blood sugar (2-h pp BS), lipid profile (triglycerides [TG], cholesterol, low-density lipoprotein [LDL], high-density lipoprotein [HDL]). Serum albumin and HbA1C were checked at the onset and the end of the study.

Laboratory data were analysed by BTC300 automated analyzer using immunoturbidimetric method.

Statistical analysis

All analyses were performed using the SPSS 16.0 (SPSS Inc., Chicago, IL, USA) software. Categorical data were presented as frequency (percentage), continuous normally distributed data as mean ± standard deviation, and nonnormally distributed variables as median

(range: minimum–maximum). Categorical data were compared between two groups using the Chi-square test and basic continuous variables using the independent samples *t*-test.

The main statistical method used for analyzing the data was the "repeated measures analysis of variances (ANOVA)." Sphericity assumption using Mauchly's test, and when it was violated, multivariate ANOVA, was adopted for evaluating the changes over time in each group separately for studied variables (time effect), between groups' mean changes of variables (intervention effect), and interaction of time and intervention. $P < 0.05$ was considered statistically significant.

RESULTS

The mean age of the patients was 61 ± 10.80 years in placebo and 59 ± 6.25 years in curcumin. Curcumin group consisted of 27 patients (11 [41%] females and 16 [59%] males) and placebo group consisted of 19 patients (8 [42%] females and 11 [58%] males). Table 1 presents more details about basic characteristics of participants and as can be seen no significant differences were detected between the two study groups.

Table 1: Demographic and basic clinical characteristics of the patients

Variable	Placebo (*n*=19)	Curcumin (*n*=27)	*P**
Sex, male (%)	58	59	>0.05
Age (years)	61±10.80	59±6.25	0.79
Duration of DM (years)	15±10.1	16±6.86	0.53
ACEI or ARB use percentage (%)	65	75	>0.05
Blood pressure (mean±SD)	136/78	124/82	>0.05

*Resulted from independent *t*-test and Chi-square test for continuous and categorical variables, respectively. SD=Standard deviation; ACEI=Angiotensin-converting enzyme inhibitor; ARB=Angiotensin II receptor blocker; DM=Diabetes mellitus

In Table 2, it has been shown that albuminuria decreased significantly from 900.42 ± 621.91 at the baseline to 539.68 ± 375.16 at the end of the study period in the curcumin group (P_{Time} = 0.002); however, no statistically significant changes were observed in the placebo group (519.94 ± 214.33 at the baseline vs. 444.00 ± 219.10 at the end of the trial; P_{Time} = 0.43), and the decrease was significantly higher in the curcumin group than that of the placebo group ($P_{Intervention}$ = 0.01) [Figure 1]. Other nephrological specific variables did not show significant differences between the two groups, although we observed marginally significant more decrease in terms of Cr in curcumin group ($P < 0.1$).

In Table 3, the mean values of blood sugar, 2-h pp, HbAIC, serum albumin, and lipid profile (TG, cholesterol, LDL, and HDL) have been compared between the curcumin and placebo groups, and no significant differences were found between the placebo and curcumin groups.

DISCUSSION

Constant and progressive albuminuria is characteristic of DN. When nephropathy exceeds the cardiovascular disease, it leads to mortality and decline in the GFR, thereby resulting in ESRD. The deterioration of renal function is partly due to the toxic effects of persistent proteinuria, which may cause tubular epithelial injury through tubular apoptosis, secondary generation of inflammatory mediator, and peritubular inflammation.[19]

In the experimental studies, curcumin (diferuloylmethane; 1,7-bis (4-hydroxy-3-methoxyphenyl) hepta-1,6-diene-3,5-dione),[20] which is the major active component in turmeric, has been shown to ameliorate DN by blocking cytokines, including the TGF-β signaling cascade in renal cells, and prevent renal fibrosis and delay apoptosis by

Table 2: Comparison of nephrological specific outcomes during the study period between the two studied groups

Variable	Group	Mean±SD Median (range)			P^a	P^b	P^c
		Baseline	After 2 months	After 4 months			
Albuminuria	Curcumin	900.42±621.91 769 (303-2568)	661.51±402.73 589 (48-1669)	539.68±375.16 454 (49-1416)	0.002 0.485	0.0184	0.006
	Placebo	519.94±214.33 511 (220-1013)	484.36±232.04 520 (101-844)	444.00±219.10 463 (126-745)			
BUN	Curcumin	18.35±5.53 18 (9-34)	19.54±5.53 20 (10-32)	21.24±6.37 21 (12-37)	0.021 0.137	0.936	0.515
	Placebo	17.77±4.84 17 (11-32)	19.71±7.04 19 (9-39)	19.94±4.94 19 (12-35)			
Cr	Curcumin	1.23±0.37 1.20 (0.65-2.10)	1.28±0.45 1.10 (0.64-2.20)	1.34±0.45 1.20 (0.80-2.50)	0.074 0.095	0.520	0.09
	Placebo	1.19±0.396 1.10 (0.70-2.30)	1.40±0.51 1.25 (0.75-2.50)	1.49±0.50 1.30 (0.80-3.00)			

[a]Time effect; [b]Intervention effect; [c]Time × intervention effect. *P* values resulted from repeated measures ANOVA. ANOVA=Analysis of variances; BUN=Blood urea nitrogen; Cr=Creatinine; SD=Standard deviation

Table 3: Comparison of serum albumin, fasting blood sugar, hemoglobin A1C, and lipid profile in the placebo and curcumin groups

Variable	Group	Mean±SD Median (range)			P^a	P^b	P^c
		Baseline	After 2 months	After 4 months			
Serum albumin	Curcumin	3.97±0.47 4.00 (3.10-4.80)	4.03±0.41 4.10 (3.20-4.70)	4.09±0.44 4.20 (3.10-4.80)	0.357 0.874	0.155	0.578
	Placebo	4.10±0.33 4.20 (3.30-4.60)	4.16±0.50 4.35 (3.10-5.00)	4.20±0.48 4.30 (3.00-4.80)			
FBS	Curcumin	183.55±75.37 164 (78-381)	186.92±81.30 178 (76-400)	201.95±86.61 186 (47-434)	0.720 0.120	0.811	0.89
	Placebo	176.05±73.02 160 (71-398)	214.05±93.64 206 (99-384)	173.63±66.28 158 (78-298)			
HBA1C	Curcumin	9.46±2.25 8.7 (6.20-14.90)	9.91±2.42 9.50 (6.10-16.20)	9.49±2.54 9.50 (5.10-15.70)	0.436 0.255	0.730	0.558
	Placebo	13.01±14.17 10 (6.20-69)	8.75±2.17 9.3 (5.10-11.70)	8.53±1.75 8.30 (6.40-12)			
TG	Curcumin	187.85±70.01 195 (86-354)	173.28±76.85 149 (57-363)	191.08±99.80 167 (47-421)	0.457 0.373	0.959	0.716
	Placebo	202.21±144.85 147 (76-659)	163.55±74.13 161 (53-320)	183.00±120.19 136 (65-449)			
Cholesterol	Curcumin	173.85±40.00 187 (98-247)	174.44±49.95 158 (98-282)	172.56±47.81 168 (103-278)	0.375 0.489	0.341	0.865
	Placebo	181.89±44.73 172 (114-261)	168.45±41.06 164 (106-239)	177.27±49.82 168 (118-294)			
LDL	Curcumin	96.92±34.99 94.00 (35-150)	98.32±40.74 90 (52-211)	90.94±37.28 83 (50-208)	0.151 0.959	0.924	0.524
	Placebo	98.26±46.87 90 (40-183)	97.45±39 90 (36-169)	92.72±35.59 82 (45-188)			
HDL	Curcumin	40.07±8.62 39 (26-63)	38.96±10.28 37 (26-69)	39.56±8.66 37 (24-56)	0.337 0.951	0.388	0.596
	Placebo	42.10±11.72 41 (23-72)	41.75±13.77 40 (23-76)	43.27±14.33 42 (18-75)			

[a]Time effect; [b]Intervention effect; [c]Time × intervention effect. *P* values resulted from repeated measures ANOVA. HBA1C=Hemoglobin A1C; FBS=Fasting blood sugar; LDL=Low-density lipoproteins; HDL=High-density lipoproteins; TG=Triglycerides; SD=Standard deviation; ANOVA=Analysis of variances

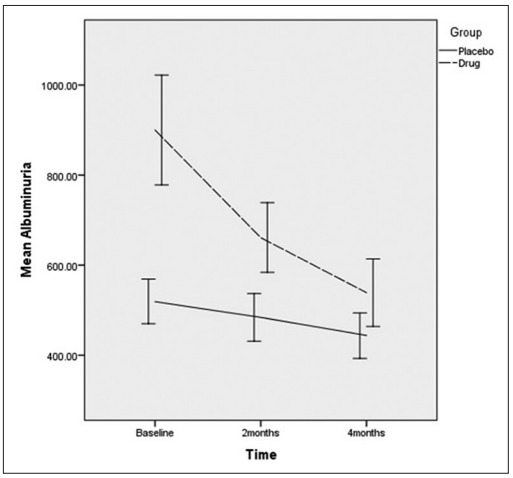

Figure 1: The mean values of albuminuria in two study groups over the study periods

decreasing the mRNA expression of TNF-α.[5,6,21-23] The experimental studies indicated that turmeric inhibits IL-8 production.[7]

Hyperglycemia-induced oxidative stress can cause renal cell dysfunction. Curcumin, as a polyphenol[8] antioxidant (same as allopurinol and N-acetylcysteine), reduces renal inflammation and fibrosis in experimental models of DN and inflammatory responses and contributes to the oxidative stress in ESRD condition.[24]

Three studies in Shiraz University were done, about the curcumin in different conditions. One study demonstrated that turmeric decreases the proteinuria and systolic hypertension in recurrent lupus nephritis without any effect on the activity of lupus.[17]

The useful effect of curcumin on oxidative stress was observed in the preservation function of the mitochondrial enzyme complex and in decreasing the active oxygen released that results in an antioxidant effect.

In the other study, turmeric was used on dialysis patients to decrease the hs-CRP level and improve pruritus.[9]

Another study conducted on DN during a 2-month period showed that curcumin decreases proteinuria, serum and urine IL-8, and serum TGF-β; hence, curcumin can be administrated as a safe alternative treatment.[16] In this

study, blood sugar and lipid profile didn't find significant differences between the placebo and curcumin groups, similar to our study.

Our study has similar effect on proteinuria in contrast to Shiraz studies on lupus nephritis and diabetic patients, but only one different result was found on BP in recurrent lupus nephritis which may be due to diuretic administration in all of them.

An animals based review article about drug-induced nephrotoxicity showed that curcumin had a renoprotective effect against cisplatin and acetaminophen.[25] In the other study, the protective effects of curcumin against cyclophosphamide-induced cytogenetic damage were shown.[26]

The extent of persistent proteinuria correlates quite closely with the rate of decline of Cr clearance; curcumin limiting the Cr clearance results in a slower renal function impairment, and possibly, a reversal of the fibrotic lesions.[21,22,27] The experimental studies have shown that dietary turmeric ameliorates DN and the renal lesions associated with it.[28]

The duration of our study was 4 months, and it evaluated the antiproteinuric effect of turmeric and determined its effect on the renal function of the 46 type 2 diabetic patients suffering from clinical DN. A significant decrease in the urinary protein excretion was found in the trial group comparing pre- and postsupplementation values, but there was no significant change in the serum Cr and GFR levels.

Oral administration of curcumin seems to be a promising alternative therapy for type 2 DN. Longer duration of our study was in order to provide more evidence and to clarify the effects of turmeric on renal function. Based on the findings of this study, turmeric can be used as a safe and effective adjuvant therapy for ameliorating proteinuria in patients suffering from T2DM, even when patients have poorly controlled diabetes.

The only side effect of curcumin in the study was epigastric pain due to GI system in one case.

We must discover other participatory mechanisms that result in proteinuria decrement. In traditional medicine, in addition to providing support to the kidney, concurrent liver amplification occurs while decreasing proteinuria. One hypothesis about curcumin is that it resolves mechanical or functional obstruction of the liver vessels by decreasing the inflammatory mechanism. Moreover, we require a comprehensive theoretical and experimental study on the other parts of the plant because, theoretically, other parts of the plant can be used to reinforce drug effect and decrease the adverse effects.

The limitation of our study was the relatively small number of the patients. We recommend a larger study with more population and longer duration of therapy for definite results.

CONCLUSION

Curcumin, an active turmeric metabolite, is a safe adjuvant therapy for ameliorating macroscopic proteinuria in type 2 diabetic patients. Its effect may appear after short-term (2 months) therapy and even in patients with a mild decrease in GFR.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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