The Effects of Nano-curcumin on Metabolic Status in Patients With Diabetes on Hemodialysis, a Randomized, Double Blind, Placebo-controlled Trial

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Original Paper

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Introduction. This study evaluated the effects of nano-curcumin intake on metabolic status in patients with diabetes on hemodialysis (HD).
Methods. This randomized, double-blind, placebo-controlled clinical trial was performed on 60 patients with diabetes on HD. Participants were randomly divided into two groups to take either 80 mg/d nano-curcumin (n = 30) or placebo (n = 30) for 12 weeks.
Results. Nano-curcumin significantly decreased fasting plasma glucose (β = -19.68 mg/dL, 95% CI: -33.48 to -5.88; $P < .05$) and serum insulin levels (β = -1.70 μIU/mL, 95% CI: -2.96 to -0.44; $P < .05$) when compared with patients who received placebo. Nano-curcumin treatment was associated with a significant reduction in triglycerides (β = -16.13 mg/dL, 95% CI: -31.51 to -0.75; $P < .05$), VLDL-cholesterol (β = -3.22 mg/dL, 95% CI: -6.30 to -0.15; $P < .05$), total cholesterol (β = -17.83 mg/dL, 95% CI: -29.22 to -6.45; $P < .05$), LDL-cholesterol (β = -15.20 mg/dL, 95% CI: -25.53 to -4.87; $P < .05$), and total-cholesterol/HDL-cholesterol ratio (β = -1.15, 95% CI: -0.2.10 to -0.21; $P < .05$) when compared with the placebo. Nano-curcumin also resulted in a significant reduction of serum high sensitivity CRP (β = -0.78 mg/L, 95% CI: -1.41 to -0.15; $P < .05$), and plasma malondialdehyde (β = -0.25 μmol/L, 95% CI: -0.45 to -0.04; $P < .05$); but also with a significant increase in plasma total antioxidant capacity (β = 52.43 mmol/L; 95% CI: 4.52 to 100.35; $P < .05$) and total nitrite levels (β = 3.62 μmol/L, 95% CI: 2.17 to 5.08; $P < .001$) when compared with placebo.
Conclusion. Nano-curcumin intake for 12 weeks had beneficial effects on metabolic profile in patients with diabetes on HD.

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INTRODUCTION

Diabetes mellitus is one of the leading causes of chronic kidney disease (CKD) worldwide. Diabetic nephropathy (DN) is the most common risk factor for developing end-stage renal disease (ESRD). Approximately 95% of these patients are treated with hemodialysis (HD).[1] Hyperglycemia is the primary cause for developing DN because it increases generation of reactive oxygen species and causes oxidative damage, which are more expressed in HD patients. In addition to oxidative stress, other factors such as malnutrition, inflammation, and the reduced production of nitric oxide (NO) promote endothelial dysfunction and atherosclerosis in these patients.[2-4] Moreover, changes of lipoproteins, both quantitative and qualitative, are often found in

CKD patients and are more pronounced in end-stage of the disease.[5-7] However, diabetes per se, particularly type 2 diabetes mellitus (T2DM), is very often associated with atherogenic dyslipidemia which is characterized by hypertriglyceridemia, low HDL-cholesterol and moderately elevated or even normal LDL-cholesterol but LDL particles are small, dense and more atherogenic.[8-10] CKD is associated in patients with diabetes with higher levels of plasma triglycerides and lower levels of HDL-cholesterol even among patients with good control of LDL- cholesterol.[11]

Curcumin is the active compound of the traditional dietary and medicine plant named turmeric.[12,13] Curcumin has a wide variety of pharmacological and biomedical effects in various conditions such as inflammatory diseases, metabolic syndrome, obesity, dyslipidemia, cardiovascular diseases, and cancer.[14-16] This natural compound has attracted attention because of its beneficial properties in treatment of diabetes and its complications due to its hypoglycemic, lipid-lowering, anti-inflammatory and antioxidant effects.[17,18] Curcumin improves insulin resistance and glucose homeostasis by enhancing β-cells function and insulin secretion affecting glycolysis, glyconeogenesis and lipids metabolism in liver.[19] Lipid-lowering effects of curcumin are due to its ability to increase the activity of lipoprotein lipase, to reduce lipid peroxidation, plasma total cholesterol and triglycerides concentrations and to elevate HDL-cholesterol levels.[20,21] There are indications that curcumin can modulate the expression of some genes related to glucose and lipid metabolism such as peroxisome proliferator-activated receptor (PPAR-γ) and LDL receptor (LDLR).[22,23]

Despite of potential positive effects of curcumin, its oral bioavailability is low. Nano formulated curcumin is a novel way to improve its bioavailability.[24] Therefore, based upon reported beneficial effects of curcumin, we tried to evaluate the effects of Nano-curcumin intake on metabolic status in patients with diabetes mellitus on hemodialysis (HD).

MATERIALS AND METHODS

Trial Design and Participants

This study, registered in the Iranian website for clinical trials (http://www.irct.ir: IRCT20150606022562N6), was a randomized, double-blind, placebo-controlled clinical trial performed on 60 patients with diabetes on HD; 18 to 80 years old, which were referred to the Akhavan Clinic in Kashan, Iran, between December 2018 and April 2019. All participants fulfilled The Declaration of Helsinki requirements and signed an informed consent. The ethics committee of Kashan University of Medical Sciences (KAUMS) approved this study. Patients involved with infectious, inflammatory and malignant diseases, those who were taking curcumin supplements, antioxidant and/or anti-inflammatory supplements within 3 months before participation in the study, and subjects who were receiving immunosuppressive and antibiotics medications were not included in the study.

Study Design

Patients were asked to continue their routine physical activity, and not to take any anti-inflammatory and antioxidant medications or supplements that might affect their nutritional status during the 12-week intervention. By asking participants to give back the medication containers we checked administration of curcumin and placebo during the study. All participants were reminded to take the supplement (or placebo) by sending a short SMS message every day. All partients completed both 3-day food records and physical activity records at weeks 0, 6, and 12 of the intervention. To obtain macro- and micro-nutrient intake composition of participants based on these 3-day food records, Nutritionist IV software (First Databank, San Bruno, CA) modified for Iranian foods was used.

Intervention

Patients were randomized into two groups to take either nano-curcumin capsule (80 mg/d) or placebo (n = 30, each group) for 12 weeks. Nano-curcumin and placebo capsules were purchased from Exir Nano Sina Company (Tehran, Iran). Nano-curcumin and placebo were similar in shape and package.

Assessment of Anthropometric Measures

Body weight and height were assessed after overnight fasting using the same digital scale (Seca, Hamburg, Germany) at baseline and after the 12-week of intervention. Body mass index (BMI) was

calculated by weight and height measurements [weight (kg) / height (m^2)].

Clinical Measurements

Assessment of Outcomes. Insulin resistance and insulin levels were considered as primary outcomes while serum lipoproteins, and biomarkers of inflammation and oxidative stress were considered as secondary outcomes. A 15 mL fasting blood sample was collected at baseline and at week 12 after the intervention at Kashan reference laboratory and samples were centrifuged to separate serum. Then, the samples were stored at -80°C until analysis. Serum insulin and hs-CRP levels were quantified by using ELISA kit (DiaMetra, Milano, Italy and LDN, Nordhorn, Germany) with inter- and intra-assay coefficient variances (CVs) lower than 7%. The homeostasis model of assessment-insulin resistance (HOMA-IR), and the quantitative insulin sensitivity check index (QUICKI) were determined according to the standard formula.[25] Enzymatic kits (Pars Azmun, Tehran, Iran) were used to quantify fasting plasma glucose (FPG), serum lipoproteins, creatinine and blood urea nitrogen (BUN) with inter- and intra-assay CVs less than 5%. Total nitrite was estimated using Griess method,[26] total antioxidant capacity (TAC) by the method of ferric reducing antioxidant power developed by Benzie and Strain,[27] total glutathione (GSH) using the method of Beutler *et al*.[28] and malondialdehyde (MDA) concentrations were determined by the thiobarbituric acid reactive substances spectrophotometric test[29] with inter- and intra-assay CVs lower than 5%. Systolic (SBP) and diastolic blood pressure (DBP) was measured using the same sphygmomanometer (ALPK2, Zhejiang, China). Blood pressure was measured between 08:00 and 09:00 AM by the same investigator each time.

Isolation of Lymphocytes

Lymphocytes were extracted from blood samples using 50% percoll (Sigma-Aldrich, Dorset, UK). Cell count and viability test were conducted using trypan blue, RNA and DNA extraction.

RNA Extraction and Real-time PCR (RT-PCR)

Gene expressions of PPAR-γ, LDLR and transforming growth factor beta (TGF-β) were assessed by quantitative RT-PCR in peripheral blood mononuclear cells (PBMCs), using the LightCycler technology (Roche Diagnostics, Rotkreuz, Switzerland) with SYBR green detection and Amplicon Kit (Table 1). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) primers were used as a housekeeping gene. Primer Express Software (Applied Biosystems, Foster City, USA) and Beacon designer software (Takaposizt, Tehran, Iran) were used to design primers. Relative transcription levels were calculated using the method of Pffafi.

Sample Size

In this study, we used a randomized clinical trial sample size calculation formula where type one (α) and type two errors (β) were 0.05, and 0.20 (power = 80%); respectively. According to our previously published trial,[30] we used 0.170 as the SD and 0.135 as the change in mean (d) of HOMA-IR as a primary outcome. Based on the formula, we needed 25 participants in each group. After allowing for 5 dropouts in each group, the final sample size was 30 persons in each group.

Table 1. Specific Primers Used for Real-time Quantitative PCR

Gene	Primer	Product Size (bp)	Annealing Temperature (°C)
GAPDH	F: AAGCTCATTTCCTGGTATGACAACG	126	61.3
	R: TCTTCCTCTTGTGCTCTTGCTGG		
PPAR-γ	F: ATGACAGACCTCAGACAGATTG	210	54
	R: AATGTTGGCAGTGGCTCAG		
LDLR	F: ACTTACGGACAGACAGACAG	223	57
	R: GGCCACACATCCCATGATTC		
TGF-β	F: TTGAGACTTTTCCGTTGCCG	227	56
	R: CGAGGTCTGGGGAAAAGTCT		

GAPDH, glyceraldehyde-3-Phosphate dehydrogenase; LDLR, low-density lipoprotein receptor; PPAR-γ, peroxisome proliferator-activated receptor gamma; TGF-β, transforming growth factor beta.

Randomization

Computer-generated random numbers were used for randomization. The researchers and patients were not aware of randomization details until the final analyses were completed. The enrolling of participants, randomized, and allocating them to treatment or placebo were performed by trained staff at the dialysis clinic.

Statistical Methods

The Kolmogorov-Smirnov test was done to determine the normality of data. To detect the differences in anthropometric parameters, dietary intakes and gene expression between two groups, we used the independent-samples *t*-test. Paired-samples *t*-test was used to detect within-group changes. Multiple linear regression models were used to assess treatment effects on study outcomes. The effect sizes were presented as the mean differences with 95% confidence intervals. *P* values < .05 were considered statistically significant. All statistical analyses were done using the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

RESULTS

Four patients in the Nano-curcumin group and 3 in the placebo group withdraw from the trial, due to personal reasons; thus 53 patients [nano-curcumin (n = 26) and placebo (n = 27)] completed the study (Figure 1). The compliance rate was high, more than 90% of capsules were taken during the course of the trial in both groups. No side effects were reported following the consumption of Nano-curcumin in patients with diabetes on HD during the study.

Distribution of gender, mean age, height, baseline weight and BMI were not statistically different between the two groups (Table 2).

Based on the 3-day dietary records obtained during the treatment period, we found no significant change in dietary macro- and micro-nutrient intake (data not shown).

Nano-curcumin significantly decreased FPG (β = -19.68 mg/dL, 95% CI: -33.48 to -5.88; *P* < .05) and serum insulin levels (β = -1.70 μIU/mL, 95% CI:

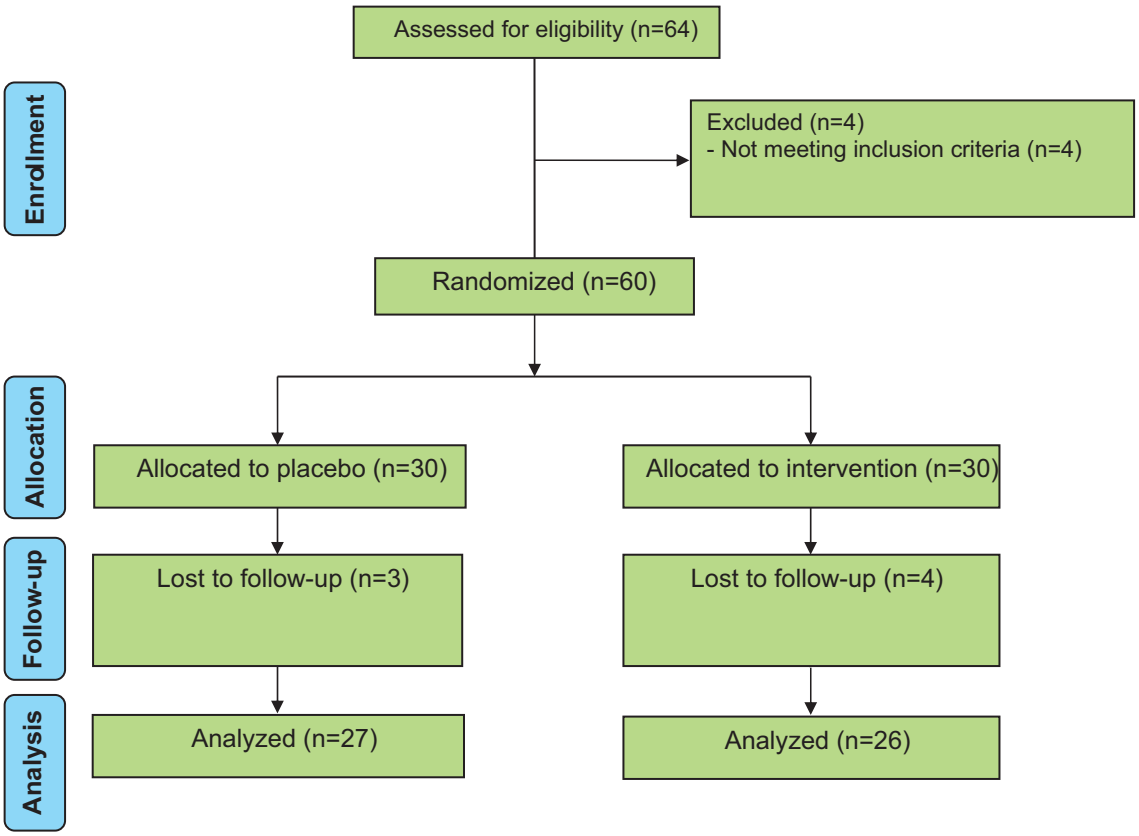

Figure 1. It shows summary of patients' flow diagram.

Table 2. General Characteristics of Study Participants

	Placebo Group (n = 27)	Nano-curcumin Group (n = 26)	*P*[1]
Gender (%)			
Males	15 (55.6)	17 (65.4)	> .05[†]
Females	12 (44.4)	9 (34.6)	
Age, years	56.2 ± 9.8	58.3 ± 9.4	> .05
Height, cm	165.5 ± 7.2	167.5 ± 7.3	> .05
Weight at Baseline, kg	73.9 ± 10.7	78.6 ± 15.9	> .05
Weight at the End of Trial, kg	74.9 ± 10.8	77.8 ± 15.4	> .05
Weight Change, kg	0.1 ± 1.4	-0.8 ± 1.5	< .05
BMI at Baseline, kg/m^2	27.1 ± 4.2	27.9 ± 4.9	> .05
BMI at the End of Trial, kg/m^2	27.1 ± 4.3	27.6 ± 4.7	> .05
BMI Change, kg/m^2	0.03 ± 0.5	-0.3 ± 0.5	< .05

Data are means ± SD.
[1]Obtained from independent *t*-test.
[†]Obtained from Pearson Chi-square test.

-2.96 to -0.44; $P < .05$) when compared with placebo (Table 3). Nano-curcumin was also associated with a significant reduction in triglycerides (β = -16.13 mg/dL, 95% CI: -31.51 to -0.75; $P < .05$), VLDL-cholesterol (β = -3.22 mg/dL, 95% CI: -6.30 to -0.15; $P < .05$), total cholesterol (β = -17.83 mg/dL, 95% CI: -29.22 to -6.45; $P < .05$), LDL-cholesterol (β = -15.20 mg/dL, 95% CI: -25.53 to -4.87; $P < .05$), and total-/HDL-cholesterol ratio (β = -1.15, 95% CI: -0.2.10 to -0.21; $P < .05$) when compared with placebo. Nano-curcumin significantly reduced serum hs-CRP (β = -0.78 mg/L, 95% CI: -1.41 to -0.15; $P < .05$) and plasma MDA (β = -0.25 µmol/L, 95% CI: -0.45 to -0.04; $P < .05$); and significantly increased plasma TAC (β = 52.43 mmol/L, 95% CI: 4.52 to 100.35; $P < .05$), and total nitrite levels (β = 3.62 µmol/L, 95% CI: 2.17 to 5.08; $P < .001$) when were compared with the placebo. Nano-curcumin intake did not change other metabolic parameters.

Baseline levels of HDL-cholesterol ($P < .05$), total-/HDL-cholesterol ratio ($P < .05$), and creatinine ($P < .05$) were significantly different between the two groups. Therefore, we adjusted the analyses for the baseline levels. However, after this adjustment no significant changes in our findings occurred (data not shown).

Nano-curcumin intake upregulated gene expression of PPAR-γ ($P < .05$) and LDLR ($P < .05$) in PBMCs of patients with diabetes on HD, when compared with placebo. Nano-curcumin did not affect gene expression of TGF-β (Figure 2).

DISCUSSION

In this study, we analyzed the effects of Nano-curcumin intake on metabolic profiles in patients with diabetes on HD. We found that Nano-curcumin supplementation during 12 weeks in these patients had beneficial effects on FPG, insulin levels, HOMA-IR, triglycerides, VLDL-cholesterol, total cholesterol, LDL-cholesterol, total-/HDL-cholesterol ratio, hs-CRP, total nitrite levels, TAC and MDA, and gene expression of PPAR-γ and LDLR, but did not affect other metabolic parameters and gene expression of TGF-β.

Effects on Glycemic Control and Serum Lipids

Our findings indicated that nano-curcumin intake during 12 weeks significantly reduced FPG, insulin

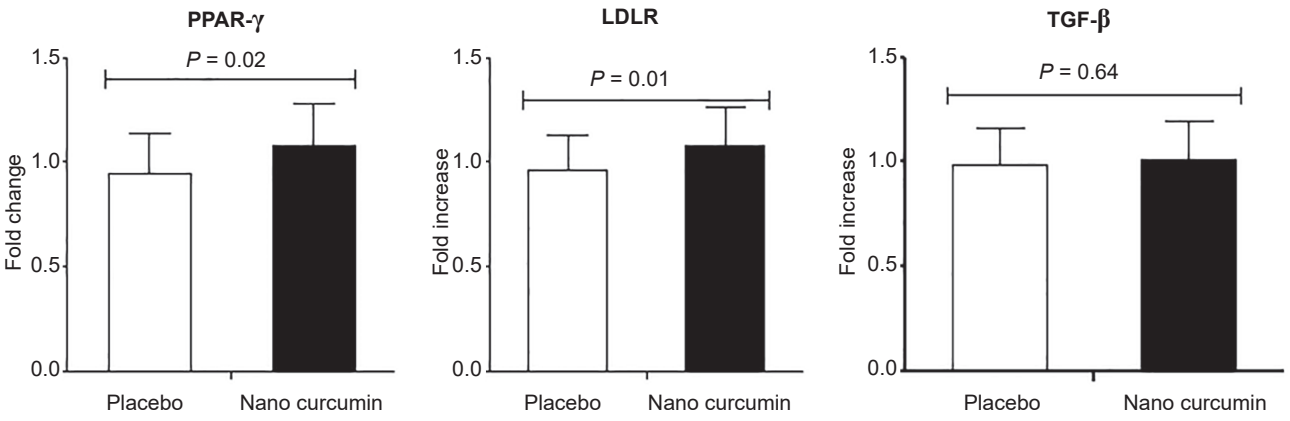

Figure 2. It determined effect of the 12-week supplementation with nano-curcumin or placebo on expression ratio of PPAR-γ, LDLR, and TGF-β gene in PBMCs of patients with diabetes on HD
(LDLR, low-density lipoprotein receptor; HD, hemodialysis; PBMCs, peripheral blood mononuclear cells; PPAR-γ, peroxisome proliferator-activated receptor gamma; TGF-β, transforming growth factor beta).

Table 3. Metabolic Profiles, Biomarkers of Inflammation and Oxidative Stress at Baseline and After the 12-week Intervention in Patients with Diabetes on Hemodialysis Who Received Either Nano-curcumin or Placebo

Variables	Placebo Group (n = 27)			Nano-curcumin Group (n = 26)			Difference in Outcome Parameters Between Nano-curcumin and Placebo Groups[1]	
	Baseline	Week 12	*P*[2]	Baseline	Week 12	*P*[2]	β (95% CI)	*P*[3]
FPG, mg/dL	126.2 ± 39.4	128.6 ± 39.2	> .05	139.8 ± 40.2	119.1 ± 38.0	< .05	-19.68 (-33.48 to -5.88)	< .05
Insulin, μIU/mL	10.4 ± 3.7	10.9 ± 3.6	> .05	11.4 ± 4.8	10.0 ± 4.2	< .05	-1.70 (-2.96 to -0.44)	< .05
HOMA-IR	3.2 ± 1.7	3.4 ± 1.6	> .05	3.8 ± 1.8	3.5 ± 1.8	> .05	-0.41 (-0.830 to -0.006)	> .05
QUICKI	0.33 ± 0.04	0.32 ± 0.02	> .05	0.32 ± 0.03	0.33 ± 0.03	> .05	0.008 (-0.002 to 0.0100)	> .05
Triglycerides, mg/dL	142.1 ± 77.8	138.9 ± 76.7	> .05	153.3 ± 72.1	132.3 ± 61.7	< .05	-16.13 (-31.51 to -0.75)	< .05
VLDL-cholesterol, mg/dL	28.4 ± 15.6	27.8 ± 15.3	> .05	30.7 ± 14.4	26.4 ± 12.3	< .05	-3.22 (-6.30 to -0.15)	< .05
Total Cholesterol, mg/dL	138.6 ± 37.5	146.1 ± 37.0	> .05	147.8 ± 40.3	133.9 ± 24.4	< .05	-17.83 (-29.22 to -6.45)	< .05
LDL-cholesterol, mg/dL	79.6 ± 29.9	86.8 ± 32.3	> .05	91.2 ± 34.5	78.4 ± 18.6	< .05	-15.20 (-25.53 to -4.87)	< .05
HDL-cholesterol, mg/dL	30.6 ± 6.1	31.6 ± 6.5	> .05	26.0 ± 6.2	29.1 ± 5.9	< .05	0.59 (-2.15 to 3.33)	> .05
Total-/HDL-cholesterol Ratio	4.7 ± 1.4	4.9 ± 2.6	> .05	5.9 ± 2.0	4.7 ± 1.0	< .001	-1.15 (-2.10 to -0.21)	< .05
hs-CRP, mg/L	6.3 ± 3.6	6.1 ± 3.5	> .05	5.4 ± 2.5	4.5 ± 2.0	< .05	-0.78 (-1.41 to -0.15)	< .05
Total Nitrite Level, μmol/L	40.8 ± 6.3	41.1 ± 6.0	> .05	39.6 ± 5.0	43.6 ± 5.2	< .001	3.62 (2.17 to 5.08)	< .001
TAC, mmol/L	1088.8 ± 203.7	1076.9 ± 225.9	> .05	1140.6 ± 187.7	1176.1 ± 159.6	> .05	52.43 (4.52 to 100.35)	< .05
GSH, μmol/L	493.7 ± 107.1	497.1 ± 120.7	> .05	408.8 ± 88.5	451.5 ± 88.6	< .05	28.21 (-10.00 to 66.43)	> .05
MDA, μmol/L	2.9 ± 0.8	2.9 ± 0.9	> .05	2.6 ± 0.4	2.4 ± 0.4	< .05	-0.25 (-0.45 to -0.04)	< .05
AGEs, AU	357.6 ± 124.5	364.6 ± 135.0	> .05	400.1 ± 106.2	379.8 ± 76.0	> .05	-21.20 (-48.49 to 6.09)	> .05
Creatinine, mg/dL	7.3 ± 2.5	6.7 ± 2.1	< .05	8.6 ± 1.9	7.5 ± 1.8	< .001	-0.24 (-0.84 to 0.35)	> .05
BUN, mg/dL	51.5 ± 13.7	48.8 ± 12.8	> .05	58.4 ± 12.1	48.7 ± 11.3	< .001	-3.92 (-9.53 to 1.67)	> .05
SBP, mmHg	133.9 ± 14.1	132.2 ± 11.5	> .05	138.8 ± 13.6	133.5 ± 14.4	< .05	-3.08 (-7.70 to 1.53)	> .05
DBP, mmHg	82.6 ± 10.2	81.3 ± 8.3	> .05	79.2 ± 6.9	76.5 ± 6.3	< .05	-2.74 (-5.68 to 0.19)	> .05

Data are mean ± SD.

[1]"Outcome measures" refers to the change in values of measures of interest between baseline and week 12. β shows difference in the mean outcome's measures between treatment groups (nano curcumin group = 1 and placebo group = 0).

[2]Obtained from paired-samples t-tests.

[3]Obtained from multiple regression model (adjusted for baseline values of each biochemical variables).

AGEs, advanced glycation end products; BUN, blood urea nitrogen; DBP, diastolic blood pressure; FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-insulin resistance; HDL-cholesterol, high density lipoprotein-cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-cholesterol, low density lipoprotein-cholesterol; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; VLDL-cholesterol, very low density lipoprotein-cholesterol; SBP, systolic blood pressure; TAC, total antioxidant capacity.

levels, HOMA-IR, triglycerides, VLDL-cholesterol, total cholesterol, LDL-cholesterol, and total-/HDL-cholesterol ratio. A meta-analysis showed that curcumin intake in subjects with prediabetes and T2DM can reduce FPG, but did not change HOMA-IR.[31] Another study reported that 300 mg curcumin administration during 3 months to patients with (T2DM) significantly decreased FPG and HOMA-IR.[32] However, Kocher *et al*.[33] reported that 294 mg micellar curcumin intake for 6 weeks in moderately hyperlipidemic individuals did not show any glucose-lowering effect. A recent meta-analysis suggested that turmeric and curcumin in patients with cardiovascular risk factors was associated with a significant reduction in total cholesterol, LDL-cholesterol, and triglycerides; but did not affect HDL-cholesterol levels.[34] In a clinical study, 1,000 mg curcumin plus 10 mg piperine intake during 12 weeks reduced total cholesterol; non-HDL-cholesterol, lipoprotein A and elevated HDL-cholesterol levels, but failed to change LDL-cholesterol and triglycerides levels in T2DM patients.[35] In contrast to these results, an earlier meta-analysis on a heterogeneous population reported that curcumin administration did not significantly change any lipoproteins.[36] On the other hand, 40 mg nano-curcumin during 3 months in overweight/obese subjects with non-alcoholic fatty liver disease (NAFLD) resulted in a significant reduction in FPG, HOMA-IR, total- and LDL-cholesterol, and triglycerides levels as well as an elevation in HDL-cholesterol concentrations.[30] Several factors including the type of the study, curcumin dosage and intervention duration may account for these conflicting results of different studies. Hyperglycemia is the most important factor in the development of DN because it increases oxidative stress and inflammation. Insulin resistance is an independent predictor for cardiovascular disease and mortality in patients with CKD. Besides changed glucose, changes in plasma lipoproteins are frequent in early stages of kidney disease and are more severe in end stages.[37,38] Curcumin improves hyperglycemia by lowering oxidative stress.[39] Curcumin can also affect β-cells function increasing production and secretion of insulin.[40] The beneficial effect of curcumin on insulin resistance is mediated by stimulation of glycolysis and inhibition of glyconeogenesis in the liver.[19] The results of many studies suggested that curcumin can influence cholesterol absorption and excretion by the bile as well as to decrease lipid peroxides.[41] Nano-curcumin supplementation increased gene expression of PPAR-γ and LDLR. LDLR is involved in LDL-cholesterol catabolism and therefore its increased expression decreases plasma LDL-cholesterol levels. Furthermore, PPAR-γ induction is one of the main mechanisms by which glucose-lowering effect of curcumin can be explained.[42] Since curcumin can upregulate PPAR-γ and LDLR this might explain the improvement of lipoproteins and glucose metabolism.

Effects on Inflammation and Oxidative Stress Biomarkers

The results of our study suggest that Nano-curcumin during 12 weeks significantly reduced hs-CRP and MDA, and increased total nitrite and TAC levels, but did not affect GSH levels and gene expression of TGF-β in patients with diabetes on HD. In a meta-analysis, we have previously documented that taking curcumin-containing supplements could have anti-inflammatory and antioxidant effects which are achieved by a significant decrease in IL-6, hs-CRP, and MDA concentrations.[43] A significant reduction in hs-CRP, IL-6, and TNF-α concentrations following the intake of 1,500 mg/d turmeric for 12 weeks in HD patients was seen in another study, but there was no significant difference between intervention and control groups.[44] Short-term therapy with curcuminoids (500 mg/d for 4 weeks) resulted in suppressing systemic inflammation in subjects suffering from sulfur mustard-induced chronic pulmonary complications.[45] In another study on patients with T2DM, 2 g/d turmeric treatment for 4 weeks significantly reduced MDA concentrations.[46] However, in a meta-analysis; turmeric or curcumin intake did not reduce inflammatory cytokines in subjects with chronic inflammatory diseases.[47] Discrepancies in might be because of different characteristics of study populations, because of differences in study design, dosage and kind of curcumin-containing supplements used, quality of curcumin used and duration of the intervention. Earlier studies suggested that different factors, including dialysis clearance inflammation and oxidative damage are associated with morbidity and mortality in HD patients.[48,49] High rate of morbidity has been correlated with high concentrations of

CRP and other inflammatory markers such as IL-1 or IL-6 in these patients.[48,50] Curcumin is a natural antioxidant that has protective effects due to both increasing biological antioxidant defense system and free radical scavenging.[51] Curcumin intake may also reduce oxidative damage by chelating the redox-active metals and suppressing chain reactions producing metal ion-induced radicals.[52]

This study has some limitations. Due to budget restrictions, we did not check complience to Nano-curcumin intake by a biomarker. We were also unable to determine the effects of Nano-curcumin administration on other biomarkers of oxidative stress and inflammation.

CONCLUSION

We found that nano-curcumin supplementation for 12 weeks to patients with diabetes on HD had beneficial effects on FPG, insulin levels, HOMA-IR, triglycerides, VLDL-cholesterol, total cholesterol, LDL-cholesterol, total-/HDL-cholesterol ratio, hs-CRP, total nitrite, TAC and MDA, and gene expression of PPAR-γ and LDLR; but did not affect other metabolic parameters and gene expression of TGF-β.

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Not applicable.

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CONFLICT OF INTEREST

No conflicted.

AUTHOR CONTRIBUTIONS

FB and ZA contributed in conception, design, statistical analysis, and manuscript drafting. RS, ZR, AS, and EA contributed in data collection and manuscript drafting. All authors approved the paper for submission

CLINICAL REGISTRATION

http://www.irct.ir: IRCT20150606022562N6.

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