Original Article

The Effects of Curcumin Administration on Carotid Intima-Media Thickness and Pulse Wave Velocity in Diabetic Hemodialysis Patients: A Randomized, Double-Blinded, Placebo-Controlled Trial

Abstract

Background: Prior studies have reported that curcumin is inversely associated with reduced markers of atherosclerosis risk, including carotid intima-media thickness (CIMT). This study was designed to assess the effects of curcumin on CIMT and pulse wave velocity (PWV) in diabetic hemodialysis (HD) patients. **Methods:** This randomized, double-blinded, placebo-controlled trial was conducted on 39 diabetic HD patients. People were assigned to receive curcumin or placebo (starch) for 24 weeks. Individuals in the curcumin group (n = 26) received 80 mg/day. CIMT and PWV levels were taken at baseline and after 24 weeks of intervention. **Results:** After 24 weeks of intervention, curcumin intake did not affect mean levels of left (P = 0.83) and right (P = 0.47) CIMT and maximum levels of left (P = 0.84) and right (P = 0.11) CIMT, and PWV (P = 0.12) compared to the placebo. Furthermore, within-group difference demonstrated a significant reduction in mean levels of PWV (P = 0.01) in the curcumin group. We did not observe any significant change in C-reactive protein (CRP) concentrations after curcumin intake (P = 0.69). **Conclusions:** Curcumin intake did not affect mean levels of left and right CIMT and maximum levels of left and right CIMT, PWV, and CRP levels compared to the placebo. Additionally, within-group difference demonstrated a significant reduction in mean levels of PWV in the curcumin group.

This trial was registered at www.irct.ir as http://www.irct.ir: IRCT20200527047584N1.

Keywords: *Carotid intima-media thickness, curcumin, diabetic hemodialysis*

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Introduction

Increased oxidative damage and inflammation in chronic kidney disease (CKD) and diabetic hemodialysis (HD) patients are important independent risk factors of cardiovascular morbidity.[1,2] Endothelial dysfunction is one of the first steps in the developmental process of arterial atherosclerosis, and it is directly associated with an increase in cerebrovascular, cardiac, and peripheral artery disease.[3] Risk factors such as hypertension, diabetes, smoking, dyslipidemia, sedentary lifestyle, among others, contribute to elevated reactive oxygen species, favoring the release of vasoconstrictors, pro-aggregant substances, pro-inflammatory factors, and increased oxidized low-density lipoprotein (Ox)-LDL levels that lead to atherosclerosis.[4]

Carotid intima-media thickness (CIMT) and pulse wave velocity (PWV) are regarded as the footprints of arteriosclerosis.[5] Additionally, PWV is the good standard for non-invasive evaluation of aortic stiffness and is a modifiable cardiovascular risk factor. It has been reported that curcumin has a major component of turmeric, which is known to have anti-inflammatory and antioxidative properties.[6] Since arterial stiffness and CIMT are influenced by increased damage of oxidative stress and inflammation,[7] it may be improved through curcumin intake. In a study conducted by Alidadi *et al*.,[8] it was documented that the daily intake of 500 mg of curcumin for 12 weeks led to the improvement of PWV and weight management in patients with metabolic syndrome. In few another studies, taking curcumin significantly decreased vascular dysfunction (increased EDD and/or decreased arterial stiffness) in rats with nitric oxide deficiency,[9] diabetic rats,[10] and male mice for 4 weeks that were given normal or curcumin supplemented (0.2%) chow.[11] In addition to this, taking curcumin (2,000 mg/day) for 12 weeks by healthy

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men and postmenopausal women significantly reduced vascular dysfunction by decreasing oxidative damage and elevating vascular nitric oxide bioavailability.[12] Also, curcumin administration decreased histological evidence of kidney damage at a dosage of 80 mg per kg body weight in diabetic rats for 45 days[13] and in nephrectomized rats by its anti-inflammatory property.[14]

To our knowledge, data from studies evaluating the effects of curcumin on CIMT and PWV in diabetic HD patients are limited. Therefore, the current study was aimed to evaluate the effects of curcumin on CIMT and PWV in diabetic HD patients.

Methods

Trial design and patients

This research, registered in the Iranian website for clinical trials (http://www.irct.ir: no: IRCT20200527047584N1), was a randomized, double-blinded, placebo-controlled clinical trial that enrolled patients with glomerular filtration rate between 15 and 89, systolic blood pressure between 140 and 160, and diastolic blood pressure between 90 and 100 mmHg, who were not pregnant or lactating, who had no history of smoking or alcohol abuse, no underlying condition, including cardiovascular diseases, cancer, autoimmune disorders and thyroid function abnormalities, who did not have an underlying disease that caused proteinuria, who were 40–85 years old, and who were referred to the Beheshti Clinic in Kashan, Iran, between April 2020 and January 2021. This investigation was approved by the ethics committee of Kashan University of Medical Sciences (Ethics committee reference number: IR.KAUMS.MEDNT.REC.1398.130). Underlying diseases that caused admission to the hospital, high blood pressure using, fluvoxamine or any kind of antioxidant drugs and night worker were not included in the current study.

Study design

Patients were requested to continue their common physical activity and to not take any anti-inflammatory and antioxidant agents or supplements that could influence their nutritional status during the 24-week intervention.

Randomization

Random numbers were done by a computer. Randomization and allocation were hidden from the researchers and people until the final analyses were completed. Allocating the participants and enrolling them to interventions and the randomized allocation sequence were conducted by a trained staff at the clinic.

Intervention

Participants were randomized into two groups to take either nano-curcumin capsule (80 mg/day) or placebo for 24 weeks. Nano-curcumin and placebo supplements were purchased from Exir Nano Sina Company (Tehran, Iran). Nano-curcumin supplements and placebo capsules were the same in packaging size, shape, and color. Placebo (starch) and nano-curcumin were identical in shape and package. To assess compliance, the remaining supplements were counted and subtracted from the number of supplements provided to the participants.

Assessment of outcomes

Weight and height (Seca, Hamburg, Germany) were quantified at baseline and after intervention. BMI was calculated as the participant's weight in kilograms divided by the square of their height in meters. CIMT was considered as the primary outcome, and metabolic profiles were considered as secondary outcomes. Measurement of the CIMT was conducted in patients at the 2-cm distance of the common carotid bifurcation at baseline and after the 24-week intervention using a Doppler ultrasonography device (Samsung Madyson V20, Korea) with linear multi-frequencies of 7.5–10-MHz probe. All CIMT (mean and maximum thickness) measurements were assessed blindly by a single experienced ultrasonographer (H-RT). The intra- and inter-observer coefficient variances (CVs) for the repeated measurements of mean CIMT were 5.2% and 6.9%, respectively. Measurement of the PWV in participants was done at the beginning of the study and after the 24-week intervention using a Doppler ultrasonography device (Samsung Madyson V20, Seoul, Korea). The intra- and inter-observer CVs for the repeated measurements of mean PWV were 3.1% and 5%, respectively.

Assessment of outcomes

A 5-ml blood sample (12-h fasting) was taken at baseline and after the 6-month intervention at Kashan reference laboratory. The serum was then stored at − 80°C before analysis. C-reactive protein (CRP) values were determined using an enzyme–linked immunosorbent assay (ELISA) kit (DiaMetra, Milano, Italy and LDN, Nordhorn, Germany) with intra- and inter-assay CVs below 7%.

Statistical methods

The Kolmogorov–Smirnov test was done to determine the normality of data. To detect the differences in anthropometric measures between two groups, independent-sample *t*-test was used. To determine the effects of melatonin intake on CIMT, PWV, and CRP, we used independent-sample *t*-test. *P*-values less than 0.05 were considered statistically significant. All statistical analyses were done using the IBM SPSS Statistics version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

In the current study, 39 patients (curcumin [n = 26, of whom 14 were men and 12 were women] and placebo [n = 13, of whom 7 were men and 6 were women]) 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. Any side effects were not reported following the intake of curcumin supplements in participats with diabetic HD.

Mean anthropometric parameters of the study participants were not statistically different between the two groups (data not shown).

After 24 weeks of intervention, curcumin intake did not affect the mean levels of left ($P = 0.83$) and right ($P = 0.47$) CIMT, the maximum levels of left ($P = 0.84$) and right ($P = 0.11$) CIMT, and PWV ($P = 0.12$) compared to the placebo group [Table 1]. Additionally, within-group difference demonstrated a significant reduction in mean levels of PWV ($P = 0.01$) in the curcumin group. We did not observe any significant change in CRP concentrations after curcumin intake ($P = 0.69$).

Discussion

In the current study, we evaluated the effects of curcumin intake on CIMT, PWV, and CRP levels in diabetic HD subjects. We found that after 24 weeks of intervention, curcumin intake did not affect mean values of left and right CIMT and maximum values of left and right CIMT, PWV, and CR*P* values compared to the placebo group. Additionally, within-group difference demonstrated a significant reduction in mean values of PWV in the curcumin group. The beneficial effects of nutritional supplements on metabolic profiles in diabetic HD subjects have been reported previously.[15–17]

Effect of curcumin on CIMT and PWV levels

We demonstrated that curcumin intake of 24 weeks in participants with diabetic HD did not affect mean and maximum values of left and right CIMT and PWV values. Additionally, within-group difference demonstrated a significant reduction in mean values of PWV in the curcumin group. Overall, studies that have evaluated the effects of curcumin intake on CIMT and PWV are limited. In a study conducted by Alidadi *et al*.,[8] it was reported that a daily intake of 500 mg of curcumin for 12 weeks resulted in the improvement of PWV and weight management in patients with metabolic syndrome. A meta-analysis showed the beneficial effects of curcumin intake on improving flow-mediated dilation (FMD),

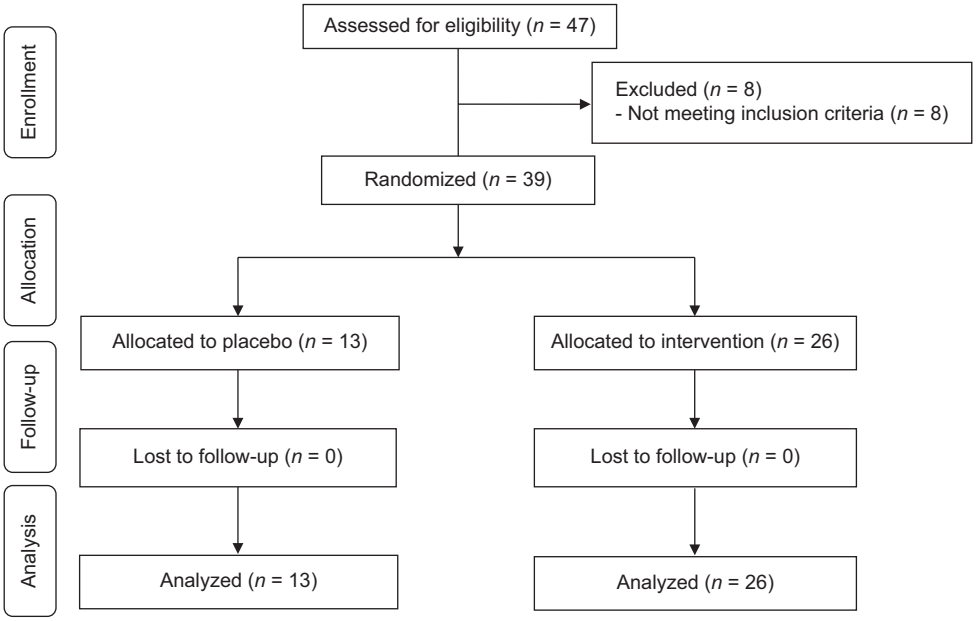

Figure 1: Summary of patient flow diagram

Table 1: CIMT, PWV, and CRP values at baseline and after 24 weeks of intervention in diabetic hemodialysis patients

	Curcumin group (*n*=26)				Placebo group (*n*=13)				*P*[2]
	Baseline	End-of-trial	Change	*P*[1]	Baseline	End-of-trial	Change	*P*[1]	
Mean left CIMT (mm)	0.638±0.120	0.655±0.122	0.017±0.065	0.18	0.625±0.153	0.650±0.128	0.025±0.169	0.59	0.83
Maximum left CIMT (mm)	0.916±0.159	0.920±0.186	0.004±0.177	0.89	0.893±0.184	0.911±0.172	0.018±0.272	0.81	0.84
Mean right CIMT (mm)	0.648±0.124	0.621±0.125	−0.026±0.093	0.15	0.626±0.091	0.621±0.096	−0.005±0.076	0.80	0.16
Maximum right CIMT (mm)	0.919±0.154	0.876±0.190	−0.043±0.173	0.21	0.869±0.155	0.912±0.148	0.043±0.111	0.18	0.11
PWV	10.58±2.76	9.51±1.93	−1.07±1.97	0.01	10.66±2.27	10.85±3.49	0.19±3.10	0.82	0.12
CRP (mg/ml)	4.5±1.7	4.4±1.7	−0.1±1.0	0.75	4.8±1.7	4.9±1.8	0.1±1.1	0.79	0.69

Values are presented as mean±SD. [1]*P*-values represent paired-sample *t*-test. [2]*P*-values represent independent-sample *t*-test. CIMT=carotid intima-media thickness; CRP=C-reactive protein; PWV=pulse wave velocity

but curcumin did not influence PWV and other factors related to endothelial function.[18] Another meta-analysis of five randomized clinical trials reported a significant effect of curcumin to increase FMD levels and, thus, endothelial function compared to a placebo group.[19] However, no significant influence of curcumin intake at a dosage of 5 g per day on FMD was seen in healthy smokers.[20] Moreover, curcumin intake at a dosage of 500 mg per day for 12 weeks among obese men did not influence PWV values.[21] The lack of conservable effect in endothelial function following the intake of curcumin was consistent with a prior intervention in postmenopausal women with a lower dose (150 mg/day) and shorter 8-week intervention.[22] These differences in these results might be partially due to the fact that the effect of curcumin intake on endothelial function might be influenced by various factors, such as duration of intervention, characteristics of the study participants, and supplementation dosage.

Effect of curcumin on CRP levels

Our study indicated that curcumin intake of 24 weeks among participants with diabetic HD did not influence CR*P* values. In line with this study, a meta-analysis reported that taking curcumin did not reduce inflammatory markers in people with inflammatory diseases.[23] Unlike our study, another meta-analysis reported that curcumin-containing supplements could have anti-inflammatory properties that are achieved by a significant decrease in high-sensitivity CR*P* values.[24] Furthermore, a significant decrease in tumor necrosis factor alpha, high-sensitivity CRP, and interleukin 6 values following the administration of 1,500 mg per day of curcumin for 12 weeks in HD patients was observed; but there was no significant change between control and intervention groups.[25] However, the beneficial effects of curcumin on metabolic profiles for 12 weeks among women with polycystic ovary syndrome were reported.[26] Short-term intervention with curcumin (500 mg/day in 4 weeks) led to suppressing systemic inflammation in subjects with sulfur mustard–induced chronic pulmonary complications.[27] Discrepancies among studies might be because of different characteristics of the study participants, differences in study design, dosage of curcumin used, the kind of curcumin-containing supplements used, the quality of curcumin, and the duration of the intervention.

This study had a few limitations. Further studies with bigger sample sizes are needed to confirm our findings. Also, we were unable to assess if curcumin supplementation improved HD state. In the present study, we did not assess the compliance to curcumin intake through the quantification of blood markers.

Conclusions

Overall, curcumin intake did not affect mean values of left and right CIMT, maximum values of left and right CIMT, PWV, and CR*P* values compared to the placebo group. Additionally, within-group difference demonstrated a significant reduction in mean values of PWV in the curcumin group.

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Conflicts of interest

There are no conflicts of interest.

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