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NEPHROLOGY - ORIGINAL PAPER

Curcumin supplementation improves oxidative stress and inflammation biomarkers in patients undergoing hemodialysis: a secondary analysis of a randomized controlled trial

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Abstract

Background and objectives Recent studies have shed light on the potential role of curcumin in mitigating inflammation in patients with chronic kidney disease (CKD). This study aimed to evaluate the effects of curcumin supplementation on plasma levels of markers of inflammation and oxidative stress in patients with CKD undergoing hemodialysis (HD).

Methods These are secondary exploratory analyses from a previous double-blind, randomized controlled pilot study registered under ClinicalTrials.gov Identifier no. NCT00123456. It included 28 hemodialysis patients from a previous study divided into two groups: curcumin group (receiving juice with 2.5 g of turmeric 3×/week for 12 weeks) and a control group. The TNF-α, IL-6 and Ox-LDL plasma levels were measured by sandwich enzyme immunoassays ELISA; lipid peroxidation was measured by the reaction between malondialdehyde (MDA) and thiobarbituric acid.

Results After 12 weeks of supplementation with curcumin, the TNF-α plasma levels were significantly reduced [from 15.0 (8.23–73.3) to 6.17 (1.11–55.0) pg/mL, $p = 0.01$].

Conclusion 12 weeks of treatment with curcumin in HD patients resulted in a reduction in the biomarker of inflammation (TNF-α), confirming our previous hypothesis that curcumin has an anti-inflammatory effect.

Keywords Chronic kidney disease · Curcumin · Inflammation · Hemodialysis

Introduction

Botanically, Curcuma Longa is related to ginger (Zingiberaceae family); it is a perennial plant with a short stem and large oblong leaves; it also features oval, piriform, or oblong rhizomes, which are often branched and brownish-yellow in color [1]. This striking color is the bioactive compound curcumin, the main component of this plant [2]. Curcuma Longa contains a class of curcuminoids, composed of curcumin, demethoxycurcumin, and bisdemethoxycurcumin, but curcumin is the most studied compound in the literature [3, 4]. Curcuma Longa is a medicinal plant widely used for thousands of years by Asian countries as a food additive, preservative, and coloring.

According to several studies, curcumin has a therapeutic potential as an anti-inflammatory, antioxidant, antidiabetic, anticancer, and anti-aging agent [5–7]. Regarding its anti-inflammatory function, curcumin can decrease the production of proinflammatory cytokines such as tumor of necrose factor-alpha (TNF-α), C-reactive protein (CRP), and interleukin (IL) 6 [8, 9]. Curcumin is a potent antioxidant that reduces the generation of reactive oxygen species (ROS) through its hydrogen-donating antioxidant activity, consequently reducing the cell damage. In addition, curcumin facilitates nuclear translocation of factor 2 related to nuclear erythroid factor-2 (Nrf2) by uncoupling of its binding protein Kelch-like ECH-associated protein 1 (Keap 1)

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and increases the expression of antioxidant enzymes, thus preventing lipid peroxidation and other damage to cellular proteins and DNA [10]. Also, curcumin seems to reduce the activation of nuclear factor κB (NF-κB), which is involved with cytokines synthesis and inflammation. Indeed, our previous study showed that curcumin reduced the expression of NF-κB [11] as well, decreased the plasma levels of *p*-cresyl sulfate (a uremic toxin produced by the gut microbiota involved with inflammation) in patients with chronic kidney disease on hemodialysis (HD) [12].

Chronic kidney disease (CKD) is a known worldwide public health problem [13] and is involved with many complications such as inflammation and oxidative stress [14], which are important risk factors for developing cardiovascular disease and accelerate kidney disease progression [15]. Regarding the activation of NF-κB in these patients, studies have shown overregulation, consequently increasing the production of proinflammatory cytokines [16].

Into the concept of food as medicine for CKD patients [17], several nutritional strategies have been proposed to these patients [11, 18–21], including the use of curcumin to mitigate inflammation as well oxidative stress [22].

Currently, some studies have shown the positive effects of curcumin supplementation in vivo models in animals and humans [23–25]. These studies demonstrated that curcumin positively regulates Nrf2 with a consequent increase in antioxidant enzymes and a reduction in inflammatory markers in CKD [23–26]. Furthermore, curcumin was also efficient in improving intestinal architecture by increasing tight junction proteins and alkaline intestinal phosphatase (IAP), leading to lower intestinal permeability and better circulation of inflammatory factors in the systemic circulation [27]. Previously we showed a reduction in NF-κB expression after curcumin treatment. Thus, we hypothesized here that curcumin supplementation decreases oxidative stress and inflammation biomarkers in hemodialysis patients. This study aims to evaluate the plasma levels of inflammation and oxidative stress markers after curcumin supplementation in patients with CKD on HD.

Methods and patients

These are secondary exploratory analyses from a previous study [11], that involved 28 HD patients from Renalcor Clinic, RJ, Brazil from March to December 2018, previously included in a study from our research group. For the sample calculation, the test power of 80% was used, with a type I error probability, and a null hypothesis test of 0.05 [11].

The Ethical Committee approved this project (number: 2346933). This study is registered in ClinicalTrials.Gov under the number NCT 03475017. Inclusion criteria were CKD patients on HD for 6 months, over the age of 18 years, and with access through an arteriovenous fistula (AVF). Exclusion criteria were pregnant patients, smokers, patients who received antibiotics in the last 3 months, antioxidant supplements and usual intake of turmeric, patients with autoimmune and infectious diseases, cancer, liver disease, and AIDS. The dialysis treatment was performed with fibre cellulose acetate dialyzers for 3.5–4.5 h/session 3×/week with 500 ml/min of dialysate flow and blood flow greater than 250 ml/min.

Patients were instructed to maintain ingested medications, as prescribed by the physician, such as simvastatin, beta receptor blockers, diuretics, metformin, and insulin, which were not changed during the study [11].

The primary outcome of the present study is the decrease in plasma levels of inflammatory markers such as IL-6, and TNF-α plasma levels and the secondary outcome is the decrease in oxidative stress markers, which are represented by oxidized low-density lipoprotein-LDL (LDL-ox) and malondialdehyde (MDA) plasma levels.

Experimental design

Patients were randomized in double-blind conditions into two groups: curcumin group, in which patients were given a juice containing 100 mL of orange juice, 12 g of carrots, and 2.5 g of turmeric extract (95% curcumin) three times per week at the end of the HD session, for 12 weeks, and the control group, which received the same juice without curcumin (Fig. 1). Adherence to the intervention was made by the researchers who checked whether the juice had been offered and consumed by the patients at the end of each dialysis session.

A trained professional performed the allocation into groups, curcumin and control, through a list of codes. The inclusion and exclusion criteria were previously applied to carry out the randomization. After this step, the patients were allocated in 1:1 branches according to the groups. Details about the study design and randomization have been published previously [11].

General data, analysis of food intake, and anthropometric data

Demographic, clinical, and biochemical data were obtained by analyzing the medical record, interviewing during consultations/reconsults, and collecting biological material (blood). The details were previously described in [11]. Food intake was assessed at the beginning and end of the intervention through 24-h food recall, and data were analyzed using NutWin® software [11] and analyzed according to KDOQI, 2020. As previously described in [11], the body mass index (BMI) was calculated.

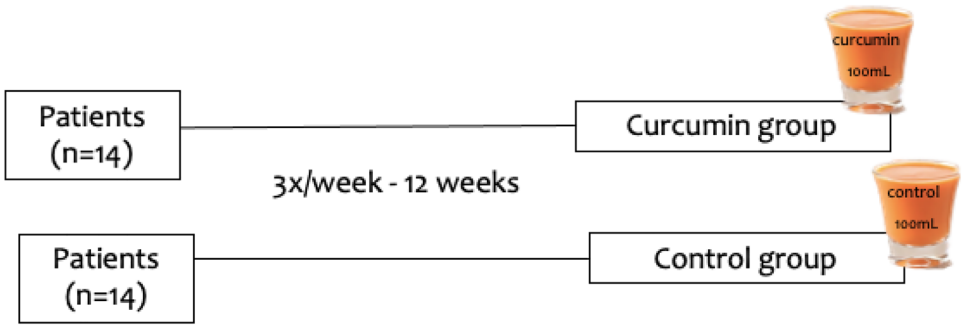

Fig. 1 Design of study with curcumin supplementation in HD patients

Sample preparation and oxidative stress and inflammation markers

Blood samples were collected in the morning, before the start of the HD session, and midweek, with patients fasting for 12 h. For plasma preparation, blood tubes were centrifuged at 2500 rpm for 10 min at 4 °C, which was distributed in identified 1.5-ml polypropylene Eppendorf, and stored at −80 °C for later analysis [11].

The markers of inflammation, IL-6, and TNF-α, were measured via ELISA sandwich enzyme immunoassays using commercially available kits (PeproTech®, Rocky Hills, NJ, USA), following the manufacturer's recommendations for the development of the experiment. The Optical Density (OD) at 405 nm was measured using a Synergy II Microplate Reader (Biotek®) [28]. LDL-ox plasma levels were measured using the Human Ox-LDL ELISA kit (Elabscience Biotechnology Co., Ltd, USA) according to the manufacturer's protocol [29]. The reaction between MDA and thiobarbituric acid was measured according to the modified Ohkawa method to evaluate the lipid peroxidation [30].

Statistical analysis

The Shapiro Wilk test was used to verify the distribution of the variables. Normally distributed variables were expressed as mean ± standard deviation, and non-normally distributed variables were expressed as median (min–max). Comparisons between the baseline of the groups were performed using the two-tailed unpaired Student *t*-Test for parametric variables, and the Mann–Whitney test for the nonparametric variables. A mixed linear model was performed, and sex and age were added as influence potentials. The statistical analyses were performed through Jamovi 1.6.3 software.

Results

Sixty-three patients were assessed for eligibility, but 32 dropped out. Then, 31 patients were randomized to the curcumin and control group. A total of 28 patients completed the 3 months of curcumin supplementation as shown in the CONSORT diagram (Fig. 2), 14 patients in the curcumin group (54.0 ± 15 years, 7 women) and 14 in the control group (53.0 ± 12 years, 7 women). No side effects were observed in any of the groups during the intervention.

There was no statistical difference in any biochemical, anthropometric, or food intake parameters between the groups at the baseline, as shown in Table 1. There was no statistical difference concerning these data before and after the intervention [11].

Table 2 shows the inflammation and oxidative stress markers in both groups. There was no difference between the baseline values in the groups, IL-6 ($p = 0.32$), TNF-α ($p = 0.94$), MDA ($p = 0.085$) and ox-LDL ($p = 0.17$).

Regarding oxidative stress markers, no statistical difference was observed concerning ox-LDL and MDA plasma levels after 12 weeks of intervention, and there was also no statistical difference in the concentration of IL-6 plasma levels (Table 2). Figure 3 demonstrates that plasma levels of TNF-α were significantly reduced after curcumin intervention.

Discussion

This secondary analysis of our previous randomized controlled trial [11] showed that curcumin supplementation for 12 weeks in HD patients reduced the plasma levels of TNF-α, an inflammatory biomarker. However, this supplementation did not change oxidative stress markers such as MDA and ox-LDL. Our previous study demonstrated that curcumin supplementation in HD patients decreased the expression of NF-κB mRNA in peripheral blood mononuclear cell (PBMC) and also the plasma levels of ultrasensitive C-reactive protein (hs-CRP), but the Nrf2 mRNA expression was not changed [11], which corroborate with the

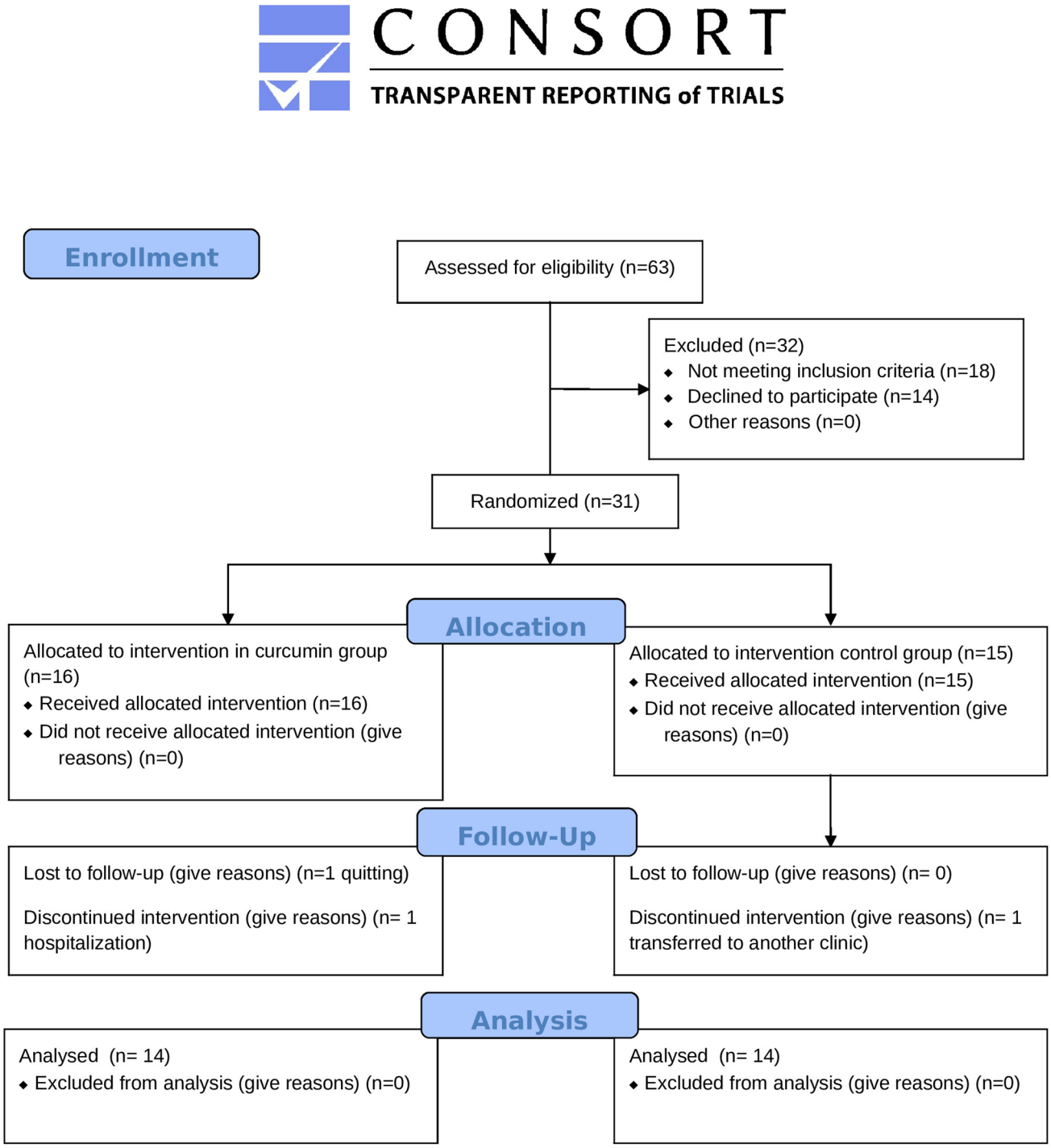

Fig. 2 CONSORT 2010 FLOW diagram

current study since there was no change in oxidative stress markers after curcumin supplementation. On the other hand, the reduction of TNF-α plasma levels may be justified due to the downregulation of NF-κB by the curcumin intervention [11].

There are some hypotheses for this TNF-α plasma levels reduction. Curcumin acts as a TNF-α suppressor mainly at the transcriptional level. Curcumin can mediate TNF-α expression by inhibiting p300/Cyclic AMP-responsive element-binding protein (CREB)-specific acetyltransferase, generating repression of histone protein acetylation and

Table 1 Characteristics of hemodialysis patients in curcumin and control groups at baseline

Parameters	Curcumin group ($N=14$) Baseline	Control group ($N=14$) Baseline	p value
General characteristics			
Age (years)	54 ± 15	53 ± 12	0.89
Gender (female/male)	7/7	7/7	1.00
Antropometric			
BMI (kg/m^2)	27.1 ± 4.0	26.4 ± 3.2	0.63
Dietary intake			
Kcal/kg	20.4 ± 6.5	20.9 ± 5.5	0.95
Carbohydrates (%)	55.1 ± 4.0	57.5 ± 5.6	0.50
Proteins (g)	64.6 ± 25.5	71.3 ± 24.2	0.30
Lipids (%)	24.3 ± 7.3	22.7 ± 7.2	0.87
Phosphorus (mg)	899.6 ± 40.9	1041.5 ± 297.5	0.30
Potassium (mg)	1675.1 ± 438.6	2135.1 ± 696.0	0.05
Biochemistry			
Hemoglobin (g/dL)	11.0 ± 2.0	10.8 ± 1.3	0.72
Albumin (g/dL)	3.7 ± 0.2	3.6 ± 0.25	0.82
Phosphorus (mg/dL)	4.3 ± 0.5	4.8 ± 1.0	0.16
Potassium (mg/dL)	4.7 ± 0.2	4.8 ± 0.3	0.67
Urea (mg/dL)	47.5 ± 11.4	43.5 ± 12.7	0.73
Glucose (mg/dL)	136.3 ± 46.6	156.8 ± 83.8	0.72
HbA1c (%)	7.7 ± 1.1	6.6 ± 1.2	0.23
Total cholesterol (mg/dL)	145.7 ± 45.7	155.9 ± 37.7	0.96
LDL-c (mg/dL)	77.6 ± 37.4	87.5 ± 32.4	0.46
HDL-c (mg/dL)	42.1 ± 12.1	40.5 ± 9.8	0.71
Triglycerides (mg/dL)	130.1 ± 49.9	139.3 ± 63.8	0.67
Kt/V	1.36 ± 0.2	1.35 ± 0.18	0.94
PTH (pg/mL)	589 (301.7–1112.5)	460 (209–1428)	0.97

Data are expressed as mean ± SD and non-parametric data shown are median (interquartile range)

$p < 0.05$ indicates a significant difference between the groups

HbA1c glycated hemoglobin; *LDL-c* low-density lipoprotein; *HDL-c* high-density lipoprotein; *PTH* parathyroid hormone

Table 2 Inflammatory and oxidative stress biomarkers in the curcumin and control groups

Parameters	Curcumin group ($n=14$)		Control group ($n=14$)		Effect of intervention					
					Intervention		Time		Time × intervention	
	Before	After	Before	After	p values	df	p values	df	p values	df
MDA (nmol/mL)	1.78 (0.27–5.97)	1.08 (0.25–4.41)	0.57 (0.15–3.28)	1.30 (0.10–2.5)	0.233	17.0	0.307	19.0	0.086	19.0
LDL-ox (pg/mL)	846 ± 104	967 ± 301	1001 ± 322	1058 ± 518	0.312	8.0	0.483	9.0	0.797	9.0
IL-6 (pg/mL)	15.2 ± 15.8	11.8 ± 9.94	13.5 ± 11.0	14.3 ± 14	0.815	23.9	0.368	22.3	0.739	22.6
TNF-α (pg/mL)	15.0 (8.23–73.3)	6.17 (1.11–55.0)	22.8 (2.04–79.4)	16.4 (2.04–98.3)	0.428	13.5	0.411	5.56	**0.010**	6.0

Data were expressed as mean ± SD. Data analysis was conducted by applying a linear mixed model

$p < 0.05$ indicates a significant difference between the groups

df degrees of freedom; *MDA* malondialdehyde; *LDL-ox* oxidized low-density lipoprotein; *IL-6* interleukin-6; *TNF-α* tumor necrosis factor alpha

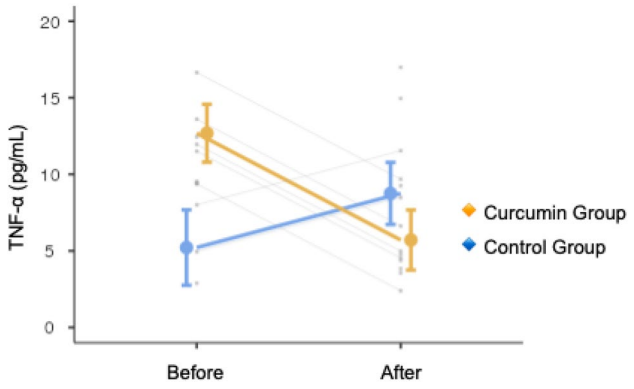

Fig. 3 TNF-α plasma levels before and after intervention in both groups

histone acetyl transferase-dependent chromatin transcription [31, 32]. Furthermore, methylation of TNF promoters by curcumin decreases their expression. The receptors involved in TNF activation, toll-like receptors (TLRs), may also have their responsiveness decreased by curcumin treatment [33]. Also, it is also well known that curcumin can decrease NF-κB activation and lead to down-regulation of this transcription factor [34]. Experimental studies in cells and animals have confirmed that curcumin decreases the inflammatory cytokines such as TNF-α [35–37]. Curcumin inhibits NF-κB activation directly by inhibiting the degradation of IκB-α and reacting with NF-kB itself [38, 39]. Consequently, the production of proinflammatory mediators, including TNF-α, is suppressed by curcumin [39, 40]. Furthermore, TNF-α can be lowered by curcumin through IKK suppression, which prevents the NF-κB translocation to the nucleus and activation [10].

In addition, TNF-α can be inhibited by binding directly to curcumin. Curcumin docks to TNF-α receptor binding sites, including Leu89, Asn90, Asp105, Asn106 and Cys129. This binding is due to non-covalent and covalent interactions, interrupting the signal transduction between TNF-α and its receptor by direct binding and suppressing the inflammation induced by this cytokine [41]. Thus, one of the hypotheses that can be raised in this study is that curcumin inhibited TNF-α by direct action, a fact that does not happen with IL-6.

Randomized clinical studies in CKD patients that evaluated the effects of curcumin supplementation on inflammation corroborate our result [24, 42–44]. Samadian et al. [24] showed that 1500 mg/day of turmeric extract (66,3 mg of curcumin) in a capsule for 12 weeks in hemodialysis patients reduced TNF-α levels, hs-PCR, and IL-6 plasma levels. Another study with patients in hemodialysis showed that 120 mg of nano curcumin for 12 weeks also decreased TNF-α and IL-6 plasma levels [43]. Thus, as in the present study, Rodrigues et al. [44] did not find a reduction in the MDA concentration before and after the 1.0 g/day of curcumin after 12 weeks.

In addition, a recent systematic review on the effects of curcumin supplementation in CKD patients demonstrated that curcumin has particularly favorable effects on inflammation and oxidative stress and also is associated with a reduction in proteinuria [45]. Inflammation plays an essential role in CKD progression, mainly due to its ability to improve the regulation of intrarenal microcirculation and perfusion distribution [46]. Furthermore, chronic inflammation in CKD patients is associated with several factors, including dysregulation of intestinal microbiota, complications associated with uremia, a diet low in fruits, vegetables, and legumes [22, 46]. In this context, curcumin appears to be a good nutritional strategy to reduce inflammation in hemodialysis patients [22, 46].

The results presented in this study must be interpreted with some limitations. We did not assess the absorption of curcumin in the plasma of patients, and its absorption may have been insufficient to find a significant difference in the concentration of MDA, Ox-LDL and IL-6. Curcumin is a polyphenol with rapid metabolism and systemic elimination, which may contribute to low plasma and tissue levels of curcumin. Despite this, according to Aggarwal et al. [34], curcumin can still manifest its effect in vivo. Some approaches could be used to improve the bioavailability of curcumin, such as the use of adjuvants that interfere with glucuronidation, the use of liposomal curcumin, nanoparticles; the use of curcumin phospholipid complex; or use of structural analogs of curcumin [47]. Unlike previously published studies, this study uses curcumin supplementation through a juice, thus preserving the concept of "foodome," the bioactive compound can be potentiated due to its ingredients and chemical structure [11, 48]. Therefore, further studies in HD patients with a larger number of participants should be encouraged.

In conclusion, curcumin supplementation for 12 weeks in hemodialysis patients decreases the plasma concentration of TNF-α and can be a good strategy to mitigate inflammation in CKD patients.

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Author contributions LA contributed to the data collection and sample analysis; performed statistical analyses; produced the tables and figures; and preparation of the manuscript. BOdaC and BRP actively contributed to samples analysis of the present study. LC participated of all analysis; restructured and revised the manuscript. DF contributed to

the interpretation, restructured and revised the manuscript. DM coordinated all the steps of research, restructured and revised the manuscript.

Declarations

Conflict of interest The authors declare no conflict of interests.

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