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Original article

# Evaluation of Curcumin's effect on inflammation in hemodialysis patients

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SUMMARY

*Objective:* Despite advances in prevention of inflammatory milieu with different anti-inflammatory modalities in hemodialysis patients the rate of inflammatory markers in this population are still high. Inflammation is considered as a major player in uremia associated with morbidity and mortality in hemodialysis patients. The aim of this study was to evaluate the turmeric s effects on reduction of inflammatory markers in hemodialysis patients.

*Methods:* Hemodialysis patients over 18 years were recruited after fulfilling the inclusion criteria. Seventy-one hemodialysis patients were randomized into two groups: the trial group (n = 35) and the controls (n = 36); a randomization numeric table was used for allocation sequence. Trial group received turmeric and control group received placebo for 12 weeks. Biochemical determinations included levels of serum albumin (Alb), potassium (K), blood urea nitrogen (BUN), serum creatinine (Cr), IL-6 level, TNF-α, and liver function tests and hs-CRP at the start and end of the study were measured.

*Results:* Although there was a significant reduction in hs-CRP level, IL-6 level and TNF-α level in turmeric group (p = 0.002, p = 0.001, p = 0.001), there was no statistical difference between intervention and control groups. Albumin level was significantly increased in turmeric group (p = 0.001) and no meaningful changes were seen in potassium or liver function tests neither within nor between groups.

*Conclusion:* Programmed ingestion of turmeric has no adverse effects and reduces plasma level of hs-CRP, IL-6 and TNF-α accompanying with increases albumin levels in hemodialysis patients. Turmeric can be considered as an effective anti-inflammatory supplement in hemodialysis patients.

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## 1. Introduction

Curcumin, a hydrophobic polyphenol derived from the rhizome of the herb *Curcuma longa* has a wide range of biomedical and pharmacological properties. Traditionally, turmeric has been used for many reasons, usually as an anti-inflammatory agent, and curcumin has been identified as the active foundation of turmeric [1]. The pharmacological safety and efficacy of curcumin makes it an appealing target for treatment and prevention of a wide variety of human diseases. It has been shown that turmeric (curcumin) has immune-stimulatory effect, and may increase in macrophage phagocytic activity. Evidence from different trials showed that turmeric/curcumin can be useful for prevention and possibly treatment of several types of cancers, and these preventive effects are largely due to antioxidant properties and hence protecting cells against damage plus its inhibitory effect on cell proliferation, and angiogenesis along with induction of apoptosis. Curcumin's beneficial effects on tumorigenesis are likely related to the inhibition of nuclear factor kappa B (NF-kB) cell signaling pathway [2]. Different studies have demonstrated a decrease in chemokine ligand 2 (CCL2), also known as monocyte chemo-attractant protein 1, after

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treatment with curcumin. CCL2 is known as a principle chemokine for macrophage recruitment, associated with increased grade of the tumor in certain cancers [2]. Also, in clinical trials it has been reported that adding turmeric to diet can improve lipid profile. In addition, more recently it has been shown that this can decrease systolic pressure in patients suffering from relapsing or refractory lupus nephritis [3]. Turmeric also inhibits the production of interleukin-8 (IL-8) thus, attenuates inflammation, prevents renal fibrosis and delay apoptosis by decreasing in mRNA expression of TNF-α, and blocks cytokines, including the transforming growth factor beta (TGF-(β) [4]. End-stage renal disease (ESRD) is a state of oxidative stress, due to uremic mediator's accumulation, the activation of phagocytic oxidative metabolism by the dialysis membrane, intravenous iron therapy and the antioxidant depletion caused by hemodialysis itself. Some trials showed a significant benefit from antioxidant therapy on cardiovascular outcome in hemodialysis patients and many researchers focused on direct exogenous antioxidants including vitamin C and vitamin E, in treatment of cardiovascular disease but most of these clinical trials showed no more beneficial effect of dietary antioxidant supplementation in prevention of cardiovascular disease in hemodialysis patients and recommended the necessity for a new approach to regulating cellular redox status in this population [5,6]. In ESRD-patients elevated levels of IL-8 may be associated with increased oxidative stress due to inflammation and it is shown that oral turmeric supplementation results in a significant decrease in both serum and urinary IL-8 levels in patients suffering from overt type-2 diabetic nephropathy. Curcumin improves diabetic nephropathy by blunting NADPH oxidase expression [7]. A cohort study followed 43 dialysis-dependent cadaver kidney recipients who had taken curcumin for 1 month. Investigators observed reduced acute rejection and neurotoxicity over the course of 6 months [8]. Although extensive in vitro and animal studies have analyzed the effect of curcumin on inflammation and inflammatory mediators (including inhibition of lipoxygenase, cyclooxygenase-2, leukotrienes, thromboxane, prostaglandins, and tumor necrosis factor 1 but we still face the few human studies which looked at this Asian present s effects on hemodialysis patients. In different studies, chronic inflammation predicts all-cause and cardiovascular mortality in hemodialysis patients. The causes of inflammation in hemodialysis are multifactorial and consist of both dialysis-related and unrelated factors. So suppression of the inflammation seems to be logical and could improve survival and diminish co-morbidity in hemodialysis patients. Because still there is a lack of data regarding turmeric effects in hemodialysis patients our group designed a three-month double blind placebo-controlled randomized clinical trial on 71 chronic hemodialysis patients. The aim of this study was to examine the anti inflammatory effects of dietary component curcumin on decreasing inflammatory markers in chronic hemodialysis patients as a potential mechanism for its benefits on dialysis efficacy. On the basis of previous literature on curcumin's anti-inflammatory activity in vitro, we hypothesized that curcumin would decrease inflammation and this would be associated with a decrease in morbidity in hemodialysis patients.

## 2. Materials and methods

This study was a double-blind placebo-controlled randomized clinical trial carried out between Jan 2014 and 2015. The trial was approved by the ethics committee of Shahid Beheshti University of Medical Sciences and carried out in accordance with the Declaration of Helsinki. The trial was registered at Clinicaltrials.gov IRCT.

Any chronic hemodialysis patients attending the Labbafinezhad dialysis center in Tehran were assessed for eligibility of enrollment in this study. Inclusion criteria were:

- Males or females undergoing maintenance hemodialysis
- Age ≥18 year
- Clinically stable and receiving adequate hemodialysis defined by a single pool Kt/V ≥ 1.20 or no less than 3 dialysis sessions per week with a total dialysis time ≥12 h per week for at least 3 month before enrollment
- Diabetic patients must be willing to commence insulin therapy if deemed necessary for plasma glucose control.

Exclusion criteria were:

- Active malignant disease (defined as less than 5 year since receiving a diagnosis of being malignancy-free)
- Critical illness as defined by the need for respiratory or circulatory support (in an intensive care unit)
- Active vasculitis
- Severe congestive heart failure (New York Heart Association class IV)
- Severe chronic systemic infectious or inflammatory disease
- Liver disease (defined as serum alanine aminotransferase or aspartate aminotransferase levels greater than three times the upper limit of normal)
- Known or suspected allergy to trial product(s) or related products
- Treatment with immunosuppressive agents or receipt of any investigational drug within one month preceding screening
- Recent or current use of anti-inflammatory corticosteroids agents
- A scheduled renal transplantation within the trial period

All the participants signed the informed consent. Seventy-two patients who met the study criteria were enrolled in the study. One patient before the start of the study dropped out due to renal transplantation. The remaining 71 patients were randomized into two groups: the trial group (n = 35) and the controls (n = 36); a randomization numeric table was used for allocation sequence. The allocation sequence was concealed from the researcher enrolling and assessing participants in sequentially numbered, opaque, sealed envelopes. Clinical investigators, laboratory personnel, and patients were all masked to the treatment assignment. Each patient in the trial group received a safe dose of turmeric (one capsule with each meal containing 500 mg turmeric, of which 22.1 mg was the active ingredient curcumin, 3 caps/day for 12 weeks) while the control group received placebo capsules for the same 12-week period. The type and dose of the individualized drugs remained unchanged during the study. All drugs and placebo capsules were similar in size, shape, weight and color. The membrane and general dialysis prescription were similar for all patients. Any medications with anti-inflammatory effect were discontinued one week before the study. A trained clinical pharmacist, who evaluated drug tolerability and any complaint, visited all the patients. All the measurements and clinical evaluations performed by the same person throughout the study (at the start, during, and end). The data collection technique was based on observation, interview and laboratory blood tests. We evaluated patients in weekly visits at the dialysis center for side effects before and at the end of the each session.

Turmeric rhizome at first was washed and dried out in a warm and dry place for a week, then powdered rhizomes were encapsulated by Clinical Pharmacy Research Center of Shahid Beheshti University of Medical Sciences, using hard gelatin capsules. Also placebo capsules were made by the same center using Sorbitol. Curcumin level of turmeric was measured by HPTLC analysis for quantification of variability in content of curcumin. Blood samples from hemodialysis patients in a fasting state were collected from

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