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Original Article

Protective effects of curcumin on kidney tissue in ischemia-reperfusion injury in rats

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Abstract

Aim: Kidney damage caused by ischemia-reperfusion (IR) is a serious clinical problem. Many studies have emphasized the antioxidant and anti-inflammatory properties of Curcumin.

Material and Methods: Wistar-Albino male rats were divided into three groups. The sham group was the group in which only laparotomy was performed, the IR group was the group in which the infrarenal aorta was clamped after laparotomy and ischemia-reperfusion was created, and the IR+ curcumin group was the group in which intraperitoneal curcumin was given 1 hour before the procedure and the same procedures were repeated with the IR group. After creating the IR, blood and kidney tissue were taken from the rats and biochemical and histopathological examinations were performed.

Results: Potassium (p=0.005), urea (p=0.050), and blood urea nitrogen (p=0.050) levels were higher in the IR+curcumin group. While total antioxidant status was found to be high in the IR+curcumin group (p=0.021), there was no difference in total oxidant status across the groups (p=0.069). Interleukin (IL)-1β and IL-6 were found to be higher in the IR group (p=0.014, p=0.022, respectively). Tumour necrosis factor-α was higher in the IR group than in other groups (p=0.020). Interferon-γ did not differ across groups (p=0.140). In the histopathological examination, the IR group had more damage to the glomerulus and tubular epithelial cells than the other groups (p<0.001).

Conclusion: Curcumin, despite its anti-inflammatory and antioxidant characteristics, had no protective effect on renal functions in IR-induced kidney injury. It was found that it suppresses the inflammatory response and is effective in preserving renal tissue structure.

Keywords: Curcumin, infrarenal aortic occlusion, renal injury, ischemia and reperfusion

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INTRODUCTION

Ischemia-reperfusion (IR)-induced kidney tissue inflammation, tubular epithelial damage, and renal failure due to microvascular disorders cause high mortality and morbidity [1,2]. Oxidative stress and subsequent inflammation due to ischemia play an important role in tissue destruction. Tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, and Interferon(IF)-γ are proinflammatory cytokines that cause apoptosis and cell damage [3].

Curcumin is a healthy and easily accessible spice that is widely used, especially in tropical areas [4]. Curcumin has anti-inflammatory and antioxidant effects, especially by lowering inflammatory cell infiltration and preventing the inflammatory response pathway [5,6]. Our aim in this study is to show the protective effect of curcumin on kidney tissue and its functions in IR damage.

MATERIAL AND METHODS

Animals

Twenty-four Wistar-Albino male rats were included in the study. Rats weighing 250-300 g (mean 267 g) were observed in a laboratory setting with 12-hour light and 12-hour dark cycle at 24ºC-26ºC and 55-60% humidity. Laboratory conditions were prepared considering the Principles and Guidelines for Experimental Animals issued by The National Health and Medical Research Council and Guide for the Care and Use of Laboratory Animals (NIH issue no. 85-23, 1985 revised) prepared by The National Institutes of Health. Food and water access were not restricted during the rats' follow-up, however, it was restricted 12 hours before the procedure. Approval was obtained from Afyon Kocatepe University Animal Experiments Local Ethics Committee for the study protocol and experimental methods (date:06.05.2020-no:49533702/260).

Study Design

Rats were randomly divided into three equal groups.

Group I (sham): The infrarenal aorta was dissected by laparotomy on rats, but the infrarenal aorta was not clamped. After that, the laparotomy incisions were closed, followed by 3 hours of waiting.

Group II (IR): Infrarenal aorta was dissected after laparotomy was performed on the rats. In order to provide ischemia, the infrarenal aorta was left clamped for 1 hour. After the clamp was removed to provide reperfusion, blood flow was regained after 2 hours of waiting.

Group III (IR+curcumin): 250 mg/kg of curcumin was administered intraperitoneally to the rats 30 minutes before laparotomy. Afterward, the procedures in the IR group were performed in the same way to produce ischemia and reperfusion.

Anesthesia and Surgical Procedure

Xylazine (Rompun; Bayer, Turkey) was injected intramuscularly at 5 mg/kg dose as premedication, and animals were anesthetized with ketamine (Ketalar; Parke-Davis, Eczacibasi, Turkey) at 40 mg/kg dose. Unlike other groups, rats in group III were given 250mg/kg of curcumin 30 minutes before laparotomy (Sigma-Aldrich: C1386, Merck KGaA, Darmstadt, Germany). The rats were placed on the operation table and positioned after being sedated. The abdominal area was cleaned with antiseptic solutions and covered with sterile drapes. Following a medial line laparotomy, intestinal structures were wrapped in warm blankets and deviated to the right. A longitudinal incision over the aorta was used to enter the retroperitoneal cavity, and the infrarenal aorta was rotated and suspended 1 cm distal to the renal artery level and 1 cm proximal to the iliac bifurcation using elastic tapes. Anticoagulation was achieved with 150 U/kg IV heparin (Coparin, Koçak Pharma, Turkey). In the 5th minute of heparin administration, the infrarenal aorta was occluded by using a microvascular clamp. After 1 hour of ischemia, the aortic clamp was removed and 1 mg/kg IV protamine sulfate (Promin, Vem, Turkey) was administered to the animals for heparin neutralization. Intestinal structures were taken into the abdomen and the peritoneal cavity was closed by using sterile drapes. The rats were sacrificed at the end of the second hour of reperfusion, and tissue and blood samples were obtained.

Kidney Tissue and Blood Samples

The inferior vena cava of the rats was punctured to obtain approximately 3 mL of blood for biochemical analyses to evaluate renal functioning and hematological parameters. The blood samples were centrifuged and stored at -70 ºC until the biochemical analysis was performed. The right kidneys of the rats were removed to analyze the histopathological alterations in the kidney tissue as well as the oxidative stress in the kidney tissue.

Biochemical Analysis

The haemoglobin, platelet, white blood cell (WBC), and hematocrit count were performed on the blood samples taken (Sysmex XN-2000; Sysmex Corporation, Germany). The estimated glomerular filtration rate (eGFR), calcium, creatinine, potassium, sodium, urea, and blood urea nitrogen (BUN) from the same blood samples were measured with an autoanalyzer (Cobas 8000; Roche, Switzerland). Kidney tissue levels of interleukin (IL)-1β, IL-6, tumor necrosis factor (TNF)-α, and

interferon(IF)-γ (E-Bioscience, Vienna, Austria) were analyzed with the ELISA technique.

Measurement of total antioxidant status (TAS) and total oxidant status (TOS).

The measurements of TAS and TOS were done with automatic colorimetric methods. TAS values were given as mmol Trolox equivalent/g protein. TOS values were calibrated with hydrogen peroxide and these values were given as micromolar hydrogen peroxide equivalent per gram prot (μmol H2O2 Eq/g prot).

Histopathologic Evaluation

The tissue samples taken from rats were fixated with 10% buffered neutral formaldehyde solution and fixation was achieved for 48 hours. The tissue samples embedded in paraffin blocks were sampled by cutting sections of 5-μm thickness. The samples were examined under the optical microscope by staining with hematoxylin-eosin (H&E).

Samples from kidney tissue were randomly examined at 200X magnification. Samples were examined for congestion, cellular vacuolization, interstitial edema, luminal debris, and intratubular detachment and were graded with scores ranging from 0 to 4 points. No abnormality was scored as 0, mild lesions affecting 25% of the kidney samples as 1, lesions affecting 25%-50% of the kidney samples as 2, lesions affecting 50%-75% were given 3, and lesions affecting more than 75% of the samples as 4 points. As a result of scoring, an evaluation was made for each group and thus the damage was recorded.

TUNEL assay

Steps recommended by the manufacturer were carried out by using In Situ Cell Death Detection Kit, POD, (Roche, cat. no. 1684 817). TUNEL method was applied to the tissue sections taken and deparaffinization was achieved by applying xylol. It was rehydrated with gradual application of ethanol. Proteinase K (pH 8.0, 10 units/mL) was applied for 10 minutes to show the breaks in the DNA chain. The sections were rinsed with phosphate-buffered saline (PBS) and then incubated in TUNEL reaction mixture containing fluorochrome at 37ºC for 1 h and were rinsed with PBS again. The preparations were placed in a light-free laboratory environment and a drop of PBS was applied and covered. Stained slides were examined under Zeiss Imager A2 microscope with fluorescence attachment. Ten different areas of cortical kidney tissue from each kidney tissue were selected and TUNEL positive cells in this region were counted.

Statistical Analysis

The data were analyzed by using SPSS for Windows 22.0 software package (SPSS Inc., Chicago, Illinois, USA). Distribution of continuous variables was examined by using the Shapiro–Wilk test. Normally distributed variables were expressed as mean, when appropriate, and non-normally distributed variables as median and categorical variables as percentages. Results for descriptive statistics were expressed as mean±standard deviation (SD). Statistical comparisons of continuous variables among the groups were performed using one-way analysis of variance (ANOVA) or Kruskal–Wallis test based on their distribution. Tukey test was performed for post hoc analysis after performing analysis of variance test. In cases where the Kruskal–Wallis test yielded statistical significance, Bonferroni-corrected Mann–Whitney U test was used to identify the groups which showed differences. Probable method was used for sampling. Kolmogorov-Smirnov test was used as normality test. Kolmogorov-Smirnov test was used as normality test. T test was used for normally distributed variables and Mann Whitney U test was used for non-normally distributed variables. Categorical variables were expressed as percentages. A P value <0.05 was considered statistically significant.

RESULTS

Biochemical Values

There was no difference between the groups in terms of haemoglobin (p=0.153), platelet count (p= 0.303), WBC (p= 0.251) and haematocrit (p=0.093) values. There was also no difference between the groups in terms of eGFR (p=0.143) and creatine (p=0.070), which show renal functions. Potassium levels were observed to be higher in the IR group than in the other groups (p=0.005), but there was also a significant difference between the sham and IR+curcumin groups (p=0.050). When compared to the other groups, the IR group had significantly lower sodium levels (p=0.001). Urea and BUN, which are other indicators of kidney function, were found to be significantly higher in the IR+curcumin group compared to the other two groups (p=0.050). Hematological and biochemical analysis results are given in Table 1.

As a result of colorimetric methods, TAS was found to be significantly higher in the IR group than in the other two groups (p=0.021). However, although TOS was higher in the IR group than in the other groups, no significant difference was observed (p=0.069). IL-1β (p=0.014), IL-6 (p=0.022), and TNF-α (0.020) were found to be higher in the IR group than in the other groups and were statistically significant, but IF-γ, another inflammatory indicator, was not different between the groups (p=0.140). Levels of inflammation markers and oxidative parameters in renal tissue are given in Table 2.

Table 1. Serum levels of hematological and biochemical values

	Sham	IR	IR+Curcumin	P
Haemoglobin	15.72±1.08	15.77±0.89	16.56±0.79	0.153
Platelet count	574.87±271.55	435.12±108.72	573.12±191.27	0.303
WBC	3.41±1.28	2.46±1.01	2.89±0.88	0.251
Haematocrit	42.52±3.85	38.45±2.20	39.11±2.19	0.093
eGFR	130.62±15.48	136.50±8.09	123.87±9.20	0.143
Creatinine	0.340±064	0.52±0.17	0.40±0.14	0.070
Calcium	10.61±0.76	9.76±1.09	10.57±0.71	0.355
Potassium	5.14±0.82	7.5±0.77	6.30±1.39	**0.005**
Sodium	149.16±13.74	126.75±8.81	134.87±5.46	**0.001**
Urea	68.68±11.78	69.78±16.28	84.67±12.87	**0.050**
BUN	32.09±5.50	32.60±7.60	39.56±6.01	**0.050**

BUN: blood urea nitrogen, eGFR:estimated glomerular filtration rate, WBC:white blood cell
Data are presented as mean±standard deviation. Dark p values are statistically significant among groups (p<0.05)

Table 2. Levels of inflammation markers and oxidative parameters at renal tissue

	Groups			
	Sham	**IR**	**IR+Curcumin**	**P**
TAS	4.58±0.37	5.10±0.62	4.28±0.51	**0.021**
TOS	5.06±0.62	5.42±0.58	4.74±0.46	0.069
IL1β	4.94±0.61	6.26±0.58	5.64±0.81	**0.014**
IL6	2.82±0.78	3.79±0.25	3.46±0.66	**0.022**
TNF-α	8.11±1.31	10.18±0.87	9.85±1.38	**0.020**
IF-γ	11.40±2.82	14.79±3.36	14.07±3.54	0.140

TAS: total antioxidant status, TOS: total oxidant status, IL: interleukin, TNF: tumor necrosis factor, IF: interferon
Data are presented as mean±standard deviation. Dark P values are statistically significant among groups (P <0.05)

Histopathology

Hematoxylin and eosin (H&E) staining

Tubular and glomerular structures were normal in the histopathologic examination of the Sham group. When the enlargement of the Bowman's space in the glomerulus, degenerative and necrotic changes in the tubular epithelial cells, vacuolization formations in glomerulus capillaries, and the infiltrations of inflammatory cells in the interstitial area were evaluated, an increased rate of tissue damage was detected in the IR group. Damage was found to be significantly higher in the IR group when compared to the IR+ alpha-tocopherol group (p<0.001). The glomerular damage and tubular changes were shown in Figures A1, A2 and A3.

TUNEL method

When compared to the other groups, TUNEL positive cell count was found to be higher in the IR group (p<0.001). Figures B1, B2, and B3 reveal that the IR group has a higher TUNEL positive cell count than the IR+ curcumin group.

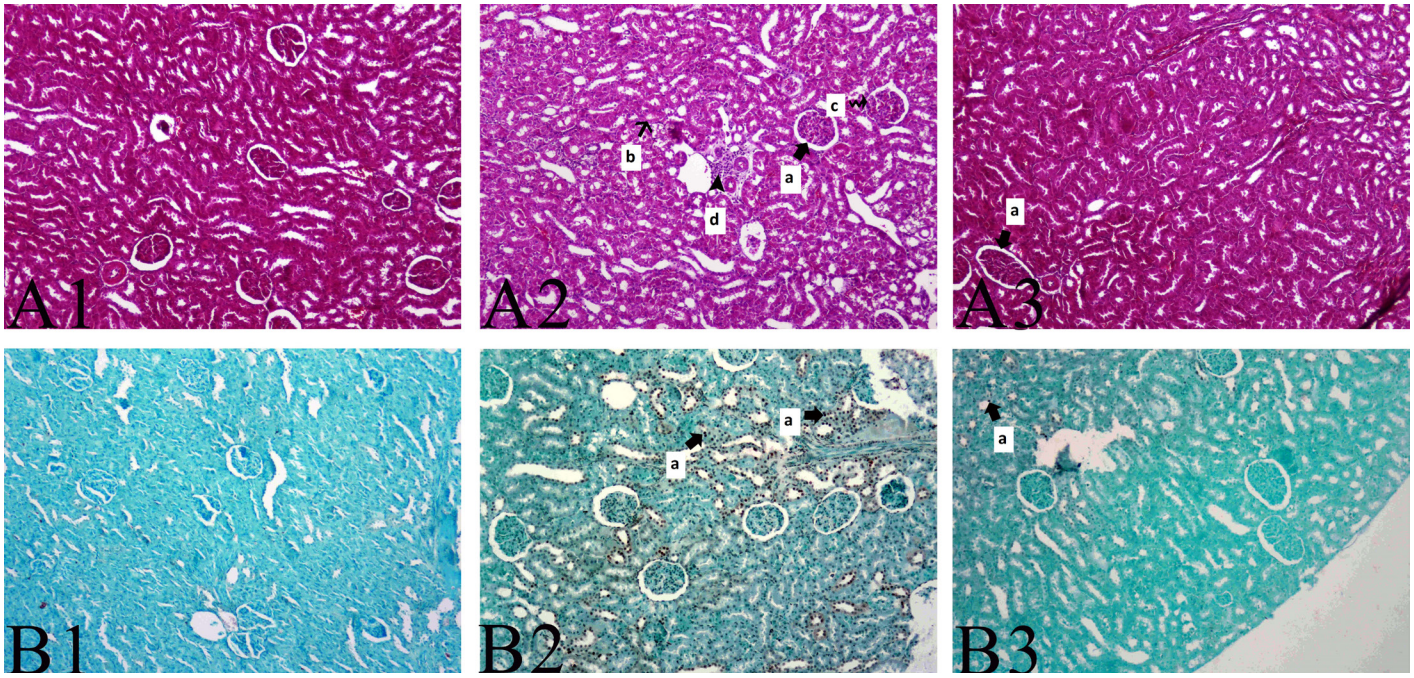

Figure 1. Histopathologic evaluation. **A:** Hematoxylin-eosin (H&E) staining, **B:** TUNNEL staining method. **A1** Group I (sham), **A2** Group II (IR), **A3** Group III (IR+ Curcumin), **B1** Group I, **B2** Group II, **B3** Group III tubular and glomerular structures. **a:** Enlargement of the Bowman space in the glomerulus, **b:** Degenerative and necrotic changes in the tubular epithelial cells, **c:** Vacuolization formations in the glomerulus capillaries, **d:** Inflammatory cell infiltration areas in the interstitial area. TUNEL positive cells are seen in **B2** and **B3**

DISCUSSION

According to the findings of our study, curcumin had no positive or negative effect on hematological parameters in rats with IR injury. When renal functions were evaluated, there was no effect on eGFR and creatine, but urea and bun values were higher in the curcumin group. It is not possible to say that curcumin has a sufficient effect in protecting renal functions in IR injury; on the contrary, it should be taken with caution because it induces high potassium levels. In the light of the results obtained, it can be said that inflammatory response is suppressed and oxidative stress is reduced. In histopathological examination, curcumin showed an effective protective effect on kidney tissue.

Although significant progress has been made in understanding the pathophysiology of kidney injury, it has not been fully clarified, and despite attempts to develop treatment methods, it remains a destructive disease with high mortality and morbidity rates all over the world [7]. Renal damage caused by IR typically arises following hypotension, hemorrhagic shock, major cardiovascular surgery, and transplants [8]. In infrarenal aortic diseases and surgery, there are a series of changes affecting the lower extremity as well as other organs [9]. This is due to both ischemia and the inflammatory response to reperfusion following ischemia [10]. Some of the precursors that cause this inflammatory response are IL-1β, IL-6, TNF-α, and IF-γ [11,12]. Many studies have been conducted to prevent kidney damage after IR [9,13]. Our study aims to investigate the effect of curcumin on kidney injury after IR.

Hematological changes that affect mortality and morbidity in cardiovascular diseases and the surgery of these disorders are critical [14]. In our study, haemoglobin (p=0.153), haematocrit (p=0.093) and platelet (p=0.303) values were higher in the curcumin group compared to the IR group, but no significant difference was found between the groups. Maintaining haemoglobin, hematocrit, and platelet levels is advantageous for cardiovascular diseases and surgery. The eGFR (p=0.143) and creatinine (p=0.070) used in the evaluation of renal functions did not differ between the groups, but both parameters were found to be higher in the IR group. Although there was no difference between the groups, these data suggest that curcumin may be protective against kidney function damage caused by IR. Calcium values did not differ between the groups (p=0.355). Potassium is an important electrolyte in terms of cardiac functions. Cardiac arrhythmias and arrests may occur in case of hyperpotasemia [15]. Hyperpotasemia was found to be significantly higher in the IR group (p=0.005), but it was also significantly higher in the curcumin group compared to the sham group (p=0.050). Curcumin has been insufficient to demonstrate the protective effect predicted for hyperpotassemia. Hyponatremia is one of the most common electrolyte disorders. It may be asymptomatic, but it also has the potential to induce neurological dysfunction by causing brain edema [16] In our study, significant hyponatremia

was seen in the IR group compared to the other groups (p=0.001), and sodium levels in the curcumin group were determined to be close to normal. We believe that measuring serum osmolarity for sodium levels is crucial to investigate whether it is hypoosmolar hyponatremia or pseudohyponatremia. Urea and BUN levels indicating renal functions were found to be significantly higher in the curcumin group (p=0.050). While eGFR and creatinine levels were not different, urea and BUN levels were found to be borderline significant. When the results obtained regarding the effect of curcumin in protecting kidney functions are evaluated, it shows that more detailed studies are needed.

When the studies in the literature are examined, curcumin has shown many positive effects on TAS and TOS with its antioxidant properties [17,18] Consistent with the literature, TAS was found to be significantly lower in the curcumin group in our study (p=0.021). Although TOS was low in the curcumin group, it was not significantly different from other groups (p=0.069). Based on our findings, curcumin is efficient in lowering the oxidative stress that develops in kidney tissue as a result of IR damage. Proinflammatory cytokines play an important role in the inflammatory response that causes IR injury. IL-1β, IL-6, TNF-α, and IF-γ are among the most important cytokines of the inflammatory response, with numerous effects both on their own and on the pathways they trigger in a variety of pathological processes [19]. These cytokines were found to be high in IR injury in studies, and many methods were used to suppress them [20]. In our study, IL-1β (p=0.014), IL-6 (p=0.022) and TNF-α (p=0.020) were found to be significantly higher in the IR group in accordance with the literature. IF-γ did not differ between groups (p=0.140). With the data we obtained, we may conclude that curcumin has an active role in suppressing the inflammatory response that occurs as a result of IR. As shown in previous studies in the literature, it is possible to prevent apoptosis and tissue damage caused by inflammatory response, thanks to curcumin [4,21].

Ischemia primarily causes functional and structural defects in tubular epithelial cells. Reperfusion causes endothelial dysfunction and microvascular injury. All of these factors result in glomerulus and tubular cell injury, and kidney functions worsen [22]. In our research, curcumin was found to reduce the enlargement of Bowman's space in the glomerulus as well as degenerative and necrotic alterations in tubular cells. In addition, it was observed that curcumin administration significantly prevents the formation of vacuolization in the glomerulus and the infiltration of inflammatory cells in the interstitial area. In accordance with the literature data, curcumin protected kidney tissue with its antioxidant and anti-inflammatory effects [4].

Limitations

In accordance with the literature, the IR durations in our study were established at 1-hour ischemia and 2-hour reperfusion, and the dose of curcumin was set to be 250mg/kg. Examination of oxidative and antioxidative mechanisms in tissue was done by evaluating TAS and TOS. Studies using more extensive parameters and variable times and doses will provide valuable information.

Conclusion

Many studies show the antioxidant and anti-inflammatory characteristics of curcumin, which are being easily accessible and being utilized safely in food. Studies on the effect of curcumin against IR injury are insufficient. The data obtained in our study gave positive results regarding the use of curcumin in IR injury. Curcumin, with its anti-inflammatory and antioxidant properties, can be used to suppress inflammation and protect the histological structure of kidney tissue in IR injury.

Ethics Committee Approval: Approval was obtained from Afyon Kocatepe University Animal Experiments Local Ethics Committee for the study protocol and experimental methods (date:06.05.2020-no:49533702/260).

Patient Consent for Publication: This study is a research using experimental animals.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: All authors contributed equally to the article.

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