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LABORATORY STUDY

Lycopene has reduced renal damage histopathologically and biochemically in experimental renal ischemia-reperfusion injury

Cem Kaya[1], Ramazan Karabulut[1], Zafer Turkyilmaz[1], Kaan Sonmez[1], Gamze Kulduk[2], Özlem Gülbahar[3], Faik Köse[1], and Abdullah Can Basaklar[1]

[1]Department of Pediatric Surgery, [2]Department of Pathology, and [3]Department of Biochemistry, Faculty of Medicine, Gazi University, Ankara, Turkey

Abstract

Background: The present study aimed to investigate whether the inflammatory and antioxidant lycopene has a therapeutic effect against renal ischemia/reperfusion (I/R) injury. *Materials and methods*: In this study, 24 Wistar-Albino rats, weighing from 200 to 250 g, were divided into four groups. All rats underwent median laparotomy under anesthesia. No procedures were performed in the control group (Group C), whereas 100 mg/kg lycopene was administered by gavage in the lycopene group (Group L). The arteries of both kidneys were clamped for 45 min in the ischemia group (Group I), whereas 100 mg/kg lycopene was administered by gavage 30 min before clamping renal arteries, and ischemia was performed in the treatment group (Group T) rats. For all rats, blood samples and renal tissues were collected at 6 h of reperfusion. Samples were used to examine serum BUN, creatinine, MDA and GSH levels, and the renal tissues were used to examine MDA and GSH levels, and renal histopathologies. *Results*: The treatment group had statistically significant lower serum MDA levels, histopathological tubular vacuolization, loss of brush border and tubular dilatation ($p < 0.05$), whereas serum BUN, creatinine, tissue MDA, and tissue and serum GSH levels were improved in favor of the treatment group, even though it was not statistically significant ($p > 0.05$). *Conclusion*: The present study demonstrated that lycopene, which was administered prior to renal I/R injury, prevented renal damage through biochemical and histopathological parameters.

Keywords

Free radical, lycopene, renal ischemia/reperfusion injury

History

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Introduction

Renal ischemia occurs in various urological interventions such as kidney transplantation, renal artery surgeries, partial nephrectomy and in clinical conditions such as trauma, shock and sepsis.[1] During ischemia and reperfusion, altered mitochondrial oxidative phosphorylation, reduced adenosine triphosphate (ATP), increased intracellular calcium (Ca^{+2}), and activation of proteases and phosphatases, which lead to the impairment of the cytoskeleton and membrane phospholipids, cause production of free oxygen radicals (FOR), resulting in oxidative stress.[2–4] Previous histopathological studies have shown increased microvascular permeability, interstitial edema, impaired vasoregulation, inflammatory cell infiltration and parenchymal cell dysfunction in the kidneys due to ischemia/reperfusion (I/R) injury and acute tubular necrosis (ATN) during or after ischemia.[5–7] FOR is produced after re-oxygenation of the tissue during reperfusion, and it increases the tissue damage by causing lipid peroxidation.[8] Free radicals and their damage to the tissues can be prevented via antioxidants. Such antioxidants may be endogenous such as catalase (CAT), superoxide dismutase (SOD), glutathione (GSH) and glutathione peroxidase (GSH-Px), or exogenous such as folic acid, vitamin C and vitamin E.[2] An important carotenoid, lycopene, is found in the highest amount in tomatoes and tomato-based products, and it is also present in fruits and vegetables like watermelon and pink grapefruit and gives their red color. Lycopene, which is found in higher amounts in the human plasma than β-carotene and other dietary carotenoids, is anti-carcinogenic, anti-inflammatory and antioxidant. Lycopene suppresses the synthesis of prostaglandin, prostacyclin, thromboxane and leukotriene by regulating cyclooxygenase and lipoxygenase, and thereby it prevents the reactions that cause inflammation.[9–13] Having protective effects against several diseases such as prostate, uterine and liver cancers, Alzheimer's disease, and cardiovascular diseases, lycopene slows the ageing process via its antioxidant activity.[14,15] This experimental study aimed to investigate the potential protective effects of lycopene on experimentally induced I/R injury in renal tissue.

Materials and methods

Twenty-four healthy Wistar-Albino female rats, weighing from 200 to 250 g, were used in the study. The animals were

Address correspondence to Ramazan Karabulut, M.D., Gezegen Sokak No: 1/10, 06670 GOP Çankaya, Ankara, Turkey. Tel: +90-312-2026210; Fax: +90-312-2026212; E-mail: karabulutr@yahoo.com

fed in the cages at constant room temperature and humidity in a laboratory setting with 12 h light and 12 h dark. There was no food or water limitation prior to the experiment.

All procedures were performed under general anesthesia and sterile conditions. For general anesthesia, 45 mg/kg ketamine hydrochloride (Ketalar, Eczacıbası, Turkey) and 5 mg/kg xylazine hydrochloride (Alfazyne 2%, Ege Vet, Turkey) were intramuscularly administered to each rat.

Twenty-four rats were divided into four groups with six animals in each group.

Control group (Group C)

Animals underwent median laparotomy under anesthesia with no procedures performed, and renal tissues and blood samples were collected.

Lycopene group (Group L)

Animals underwent median laparotomy under anesthesia 6 h after the administration of 100 mg/kg lycopene by gavage, and renal tissues and blood samples were collected.

Renal ischemia group (Group I)

Animals underwent median laparotomy under anesthesia, followed by 45 min ischemia in both the renal arteries, then renal tissues and blood samples were collected by re-anesthetizing at 6 h of reperfusion.

Lycopene treatment group (Group T)

Animals underwent median laparotomy under anesthesia 30 min after administering 100 mg/kg lycopene by gavage, followed by 45 min ischemia in both renal arteries, then renal tissues and blood samples were collected by re-anesthetizing at 6 h of reperfusion.

Experimental study model

All rats were fixed on the operation table after anesthesia, and the abdominal skin was shaved in supine position and cleared using 10% povidone-iodine, then the abdomen was opened through a 3-cm midline incision, the bilateral kidneys were removed, and the renal pedicles were dissected. In the last two groups, bilateral renal pedicles were occluded using atraumatic microvascular clamps, and renal ischemia was performed for 45 min (Figure 1). After ischemia, atraumatic microvascular clamps were removed for reperfusion. The incision line in the abdominal region was closed using 3/0 silk suture.

After 6 h, anesthesia was administered to all animals including the control group, and bilateral nephrectomy was performed via laparotomy; all blood was taken through cardiac puncture and the animals were sacrificed by injecting intracardiac anesthetic substance. For all groups, one of the kidneys removed was stored in 10% formalin for histopathological evaluation, and the other kidney was divided into two equal parts and freeze-stored at −80°C for tissue enzyme and receptor analysis. Blood samples were centrifuged at 3000 rpm for 10 min, and the urea (BUN) and creatinine levels were tested for renal function evaluation, then the sera were placed into Eppendorf tubes and stored at 80°C for MDA and GSH testing.

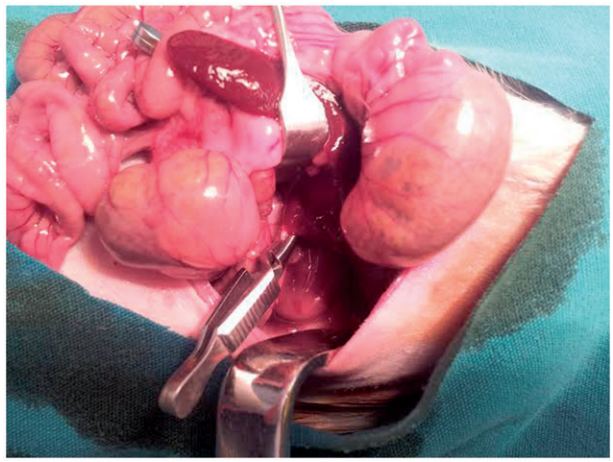

Figure 1. Placing atraumatic microvascular clamps to the renal pedicle for renal ischemia.

Histopathological evaluation

Rat kidneys were fixated in 10% buffer formalin solution for 24 h. Sections were prepared at 4 μm thickness from the paraffin blocks, which were prepared following routine tissue tracking procedure and stained with hematoxylin-eosin (H&E) and PAS. Cytoplasmic swelling of the tubular epithelium, the presence of apical cytoplasmic brush border in the proximal tubular epithelium, tubular necrosis and tubular dilatation were evaluated. Especially, the integrity of apical cytoplasmic brush border was evaluated in ''PAS''-stained preparations.

Tubular necrosis and loss of apical cytoplasmic brush border in the proximal tubular epithelium were noted as ''yes/no''. Cytoplasmic swelling of tubular epithelium and tubular dilatation were evaluated by noting the parenchymal area affected semi-quantitatively (parenchymal area with cytoplasmic swelling/total cortical area).[16]

Determination of GSH and MDA in renal tissues and blood

Renal tissue was homogenized 1/10 in cold 1.15% KCL. Protein estimation in tissues was made using a Folin reagent based on Lowry's method. The levels of MDA, a lipid peroxidation product, were studied in kidney homogenates and serum samples using thiobarbituric acid based on the method of Uchiyama and Mihara. The GSH levels were studied in kidney homogenates and serum samples using Ellman's reagent [5,5-dithiobis-(2-nitrobenzoic acid)] based on the Ellman method. The tissue MDA and GSH results were expressed as per mg protein.[17,18]

Statistical analysis of data was conducted on the computer using SPSS for Windows software. Biochemical results from blood and tissue samples were expressed as mean ± standard deviation (SD). Differences between the groups were tested using the Mann–Whitney *U*-test. Differences in the histopathological evaluation results between the groups were determined using the one-way ANOVA test. $p < 0.05$ was considered statistically significant.

Table 1. Mean ± standard deviation values in blood serum and tissue samples of animals from experimental groups.

	Urea (BUN) (mg/dL)	Creatinine (mg/dL)	Tissue MDA (nmol/mg protein)	Serum MDA (nmol/mL)	Tissue GSH (nmol/mg protein)	Serum GSH (μmol/mL)
Group C	24.81 ± 2.54	0.30 ± 0.03	3.43 ± 0.44	5.41 ± 2.26	37.98 ± 17.01	0.23 ± 0.10
Group L	17.01 ± 4.02	0.27 ± 0.04	2.00 ± 0.41	6.73 ± 2.14	27.25 ± 17.52	0.33 ± 0.13
Group I	48.70 ± 5.40	0.59 ± 0.18	3.96 ± 1.12	10.66 ± 2.45	11.46 ± 7.27	0.28 ± 0.09
Group T	41.35 ± 6.37	0.51 ± 0.11	2.61 ± 1.04	7.45 ± 1.27	13.6 ± 7.93	0.32 ± 0.15

Results

There was a significant difference in BUN between Group C, Groups L & I, and Group T ($p = 0.006$, 0.006, and 0.004, respectively). Additionally, there was a statistically significant difference between Group L and Groups I & Group T ($p = 0.004$ and 0.004, respectively). For creatinine, there was a significant difference between Groups C & L and Groups I & T ($p = 0.016$, 0.004, and 0.01–0.004, respectively). Thereby, BUN and creatinine values were lower in the treatment group compared to the ischemia group (Table 1).

The tissue MDA level was lower in the treatment group compared to the ischemia group (3.96 ± 1.12 in Group I and 2.61 ± 1.04 in Group T); however, the difference was significant only between Group L and Groups C & I ($p = 0.004$ and 0.004, respectively). For reduced serum level of MDA, there was a significant difference between Group C, Group L, and Groups T & Group I ($p = 0.006$, 0.030, and 0.025, respectively) (Table 1).

The mean values of GSH in the renal tissues were 37.98 ± 17.01 in Group C, 27.25 ± 17.52 in Group L, 11.46 ± 7.27 in Group I and 13.65 ± 7.93 in Group T. There was a significant difference between Group C and Groups I & T ($p = 0.006$ and 0.010, respectively). The mean values of GSH in blood serum samples were 0.23 ± 0.10 in Group C, 0.33 ± 0.13 in Group L, 0.28 ± 0.09 in Group I and 0.32 ± 0.15 in Group T. Tissue and serum GSH values were higher in the treatment group compared to the ischemia group, even though it was not statistically significant (Table 1).

For tubular vacuolization, there was a significant difference between Groups C & T and Group I ($p = 0.008$ and 0.011, respectively). There was a significant difference in brush border loss between Group C, Group L and Groups T& I ($p = 0.002$, 0.002 and 0.002, respectively) (Figures 2 and 3). For tubular necrosis, there was no statistically significant difference found between the groups ($p > 0.05$). For tubular dilatation, there was a significant difference found between Group C, Group L, and Groups T & I ($p = 0.000$, 0.000 and 0.000, respectively). Histopathologically, the treatment group had less tubular vacuolization, brush border loss and tubular dilatation compared to the ischemia group ($p = 0.011$, 0.002 and 0.000, respectively) (Table 2).

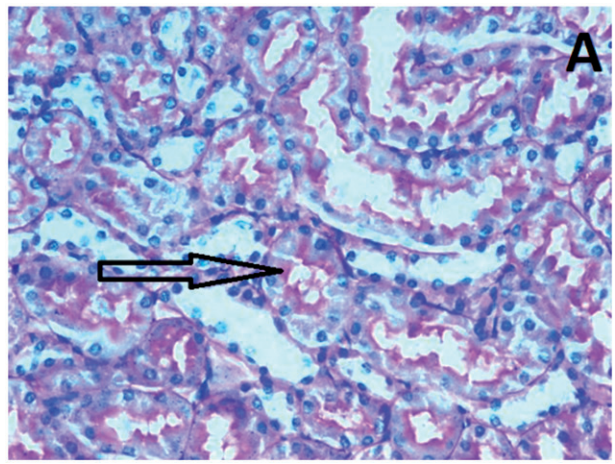

Figure 2. View of brush border in renal tissue in Group C.

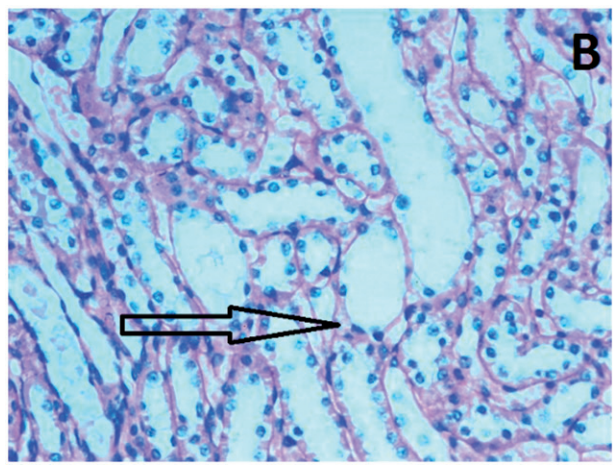

Figure 3. Brush border loss, tubular dilatation and tubular vacuolization in renal tissue after Group I.

Discussion

Renal I/R injury is a complex condition leading to functional and morphological damage of the kidneys due to chain reactions occurring in the periods of ischemia and subsequent reperfusion.[18,19] In order to avoid this damage, various substances have been used as protective before and after ischemia in the literature, such as amrinone, silymarin, celecoxib, dexmedetomidine and rosmarinic acid.[20–24] In the present experimental study, lycopene was used in order to benefit from its anti-oxidant and anti-inflammatory activities in a renal I/R model induced in rats.

The duration of ischemia–reperfusion varied in the studies, which were conducted to induce renal I/R injury. Singh et al. induced an I/R model with 40-min ischemia and reperfusion afterwards; Senbel et al. performed 45-min ischemia and reperfusion afterwards, and Ozturk et al. performed 60-min ischemia and reperfusion afterwards.[22,24,25] Williams et al. investigated the effects of reperfusion performed in different durations after 45-min ischemia on renal histology in rats and

Table 2. Mean ± SD histopathological evaluation of renal tissues of the animals from experimental groups.

	Tubular vacuolization	Brush border loss	Tubular necrosis	Tubular dilatation
Group C	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Group L	11.66 ± 19.14	0 ± 0	0 ± 0	0.83 ± 2.04
Group I	35.00 ± 25.88	1.16 ± 0.68	0.16 ± 0.40	15.83 ± 6.64
Group T	1.66 ± 4.08	0 ± 0	0 ± 0	0.83 ± 2.04

reported that the damage started at hour 4 at the earliest and reached the maximum level at hour 24.[26] Therefore, 45-min ischemia was preferred in the present study, and the procedure was terminated after 6 h of reperfusion. The present study had statistically significant differences ($p < 0.05$) in serum BUN and creatinine levels, serum and tissue MDA and GSH levels, and histopathological values between the control and ischemia groups, suggesting that the 45-min renal ischemia performed in rats is adequate.

When the BUN values were compared between the groups at the end of the experiment, the highest value was in Group I (48.7 ± 5.4 mg/dL) and the lowest value was in Group L (17.01 ± 4.02 mg/dL). When the creatinine values were compared, the highest value was in Group I (0.59 ± 0.18 mg/dL) and the lowest value was in Group L (0.27 ± 0.04 mg/dL). The increased serum levels of BUN and creatinine after ischemia are not clearly understood, but believed to result from tubular inhibition or reverse leakage in the tubules. Serum levels of BUN and creatinine increased due to renal dysfunction at the stage prior to the development of tubular necrosis, and this is an indicator of glomerular filtration ratio.[27] The increased levels of BUN and creatinine, and the statistically significant difference ($p < 0.05$) between Groups C & L and Groups I & T with I/R suggest a disorder in the renal function and the efficacy of the I/R model. The study by Pektas et al. investigated a group administered maize oil and lycopene before performing unilateral renal ischemia and found higher levels of BUN and creatinine in the lycopene group compared to the ischemia group, in contrast to the present study.[28] However, the present study found lower values in the treatment group compared to the ischemia group, even though it was not statistically significant. The difference between these two studies in the literature, in which renal ischemia was performed and lycopene was administered for treatment, may be resulted from the difference in using drugs. Lycopene was administered at a single dose and 30 min before in the present study, whereas Pektas et al. administered lycopene for 2 days.

I/R injury causes reduced ATP, increased intracellular Ca^{+2}, and consequently activation of proteases and phosphatases, and FOR production. With reperfusion, the complement system leads to leukocyte activation and chemotaxis, and stronger inflammatory response by stimulating the production of proinflammatory cytokines. FOR causes PMNL chemotaxis, while the activated leukocytes lead to more FOR production. FOR reacts with unsaturated fatty acids in the plasma and organelle membrane, resulting in lipid peroxidation and production of MDA, the final product of lipid peroxidation. GSH is the most important intracellular antioxidant compound, which is synthesized from glutamate, cysteine and glycine in several tissues, especially in the liver, and protects the cells against oxidative damage.[2,29,30] Previous studies have shown increased levels of MDA and reduced levels of GSH in the tissues using nephrotoxic agents or inducing I/R model.[22,24,31–33] The present study has found lower tissue and serum levels of GSH in the ischemia group (11.46 ± 7.27 and 0.28 ± 0.09) compared to the treatment group (13.65 ± 7.93 and 0.32 ± 0.15), and higher levels of MDA again in the ischemia group (3.96 ± 1.12 and 10.66 ± 2.45) compared to the treatment group (2.61 ± 1.04 and 7.45 ± 1.27), suggesting that lycopene has an anti-oxidant mechanism in renal ischemia. In the literature, the study by Ghavipour et al. with lycopene and obese women showed reduced inflammatory cytokines (IL-6, IL-8, TNF-alpha), and the study by Dogukan et al. investigating the effects of lycopene on cisplatin nephrotoxicity in rats demonstrated reduced levels of HSP70, which causes an NF-kB-mediated proinflammatory response.[32,34] Some previous studies, which were conducted with nephrotoxic agents (cisplatin, gentamicin and cadmium) in order to demonstrate the anti-oxidant activity of lycopene in tissues, showed reduced levels of MDA and increased levels of GSH.[31–33,35] The study by Pektas et al., which is the single study in the literature regarding the effect of lycopene on renal I/R injury, found lower levels of MDA and GSH, and insufficient anti-oxidant effect. In the present study, lycopene exhibited a complete anti-oxidant effect through positive influence on both values, as specified in the previous literature.[28] Such an anti-oxidant effect of lycopene, as stated by Rao and Agarwal, was attributed to its ability to reduce lipid, protein and DNA damage caused by FOR.[36] The primary mechanism of lycopene to inhibit the effects of FOR is the inactivation of hydrogen peroxide and nitrogen dioxide.[37] Again, another study found lycopene is effective in eliminating O_2, which causes harmful effects in the cells and the production of other free radicals by reacting with DNA, RNA, proteins, lipids, and sterols. Such anti-oxidant effects of lycopene are also supported by its anti-inflammatory effects.[32,34,38,39] Furthermore, lycopene protected all values except serum MDA and tissue GDA (no statistically significant difference) in favor of kidneys in the group in which it is administered alone without ischemia (Group L) in the present study, suggesting that lycopene has anti-oxidant and protective effects in normal life without ischemia.

When the literature is reviewed, there are a great number of articles investigating histopathological changes such as tubular dilatation, tubular vacuolization, brush border loss, glomerular necrosis and tubular necrosis after using nephrotoxic agents and renal I/R.[22–24,40,41] There are also publications investigating the efficacy of lycopene after inducing renal damage with nephrotoxic agents and demonstrating improved histopathological parameters with lycopene such as tubular vacuolization, brush border loss, tubular dilatation and tubular necrosis.[32,39,40,41] The present experimental study found significantly reduced brush border loss, tubular vacuolization and tubular dilatation in the ischemia group treated with lycopene compared to the ischemia group and has shown that lycopene is histopathologically protective in renal

ischemia. A similar study by Pektas et al. did not find these parameters significantly lower when analyzed alone and indicated that lycopene had a significantly positive effect on renal histology only in total scoring.[28] The studies by Atessahin et al. and Dogukan et al. with nephrotoxic agents demonstrated that lycopene reduced tubular vacuolization, brush border loss and tubular dilatation.[32,40] Dogukan et al. also showed that lycopene reduced the apoptotic gene Bax and increased the anti-apoptotic gene Bcl-2.[32] The improvements caused by lycopene on these histopathological parameters at cellular level can be attributed to the reflection of the total for anti-oxidant, anti-apoptotic and anti-inflammatory effects mentioned above.

With known anti-oxidant, anti-apoptotic and anti-inflammatory effects, lycopene has reduced renal damage through both histopathological and biochemical parameters in the present experimental renal ischemia–reperfusion model. Lycopene is not routinely used as medication, but it can be used for treatment and support purposes in both daily life and clinical practices, since it is abundantly consumed by humans through products such as tomatoes, tomato sauce, ketchup, grapefruits, melons and watermelons, and because it has exhibited an anti-oxidant effect in normal rats in the present experiment.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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