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The Protective Effects of Beta Glucan Against Experimental Renal Ischemia Reperfusion Injury

Beta Glukanin Deneysel Böbrek İskemi Reperfüzyon Hasarina Karşi Koruyucu Etkileri

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ABSTRACT

Aim: This study aimed to investigate the possible protective effects of beta-glucan against oxidative stress caused by ischemia and reperfusion injury in kidney tissue.
Materials and methods: In the study, 30 male Wistar albino rats weighing 300-350g were used (n=10). Rats were randomly grouped into three groups of Sham control, ischemia reperfusion group (IR), ischemia reperfusion + beta glucan group (IR + BG). Sham group had left nephrectomy, the right kidney taken for histopathologic and biochemical examination. After left nephrectomy in IR group, ischemia procedure was applied for 45 minutes via nontraumatic microvascular clamp, then reperfusion was applied for 60 minutes in the right kidney. In the IR+BG group, rats were administered 100 mg/kg beta glucan via gastric gavage for 10 days. Reperfusion was applied for 60 minutes after 45 minutes of ischemia to the right kidney under anesthesia.
Results: As a result of biochemical examination MDA values showed a significant increase in IR group compared to Sham group (p<0,05). In IR+BG group, there was a significant decrease compared to IR group (p<0,05). Tissue MPO values in IR group showed a significant increase compared to Sham group, whereas in the IR+BG group there was not a significant decrease. Also, there was not a significant difference in tissue catalase levels. Tissue GSH values showed a significant decrease in IR group compared to Sham group (p<0,05). In the IR+BG group a significant increase was found compared to IR group (p<0,05). Less damage has been revealed in the IR+BG group compared to IR group in histopathologic examination.
Conclusion: All these data show that beta glucan may have an antioxidant effect on renal ischemia reperfusion injury.

Keywords: Antioxidant, Beta glucan, İschemia, Kidney, Reperfusion

ÖZ

Amaç: Bu çalışma, böbrek dokusunda iskemi ve reperfüzyon hasarının neden olduğu oksidatif strese karşı beta glukanın olası koruyucu etkilerini araştırmayı amaçlamaktadır.
Materyal ve metod: Çalışmada 300-350 gr ağırlığında 30 adet erkek Wistar albino sıçan kullanıldı (n=10). Sıçanlar rastgele Sham kontrol, iskemi reperfüzyon grubu (İR), iskemi reperfüzyon + beta glukan grubu (IR + BG) olmak üzere üç gruba ayrıldı. Sham grubuna sol nefrektomi yapıldı, sağ böbrek histopatolojik ve biyokimyasal inceleme için alındı. İR grubunda sol nefrektomi sonrası travmatik olmayan mikrovasküler klemp ile 45 dakika iskemi prosedürü uygulandı, ardından sağ böbrekte 60 dakika reperfüzyon uygulandı. IR+BG grubunda, sıçanlara 10 gün süreyle 100 mg/kg beta glukan gastrik gavaj yoluyla uygulandı. Anestezi altında sağ böbreğe 45 dakikalık iskemi sonrası 60 dakika reperfüzyon uygulandı.
Bulgular: Biyokimyasal inceleme sonucunda MDA değerleri IR grubunda Sham grubuna göre anlamlı artış gösterdi (p<0,05). IR+BG grubunda IR grubuna göre anlamlı azalma oldu (p<0,05). IR grubunda doku MPO değerlerinde Sham grubuna göre anlamlı bir artış görülürken, IR+BG grubunda anlamlı bir azalma olmadı. Ayrıca doku katalaz seviyelerinde de anlamlı bir fark yoktu. Doku GSH değerleri IR grubunda Sham grubuna göre anlamlı düşüş gösterdi (p<0,05). IR+BG grubunda IR grubuna göre anlamlı artış bulundu (p<0,05). Histopatolojik incelemede IR+BG grubunda IR grubuna göre daha az hasar saptandı.
Sonuç: Tüm bu veriler, beta glukanın renal iskemi reperfüzyon hasarı üzerinde antioksidan etkiye sahip olabileceğini göstermektedir.

Anahtar Kelimeler: Antioksidan, Beta glukan, İskemi, Böbrek, Reperfüzyon

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INTRODUCTION

Ischemia is an oxygen deprivation caused by decreased arterial and venous blood flow. Interruption of blood flow to the tissue decreases cellular oxidative phosphorylation, adenosine triphosphate (ATP) and phosphocreatine [1]. During ischemia and reperfusion, oxidative stress damage occurs with decreased ATP, increased intracellular calcium, increased activity of protease and phosphatase that cause degradation of membrane phospholipids and in particular, releasing reactive oxygen species [1,2]. The severity of ischemic damage is split into two categories, reversible and irreversible ischemic injury. Cellular functions are conducted by aerobic mechanism due to oxygen and high energy phosphate bonds in normoxia. In hypoxia, ATP stores are depleted and ATP production cannot be produced, therefore structural disorders occur in the cell. Increase in membrane permeability results in morphological deterioration [3]. Reperfusion is the re-oxygenation of tissue by re-flowing blood to ischemic tissue. The arrival of oxygenated blood into the tissue initiates a process that leads to more damage for tissue than the ischemic period [2]. In the ischemic period, metabolic and structural changes in the cell (such as increase in proinflammatory cytokines and leukocyte adhesion molecules, decrease in antioxidant enzymes) make the cell vulnerable to damage during the reperfusion period. Membrane lipids, proteins, nucleic acids and DNA molecules are the cellular structures that are most susceptible to reperfusion injury [4].

Beta glucans are carbohydrates composed of glucose chains found in the cell walls of yeast, bacteria, fungus and grains. They consist of 1,3 1,4 1,6 chain glycopyrrolate units. Beta glucan, which has the most biological effects, is obtained from baker's yeast - Saccharomyces cerevisiae [5]. Beta glucans strengthen the immunity by activating the macrophage and complement system when taken from outside and have effects on natural and adaptive immunity [6]. Beta glucan has been described as a potent immunostimulatory with no toxic effects or adverse effects, as well as antioxidant and organ protective properties [7]. The determination of possible positive results of beta glucan in the treatment of renal ischemic injuries will appear as an added value on antioxidant treatment area. As a result of further studies on the subject, multidisciplinary approaches are expected to be developed and a useful scientific study for humanity will be put forward.

The aim of this study was to investigate the protective effects of beta glucan on renal ischemia reperfusion injury. Since a study investigating the effects of beta glucan on renal ischemia reperfusion injury has not been found in the literature, therefore the results of this study will be a reference for further studies.

MATERIALS AND METHODS

This experimental study was carried out in Aydın Adnan Menderes University, Faculty of Medicine, Department of Physiology, with 30 male Wistar rats weighing 300-350g. The decision of the ethics committee was approved by the decision of 64583101/2015/099 Animal Experiments Local Ethics Committee dated 14 august 2015 and numbered 64583101. Rats were kept in a circadian rhythm of 12 hours a night, 12 hours a day, at a temperature of 22±2ºC and a humidity of 45-50%. Standard pellet feed and drinking water were used in the diet of the rats. In the experimental groups, 30 male Wistar albino rats were randomly divided into 3 groups (n=10). Right kidneys were analyzed in histology and biochemistry laboratories.

Sham Control Group: Left nephrectomy was applied at the end of the experiment without any application.

Ischemia-Reperfusion (IR) Group: The left kidneys were removed by nephrectomy at the end of the experiment without any application, the right kidney was exposed to ischemia with a nontraumatic microvascular clamp for 45 minutes, followed by 60 minutes of reperfusion [8 9].

Beta-Glucan + Ischemia-Reperfusion (IR+BG) Group: The group administered beta-glucan per oral (p.o.) once a day by the gastric gavage method for 10 days. After left nephrectomy on the day of the experiment, the right kidney was exposed to ischemia for 45 minutes with a nontraumatic microvascular clamp, followed by 60 minutes of reperfusion.

Beta Glucan Administration: Beta glucan dosage

was 100 mg/kg/day to rats in the IR+BG group [8-10-11]. Beta glucan 50 mg capsule Imuneks® (Gensenta Pharmaceutical I.C) was dissolved in drinking water and applied with intragastric gavage [12-13].

Ischemia-Reperfusion Induction: 50 mg/kg ketamine and 10 mg/kg xylazine were administered to the rats that were not fed 24 hours before the experiment day of ischemia-reperfusion. The midabdominal region of the rats was incised, the left kidneys were removed by nephrectomy and the right kidneys were clamped at the level of the hilus with a nontraumatic microvascular clamp and exposed to ischemia for 45 minutes. After 45 minutes, the nontraumatic microvascular clamp was removed and 60 minutes of reperfusion was achieved. 0,09% saline water was administered to prevent dehydration during the operation.

Tissue Collection: The rats were sacrificed under anesthesia with cervical dislocation after the kidney tissues were collected. Tissues were separated and stored at -80ºC for biochemical analysis and in 10% formaldehyde solution for histology examination.

Biochemical Analysis of Kidney Tissue Samples: Homogenization of tissues: after the kidney tissues in the experimental group and the control group were weighed and homogenized separately with the 'Ultra Turnax, IKA-WERKE, Germany' brand tissue homogenizer. Afterwards, PBS (phosphate buffer saline) was added for the calculation of MDA (Cat. No: K739, BioVision®, Milpitas, CA, United States), MPO (Cat. No: K744, BioVision®, Milpitas, CA, United States), CAT (Cat. No: K773, BioVision®, Milpitas, CA, United States) and GSH (Cat. No: K264, BioVision®, Milpitas, CA, United States) activities. [14,15]. The tissue homogenates were centrifuged at 1500 rotational speed (rpm) for 15 minutes at 40C. Supernatants were stored for analysis at -80oC. ELISA method 'Diagnostic Automation, Inc./ELx800TM brand model has been used.

Histological Analysis of Kidney Tissue Samples: Kidney tissues were kept in 10% formaldehyde until the day of examination. Tissue samples using routine histological follow-up method were embedded in paraffin and sections of 5 µm were cut with microtome (HistoPlusTM Specimen). The preparations stained using the hematoxylin eosin staining technique were covered with entellan. Histological examination was taken with the "Olympus DP20 Digital camera" mounted on the "Olympus B*51" microscope at the light microscope level.

Statistical analysis: Statistical analysis of all data obtained was made using Graphpad Prism® 6 package program. In the Kolmogorov Smirnov test, the data showed a normal distribution. Statistical evaluation between groups was made using the Mann Whitney U test. A p value of <0.05 was considered statistically significant.

RESULTS

Biochemical Results

MDA, the final product of lipid peroxidation, was 12.81±0.2578 nmol/mg in the Sham group; 14.53±0.3000 nmol/mg in the IR group; in the IR+BG group, it was measured as 13.46±0.3157 nmol/mg. When the Sham group and the IR group were compared; MDA value increased significantly in the IR group compared to the Sham group ($p<0.05$). The IR+BG group has a significantly lower MDA value compared to the IR group ($p<0.05$).

MPO values in Sham group were 8.643±0.4565 nmol/mg; 12.78±0.8489 nmol/mg in the IR group; It was measured as 11.86±0.6620 nmol/mg in the IR+BG group. When the Sham group and the IR group are compared; The MPO level was significantly decreased in the Sham group compared to the IR group ($p<0.05$). MPO values decreased in the IR+BG group compared to the IR group but did not make a significant difference ($p>0.05$).

Measured catalase levels, Sham group 2.456±0.2225 nmol/mg, IR group 2.453±0.2334 nmol/mg, IR+BG group 2.825±0.2413 nmol/mg. There was no significant difference between the Sham group and the IR group in terms of measured catalase values ($p>0.05$). No significant difference was found between the IR group and the IR+BG group ($p>0.05$).

Glutathione levels were 17.46±0.4148 nmol/mg in the Sham group, 7.466 ± 0.4884 nmol/mg in the IR group, and 8.879±0.3216 nmol/mg in the IR+BG

group. When the measured GSH levels were compared with the Sham group and the IR group, a significant decrease was observed in the IR group ($p<0.05$). When the IR group and the IR+BG group were compared, a significant increase was observed in the IR+BG group compared to the IR group ($p<0.05$).

All measured values are shown in detail in Table 1.

Table 1. Tissue MDA, MPO, CAT and GSH Values.

	Sham	IR	IR+BG
MDA (nmol/mg)	12,81±0,2578	14,53±0,3000*	13,46±0,3157†
MPO (nmol/mg)	8,643±0,4565	12,78±0,8489*	11,86±0,6620
CAT (nmol/mg)	2,456±0,2225	2,453±0,2334	2,825±0,2413
GSH (nmol/mg)	17,46±0,4148	7,466±0,4884*	8,879±0,3216†

* For IR group compared to Sham group: p≤0.001

† For IR+BG group compared to IR group: p≤0.05

Histological Results

Cortical degeneration, glomerular degeneration, tubular damage, medulla degeneration and congestion in kidney tissues were evaluated. Histological scoring was evaluated as 0: no damage, 1: mild, 2: moderate and 3: extensive damage. Mild cortical degeneration and mild glomerular smallness were observed in the Sham group (figure 1), moderate cortical, medullary, tubular and glomerular degeneration and congestion were detected in the IR group (figure 2), mild cortical and medullary degeneration and mild tubular degeneration were observed in the IR + BG group (figure 3). Detailed scoring of all groups is shown in Table 2.

Table 2. Histological Scores

	Sham	IR	IR+BG
Congestion	0	2	0
Cortical Degeneration	1	2	1
Gromerular Degeneration	1	1	0
Tubular Damage	0	2	1
Medulla Degeneration	0	2	1

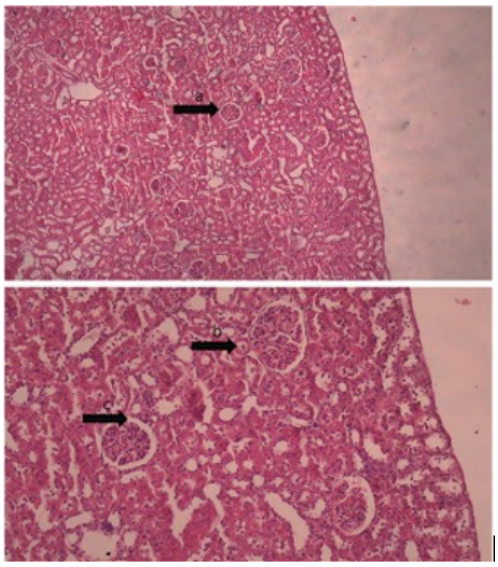

Figure 1. Sham group histopathological sample: kidney morphological structures are preserved a:glomerule (40X,H&E), b:distal tubule (100X,H&E), c:Bowman's capsule (100X,H&E).

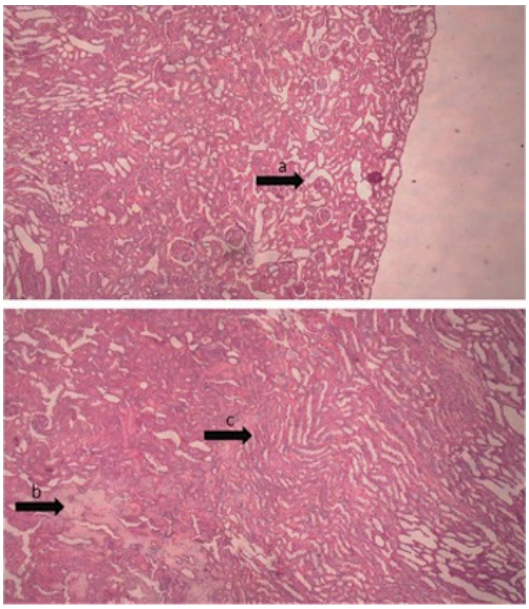

Figure 2. IR group histopathological sample (40X, H&E); Moderate morphological degeneration is observed in the kidney. a:disruption in glomerular integrity, b:ischemic focus, c:medullary degeneration.

DISCUSSION

Beta glucans became an important subject of research in recent years and significant beneficial results have been obtained. Numerous studies showed that beta glucans have beneficial effects on human health against a number of diseases, such as cancer, infection, wound healing and others [16]. Clinical studies on beta glucan have also been increasing in recent years and it is being used in many supportive treatments

[17]. We investigated the possible effects of beta glucan administration as pre-treatment like various studies performed by other researchers [18,19]. Renal ischemia can be observed in clinical situations such as kidney transplantation, partial nephrectomy, sepsis, cardio-pulmonary bypass, various urological procedures and hydronephrosis. As a result of studies on kidney, the critical time period determined for permanent damage was determined to be 30 minutes [20]. Mitochondrial disorders are irreversible after approximately 30-40 minutes of ischemia [21]. In our study rats were exposed to ischemia for 45 minutes, with irreversible damage. Rats were applied reperfusion for 60 minutes after ischemia and histological and biochemical results supported by previous research [8,9].

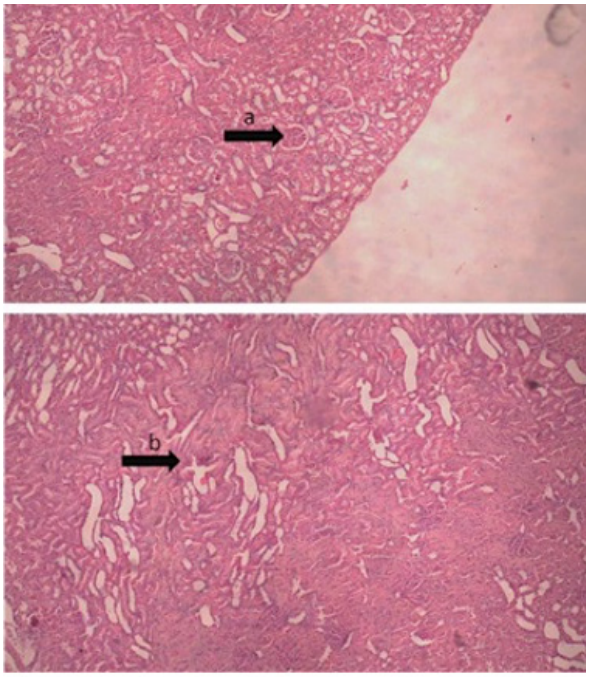

Figure 3. IR+BG group histopathological sample (40X,H&E); Glomerular structures are largely preserved by observing low-level degeneration areas in the morphological structure. a:glomerulus, b:medullary degeneration.

The dosage of beta glucan is specified as 40-3000 mg per day, which is accepted by the FDA on the GRAS category and 2-6 mg/kg of body weight has been considered [12]. Suzuki et al. reported that beta glucan should be applied over 80 mg doses and should be applied for 5-10 days [13]. Amany et al. and Alkhalidi et al. applied the beta glucan the dose of 100 mg/kg by oral administration [10,11]. In our study we also applied beta glucan orally and the dose was 100 mg/kg as well. We investigated pretreatment effects of beta glucan for 10 days, as per Yücel et al. and Çetin [8,19].

Beta glucan shows its antioxidant effects as a powerfully intracellular reactive oxygen species scavenger and has a protective effect on oxidative damage, by suppressing lipid peroxidation [22]. In a study by Şener et al. [6] it was shown the beta glucan prevents the increase of MDA, the final product of lipid peroxidation in tissue. In our study, tissue MDA values increased significantly in the IR group compared to the Sham group and decreased significantly in the IR+BG group compared to the IR group. These results show that beta glucan can have protective effects on oxidative damage. Toklu et al. [23] studied the effects of beta glucan on kidney injury and they found significantly decreased MDA values in tissue, as we have. MPO is an enzyme localized in leukocytes and is considered to be an indicator of neutrophil infiltration [23]. In our study, tissue MPO values in the IR group showed a significant increase compared to the Sham group, whereas in the IR+BG group there was not a significant decrease. MPO values decreasing but not with a significant difference may be due to the rats' count of group numerically. Erkol et al.'s study-on beta glucan as both prophylactic and therapeutic and it was found that beta glucan administration in the postoperative group decreased MPO, while in the prophylactic group did not provide a significant reduction for MPO [24]. MPO values not significantly decreasing may be the result of the administration of beta glucan prophylactically in our study.

Catalase, an enzyme which is found in high rates in kidney and blood, allows hydrogen peroxide to hydrolyze [25]. In our study, there was not a significant difference in tissue catalase levels. İlhan et al. [26] and Rausher et al. [25] also studied oxidative damage and could not find any significant change on CAT activity. Catalase may affect by the administration of the duration and dosage of the antioxidant substance.

Glutathione is a protective component against oxidative damage [27]. In our study, tissue GSH values showed a significant decrease in the IR group compared to the Sham group ($p<0,05$). In the IR+BG group a significant increase was found

compared to the IR group (p<0,05). Şener et al. [5], Erkol et al. [27], Toklu et al. [23] studied beta glucan and they found high GSH values, as we did.

In our study, less damage was revealed in the IR+BG group compared to the IR group in the histopathologic scores. Bedirli et al. [2] reported in their study that beta glucan provided healing histopathological on congestion, hemorrhage and infiltration. Şener et al. [4] reported the histopathological on interstitial inflammatory infiltration, glomerular necrosis and Bowman's capsule degeneration, were decreased significantly.

Limitations: The limitations of the study can be listed as follows: there are dietary and digestive system differences between rats and humans, therefore the absorption of beta glucan may cause differences. Rats are fed with a single type of food, so the effects of beta glucan on humans may vary as a result of nutritional diversity and substance interactions. Finally, the long-term effects of beta glucan may need to be investigated: the effects in different forms (encapsulated, ready-made liquid form), different administration forms (intraperitoneal), different durations (acute, subchronic and chronic) and different doses (low, optimal, high) should be investigated in further studies.

CONCLUSION

Considering its proven safety and low toxicity, beta glucan administration has increased in recent years and its effectiveness has been demonstrated with different experimental methods. The antioxidant effects of beta glucan decreased lipid peroxidation and accordingly, tissue MDA levels changed significantly in our study. MPO which is responsible for neutrophil infiltration, also decreased in the beta glucan group. In addition, positive changes were observed of histological examinations in the beta glucan group. It is shown that beta glucan prevents cortical, medullary and tubular damage histopathological, after renal ischemia reperfusion injury. All this data shows that beta glucan may have an antioxidant effect on renal ischemia reperfusion injury. The effects of clinical studies on different experimental models need to be investigated.

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Ethics Committee Approval: In this study, national and international ethical rules are observed. This study was approved by the Experimental Research Ethics Committee of Aydin Adnan Menderes University. Date: 14.08.2015, number: 64583101/2015/099

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