Original Article

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# Selenium Pretreatment Protects Against Renal Ischemia Reperfusion Injury by Inducing Mitochondrial Biogenesis

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**ABSTRACT**

**Background & Objective:** Acute kidney injury (AKI) is a rapid loss of kidney function that is associated with high morbidity and mortality. Oxidative hazard, inflammation, mitochondrial deterioration and depletion of cellular energy stores, which terminate in organ dysfunction, are the major hallmarks of AKI. The current experimental investigation attempted to evaluate the effects of selenium (Se), a pivotal micronutrient, on the ischemia/reperfusion (IR)-induced kidney damage emphasizing on the biogenesis of mitochondria.

**Materials & Methods:** Male Wistar rats (n = 18) were randomly allocated into three groups: sham, IR, and Se + IR. Rats in the last group 1 h before IR induction, were treated with Se (0.5 mg/kg) intraperitoneally. Six hours after reperfusion blood and kidney tissue samples were collected, and animals were euthanized. In addition to the evaluation of biochemical factors and histopathology, the protein levels of sirtuin1 (SIRT-1), and peroxisome proliferator-activated receptor-gamma coactivator 1-α (PGC-1α) of the kidney tissues were determined via western blotting.

**Results:** Pre-treatment with Se could significantly improve IR-induced kidney function markers (creatinine and BUN) as well as the pathological alteration in comparison with the IR group ($P < 0.05$). Moreover, in the Se + IR group, a substantial surge of the Sirt-1 and PGC-1α at the protein level was recorded compared to the IR group.

**Conclusion:** The results proposed that Se displays a protective role against renal IR injury via up-regulating proteins involved in mitochondrial biogenesis. Due to the pivotal role of mitochondria in renal tubules, these results offer insight into the plausible preventative and/or therapeutic effects of Se against AKI after further studies.

**Keywords:** Selenium, Ischemia, Reperfusion Injury, Mitochondria, Sirtuins



## Introduction

Leishmaniasis is a worldwide parasitic disease that Renal ischemia/reperfusion (IR) injury is a major cause of acute kidney injury (AKI), a frequently occurring event under extensive surgeries, transplantation and infections (1, 2). Also, ischemic AKI is accompanied by high morbidity and mortality, for instance, it can turn into chronic kidney disease or increase the risk of graft rejection after transplantation (3). Reactive oxygen species (ROS) production, tubular epithelial cell (TEC) damage, mitochondrial dysfunction, and the inflammatory cascade are involved in the pathophysiology of IR (4). Currently, there is no effective therapeutical option to target the underlying pathophysiology of ischemic AKI.

Taking into account that mitochondrial damage and subsequent energy depletion are among the key elements involved in the pathogenesis of AKI, the role of mitochondrial biogenesis and its main regulators [e. g. peroxisome proliferator-activated receptor-gamma coactivator-1alpha (PGC-1α) and sirtuins (SIRTs)] are essential in the recovery of renal function (5, 6). SIRTs are pivotal regulatory proteins that mediate diverse biological processes such as metabolism, oxidative balance,

inflammation, mitochondrial energetics, and aging (7). Among seven types of SIRTs, SIRT1 and SIRT3 are highly expressed in the renal proximal tubules, preserving the integrity of cellular mitochondrial content and homeostasis (8).

So far, extensive research has been done to develop effective pharmacological agents for the prevention/treatment of IR injury (3, 9, 10). Accordingly, oxidative stress, inflammatory cascade and the apoptotic machinery have been considered as the main targeted signaling pathways to be addressed (11-13).

Selenium (Se) as a well-known trace element with diverse biological actions (cofactor of selenoproteins, ROS scavenging, and anti-inflammatory function) is abundantly found in meat products, seafood, and cereals (14). It has been demonstrated that Se deficiency is connected with the pathogenesis of several human diseases including metabolic disorders, cancer and renal diseases (15, 16). Recent studies have enlightened the role of the kidney in the metabolism of Se since different selenoproteins such as glutathione peroxidase are synthetized in the kidney (17). Therefore, a tight connection between the plummeted level of Se and the defects in selenoproteins has been detected. Moreover, it has been suggested that Se supplement can significantly reduce the severity of chronic diseases (18). However, the possible role of Se in preventing renal ischemic injury via the modulation of mitochondrial biogenesis-related signals remains to be evaluated. In light of these considerations, this study aimed to evaluate the effect of Se on a kidney model of IR injury.

## Materials and Methods

In the current in vivo experiment, eighteen Wistar male adult rats were obtained from Pasture Institute (Tehran, Iran). Rats (220 ± 10 gr) randomly were divided into three groups ((i) Sham, (ii) IR, (iii) Se + IR groups) after 10 days of adaptation to the new environment. A single dose of Se (5 mg/kg) was intraperitoneally injected 1 h before the induction of IR induction in groups ii and iii [19]. Animals were housed according to the Laboratory Animals Care standards of the National Institutes of Health [20], and the Helsinki declaration of ethics in medical research. Also, all procedures in this study were approved by the Ethics Committee at Tabriz University of Medical Sciences (IR.TBZMED.VCR.REC.1400.228).

### Induction of ischemia reperfusion (IR) injury

In vivo, kidney IR was induced according to the previously described methods [20, 21]. In brief, the combination of xylazine (10 mg/kg) and ketamine (90 mg/kg) (via intraperitoneal injection) was utilized to anesthetize the animals. In the Sham group, only kidney vascular manipulation without clamping was performed. In the IR group, unilateral IR injury was established via non-traumatic vascular forceps to block the left kidney vascular for 45 min. The ischemic kidney was distinguished when the red-colored kidneys got pale, then the forceps were removed and the abdominal area was stitched. Six h later blood samples were collected and kidney tissue were separated after animals were euthanized via intraperitoneal thiopental sodium (200 mg/kg) injection.

### Biochemical and histopathological assessment

Bio-Merieus colorimetric assay kits were used to evaluate serum levels of BUN and creatinine. To assess the pathological changes in the kidney, paraffinated samples were stained by H&E (hematoxylin and eosin) and examined under a light microscope (Olympus, Japan).

### Evaluation of mitochondrial proteins

The effect of Se on protein levels of SIRT-1 and PGC-1α was determined using western blotting as described previously according to Santa Cruz Biotechnology, Inc. [22]. Beta-actin was used as a housekeeping protein (sc-47778, Santa Cruz Biotechnology Inc).

### Statistical analysis

The graphPad Prism 9 Software was applied to analyze the data (SPSS, Inc.). The values were indicated as the mean ± SEM. One-way ANOVA test was used to compare the differences between the groups, followed by multiple comparisons with Tukey's post-hoc. A P-value<0.05 was considered statistically significant.

## Results

The effects of Se on kidney function and histopathology Augmented serum levels of BUN and creatinine 6 h after IR induction confirmed the negative effect of IR on kidney function. Pretreatment with Se 1 h prior to IR induction considerably could decrease serum BUN and creatinine compared to the IR group ($P < 0.05$ Table 1). The effects of Se pretreatment on the histopathology of IR-induced kidney tissues are presented in Figure 1. Intact renal cells and normal histological appearance were observed in the Sham group; while elevated immune cell infiltration, formation of hyaline cast, epithelial cell damages and glomerular injuries were detected in the IR group. Pretreatment with Se could lessen the histological damages due to IR kidney injury (Figure 1).

**Table 1. Kidney function markers in the studied groups**

| | Creatinine (mg/dl) | BUN (mg/dl) |
|---|---|---|
| Sham | 0.62±0.14 | 19.8±6.8 |
| IR | 1.7±0.27* | 46.2±8.1* |
| Se + IR | 0.88±0.19# | 32±5.5# |

Ischemia reperfusion (IR), Selenium (Se).

*Significantly different ($p< 0.05$)

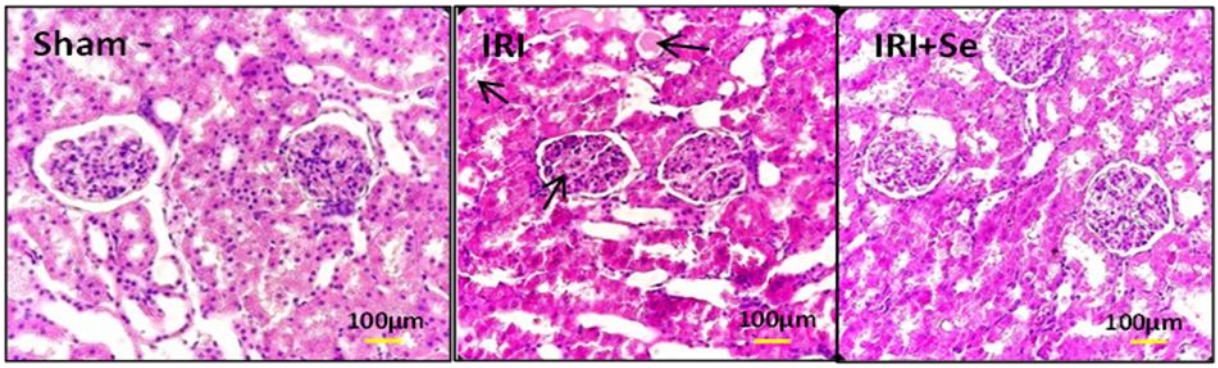


**Figure 1. Evaluation of kidney histopathological alterations in the studied groups. Ischemia reperfusion (IR), Selenium (Se). The arrows indicate hyaline crystals in tubules, damages in the membrane of epithelial cells and glomerular injuries in IR group.**

### The effects of Se on mitochondrial biogenesis

Figure 2 illustrates the protein expression of SIRT-1 and PGC-1α in different experimental groups. Accordingly, a significant decrease in the SIRT-1, and PGC-1α levels was observed in the kidney of IR rats compared to the control group. In Se + IR treated animals, a significantly higher level of SIRT-1 PGC-1α content was found compared to the IR group (Fig. 2 A& B).

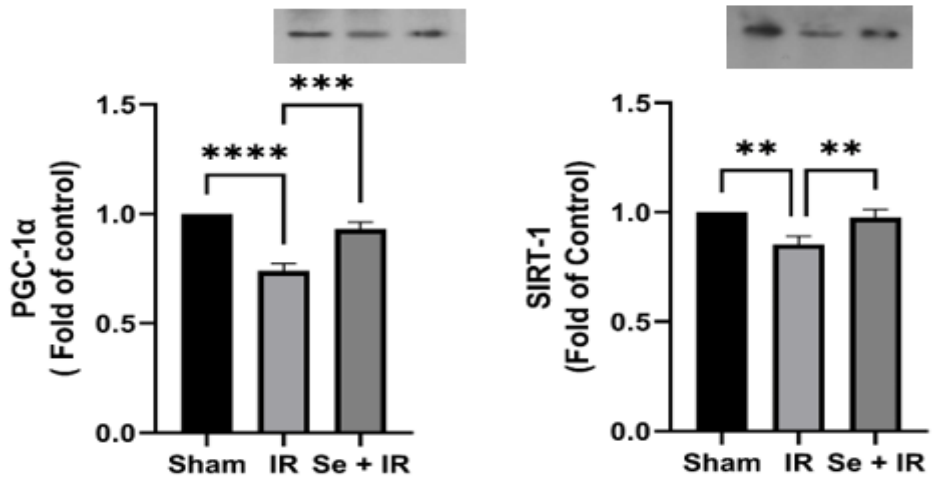


**Figure 2. Effect of Se on protein levels of PGC-1α (A), SIRT-1 (B). β-actin was used as a housekeeping control. Data are presented as mean ± SEM. Selenium: Se; ischemia/reperfusion: IR, PGC-1α: Peroxisome proliferator-activated receptor gamma coactivator 1-alpha, Sirtuin-1: SIRT-1.**

## Discussion

IR injury is the leading cause of AKI. Several signaling pathways are responsible for IR kidney damage. Among them, oxidative stress, inflammatory response and mitochondrial dysfunction are of great importance (3, 23). Therefore, the administration of antioxidant agents which can also affect other signaling cascades is considered an effective therapeutic approach against free radical-induced damage and its consequences (24). Se is a strong antioxidant micronutrient with proven protective effects against multiple human diseases such as IR injury (in the brain, bladder and heart), myocardial infarction, and organ

transplantation (25, 26). Thus, the current study aimed to evaluate the plausible beneficial impact of Se in renal IR with a focus on the main pathways related to the biogenesis of mitochondria in vivo. Our results indicated that Se could efficiently improve biochemical kidney function markers in IR rats. Previous research has shown that antioxidants are effective compounds in reliving post-IR renal function parameters (27, 28). So, it could be suggested that the diminution of renal function markers in serum might be related to the antioxidant properties of Se. Also, it should be mentioned that glutathione and thioredoxin systems as key constituents of the endogenous antioxidant network contain selenoprotiens (glutathione peroxidase (GPx) and thioredoxin reductase (TrxR)) that encompass selenocysteine at their active site responsible for their enzymatic activity (29). Our result also demonstrated that Se lowers the infiltration of inflammatory cells and, improves kidney damage in histopathological analysis.

Mitochondrial deterioration is one of the key events in charge of the stimulation of cell death pathways during ischemic injuries (30). Trace element selenium has been revealed to reverse neural cell death in hypoxic/ischemic injury of the brain via modulating mitochondrial function and biogenesis (31). Also, Se has significantly reduced heavy metal–induced nephrotoxicity via ameliorating oxidative stress and mitochondrial dysfunction (32). Stressed mitochondria can return to their normal function through anti-oxidant defenses, using selective removal of injured macromolecules and undergoing the unique process of fusion and consequent fission. In case of unsuccessful recovery, the autophagy system eliminates the injured mitochondria. If the mitochondrial disruption is extensive and severe, apoptosis and cell death cascades initiate (33). Considering the abundance of mitochondrial content in proximal tubules, this series of events is critical to cell turnover in the human kidney (34). Mitochondrial respiration evaluation has revealed that Se supplementation substantially escalates mitochondrial content and up-regulates mitochondrial biogenesis mediators in trophoblasts (35). In this study, Se could surge the master factor of mitochondrial biogenesis (PGC-1α) in comparison with the IR group insignificantly. The role of Sirtuins in the kidneys has gained great attention as the factor of protection in younger animals over their older equivalents in enduring IR injury (36). The activity of SIRT-1 relies on the NAD+ for enzymatic deacetylation that confers its ATP-sensing features, thereby linking the energy status of the cells to other biological processes, such as inflammation, metabolism and apoptosis, (37, 38). In the current investigation, Se could significantly enhance the SIRT-1 level to prohibit ROS formation and maintain post-IR intracellular ATP levels.

## Conclusion

Collectively, this empirical study showed that the pretreatment with trace element, Se, before the induction of renal IR injury, could significantly improve renal function markers, ameliorate histopathological alteration and stimulate the expression of proteins connected with mitochondrial biogenesis. Since the formation of excess ROS during IR results in the diminution of mitochondrial biogenesis, considering the antioxidant role of Se, it could be proposed that Se can enhance mitochondrial turnover through its ROS-scavenging properties. However, it is important to design a dose-dependent study and investigate more detailed signaling pathways of Se in kidney IR injury for its possible use in the prevention and/or treatment of AKI in a clinical setting.

In conclusion, data from several primary investigations demonstrated that *Leishmania* viability was significantly reduced in the promastigote and amastigote phases. However, further research is needed to evaluate and employ this compound as a potential leishmaniasis therapy in the future.

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## Authors' Contribution

AF Amin: Data collection or management, C Leila: Data analysis, A Telli: Data collection, M Farah: Data collection, T Vugar Ali: Data analysis, A Elham: Protocol/project development, Manuscript writing/editing.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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## Ethics Approval and consent to participate

The Helsinki declaration of ethics in medical research was honored in this study. Protocols of the experiment were planned according to the standards of the National Institute of Health for Laboratory Animals Care. The study was approved by the Ethics committee of Tabriz University of Medical Sciences. Tabriz, Iran (IR.TBZMED.VCR.REC.1400.228).

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