

# The effects on bacterial translocation and tissue damage of selenium treatment in an experimental intestinal ischaemia-reperfusion model

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## ABSTRACT

**BACKGROUND:** The free oxygen radicals formed with reperfusion following intestinal ischaemia are extremely toxic for the cells. Glutathione peroxidase, an important enzyme that prevents the formation of reactive oxygen species, requires selenium as a co-factor. This study aims to demonstrate the effects of selenium administration on reducing ischaemia-reperfusion damage.

**METHODS:** In this study, 28 male Wistar rats were separated into four groups. To Groups 3 and 4, sodium selenite at the dose of 10 µg/kg/day was administered intraperitoneally for five days. In Groups 1 and 3, laparotomy was applied, and in Groups 2 and 4, following laparotomy, ischaemia was created by clamping the superior mesenteric artery for 45 mins, then reperfusion was provided for 90 mins. Blood, liver and ileum samples were taken from all the animals for examination of malondialdehyde. For examination of bacterial translocation, liver, spleen and mesenteric lymph node tissue samples were taken. A sample taken from the ileum was examined histopathologically.

**RESULTS:** There was determined to be significantly more bacterial translocation in the mesenteric lymph nodes of the ischaemia-reperfusion group ( $p<0.05$ ). In the histopathological evaluation, the score in the ischaemia-reperfusion group was significantly higher than the scores in the other groups ( $p<0.05$ ). Elevated serum, liver and ileum malondialdehyde levels in the ischaemia-reperfusion group were significantly higher than those in the other groups ( $p<0.05$ ).

**CONCLUSION:** Selenium was seen to have decreased serum and tissue malondialdehyde levels and increased the histopathological damage developing in the intestines with ischaemia-reperfusion and thereby increased bacterial translocation.

**Keywords:** Bacterial translocation; ileum; ischaemia; reperfusion; selenium.

## INTRODUCTION

Ischaemia is defined as reduced blood flow to the target organ or complete removal from the environment. This results in the absence of oxygen in the tissue. Intestinal ischaemia may develop in several clinical situations, such as acute mes-

enteric ischaemia, hemorrhagic shock, necrotising enterocolitis, trauma and strangulated hernia. Ischaemia-reperfusion (I/R) damage is defined as the changes forming with blood flow and oxygenation provided again in tissue that has been temporarily exposed to ischaemia.<sup>[1,2]</sup> Damage caused by ischaemia in the intestines develops in two stages. First, hypox-

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ia and hyponutrition may occur in the ischaemia period. In this situation, energy production with aerobic metabolism is impaired, adenosine triphosphate (ATP) production is reduced, adenosine monophosphate (AMP) increases, and then lactic acid accumulates, leading to metabolic acidosis.<sup>[3,4]</sup> In the second stage, reperfusion is provided with blood flow to the ischaemic tissue, and oxygen is re-introduced. In parallel to this, reactive oxygen species (ROS) production increases because of a lower antioxidative agent concentration in the ischaemic cells. ROS and endothelial dysfunction may cause oxidative stress supporting DNA damage and local inflammatory response. Inflammatory cascades and oxidative stress may cause a subsequent cytokine storm and this causes cell death by damaging cellular structures.<sup>[5]</sup>

Potential mechanisms of I/R damage include insufficient oxygenation at the cellular and tissue level and the formation of ROS and the emergence of inflammatory mediators with activation of the xanthine oxidase system following reperfusion.<sup>[6]</sup> Although reperfusion of ischaemic tissues is necessary for repair mechanisms, it has been shown to worsen the acute ischaemic injury of ROS expression. ROS plays a role in the pathogenesis of structural and functional changes that occur in the tissues associated with various pathological processes, primarily mesenteric I/R damage.<sup>[7,8]</sup> The cell response in I/R damage depends on the severity of the total tissue damage.<sup>[9]</sup> As the duration of ischaemia increases, so the damage formed also increases. The cell damage caused by reperfusion following long-term ischaemia may lead to apoptosis, autophagia, necrosis and necroptosis.<sup>[10,11]</sup>

In normal conditions, the intestinal mucosa is a barrier preventing the passage of bacteria and endotoxins from the intestinal lumen to systemic tissue and organs. However, in conditions of intestinal I/R, trauma, burn, or infection, bacteria cross this barrier causing systemic infection, and consequently, multiorgan dysfunction syndrome (MODS) and multiorgan failure syndrome (MOFS) may develop.<sup>[12,13]</sup> In the majority of patients who die because of systemic inflammatory response syndrome (SIRS), MODS or MOFS in which a septic focus cannot be identified, bacteremia has been determined.<sup>[12]</sup> This observation suggests that the bacteria and endotoxins could originate from the gastrointestinal system.

The intestine plays an important role in protecting the nutritional and physiological functions of the organism, participates in the stress reaction following trauma, and is the source of MODS.<sup>[14]</sup> In addition to the other effects of I/R damage, increasing bacterial translocation from the intestine also leads to systemic infections. ROS, which is responsible for I/R damage and causes this much damage, are free radicals of oxygen origin. Reactive oxygen species include superoxide, hydrogen peroxide, hydroxyl radical, nitric oxide, singlet oxygen, hypochlorous acid, alcoxyl and peroxy.<sup>[15]</sup> ROS are produced endogenously in the organism, associated with immune system activation, inflammation, stress, excessive ex-

ercise, ischaemia, infection, cancer and aging.<sup>[16]</sup> When the capacity of the antioxidant defence mechanism in the body is exceeded, they may lead to various impairments. Through interaction with all cell components and all classes of biomolecules, such as carbohydrates, lipids, proteins and DNA, ROS causes structural and metabolic changes in cells.<sup>[17]</sup> When ROS enters into a reaction with cholesterol and unsaturated fatty acids in the cell membrane, lipid peroxidation is initiated. Lipid peroxidation may damage the cell membrane by impairing the viscosity and permeability of the membrane. Thus, severe tissue damage develops following ischaemia.<sup>[15,17]</sup>

There is a defence system in the organism against the formation of ROS, and the formation of lipid peroxides is prevented in this way. The three main enzyme systems preventing the formation of ROS are superoxide dismutase, catalase and glutathione peroxidase (GPx). By superoxide dismutase metabolising superoxide radical and catalase metabolising hydrogen peroxide, accumulation in the body is prevented. GPx prevents the start of lipid peroxidation and prevents the progression of peroxidation by metabolising lipid hydroperoxides which form as a result of peroxidation.<sup>[18,19]</sup> Selenium (Se), which was previously known to have toxic and carcinogenic properties, has been evaluated as a significant and useful element for biological systems as the result of recent studies.<sup>[20]</sup>

Se is primarily found in hemoglobin and in the antioxidant property of the structure of GPx enzyme, which plays a role in the prevention of some metabolic diseases and cancer types. The biological importance of Se is that it is a co-factor of this enzyme. In each subunit, GPx contains one atom of Se in the form of selenocysteine, which plays a role in the breakdown of hydrogen peroxide ( $H_2O_2$ ) to water within the cell.<sup>[21]</sup> Selenium deficiency decreases GPx activity and changes the response of the tissue to oxidative stress.<sup>[6]</sup> Se can support the protection of cells and macromolecules against oxidative damage.<sup>[22]</sup> In animal models and human trials of selenium deficiency, it has been emphasised that selenium supplementation is beneficial in improving the selenium status of the body.<sup>[23-25]</sup> In the light of this information, this study aims to investigate the effects of selenium on ileum histology, bacterial translocation and lipid peroxidation in an experimental I/R model in rats.

## MATERIALS AND METHODS

To conduct this study, ethical approval was granted by the Local Ethics Committee. In this study, 28 adult male Wistar rats, each weighing 250–300 gr, were used. The animals were separated into four groups as the control group (n=6, Group 1), the I/R group (n=6, Group 2), the selenium injection group (n=8, Group 3) and the I/R+selenium injection group (n=8, Group 4). The animals were kept at room temperature under a 12-hour light/dark cycle. All the rats were anaesthetized with 50 mg/kg ketamine and 7 mg/kg rompun was administered intramuscularly; then, a laparotomy was performed under sterile conditions.

The Group 1 subjects were applied with laparotomy only under sterile conditions. In Group 2, after the laparotomy, the superior mesenteric artery was clamped for 45 mins to create ischaemia; then reperfusion was provided for 90 mins. The Group 3 subjects were administered 10 µg/kg/day sodium selenate intraperitoneally for five days before the laparotomy. The Group 4 subjects were administered 10 µg/kg/day sodium selenate intraperitoneally for five days; then the laparotomy was applied, during which the superior mesenteric artery was clamped for 45 mins to create ischaemia; then reperfusion was provided for 90 mins.

After completion of these periods, a thoracotomy was applied to all the rats, and a blood sample was taken from the heart of each animal for biochemical analysis. The blood samples taken were assayed for malondialdehyde (MDA). Samples were taken from the ileum and liver tissues and frozen in liquid nitrogen for the measurement of MDA and selenium absorption. Samples for histopathological examinations were taken from the distal ileum and stored in 10% formaldehyde. Mesenteric lymph node, liver and spleen tissue samples were taken under sterile conditions for microbiological examination for the evaluation of bacterial translocation.

### Histopathological Evaluation

The ileum samples were fixed in 10% formaldehyde; then slices were prepared and stained with hematoxylin-eosin. Mucosal damage, hyperemia/hemorrhage and inflammation degree were evaluated by a pathologist blinded to the sample groups using the scoring system described by Chui et al.<sup>[26]</sup>

### Microbiological Evaluation

The liver, spleen and mesenteric lymph node samples were placed in 2ml Brain Heart Infusion Broth; then weights were measured and homogenised. The samples were then seeded in blood agar and Eosin-Methylene-Blue-Lactose-Sucrose agar, and the cultures were incubated in aerobic conditions. Bacterial production was checked at 24 and 48 hours, and the bacteria strains were identified. Colonisation was stated as the number of colony-forming units per milliliter of tissue (CFU/ml tissue).

### Biochemical Evaluation

The biochemical evaluation was based on the level of MDA, which is a lipid peroxidation product. By measuring the MDA level in tissue, blood and bodily fluids, the lipid peroxidation and thereby oxidative stress were objectively evaluated.<sup>[27]</sup> Serum MDA levels were measured with the thiobarbituric acid (TBA) method. The results were stated as nmol MDA/ml.<sup>[28]</sup>

MDA levels in the intestinal mucosa of liver tissue were measured spectrophotometrically with the TBA method in liver homogenates prepared with 1.15% KCL solution. The results were calculated as nmol/MDA/gram.<sup>[29]</sup>

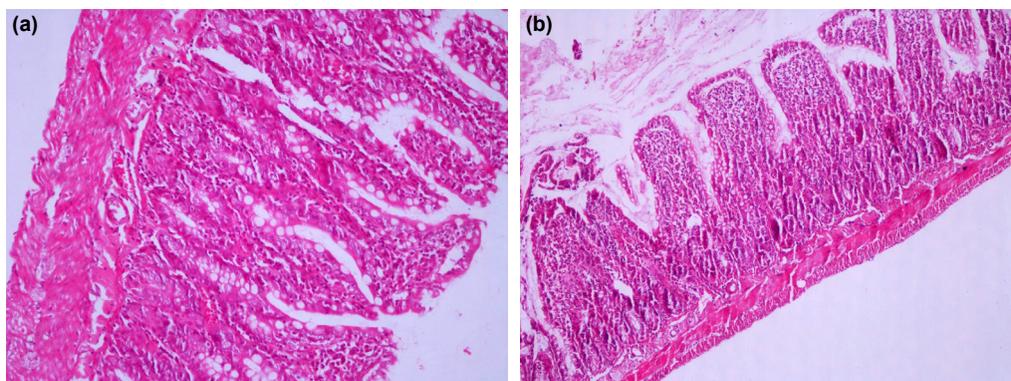
For the measurement of selenium atomic absorption in intestinal mucosa and liver tissue, the samples were mixed with nickel nitrate and surfactant; then placed in a granite oven. The light formed from selenium transmitted from a hollow cathode lamp was absorbed in proportion to the amount of selenium in the solution at a specific wavelength. The amount of absorbed energy was directly proportional to the selenium concentration. The results were calculated as ngSe/gr tissue.<sup>[30]</sup>

### Statistical Analysis

The measurements were compared according to the mean and standard deviation values of the variables. The data of the variables were determined to conform to a normal distribution, so to investigate differences between groups, the Kruskal Wallis test was used. To determine from which group a difference originated, the Mann-Whitney U test and the Tukey B test were applied. In the comparison of categorical variables, ratios were used, and to evaluate whether or not there were any differences between ratios. The Pearson Chi-square test was applied. A value of  $p < 0.05$  was accepted as statistically significant.

## RESULTS

In the histopathological evaluation, there was evident mucosal damage and leukocyte clustering in the ileum samples of Group 2 (Fig. 1). The histopathological scores of Group 2



**Figure 1.** (a) Ischaemia-reperfusion group; intense inflammation and neutrophil aggregation in the ileum section, stained with hematoxylin-eosin, 20X, (b) Ischaemia-reperfusion+Selenium injection group; preserved intestine close to normal, 10X.

**Table 1.** Histopathological scores

Groups	Histopathological scores
Control group	2.3±0.13
Ischaemia-reperfusion group	7.2±0.47
Selenium injection group	2.8±1.8
Ischaemia-reperfusion + Selenium injection group	1.6±0.74

were statistically significantly higher than the scores of the other groups ( $p<0.05$ ). The histopathological scores are shown in Table 1.

In the microbiological examination, production was seen in the mesenteric lymph nodes of nine (32.1%) of the 28 subjects. Mesenteric lymph node production was seen in each of the six subjects in Group 2 (100%). There was determined to be statistically significantly more bacterial translocation in the mesenteric lymph nodes of Group 2 than in the other groups ( $p<0.05$ ). The micro-organisms produced were *Escherichia coli* and enterococci. No production was determined in the spleen, and there was production in the liver in two subjects (7.1%) in Group 2, with no statistically significant difference determined between the groups.

The MDA values are shown in Table 2. When the serum, ileum, and liver MDA values were compared, the MDA values in Group 2 were statistically significantly higher than those of the other groups ( $p<0.001$ ).

The liver selenium values in Groups 3 and 4, which received the selenium injections, were 2-fold higher than those of the groups that did not receive the injections. The mean selenium atomic absorption in Groups 1–4 was 865.4, 828.2, 1674.8 and 1661.1 ngSe/g, respectively. The ileum selenium atomic absorption mean values in Groups 3 and 4 were statistically significantly higher than Groups 1 and 2 ( $p<0.001$ ). The ileum selenium atomic absorption mean values in Groups 1–4 were 206.6, 222.2, 301.2 and 303.3 ngSe/g, respectively.

## DISCUSSION

Ischaemia reperfusion damage is the result of blood flow re-starting in tissue that was previously ischaemic, paradoxically causing cell dysfunction and death. I/R damage is not limited to local damage to organs, such as the heart, lungs, kidneys, brain and intestines, but also has the potentially fatal effects of systemic damage in distant organs and multiple organ failure. Although the effects of I/R damage have been shown to have been successfully reduced in experimental animal models, clinical studies have not been as promising.<sup>[31]</sup>

Several studies have shown that oxygen-derived free radicals are the mediators responsible for the reperfusion component in I/R damage.<sup>[3,4,32,33]</sup> With the evident status of the ROS concept and perfusion damage mechanism, the question of how the damage can be prevented has come to prominence. The gastrointestinal system has antioxidant enzymes, which prevent the system that creates ROS. One of these enzymes is GPx, which catalyses ROS destruction. Selenium is a co-factor of this enzyme, and when it is deficient, enzyme activity is reduced.<sup>[34]</sup>

When intestinal I/R damage forms, it has been shown that as a source of gastrointestinal system bacteria and endotoxemia, it may lead to MODS and sepsis.<sup>[35]</sup> Selenium is a basic element in several physiological functions and has an antioxidant effect as a critical co-factor for the function of the glutathione peroxidase enzyme, which plays a role in glutathione oxidation. It has been shown that selenium could be effective in preventing I/R damage in the heart, lungs and kidneys.<sup>[36–38]</sup> Schoenberg et al. showed that mucosal lesions developed with reperfusion two hours after intestinal ischaemia. In that study, it was stated that hypoxia caused mucosal lesions and the intestinal functions deteriorated with reperfusion.<sup>[39]</sup> In an experimental model of ischaemia reperfusion damage, Bauer et al.<sup>[40]</sup> created ischaemia by clamping the superior mesenteric artery in rats. There was determined to be a decrease in mean blood pressure after reperfusion an increase in plasma lactate levels, and a reduction in erythrocyte GPx levels. In the group administered selenium, the decrease in blood pressure and increase in plasma lactate levels were lower, and the

**Table 2.** MDA levels in serum and tissue

Groups	MDA value [Mean±SD (nmol/g)]		
	Serum	Ileum	Liver
Control group	25.6±2.3	14±1	15.6±1.9
Ischaemia-reperfusion group	37±5.2*	20.6±5.9*	25.5±1.7*
Selenium injection group	18.4±4.2	12±2.8	13.5±1
Ischaemia-reperfusion + Selenium injection group	23.6±2.8	15.8±3.5	19.8±2.4
p-value	<0.001	<0.003	<0.001

MDA: Malondialdehyde; SD: Standard deviation.

fall in GPx levels was seen to be less. Akman et al.<sup>[41]</sup> created invagination in an experimental rat model, and reported that selenium prevented the oxidative damage formed in invagination by increasing antioxidant enzyme activity. In another study conducted on rats by Erbil et al.,<sup>[42]</sup> selenium treatment in the ischaemia model created was shown to reduce oxidative stress. Similarly, in a study of cerebral ischaemia by Mehta et al.,<sup>[43]</sup> selenium was shown to have protected mitochondrial function following focal cerebral ischaemia, stimulated mitochondrial biogenesis and reduced infarct volume.

In the current study, while mucosal destruction, separation and loss of mucosa, and leukocyte clustering increased in the I/R group, the appearance of the intestinal mucosa was close to normal in the group administered with selenium, and there was increased selenium atomic absorption in the intestines and liver. The blood, ileum and liver MDA levels in the selenium group were at the same level as those of the control group. These results suggest that selenium assists in the prevention of lipid peroxidation by GPx.

Oztürk et al.<sup>[38]</sup> reported that intraperitoneal selenium supplementation significantly reduced intestinal damage of I/R origin in rats and prevented I/R-related bacterial translocation. I/R damage in the small intestine causes the production of local cytokines and ROS which induce endothelial responses which pull neutrophils in the circulation to the damaged region.<sup>[8,15]</sup> This includes a complex interaction between intestinal wall integrity and bacterial translocation. In a study by Lelli et al.,<sup>[44]</sup> iron deferoxamine, which is an antioxidant like selenium, was used to limit lipid peroxidation mediated by specific oxidant to the organ in post-chemical injuries to the intestines in neonatal rats. Albrecht et al.<sup>[45]</sup> suggested that peroxynitrite could be directly neutralised by selenium. It was shown in their study that pre-treatment with selenium protected intestinal integrity and reduced bacterial translocation with a mechanism probably started by preventing lipid peroxidation after I/R. In the current study, the bacterial translocation that occurred following the failure of the barrier in the intestine was significantly reduced in the mesenteric lymph nodes in the group that received selenium.

In conclusion, the results of this study of ischaemia-reperfusion damage in the intestines showed that selenium reduced MDA levels, and the mucosal damage developing associated with I/R damage and thereby reduced bacterial translocation.

**Ethics Committee Approval:** Approval for this study was granted from local ethics committee in Feb 2003 (reg: 821).

**Peer-review:** Internally peer-reviewed.

**Authorship Contributions:** Concept: İ.Ö., E.Y.; Design: E.Y.; Supervision: E.Y., İ.Ö.; Materials: E.Y., H.Ö.; Data: E.Y., H.Ö.; Analysis: E.Y., T.Y.; Literature search: E.Y., A.K., Writing: E.Y.; Critical revision: E.Y., H.Ö., İ.Ö.

**Conflict of Interest:** None declared.

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## DENEYSEL ÇALIŞMA - ÖZ

### Deneysel intestinal iskemi-reperfüzyon modelinde selenyum tedavisinin bakteriyel translokasyon ve doku hasarı üzerinde etkileri

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**AMAÇ:** İntestinal iskemi sonrası reperfüzyon gerçekleşmesi ile oluşan serbest oksijen radikalleri hücre için son derece toksiktir. Glutatyon peroksidaz ise reaktif oksijen türlerinin oluşumunu engelleyen önemli enzimlerdendir ve kofaktör olarak selenyuma ihtiyaç duyar. Çalışmamızın amacı selenyum uygulamasının iskemi-reperfüzyon hasarını azaltıcı etkisini göstermektir.

**GEREÇ VE YÖNTEM:** Çalışmada 28 adet erkek Wistar sıçan kullanıldı. Denekler dört gruba ayrıldı. Üçüncü ve dördüncü gruba beş gün süre ile 10 mikrogram/kg/gün sodyum selenat intraperitoneal olarak verildi. Birinci ve üçüncü grup deneklere laparotomi yapıldı, ikinci ve dördüncü gruptaki deneklere ise laparotomi sonrası superiyor mezenterik arter 45 dakika klempe edilip iskemi oluşturuldu, ardından 90 dakika reperfüzyon sağlandı. Deneklerden malondialdehit için kan, karaciğer ve ileum örneği alındı. Bakteriyel translokasyon için karaciğer, dalak ve mezenterik lenf nodu doku örnekleri alındı, ayrıca ileumdan alınan örnek ile histopatolojik inceleme yapıldı.

**BULGULAR:** İskemi-reperfüzyon grubunda mezenterik lenf nodlarında bakteriyel translokasyon diğer gruplardan anlamlı derecede fazla idi ( $p < 0.05$ ). Histopatolojik değerlendirmelere bakıldığında yine iskemi-reperfüzyon grubunda skor diğer gruplardan anlamlı derecede yüksekti ( $p < 0.05$ ). Serum, karaciğer ve ileum malondialdehit düzeyleri de iskemi-reperfüzyon grubundaki yüksekliğe bağlı olarak gruplar arasında anlamlı farklılık gösterdi ( $p < 0.05$ ).

**TARTIŞMA:** Çalışmamız selenyumun serum ve doku MDA düzeylerini düşürdüğü, bağırsaklarda iskemi-reperfüzyon hasarı ile gelişen histopatolojik hasarı ve buna bağlı bakteriyel translokasyonu azalttığı göstermiştir.

**Anahtar sözcükler:** Bakteriyel translokasyon; ileum; İskemi; reperfüzyon; selenyum.

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