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ARAŞTIRMA / RESEARCH

Ileal interposition reduces oxidative stress via oxidant-antioxidant enzymes in rats with metabolic syndrome

İleal interpozisyon, metabolik sendromlu sıçanlarda oksidan-antioksidan enzimler yoluyla oksidatif stresi azaltır

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Abstract

Purpose: This study aims to examine the effect of ileal transposition (IT) on plasma levels of the total antioxidant status (TAS), total oxidant status (TOS), Oxidative Stress Index (OSI), Superoxide dismutase (SOD), Nicotinamide adenine dinucleotide phosphate oxidase (NOX), Catalase (CAT), Reduced Glutathione (GSH) in both rats with Metabolic syndrome (MetS) and healthy controls.

Materials and Methods: In the MetS model, newborn male Wistar albino rats were given MSG (4 g/mg) on days 0, 2, 4, 6, 8, and 10. The control group was injected only saline. In the 5th month, sham and IT animals underwent selected surgery. 2 months after surgery TOS, TAS, OSI, SOD, NOX, CAT, and GSH levels were assessed in the plasma.

Results: IT procedure significantly increased SOD and CAT levels in MetS + IT group when compared to the MetS group (SOD; MetS 1.75 ± 0.04, MetS+IT 2.1 ± 0.15, CAT; MetS 32.02 ± 1.73, MetS+IT 41.64 ± 1.18,). As expected, while GSH levels was increased in MetS+IT rats compared to MetS rats, but the difference was not significant (MetS 243.31 ± 6.36, MetS+IT 269.76 ± 9.17). The NOX activity was significantly lower in MetS+IT group than MetS and MetS+S groups (MetS 610.35 ± 26.25, MetS+IT 348.86 ± 14.12).

Conclusion: These data revealed the healing effect of IT surgery against oxidative stress associated with MetS. The available data endorses IT surgery as an effective strategy to reduce oxidative damage in rats with MetS by modulating systemic oxidant and antioxidant responses.

Keywords:. Metabolic syndrome, ileal interposition, oxidative stress, monosodium glutamate

Öz

Amaç: Bu çalışmanın amacı ileal transpozisyonun (IT) hem metabolik sendrom (MetS) sıçanları hem de sağlıklı kontrollerdeki toplam antioksidan durum (TAS), toplam oksidan durum (TOS), Oksidatif Stres İndeksi (OSI), Süperoksit dismutaz (SOD), Nikotinamid adenin dinükleotid fosfat oksidaz (NOX), Katalaz (CAT), İndirgenmiş Glutatyon (GSH)'un plazma seviyeleri üzerindeki etkisini incelemektir.

Gereç ve Yöntem: MetS modeline göre, yeni doğan erkek Wistar albino sıçanlara 0, 2, 4, 6, 8 ve 10. günlerde monosodyum glutamat (MSG) (4 mg/g) verildi. Kontrol grubuna sadece salin enjekte edildi. 5. ayda sham ve IT hayvanlara seçilmiş cerrahi uygulandı. Ameliyattan 2 ay sonra plazmada TOS, TAS, OSI, SOD, NOX, CAT, GSH seviyeleri değerlendirildi.

Bulgular: IT prosedürü MetS + IT grubunda MetS grubuna kıyasla SOD ve CAT düzeylerini önemli ölçüde artırdı (SOD; MetS 1.75 ± 0.04, MetS+IT 2.1 ± 0.15, CAT; MetS 32.02 ± 1.73, MetS+IT 41.64 ± 1.18). Beklendiği gibi, MetS+IT sıçanlarda MetS sıçanlara göre GSH seviyeleri artarken, aradaki fark anlamlı değildi (MetS 243.31 ± 6.36, MetS+IT 269.76 ± 9.17). NOX aktivitesi MetS+IT grubunda MetS ve MetS+S gruplarına göre anlamlı derecede düşüktü (MetS 610.35 ± 26.25, MetS+IT 348.86 ± 14.12).

Sonuç: Bu veriler, IT cerrahisinin MetS ile ilişkili oksidatif strese karşı iyileştirici etkisini ortaya koydu. Mevcut veriler, sistemik oksidan ve antioksidan yanıtları modüle ederek MetS'li sıçanlarda oksidatif hasarı azaltmak için IT cerrahisini etkili bir strateji olarak desteklemektedir.

Anahtar kelimeler: Metabolik sendrom, ileal interpozisyon, oksidatif stres, monosodyum glutamat

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INTRODUCTION

Metabolic syndrome (MetS) is a co-occurrence of abdominal obesity, increased fasting blood sugar, insulin resistance, atherogenic dyslipidemia, and hypertension[1]. According to the National Cholesterol Education Program Adult Treatment Panel III definition, defined as the presence of at least three of the five risk factors[2]. The development of MetS is not fully understood, but there are several hypothesized mechanisms for the underlying pathophysiology of MetS. The most widely accepted of these are insulin resistance, obesity, low-grade chronic inflammation, and oxidative stress[3].

Recent studies emphasize the critical role of oxidative stress in the development of obesity and its metabolic complications[4]. In addition, accumulation of excessive free fatty acid (FFA) in adipocytes leads to activation of nicotinamide adenine dinucleotide phosphate oxidase (NOX) enzyme and generation of excessive reactive oxygen species (ROS). Reported results support the concept that increased oxidative stress may play an important role in MetS-related manifestations, including atherosclerosis, hypertension, and diabetes mellitus[5]. Oxidative stress is associated with adiposity, and insulin resistance in individuals with MetS, suggesting that ROS production could be an early event in the pathology of chronic diseases[6].

Oxidative stress referred to as a ROS-antioxidant imbalance, occurs when the total amount of ROS exceeds the antioxidant capacity. It was shown that protein/lipid oxidation products are very cytotoxic, leading to damage of cellular macromolecules and affecting cellular functions and viability[7,8]. Therefore, several antioxidant systems protect cells against oxidative stress. Antioxidants not only inhibit ROS-induced oxidation but also repair some forms of oxidative modification in biomolecules. The most important blood antioxidants include (superoxide dismutase) SOD, catalase (CAT), glutathione peroxidase (GPx), glutathione reductase (GR), and glutathione (GSH)[9].

Recently, the digestive system is an important subject of research on MetS pathogenesis and the development of new treatment methods[10-13]. Ileal transposition (IT) is an effective metabolic surgery procedure. IT is recommended to treat comorbid conditions related to morbid obesity[14,15]. Its main benefits to patients are early satiety center stimulation and healing of the MetS parameters with the effective decrease in the excess weight[16]. However, the exact reason for these changes is still unknown. It is postulated that the improvement of obese patients is associated with the reduction of oxidative stress levels[17,18].

In recent years, oxidative stress has been intensively investigated and provided important mechanistic insights into the pathogenesis of MetS[19]. Despite the well-known positive effects, there is insufficient information about the effects of IT on MetS. Therefore, in the present study, we sought to investigate the influence of IT procedure on the oxidant-antioxidant activity in MetS-induced rats. For this purpose, we examined total oxidant status (TOS), total antioxidant status (TAS), oxidative stress index (OSI), and other oxidative stress markers such as SOD, NOX, CAT, and GSH in MetS-induced rats and compared them to healthy controls. Additionally, the primary goal of this process is to alleviate oxidative stress by lowering oxidants and raising antioxidant levels in response to the IT metabolic processes.

MATERIALS AND METHODS

Animals

Procedures and animal care were performed according to the guidelines of the Animal Care and Use Committee of the Pamukkale University (PAUHADYEK-2017/16). Animals were housed in groups of four to five rats in stainless-steel cages in standard conditions (24±2°C and 50±5% humidity) with a 12-h light-dark cycle and fed ad libitum with food and tap water.

Experiment design

Twenty-six Wistar albino newborn male rats were used throughout all experiments. The animals were divided into two groups: a control group (C) (5 animals) and a metabolic syndrome group (MetS) (21 animals). MetS were produced in rats by neonatally the administration of the monosodium glutamate (MSG) (4 mg/g body weight, s.c., Sigma) via subcutaneous injection during the first 0, 2, 4, 6, 8, 10 days of life. For the C group was injected with saline solution (0.9% NaCl, 0.1 ml/g body weight) on the same days. After the animals were weaned on the 21st postnatal day, they were kept in their cages for 5

months for Mets development. At the end of 5 months, MetS were confirmed to have developed in the rats given MSG by measuring oral glucose tolerance tests (OGTT), fasting plasma insulin, triglyceride (TG), total cholesterol (TCHOL), high-density lipoprotein (HDL) levels, Lee index, and homeostatic model assessment for insulin resistance (HOMA-IR) score. These Mets confirmation results were shared with the scientific community in a previous study by our group[20].

Surgical procedures

At this stage, we underwent IT surgery as a metabolic surgery on rats with MetS. The MetS rats were assigned to three experimental groups: metabolic syndrome group; MetS (n=7), sham group; MetS+Sham (MetS+S) (n=7), and ileal transposition group; MetS+IT (n=7). Rats undergoing surgery have fasted for 12 hours. Rats were fed a liquid diet 3 days before the surgical procedure and 15 days after the surgeries. Anesthetic induction and maintenance were performed with sevoflurane (2–5%). A midline abdominal incision was performed, and a segment of the ileum (~15 cm) 10 cm proximal to the ileocecal valve was transected. The ends of the ileum were anastomosed using a 7-0 polydioxanone. The isolated ileal transaction was then interposed 5 cm distal to the ligament of treitz with its vasculature supply. Rats that underwent sham surgery were subjected to the same protocol; however, transactions made in the identical location were anastomosed in their original position without translocation. After the operation, all rats were given analgesic (Anaflex 0.5%) and antibiotics (Baytril-K, 5%) intraperitoneally for five days.

Plasma biochemical parameters

In the 2nd month after metabolic surgery, animals have fasted overnight for the blood draw. Blood was collected from the tail. The levels of fasting plasma SOD (Cat. No #YLA0115RA), NOX (Cat. No #YLA01501RA), GSH (Cat. No #YLA0121RA), CAT (Cat. No #YLA0123RA) were determined by commercial kits (Cat. No E-BC- K238,109; Cat. No YLA0495RA). Plasma TAS and TOS were determined with kits (Rel Assay Diagnostics kit; Turkey) developed by Erel and OSI values were calculated. Plasma TAS levels were determined using a novel automated measurement method, developed by Erel. In this method, the antioxidative effect of the sample against the potent free radical reactions, which are initiated by the produced hydroxyl radical, is measured. The results are expressed as μmol Trolox Eq/L[21]. Plasma TOS values were determined using a novel automated measurement method, such as TAS, developed by Erel. The color intensity, which can be measured spectrophotometrically, is related to the total amount of oxidant molecules present in the sample. The assay is calibrated with hydrogen peroxide (H_2O_2) and the results are expressed in terms of micromolar hydrogen peroxide equivalent per liter (μmol H2O2 Eq/L). The OSI was defined as the ratio of the TOS level to the TAS level. Specifically, OSI (arbitrary unit) = TOS (μmol H2O2 Eq/L)/TAS (μmol Trolox Eq/L)[22].

Statistical analysis

The data were analyzed with the software package SPSS 25.0. Continuous variables are expressed as the mean ± standard error (SEM). The Shapiro-Wilk test was used to determine whether the data had a normal distribution. For parametric tests, we used a one-way analysis of variance (Tukey test for post-hoc examinations) (TOS, TAS, NOX). For non-parametric tests, we used Kruskal-Wallis variance analysis (Bonferroni-corrected Mann-Whitney U test for post-hoc examinations) (OSI, GSH, CAT, SOD). In all analyses, $p<0.05$ was considered statistically significant. According to the reference study results, they had a large effect size for Total SOD results (d=11.1). We planned our study for four groups and a four-group comparison large effect size value (f=0.6), a power analysis was performed before the study. Accordingly, when at least 24 rats (at least 6 rats for each group) were included in the study, that would result in 80% power with a 95% confidence level.

RESULTS

According to our results, the MetS increased significantly the TOS amount in comparison to the C group (C 1.27 ± 0.09, MetS 3.62 ± 0.12, $p<0.001$). MetS+IT group showed a lower TOS levels compared to MetS (MetS+IT 1.15 ± 0.14, $p<0.001$) and MetS+S group (MetS+S 1.58 ± 0.02, $p<0.05$) (Figure 1). The TAS were comparable in groups C, MetS, MetS+S, and MetS+IT, whereas there was no significant difference between C and MetS groups (C 2.46 ± 0.08, MetS 2.23 ± 0.03, $p>0.05$). MetS+IT rats had significantly higher levels of TAS than MetS+S animals (MetS+IT 1.97 ± 0.005, MetS+S 1.16 ± 0.09) (Figure 2). The OSI was defined as the ratio of the

TOS level to TAS level. Specifically, OSI (arbitrary unit) = TOS (µmol H2O2 Eq/L) / TAS (µmol Trolox Eq/L). The C and MetS+IT groups showed a significantly lower OSI amount assessed in the plasma than MetS and MetS+S animals (C 0.052 ± 0.004, MetS 0.163 ± 0.006, MetS+S 0.147 ± 0.014, MetS+IT 0.058 ± 0.007, p<0.001) (Figure 3).

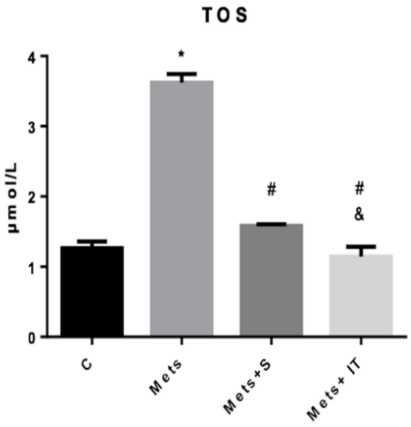

Figure 1. Effect of ileal transposition and sham operations on TOS.

Data are the means ± SEM (p<0.05). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group and &indicates groups that differ from S group; C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

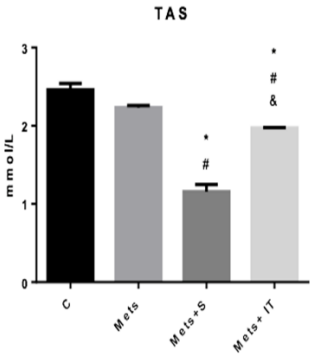

Figure 2. Effect of ileal transposition and sham operations on TAS.

Data are the means ± SEM (p<0.05). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group and &indicates groups that differ from S group; C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

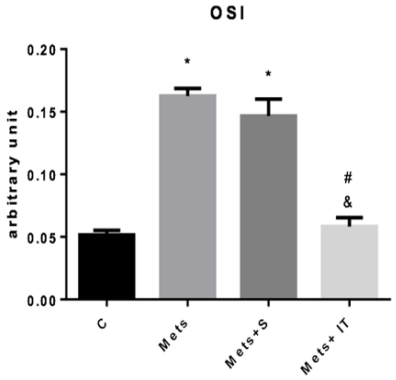

Figure 3. Effect of ileal transposition and sham operations on OSI.

Data are the means ± SEM (p<0.05). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group and &indicates groups that differ from S group; C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

In present study, the activity of plasma SOD and CAT was significantly decreased in MetS group compared to C group (p<0.001). Moreover, MetS+IT, MetS+Sham rats had significantly higher plasma SOD and CAT levels than MetS rats (SOD; MetS 1.75 ± 0.04, MetS+IT 2.1 ± 0.15, p<0.05, CAT; MetS 32.02 ± 1.73 MetS+IT 41.64 ± 1.18, p<0.001) (Figure 4 and 5 respectively).

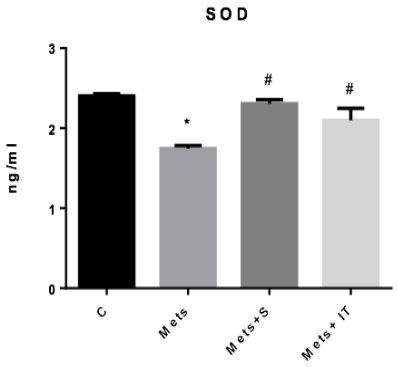

Figure 4. Effect of ileal transposition and sham operations on plasma SOX status.

Data are the means ± SEM (p<0.05). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group, C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

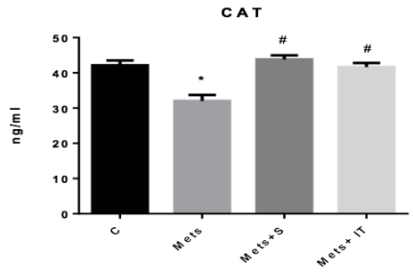

Figure 5. Effect of ileal transposition and sham operations on plasma CAT status.

Data are the means ± SEM ($p<0.05$). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group, C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

It is found that GSH decreased significantly as a result of MetS (C 288.98 ± 5.4, MetS 243.31 ± 6.36, $p<0.01$). In addition, the increase in GSH level was observed in MetS animals undergoing IT operation (MetS+IT 269.76 ± 9.17). But this increase did not reach a statistically significant level (Figure 6). In our study, we observed that significantly increased in MetS group NOX levels compared to C (C 424.38 ± 23.99, MetS 610.35 ± 26.25, $p<0.001$). On the other hand, IT operation significantly inhibited the increase in NOX enzyme caused by Mets (MetS+IT 348.86 ± 14.12, $p<0.001$) (Figure 7).

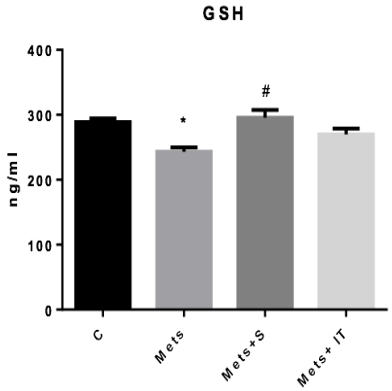

Figure 6. Effect of ileal transposition and sham operations on plasma GSH status.

Data are the means ± SEM ($p<0.05$). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group, C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

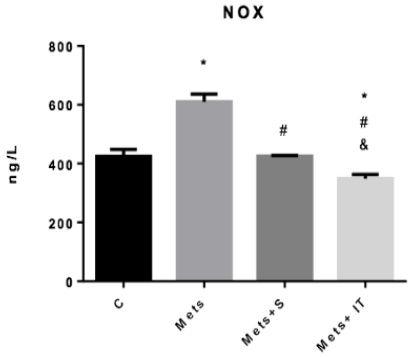

Figure 7. Effect of ileal transposition and sham operations on plasma NOX status.

Data are the means ± SEM ($p<0.05$). The letters over the bars represent significant differences. *indicates groups that differ from C group, #indicates groups that differ from MetS group and ampersand indicates groups that differ from S group; C: control, (n = 5); MetS: metabolic syndrome, (n = 7); S: sham, (n = 7); IT: ileal transposition, (n = 7).

DISCUSSION

The results of the present study indicate that there is a marked effect of IT metabolic surgery on oxidant-antioxidant levels in rats with MetS. We demonstrated the effects of IT on plasma oxidative stress levels. The obtained results in our study show that IT surgery reduced oxidative stress index in rats with MetS. Also, there is a marked stimulating effect of IT surgery on various antioxidant enzyme activities and has a significant inhibitory effect on the oxidant enzyme NOX activity in MetS rats.

MSG creates a neurotoxic effect in the brain and causes damage to the hypothalamus, especially neurons in the arcuate nucleus[23]. Decreased release of damage-induced growth hormone-releasing hormone causes impaired pulsatile growth hormone secretion from the anterior pituitary[24]. Therefore, MSG-treated animals were shorter and lighter compared to healthy animals[25]. As a result, MSG injection affects energy balance and fat metabolism in animals[26,27]. Furthermore, MSG-injected animals develop obesity, which becomes apparent at eight weeks of age and gets worse with time. TG level, insulin resistance, and inflammatory conditions in animals increase as a result of degeneration caused by MSG[28].

Oxidative stress is induced by pathophysiological conditions such as overweight, T2DM, cardiovascular disease, and atherogenic processes[29,30].

Human studies proved the correlation between visceral fat accumulation and the enhanced oxidative status[31,32]. Metabolic surgery is currently one of the leading treatment options for morbid obesity, giving efficient and long-lasting results in weight loss and glycemic control[33,34]. Literature data unequivocally show that metabolic surgery leads to a marked reduction in adipose tissue mass, followed by an improvement in systemic inflammation[35]. Human studies have found that oxidative stress was significantly reduced 6 months after metabolic surgery[36,37]. Our study provides an understanding of the balance between oxidative stress and antioxidant/oxidant enzymes 2 months after surgery as a response to IT and sham surgical procedures. In this study, while total oxidant capacity increased as a result of MetS, IT surgery significantly decreased this effect on TOS levels. IT operation inhibited the OSI in MetS rats compared to MetS and MetS+S groups. This result fosters evidence proposing that reduced oxidative stress after the IT procedure may be the main contributor to ameliorating insulin resistance and obesity conditions. Reduced ROS content in IT-operated Mets rats probably results from the increased scavenging of free radicals and other toxic species by the antioxidant enzymes. We believe that the IT procedure showed a beneficial effect on the TOS amount in comparison to the sham. The sham operation, which is a surgical method without therapeutic consequences, results in elevated stress conditions. Interestingly, we noticed effects in the S group that was comparable to the effect of IT surgery on TOS level. These findings indicate that a sham procedure performed alone may have some beneficial benefits on TOS levels in particular. Werner et al. confirmed this discovery by seeing substantial effects of sham surgery in rats and hypothesizing that this effect may be a result of surgical stress[38]. Although the TAS level was found to be significantly lower in the sham group than in the control, IT was found to reverse this decrease in the sham group. TAS reduction in the sham group can be considered an effect of surgery alone. It can be thought that the reversal of this decrease by IT surgery may be an effect of metabolic surgery.

Under the conditions of long persisting obesity, the pool of antioxidant sources can be diminished, further affecting the activity of enzymes such as superoxide dismutase (SOD). In this study, which is an animal model of obesity, the SOD levels measured in the MetS group were significantly decreased in comparison to the C group. In human subjects, the activity of SOD in obese individuals was significantly reduced in comparison to that in healthy subjects, intensifying the development of obesity-related health problems. Increased SOD activity with IT surgery is a compensatory factor of elevated oxidative stress resulting from MetS. This result suggests that the increase in SOD activity has an important role in reducing oxidative stress. There was a significant increase in CAT enzymatic activity in IT-operated animals. This can be a positive effect of the IT surgery on the CAT-related anti-oxidative defense system. It was reported that increased adipose tissue can inhibit the CAT activity[29]. It is suggested that long-term effects of metabolic surgery such as reduction in adipose tissue mass may control the antioxidant response. Previous studies have reported an impairment of the main antioxidant systems in morbid obesity, including SOD, and GPX[39,40], which are considered the front line of enzymatic ROS scavenging. In this study, the GSH level was non-significantly increased in MetS animals undergoing IT operation. IT surgery may reduce oxidative stress by triggering ROS-sensitive glutathione metabolism. It is essential to indicate that an increase in total SOD, CAT, and GSH activities after metabolic surgery can be related to the reduction of adipose tissue. Obesity has been associated with increased expression of NADPH oxidase and a reduction in the expression of several antioxidant proteins[37]. In line with these data, in this study, we observed a decrease in NOX activity in MetS rats after IT surgery. To conclude, metabolic surgery is an effective strategy for bodyweight reduction and recovery from metabolic diseases in obese subjects. These results are in line with several studies that have demonstrated that metabolic surgery can effectively and safely control diabetes in the short term and long term and even prevent its occurrence[41,42].

This study also has its limitations. The low number of animals is one of the most important limitations of the study. In addition, the fact that the endogenous antioxidant (Glutathione peroxidase and Glutathione reductase) levels were not determined is a limitation of the study. Another limitation is that detailed molecular analyzes could not be performed due to financial insufficiency. For example, measurement of blood pressure, which is a metabolic syndrome parameter, and further determination of oxidative stress could not be made.

We conclude that the IT procedure had a positive impact on the reduction of oxidative stress, measured

by TOS and OSI parameters in the plasma of MetS rats. The protective mechanisms of enzymatic antioxidant systems were observed after the IT surgery. In summary, IT surgery has reversible effects on augmented oxidant stress in rats with MetS. Studies investigating the effects of IT on the oxidant-antioxidant system should be continued using different study methods. In addition, after metabolic surgery, oxidative stress parameters can be evaluated at different experimental times and the appropriate time can be determined. This is a conclusion that needs further work to elucidate the mechanisms of these observations. The present study is thought to be a guide for future studies.

Yazar Katkıları: Çalışma konsepti/Tasarımı: VK, MTA; Veri toplama: MTA, AÇD; Veri analizi ve yorumlama: VK, ÖD; Yazı taslağı: MTA, VK, İHA; İçeriğin eleştirel incelenmesi: AÇD, ÖD; Son onay ve sorumluluk: MTA, EÇD, BÖD, İHB, VK; Teknik ve malzeme desteği: MTA, VK; Süpervizyon: VK; Fon sağlama (mevcut ise): yok.
Etik Onay: Bu çalışma için Pamukkale Universitesi Tıp Fakültesi Klinik Araştırmalar Etik Kurulundan 24/08/2021 tarih ve 2021/07 sayılı toplantıda görüşülmüş ve E-60758568-020-93115 sayılı kararla etik onayı alınmıştır.
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Author Contributions: Concept/Design : VK, MTA; Data acquisition: MTA, AÇD; Data analysis and interpretation: VK, ÖD; Drafting manuscript: MTA, VK, İHA; Critical revision of manuscript: AÇD, ÖD; Final approval and accountability: MTA, EÇD, BÖD, İHB, VK; Technical or material support: MTA, VK; Supervision: VK; Securing funding (if available): n/a.
Ethical Approval: This study was discussed at the Pamukkale University Faculty of Medicine Clinical Research Ethics Committee at the meeting dated 24/08/2021 and numbered 2021/07 and ethical approval was obtained with the decision numbered E-60758568-020-93115.
Peer-review: Externally peer-reviewed.
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