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The Evaluation of Oxidative Stress and Lipid Peroxidation Status in Experimental Pancreatitis

Deneysel Pankreatitte Oksidatif Stres ve Lipid Peroksidasyon Durumunun Değerlendirilmesi

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ABSTRACT

Aim: Currently, acute pancreatitis pathogenesis remains a matter of debate. Our study aims to investigate the oxidative stress and lipid peroxidation state in taurocholate-induced acute pancreatitis, and we used oxidized LDL as a biomarker of oxidative stress.

Material and Methods: We used twenty-six Wistar albino rats divided into four groups. Sham-operated rats, control group (group 1), and experimental group with sodium taurocholate-induced acute pancreatitis; were sacrificed at 24 hours (group 2), 48 hours (group 3), and 72 hours (group 4). We evaluated pancreatic tissue malondialdehyde (MDA) levels as an indicator of lipid peroxidation. Then, using the immunofluorescence staining, we determined the presence of ox-LDL in pancreatic tissues, which we used to compare the histopathological analysis of pancreatitis.

Results: We found that MDA levels in pancreatic tissue and serum amylase, ALT, and AST were significantly higher in groups 2, 3, and 4. Histopathological findings of groups 2, 3, and 4 were compatible with pancreatitis, and we encountered the level of ox-LDL accumulation. We found acorrelation between the level of ox-LDL accumulation in pancreatic tissue and the severity of pancreatitis in groups 2, 3, and 4.

Conclusion: This study demonstrates the accumulation of ox-LDL molecules in pancreatic tissue in a taurocholate-induced acute pancreatitis model. According to these byproducts, including ox-LDL, we conceive that treatment modalities might have beneficial effects in improving not only local but systemic complications of acute pancreatitis.

Keywords: Experimental pancreatitis, Oxidative stress, Lipid peroxidation, Oxidized low-density lipoprotein, Malondialdehyde

ÖZ

Amaç: Günümüzde,halenakut pankreatitpatogenezi tartışma konusu olmaya devam etmektedir. Çalışmamız, taurokolataile oluşturulan deneysel akut pankreatit modelinde oksidatif stres ve lipidperoksidasyon durumunu araştırmayı amaçlamaktadır. Araştırmamızda oksidatif stresin biyobelirteçi olarak, okside LDL'yi kullandık.

Gereç ve Yöntemler: Çalışmamızda dört gruba ayrılmış yirmi altı Wistar albino sıçan kullandık. Sham gurubu, kontrol grubu (grup 1) ve sodyum taurokolata ile akut pankreatit oluşturulan deney

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grubu; 24. saatte (grup 2), 48. saatte (grup 3) ve 72. saatte (grup 4) sakrifiye edildi. Pankreas dokusu malondialdehit (MDA) düzeylerini lipidperoksidasyonunun bir göstergesi olarak değerlendirdik. İmmünofloresan boyama kullanarak pankreas dokularında ox-LDL varlığını belirledik ve pankreas dokularının histopatolojik analizi ile karşılaştırdık.

Bulgular: Pankreas dokusunda MDA ve serum amilaz, ALT ve AST düzeylerinin grup 2, 3 ve 4'te anlamlı olarak yüksek olduğunu ve histopatolojik bulgularının da pankreatit ile uyumlu olduğunu gördük. Histopatolojik bulgular ile ox-LDL birikim düzeyini karşılaştırdık ve Grup 2, 3 ve 4'te pankreas dokusunda ox-LDL birikimi düzeyi ile pankreatit şiddeti arasında paralellik bulduk.

Sonuç: Bu çalışma, taurokolata bağlı akut pankreatit modelinde pankreas dokusunda ox-LDL moleküllerinin birikimini göstermektedir. Ox-LDL dahil olmak üzere bu yan ürünlere göre, tedavi modalitelerinin akut pankreatitinlokal değil sistemik komplikasyonlarını iyileştirmede faydalı etkileri olabileceğini düşünüyoruz.

Anahtar Sözcükler: Deneysel pankreatit, Oksidatif stres, Lipidperoksidasyonu, Okside düşük, Malondialdehit

INTRODUCTION

Acute pancreatitis is an inflammatory process and may lead to a severe systemic inflammatory response. While a wide variety of stimuli initiates acute pancreatitis, the majority of the fundamental mechanisms underlying the inflammatory state are unknown. The most common causes are gallstones and alcohol misuse (1, 2). Other infrequent causes of AP include endoscopic retrograde cholangiopancreatography (ERCP), drug therapy, infection, hypercalcemia, hypertriglyceridemia, tumors, vascular abnormalities, and abdominal trauma (1). Acinar cell damage, interstitial edema, hemorrhage, and necrosis are seen in AP and vary in proportion to the severity of the disease (3). In addition, many factors such as ischemia, pancreatic enzyme self-digestion, complement activation, cytokines, and oxygen-free radicals are thought to play a role in the pathogenesis of AP. However, it is still unclear how these factors play a crucial role in the development of the disease (4). Among these factors, oxidative stress is considered a significant mediator in triggering the systemic inflammatory response syndrome at the early stages of AP (5).

Oxidative stress results from the deterioration of the oxidative balance due to the increase of reactive oxygen species (ROS) formed during cellular metabolism and the insufficiency of antioxidants to detoxify ROS (6). Excessive ROS production leads to lipid peroxidation, impairing cellular membrane integrity, signal transduction, and cell viability. Accordingly, the evaluation of lipid peroxidation in mitochondria, cells, and tissues provides some explanation of the extent of oxidative stress in the cell (7). Oxidized low-density lipoprotein (ox-LDL) is an early product of lipid peroxidation, and it is known as the antigenic element in atherosclerosis (8). Moreover, ox-LDL has been proposed to play an essential role in inflammatory processes and fibrogenesis (9). Modified LDL is formed due to the oxidation of low-density lipoproteins (LDL).

This study investigates the relationship between pancreatitis severity and changes in histopathology based on the accumulation of ox-LDL. On the other hand, another aim of the study is to examine whether this ox-LDL in pancreatic tissue has an essential role in the immunological and inflammatory events of experimental pancreatitis.

MATERIAL and METHODS

Experimental Design

This study has been performed under the ethical standards in the 1964 Declaration of Helsinki, and its later amendments are approved by the Ethics Review Board (protocol no: 2021/5-7).

An experimental investigation was conducted using Wistar albino rats weighing 200-230 gr (Experimental Medical Research Laboratory of Zonguldak Bulent Ecevit University). We created three experimental groups, each consisting of seven rats and a control group composed of five rats in the study. The sterile conditions were created by following the principles of asepsis and antisepsis. For anesthesia, intraperitoneal ketamine-HCl (Ketalar-Parke Davis, Morris Plains, NJ, USA) at a dose of 50 mg/kg was used. The Taurocholate Induced Pancreatit model described by Wittel et al. was applied to create Pancreatitis (10). The duodenum was exposed with a 12 mm midline incision. After puncturing the duodenum wall with a 24 gauge catheter (Novacath, Medipro A.Ş, Istanbul, Turkey), we advanced the catheter 5 mm from the papilla Vateri to the Common canal (Figure 1). We induced AP by retrograde infusion of freshly prepared taurocholic acid (Sigma, # T-9034) by dissolving 5% concentration in physiological saline. Afterward, this prepared solution was injected into the common bile duct by infusion at 25-30 mmHg pressure and a 1 ml/min rate, depending on the infusion pump. The central hepatic duct just below the liver was clamped during the intraductal infusion period to prevent leakage into the biliary system. All experimental group rats underwent the same surgical procedure by the same surgeon. All methods described above were performed in the same fashion in the sham group but were given the same amount of saline (0.9% NaCl) instead of taurocholic acid. After the procedure, we closed the midline incisions using 3/0 polypropylene sutures and left the rats in their cages with water and food. The sacrification was initiated at 24, 48, and 72 hours after induction of AP

in experimental Groups-2 (24 hours), Groups-3 (48 hours), and Groups-4 (72 hours), respectively. The blood and pancreatic tissue samples were excised for biochemical and pathological evaluation.

Blood Biochemistry

Serum activity levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), and amylase were performed with available kits on Advia 2400 automated analyzer (Siemens Healthcare Diagnostics, Tarrytown, New York, USA).

Histopathologic Analysis

10% formalin solution was used to fix pancreatic tissue samples and embedded them in paraffin to make them suitable for sectioning. Afterward, we took sections with cuts made at five µm intervals. The hematoxylin and eosin staining was used for the sections, and finally, these sections were examined under a light microscope by an independent observer unaware of the study. The point counting techniques carried out for themorphometric analysis of the histological sections obtained from the study. Pancreatic sections were evaluated for parenchymal hemorrhage, edema, parenchymal and perivascular inflammation, fat necrosis, and acinar necrosis, as described by Schmidt et al. (11).

Immunofluorescent Staining Method

The presence of ox-LDL in the pancreas tissue sections of the operated rats was evaluated using the immunofluorescent staining method. Sections of 7-micron thickness were prepared from pancreatic tissue stored in a deep freezer at -80°C. We randomly selected the sections obtained in the study and divided them into a test group and a negative control group. Thirty microliters of Human polyclonal anti-oxLDL immunoglobulin (Ig) G (IMMCO Diagnostics, New York, NY, USA) was added to sections in the test group, and we applied phosphate-buffered solution (PBS) to the sections in the negative control group. After a 30-minute incubation period, control and test sections were washed with PBS at room temperature. Then, 30 mL of fluorescent isothiocyanate-labeled antihuman IgG was applied as a conjugate substance. Sections were left at room temperature for an additional 30 minutes, washed with standard phosphate-buffered saline solution, and left to dry. A fluorescent microscope (Leica DMRX, Wetzlar, Germany) was used for examination.

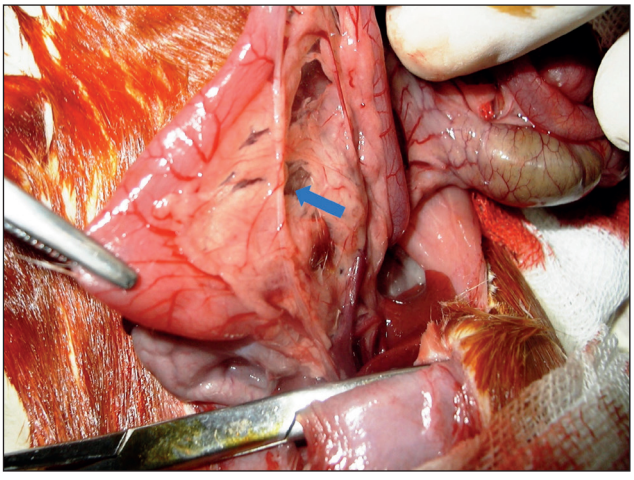

Figure 1: The canulization of the common duct through the papilla Vateri to induce AP by retrograde infusion of taurocholic acid.

Tissue Malondialdehyde Measurement

In the presented study, to measure MDA levels in pancreatic tissue, we took the model described by Uchiyama and Mihara as a basis and made measurements and evaluations by this model (12).

Statistical Analysis

The IBM SPSS Version 20.0 package program was performed for data analysis in our study. The data obtained was evaluated via the Kolmogorov-Smirnov test to conform to the normal distribution. The descriptive statistics were presented with median and interquartile range (IQR) values and Kruskal Wallis test was used to compare the four groups. On the other hand, we used the Mann-Whitney U test to compare the two groups. The results were given at a 95% confidence interval and $p<0.05$ was accepted as a significant difference.

RESULTS

No deaths were observed. Pancreatic tissue MDA levels were evaluated according to the model described by Uchiyama and Mihara. When the control group and other groups were compared in terms of pancreatic tissue MDA level, we observed that the MDA level in groups 2, 3, and 4 was significantly higher than the control group (group 1), as shown in Figure 2 according to the data obtained ($p<0.05$). In the study, we measured serum ALT, AST, and amylase levels in the experimental groups (groups 2, 3, and 4) and the control group (group 1) and compared the results. We observed that serum amylase, ALT, and AST levels in the experimental group increased significantly compared to the control group (Table 1, $p<0.05$). We did not detect significant positive immunofluorescent staining for ox-LDL in the pancreatic tissues of the control group.

On the other hand, in the groups in which we experimentally created acute pancreatitis, we observed a significant positive immunofluorescence staining for ox-LDL in pancreatic tissues and the severity of pancreatitis and ox-LDL in pancreatic tissues seemingly increased with disease severity (Figure 3). Based on the model described by Schmidt et al., we performed the histopathological evaluation of pan-

creatic tissue. Accordingly, we found widespread edema with parenchymal and perivascular inflammation in group 2, typical fat necrosis accompanying inflammation in group 3, and parenchymal hemorrhage and acinar necrosis in group 4 (Figures 4-6).

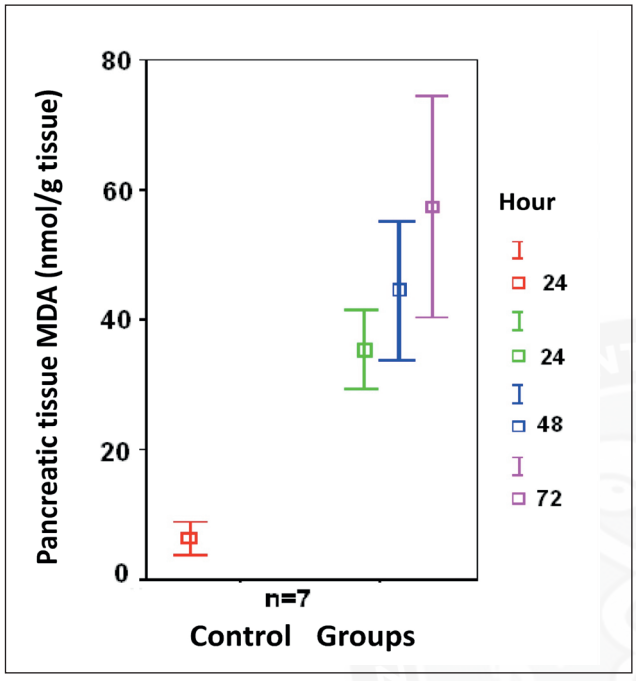

Figure 2: The comparison of pancreatic tissue MDA levels in experimental groups and controls.

DISCUSSION

Acute pancreatitis creates a significant financial burden on the healthcare system due to the high mortality rate and care costs (13). Oxidative stress and overproduction of reactive oxygen and nitrogen species (RONS) play an important role in the pathogenesis of pancreatitis, which Leung and Chan have previously demonstrated (14). Oxidative stress causes the production of ROS, which are highly reactive molecules resulting from normal metabolism within the cell, especially in mitochondria, or due to ischemia-reperfusion-induced aging, radiation, high oxygen pressure, inflammation, and exposure to chemical agents (15-19).

ROS initiate lipid peroxidation by causing oxidation of polyunsaturated fatty acids (PUFA) in biological membranes (20). Ox-LDL is an early lipid peroxidation product. It is a highly immunogenic substance (21) with properties such as the ability to stimulate monocyte and macrophage chemotaxis (22) and the expression of proinflammatory cytokines (23, 24). Oxidative damage to lipids has generally been evaluated via TBA-reactive substances assays (25). The tissue MDA content is a predictor to detect the presence of lipid peroxidation in any tissue due to oxidative stress. However, the accuracy of the methods for measuring lipid peroxidation used in biomedical research is not satisfactory (13). In the presented study, to overcome this issue, ox-LDL accumulation was evaluated as a different approach to detect lipid peroxidation in the pancreatic tissue level via a special immunofluorescent staining method. In the pre-

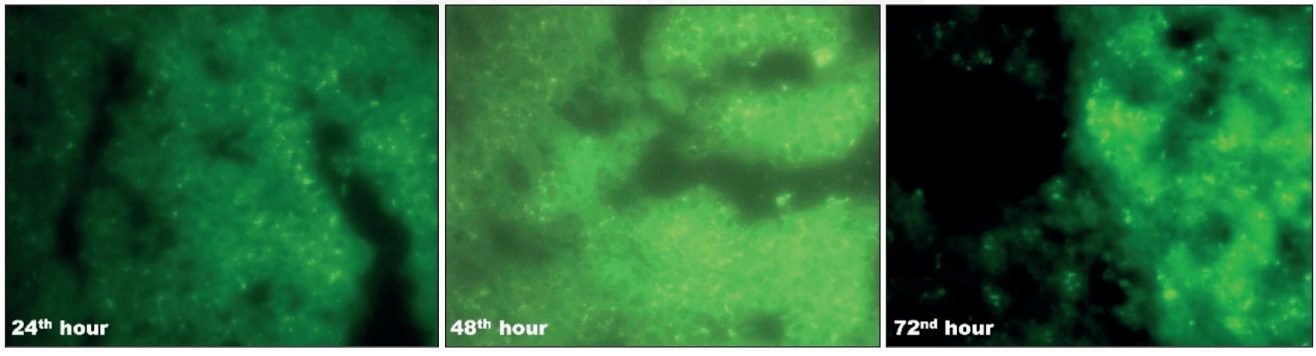

Figure 3: Immunofluorescence microscopic view of pancreatic tissue at 24th, 48th, and 72nd hours demonstrated intense ox-LDL accumulation accordant with time.

Table 1: The biochemical analysis.

Parameter Group	Group 1 (n=5)	Group 2 (n=7)	Group 3 (n=7)	Group 4 (n=7)	p*
ALT (U/L)	45.8 (6.7)	130.7 (13.7)	139.1 (16.6)	167.3 (11.2)	0.0018
AST (U/L)	34.7 (12.1)	538.2 (88.1)	586.4 (32.8)	635.2 (55.4)	0.0005
Amylase (U/L)	409.1 (78.3)	3298.8 (908.3)	3742.5 (886.7)	4095.1 (944.5)	0.0008

*Kruskal Wallis test was used to compare groups (df=3). All results of Table 1. Are presented with median interquartile range (IQR).
AST: Aspartate aminotransferase, **ALT:** Alanine aminotransferase, **Group 1:** Control group

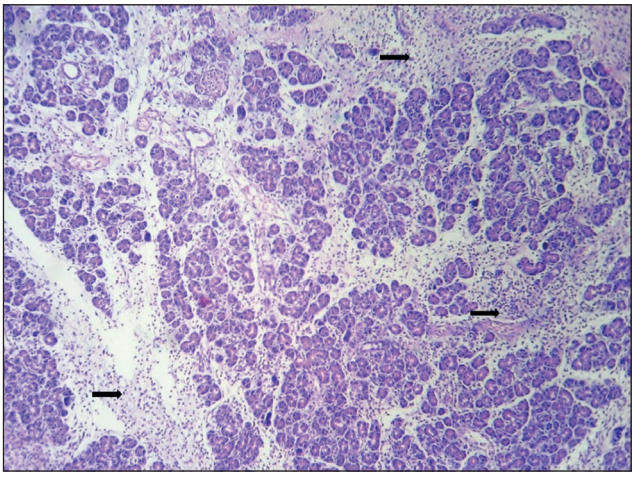

Figure 4: Parenchymal and perivascular inflammation with intense edema (arrows) at 24th hour after induction of AP (H&E, X100).

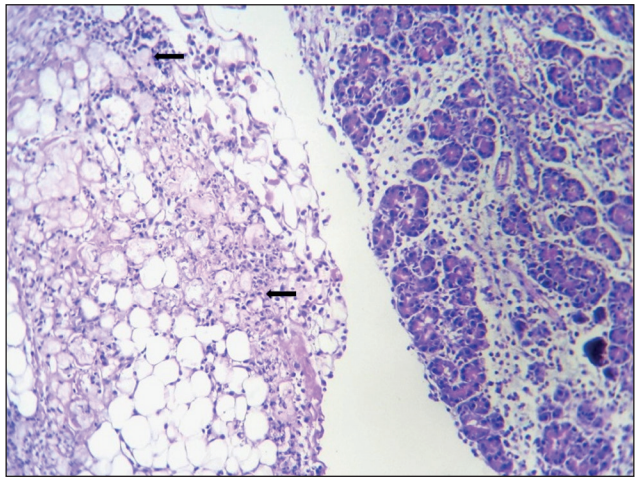

Figure 5: Fat necrosis is associated with inflammation (arrows) at 48th hour (H&E, X200).

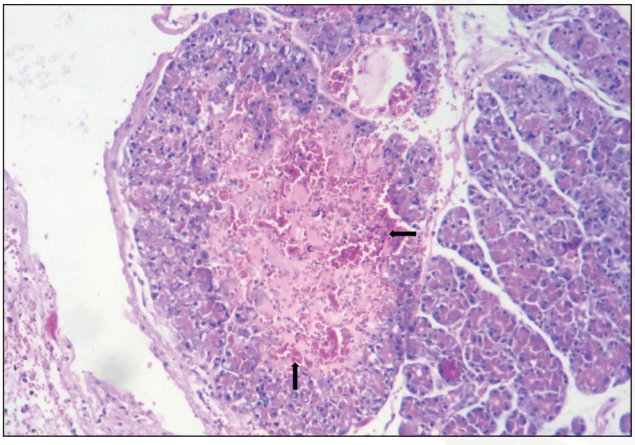

Figure 6: Parenchymal hemorrhage and acinary necrosis (arrows) at 72nd hour (H&E, X200).

sented study, positive immunofluorescent staining in the pancreatic tissue of the control group (group 1) was not observed. However, significant positive immunofluorescent staining for ox-LDL was detected in AP groups with higher levels of MDA as an indicator of lipid peroxidation in tissues. Compared with the control group, pancreatic tissue MDA levels and serum amylase, ALT, and AST levels were significantly higher in the AP group. In all experimental models of AP studies, edema is the earliest change, followed by leukocytic infiltration, parenchymal and peripancreatic fat necrosis (26). Early histopathological changes observed in taurocholate-induced acute pancreatitis are focal hemorrhage, parenchymal necrosis, neutrophil infiltration, and changes at 72 hours acinar necrosis, edema, fibrin deposition, and inflammatory cell infiltration (26). We found similar histopathological findings in our study. This study was carried out to examine the relationship between the severity of pancreatitis and the changes in histopathology based on the assumption of the accumulation of ox-LDL in pancreatic tissue. ROS is produced in the early stages of the disease in all types of experimental pancreatitis models. Moreover, indirect observations show that ROS is produced in acute, recurrent, and chronic pancreatitis in humans and contributes to the damage (27).

Oxidative stress associated with ROS appears effective in the onset of acute pancreatitis. Increased oxidative stress develops early in acute pancreatitis and lasts longer than clinical indicators (28). Likely, cell damage due to lipid peroxidation caused by oxidative stress and intermediate products will provide valuable information on the prognosis of the disease process. In the light of the previous studies, the presented study evaluated the changes in pancreatic tissue caused by oxidative stress in an experimental setting and the relationship between ox-LDL accumulation and the severity of the disease with different parameters. One of the major concerns is the lack of quantitative analysis of immunofluorescent staining to detect ox-LDL accumulation, which was evaluated individually by a single histopathologist without enough accuracy to correlate the degree of accumulation to the severity of the disease. However, in the histopathological evaluation, we observed significant positive immunofluorescent staining showing the accumulation of ox-LDL proportional to the pathological severity of AP. Therefore, we evaluated the accumulation of ox-LDL as an essential indicator in assessing the severity of the disease.

The fact that ox-LDL is an early lipid peroxidation product would enable us to detect the severity of tissue destruction due to oxidative stress in the early period. This data would potentially predict the disease process and prognosis within the first few days after disease initiation. They would act as

a crucial factor in designing individualized treatments in the very early course of the disease. This study created more research questions regarding the time and level of ox-LDL accumulation with disease extent and severity, which would be the topic of further studies. The limitation of our study was that we did not evaluate reactive oxygen species and other oxidative stress parameters. These parameters could have helped us understand the relationship between pancreatitis severity and changes in histopathology based on the accumulation of ox-LDL better. In addition, the inability to use more animals for the study increases the limitation of this study.

Lipid peroxidation associated with oxidative stress plays a pivotal role in the pathogenesis of the disease. Ox-LDL accumulation in pancreatic tissue might be an essential indicator of excessive immunoinflammatory events during AP as an oxidative stress byproduct. Considering the morbidity and mortality of the disease, we think that treatment modalities according to these byproducts, including ox-LDL, may have beneficial effects in alleviating the disease's systemic complications and potentially help reduce mortality with the use of early treatment.

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None

Author Contributions

Concept: **Hakan Balbaloglu,** Design: **Hakan Balbaloglu, Guldeniz Karadenız Cakmak,** Data collection or processing: **Hakan Balbaloglu, Oge Tascılar,** Analysis or Interpretation: **Ishak Ozel Tekın, Sereften Acıkoz, Burak Bahadır,** Literature search: **Hakan Balbaloglu, Guldeniz Karadenız Cakmak,** Writing: **Hakan Balbaloglu, Guldeniz Karadenız Cakmak,** Approval: **Oge Tascılar.**

Conflicts of Interest

The authors have no conflict of interest in this study.

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Ethical Approval

The study was approved by the Ethics Committee of Zonguldak Bulent Ecevit University, protocol number:(2021/5-7).

Review Process

Extremely peer-reviewed and accepted.

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