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Effect of Bisphenol-A on Oxidative Status and Certain Inflammatory Markers in Rats: Experimental Study

Bisfenol-A'nın Sıçanlarda Oksidatif Durum ve Bazı İnflamatuar Belirteçler Üzerine Etkisi: Deneysel Çalışma

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ABSTRACT Objective: Bisphenol-A (BPA) is a public health concern due to its widespread use in the living world and consumer products. It aimed to study the effect of ingested BPA on oxidative status and certain inflammatory markers in rats. **Material and Methods:** In this study, 24 Wistar Albino rats were used, and divided into 4 groups (control, sham, BPA25, BPA50). While no application was made to the first of these groups, corn oil was given to the second group (sham). In the first of the experimental groups, BPA dissolved in corn oil was administered at 25 mg/kg/day, and in the second at 50 mg/kg/day by oral gavage for one month. At the end of the experiment, the animals were anesthetized. Blood samples were taken from the heart and the sera were separated. Total antioxidant capacity, the total oxidative state, tumor necrosis factor-alpha, interleukin (IL)-1 beta, and IL -6 levels were determined by enzyme-linked immunosorbent assay. **Results:** When BPA was administered in doses of 25-50 mg/kg/day, serum total antioxidant capacity levels significantly decreased, while an increase was seen in total oxidative status and Oxidative Stress Index reflects harmful effects of BPA. Furthermore, serum tumor necrosis factor-alpha, IL-1-beta, and IL-6 levels increased significantly ($p \leq 0.05$). **Conclusion:** These results suggest that BPA exposure induces inflammatory markers. BPA also may causes oxidative stress, not only by promoting the production of oxidative compounds but also by reducing antioxidant capacity compared to the control group. All these biochemical changes may lead to damage to macromolecules in the tissues of living organisms.

Keywords: Bisphenol-A; inflammatory markers; oxidative stress

ÖZET Amaç: Bisfenol-A [Bisphenol-A (BPA)], canlı dünyasında ve tüketici ürünlerinde yaygın kullanımı nedeniyle bir halk sağlığı sorunudur. Bu çalışmada, sindirilen BPA'nın sıçanlarda oksidatif durum ve bazı inflamatuar belirteçler üzerindeki etkisinin araştırılması amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışmada, 24 adet Wistar Albino rat kullanıldı ve 4 gruba (kontrol, sham, BPA25, BPA50) ayrıldı. Bu gruplardan birincisine herhangi bir uygulama yapılmazken, ikinci gruba (sham) mısır yağı oral gavajı uygulandı. Deney gruplarından birincisine mısır yağında çözünmüş BPA 25 mg/kg/gün, ikincisine 50 mg/kg/gün dozlarda oral gavaj yoluyla verildi. Deneyin sonunda hayvanlara anestezi uygulandı. Kalpten kan örnekleri alındı ve serumlar ayrıldı. Toplam antioksidan kapasite, total oksidatif durum, tümör nekroz faktörü-alfa, interlökin (IL)-1 beta ve IL-6 düzeyleri enzim bağlı immünosorbent testi ile belirlendi. **Bulgular:** BPA 25-50 mg/kg/gün dozlarında uygulandığında, serum total antioksidan kapasite düzeyleri anlamlı derecede azalırken, toplam oksidatif durumda artış görülmüş ve Oksidatif Stres İndeksi, BPA'nın zararlı etkilerini yansıtmaktadır. Ayrıca serum tümör nekroz faktörü-alfa, IL-1-beta ve IL-6 düzeyleri anlamlı olarak artmıştır ($p \leq 0,05$). **Sonuç:** Bu sonuçlar, BPA maruziyetinin inflamatuar belirteçleri indüklediğini göstermektedir. BPA ayrıca sadece oksidatif bileşiklerin üretimini teşvik ederek değil, aynı zamanda kontrol grubuna kıyasla antioksidan kapasiteyi azaltarak oksidatif strese neden olabilir. Tüm bu biyokimyasal değişiklikler, canlı organizmaların dokularındaki makro moleküllere zarar verebilir.

Anahtar Kelimeler: Bisphenol-A; inflamatuar belirteçler; oksidatif stres

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Today, exposure to chemical substances produced by humans is becoming more common all over the world, especially in industrialized societies in the world.[1] Bisphenol-A [BPA; 2,2-bis(4-hydroxyphenyl) propane] is the classified organic compound in the phenol group. BPA is widely used in many different fields; it is one of the important chemicals used in polycarbonate plastics used in food and beverage containers and epoxy resins found in some metal can liners.[2] BPA is found in so many products from food, water, and beverage cans to electronic devices and dental supplies that many people are exposed to.[3] In addition to all these, it is also used in the manufacture of many products such as baby bottles and pacifiers, eyeglasses, lenses, compact discs, window panels, including children's toys.[2]

Studies show that oral BPA is rapidly absorbed in the digestive system and metabolized in the liver and intestines. It has been reported that 28% of the BPA taken into the body is primarily excreted as glucuronide in the urine, it is glucuronidated by UDP-glucuronosyl transferase and excreted in the bile duct and reabsorbed in the caecum and colon, then excreted in the urine.[2,4] Studies have shown the relationship between high urinary BPA levels and obesity, Type II diabetes, heart diseases, changing thyroid hormones, and allergic asthma. BPA appears to modulate the immune system by acting as a thyroxine hormone receptor antagonist in mice experimentally given BPA for the development of asthma and allergy.[5] It has been proven that BPA causes different pathologies such as neurological disorders, cancers, behavioral disorders, and liver enzyme abnormalities.[6]

The assessment of general oxidative stress causes many problems due to the variety of natural antioxidant enzymes, non-enzymatic free radical scavengers, and reactive oxygen species (ROS). Different measurements of each antioxidant enzyme, antioxidant molecules, and different oxidants are laborious and expensive due to the wide variety of parameters of the oxidant-antioxidant system. This greatly hinders the assessment of the total oxidant-antioxidant balance. Therefore, the total oxidative status (TOS) parameter, which encompasses a wide range of oxidants involved in cell damage, may be more useful to assess global oxidative stress in tissue. On the other hand, evaluation of antioxidant status by non-enzymatic component can be done by measuring total antioxidant capacity (TAC). TAC and TOS analyses provide a full assessment of oxidative stress.[7,8]

BPA regulates the levels of intracellular ROS that affect some cellular responses like cellular antioxidant capacity, formation of DNA defects, mitochondrial damage, or viability decline. BPA exposure affects intracellular oxidation levels as well as the state of the cell's antioxidant system.[9]

Cytokines are protein groups with therapeutic potential, known as multifunctional polypeptides, synthesized by different cells of the body. They are effective in the pathophysiology of diseases. They play an important role in many physiological responses by controlling the relationships between immune system cells, supporting the response to inflammation, and regulating hematopoiesis. Activation of cytokines was first described in 1926, and it was reported that they are dissolved products secreted from leukocytes and affect the functions of the vessel wall.[10,11]

Tumor necrosis factor (TNF)-α regulates immune functions and is a cytokine secreted from fat cells It is a 26 kDa transmembrane protein that exerts its effect through Type I and Type II TNF-α receptors. TNF-α has been found to increase with inflammation, host parasitic diseases, septic shock, obesity and insulin resistance, and rheumatoid arthritis. It regulates hematopoiesis by increasing angiogenesis and oxidative stress in endothelial cells and accelerates the differentiation of stem cells, and the formation of osteoblasts.[12]

Interleukin (IL)-1 is a multifunctional pro-inflammatory cytokine and acts like an endogenous pyrogen. Fever over cell proliferation, differentiation as well as most innate and specific immunocompetent cell functions; hepatic acute phase response, and increased production of antibodies and lymphokines; It has various effects such as cartilage destruction.[11] IL-1 was first identified as a fever-regulating protein and was named "human leukocytic pyrogen". While the IL-1α biological form is active; IL-1β is in the

form of pro-IL-1β and has no biological activity until processed. IL-1 has two receptors, Type I and Type II. IL-1α and IL-1β may exert similar effects by binding to the Type I receptor. IL-1α and IL-1β may exert similar effects by binding to the Type I receptor. In mammals, IL-1 levels increase in response to homeostatic changes, activating the hypothalamic-pituitary-adrenal axis and playing a role in eliciting disease behaviors. Following acute injury and in chronic neurodegenerative disease the levels of IL-1 increase have been found.[13]

Due to the use of BPA in food and beverage containers, exposure is most severe through ingestion. In this study, the objective was to study the effects of ingested BPA on oxidative status and certain inflammatory markers in rats.

MATERIAL AND METHODS

MATERIALS AND EXPERIMENTAL CONDITIONS

The average weight of 200-250 gr. 24 male Wistar Albino Rats to be used as experimental animals were obtained from the Experimental Application and Research Center of Yüzüncü Yıl University [Local Ethics Committee of Van Yüzüncü Yıl University (date: November 03, 2022; no: 2022/11-01)] animals were divided into 4 groups (control, sham, BPA25, BPA50) each containing 6 animals and put in the study unit.[14] During the one-month study, daily diets (pellet feed-ad libitum nutrition) were continued as normal in all groups of experimental animals.

All animals in the study were treated humanely in accordance with the Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html) and the relevant Experimental Animals Ethics Committee Approval Report was obtained.

EXPERIMENTAL PROCEDURE

Rats were divided into 4 groups and each group contained 6 animals:

Control group: No application was made to this group.

Sham group: Corn oil was given by oral gavage.

BPA25: BPA was dissolved in corn oil was given 25 mg/kg/day.[14]

BPA50: 50 mg/kg/day doses BPA was given to rats of this group during the research trial.[14]

COLLECTION OF SAMPLES

At the end of the application, experimental animals were anesthetized using isoflurane inhalation anesthetic, blood samples were taken from hearts into biochemical tubes, and sera were separated.[15]

BIOCHEMICAL ANALYSES

TAC, TOS, TNF-α, IL-1β, and IL-6 analysis were done by enzyme-linked immunosorbent assay (ELISA) with appropriate kits method. All these kits use double antibody sandwich ELISA to measure the level of rat TAC, TOS, TNF-α, IL-6, and IL-1β.

TAC (Rat Total Antioxidant Capacity ELISA Kit, Bioassay Technology Laboratory, Cat. No. E3901Ra, China). When samples are added to the plate covered with TAC, sample binds to the antibody. biotinylated Rat TAC antibody and Streptavidin-HRP are added. bind to the biotinylated TAC antibody. After incubation it is washed. Then substrate solution is added, and color change develops. The reaction is terminated by adding acidic stop solution, and absorbance is measured at 450 nm.

TOS (Rat Total Oxidant Status ELISA Kit, Bioassay Technology Laboratory, Cat. No. E1512Ra, China), The plate has been pre-coated with rat TOS antibody, sample is added an binds to antibodies coated on the wells, then botinylated Rat TOS antibody is added and binds to TOS in the sample. Then Streptavidin-HRP is added and binds to the biotiniylated TOS antibody. After incubation unbound streptavidin-HRP is washed away, substrate solution is then added and color develops in proportion to the amount of rat TOS. The reaction is terminated by addition of acidic stop solution and absorbance is measured at 450 nm. As inflammation markers; TNF-α (Rat Tumor Necrosis Factor Alpha ELISA Kit, Bioassay Technology Laboratory, Cat. No. E0764Ra, China), This kit works by the ELISA method. Optical density is measured at a wavelength of 450 nm.

IL-6 (Rat Interleukin 6 ELISA Kit, Bioassay Technology Laboratory, Cat. No. E0135Ra, China) was performed on an ELISA device. This kit is

ELISA method. Measurement of optical density 450 nm wave is done on the neck. IL-1β (Rat Interleukin 1 Beta ELISA Kit, Bioassay Technology Laboratory, Cat. No. E0119Ra, China) ELISA kits were run. This kit use double antibody sandwich ELISA to measure the level of IL-1β. ELISA kits were run using Statfax 2600 automatic washer and Statfax 2100 reader.

The Oxidative Stress Index (OSI) was calculated using the formula:

OSI=(TOS/TAC)x100

STATISTICAL ANALYSIS

The descriptive statistics of the considered biochemical properties were expressed as mean±standard deviation. Differences between data means were examined by Duncan's multiple comparison method. The level of statistical significance was assumed to be 5% in the calculations and the SPSS 13.0 (IBM Corp, New York, USA) program was used for these calculations.

RESULTS

Findings from blood analysis of rats used in the study were presented in Table 1. The means of TAC, TOS, and OSI as parameters of oxidative stress and markers of inflammation as TNF-α, IL-6, IL-1β of control, sham, BPA25, and BPA50 were tabulated.

FINDINGS OF OXIDATIVE STRESS MARKERS

When Table 1 is examined, it is seen that the total antioxidant levels decreased in the groups given different doses of BPA. The lowest value was determined in BPA 50 mg/kg/day group, the total oxidant substances increased and followed a similar pattern and the fourth group had the lowest TAC values. Indeed, the mean values of TAC and TOS of the control and sham groups were found to be statistically significant ($p \leq 0.05$) from the groups given BPA. The calculated OSI was the highest in group 4 and there was statistical importance between all groups ($p \leq 0.05$).

FINDINGS OF INFLAMMATION MARKERS

In the case of BPA administration, there was a slight increase in TNF-α levels in groups of BPA25 and BPA50 compared to control but a statistically significant increase was observed ($p \leq 0.05$). In IL-1β analysis, only a significant increase was observed in the group given BPA50 mg/kg/day ($p \leq 0.05$). IL-6 levels were examination showed a similar manner with TNF-α Significant increases were also observed in the groups given BPA and statistical importance calculated between groups as seen in Table 1 ($p \leq 0.05$).

DISCUSSION

BPA is believed to be absorbed through the digestive tract primarily from canned foods and wine and can reach a body level of up to 9 µg/kg/day. Here, the conversion of BPA to glucuronide occurs in hepatic presystemic metabolism in humans is complete after exposure to these concentrations.[16]

It has been stated that alkylphenols such as nonylphenols and octylphenols, especially BPA, cause oxidative damage in various organs as well as damage they cause in the endocrine system.[17] HO in the induction of oxidative stress by BPA. It plays a role in forming reactive oxygen products such as O_2^- and H_2O_2. These reactive oxygen products cause oxidative damage to cell membrane lipids, DNA, and proteins. Cytotoxicity caused by BPA is related to the intracellular energy level, and mitochondria are

TABLE 1: Some serum biochemical parameters in rats given different doses of BPA.

	n	TAC (U/mL)	TOS (U/mL)	OSI (TOS/TAC ratio)	TNF-α (ng/L)	IL-1β (pg/mL)	IL-6 (ng/L)
Control	6	2.06±0.38^a	4.24±0.91^a	195.51±2.48^a	0.49±0.03^a	6.57±0.07^a	2.19±0.61^a
Sham	6	2.17±0.42^a	4.06±0.34^a	207.05±2.98^a	0.51±0.02^a	6.52±0.16^a	2.40±0.35^a
BPA25 mg/kg/day	6	1.79±0.35^b	5.79±0.24^b	315.46±3.12^b	0.56±0.04^b	6.64±0.74^a	3.73±0.63^b
BPA50 mg/kg/day	6	1.53±0.27^b	5.30±0.92^b	335.22±3.54^c	0.59±0.02^b	6.72±0.86^b	3.01±0.20^b

^{a,b,c}: The difference between the means shown with different letters in each column is statistically significant ($p<0.05$); BPA: Bisphenol-A; TAC: Total antioxidant capacity; TOS: Total oxidative status; OSI: Oxidative Stress Index; TNF: Tumor necrosis factor; IL: Interleukin.

generally important targets of this compound.[18] ROS accumulated in tissues are normally eliminated by the antioxidant defense system. However, prolonged exposure or repeated exposure damages the prooxidant and antioxidant balance in cells.[19] Exposure to BPA in living organisms has negative effects by causing oxidative stress in organs such as the brain, kidney, testicles, pancreas, and liver. In recent years the status of oxidative stress was evaluated by measuring some parameters in so many researches in veterinary and other fields because of its unique importance.

The total oxidant status parameter covers a wide range of oxidants that play a role and may be more useful to understand the situation of oxidative compounds in living organisms. On the other hand, assessment of antioxidant status by non-enzymatic component can be done by measuring TAC. In a study, on the potential protective effects of protocatechuic acid on the brain in neurotoxicity, TAC and TOS were measured for a full assessment of oxidative stress parameters. The lowest TAC and the highest TOS levels were found in the cisplatin group, and researchers have reported that cisplatin increases oxidative stress and causes antioxidant depletion.[10] In this research 25 and 50 mg/kg/day BPA also affected these parameters, a decrease in TAC and an increase in TOS were found which helps to elucidate the harmful effects of BPA on living organisms.

Yıldırım et al. investigated the effect of intramuscular alpha-lipoic acid administration on TAC and TOS levels in laminectomized rabbits.[20] It has been suggested that laminectomy causes changes in total sialic acid, and total antioxidant status (TAS) levels; on the other hand, supported plasma antioxidant capacity by increasing TAS and decreasing TOS levels in animals. BPA has dose-dependent deleterious effects, and increased amounts of TOS have been detected, as seen after laminectomy surgery. We can say operation, chemical compounds, or disease strongly aff. TAC and TOS levels changes were determined in lambs from 0^{th} to 5^{th} days of the research.[21]

Mert et al. examined ect TOS and TAC levels.[22] For example, in a study presented by Daş, the effectiveness of vitamins E and Se in addition to the treatment of enzootic pneumonia was investigated.[21]

The effect of evening primrose oil in a fructose-induced metabolic syndrome model. TAC, TOS, OSI, and some other biochemical parameters were measured. The TOS value was significantly higher in the fructose group, but the TAC value was lower. They concluded that a high-fructose diet was associated with increased development of oxidative stress.

Researchers reported that when 50 mg/kg BPA was given, the oxidative and antioxidant systems of liver tissue changed, NO and thiobarbituric acid-reactive substances levels increased, and glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT) levels decreased.[22] After BPA injection into male rats, a decrease was observed in SOD, GSH, and CAT activities in pancreatic tissue, while malondialdehyde (MDA) level increased, parallel to this, administration of BPA to rats decreased serum antioxidant capacity.[23]

In the presented study it was found that the total antioxidant levels decreased in the groups given BPA, and the total oxidant substances increased. The mean values of the control and sham groups were found to be statistically significant ($p \leq 0.05$) from the groups given BPA. These changes show that the administration of BPA creates oxidative stress in organisms, causes oxidative damage to lipids and lipoproteins, creates different oxidative substances, and subsequently, the organism goes to defense by mobilizing antioxidant substances. As a result, while oxidant substances increase, antioxidant substances decrease. Huang et al. found those high concentrations of BPA increased the levels of 8-OHdG, MDA, and protein carbonyl in KGN cells.[8] In addition, they demonstrated that the levels of 8-OHdG, MDA, and protein carbonyl were increased significantly after treatment with high concentrations of BPA analogs.

In studies, glomerular atrophy, tubular and glomerular necrosis in the kidney BPA's CAT, GSH, GPx, glutathione reductase, glutathione-S-transferase, SOD and TAC parameters and increased MDA level were detected. In addition, it has been

found that BPA dose-dependently increases blood urea and creatinine levels and decreases creatinine clearance.[24-26]

Individuals with higher total serum BPA had an enlarged spleen, an indicator of inflammation. In addition, elevated BPA levels increased chronic inflammatory markers such as fatty liver, higher C-reactive protein, IL-6, and enlarged spleen.[27] A significant increase in mRNA levels of the proinflammatory cytokines TNF-α, IL-6, and IL-1β was observed when human endometrial cells were treated with 1,000 pmol BPA. In particular, dose-dependent IL-6 increases were observed, and inflammatory cytokine gene expression by BPA exposure was significantly induced. In addition, specific cytokine secretion is increased. BPA, which is used quite frequently as an endocrine disruptor, increases oxidative stress in human endometrial cells. Again, ROS and NO production and eNOS expression, as well as expression of inflammatory genes, were induced with BPA treatment. TNF-α, IL-6, and IL-1β can be counted among these. TNF-a and IL-6 are also released during these processes.[28]

In the presented study TNF-α, IL-6, and IL-1β levels were increased. As stated in previous studies, it can be said based on the findings shown in Table 1 that the synthesis of these substances increased and BPA caused oxidative stress in the organism, resulting in a rise in proinflammatory cytokines. Indeed, statistically significant changes were found in the TNF levels in the groups given 25-50 mg/kg/day of BPA compared to the control and sham groups. In the same manner, increases were observed in IL-1 β levels as a result of BPA administration. In the group given only 50 mg BPA, the differences in the mean values of the other groups showed statistical significance. An increase was also detected in the group given 25 mg BPA, but this change was not significant compared to the controls. Again, as a result of BPA application, increases in IL-6 levels were detected. The differences in the groups given 25-50 mg/kg/day BPA compared to the control groups were statistically significant.

In many of the previous studies with the production of ROS studies with BPA exposure, some researchers found that BPA decreased antioxidant enzyme expression in human endometrial cells, but BPA induces oxidative stress in human endometrial cells. ROS produced during the metabolism of BPA is more than the intracellular antioxidant system and can exceed its stabilization rate. They concluded that exposure to BPA has harmful effects on human health.[29]

BPA administration decreased the secretion of TNF-α, IL-6, IL-1β, and IL-18, which are pro-inflammatory cytokines in the organism. A reduced production of IL-1β and IL-18 as well as an inactivation of the NLRP3 inflammatory activity was shown as a mechanism for this. Here it was suggested that BPA in the medium may act as a disruptor of inflammatory activity by regulating NF-κB/MAPK pathways and activation of the NLRP3 inflammasome.[30]

In the regulation of inflammatory disorders, many substances, including proinflammatory cytokines, are produced by macrophages, T cells, and B cells through immune responses, which play a crucial role in inflammatory events. Additionally, macrophages maintain balance in the body by regulating inflammatory mediators, including regulating ROS production in immune disorders. Macrophages are actively involved in eliciting pro-inflammatory or anti-inflammatory responses, while these processes may contribute to tissue damage or regeneration.[14,31]

Some compounds such as the NLRP3 inflammasome are implicated as a critical part of the innate immune system, mediating pro-caspase-1 activation and subsequent secretion of the pro-inflammatory cytokines IL-1β/IL-18 in response to microbial disease and cellular damage. Phosphorylation of caspase-1 through activation of NLRP3 inflammation regulates cytokine release, specifically IL-1β and IL-18.[31,32]

When the macrophages were incubated with BPA at 0.1-10 μg/mL for 24 h, the inflammatory cytokines like TNF-α, IL-6, IL-1β, and IL-18 decreased significantly. Treatment of cells with BPA-attenuated TNF-α, IL-6, IL-1β, and IL-18 mRNA expression levels compared to control cells. The

researchers' findings showed that macrophages had a profound effect on their immune response when given BPA, without impairing their immune response. They show that BPA modifies the inflammatory response by regulating the activation of the inflammatory response and plays a critical and disruptive role in the immune responses of macrophages.[14,33]

As shown in previous studies, it has been accepted that BPA modifies the inflammatory response by regulating the activation of the inflammatory response and plays a critical and destructive role in macrophage immune responses.[14,31-33] In this way, it causes an increase in cytokines. In addition, BPA induces oxidative stress in rats or ROS produced during BPA metabolism is more effective than the intracellular antioxidant system. Exposure to BPA has adverse effects on the health of living organisms.

CONCLUSION

It was concluded that BPA alters the inflammatory response by regulating the activation of the inflammatory response and may play a critical and destructive role in the immune responses of macrophages. In this way, it may cause an increase in cytokines. It has also been observed that BPA induces oxidative stress in rats or that ROS produced during the metabolism of BPA may be more effective than the intracellular antioxidant system. Exposure to BPA has harmful effects on the health of living organisms. It is recommended that public health professionals draw attention to this compound in every environment.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mecit Yörük, Halil Cumhur Yılmaz, Salih Çibuk;* ***Design:*** *Mecit Yörük, Halil Cumhur Yılmaz;* ***Control/Supervision:*** *Handan Mert, Nihat Mert;* ***Data Collection and/or Processing:*** *Leyla Mis, Halil Cumhur Yılmaz, Salih Çibuk;* ***Analysis and/or Interpretation:*** *Nihat Mert, Handan Mert, Mecit Yörük;* ***Literature Review:*** *Nihat Mert, Handan Mert, Mecit Yörük, Halil Cumhur Yılmaz;* ***Writing the Article:*** *Nihat Mert, Handan Mert, Leyla Mis;* ***Critical Review:*** *Leyla Mis, Mecit Yörük;* ***References and Fundings:*** *Halil Cumhur Yılmaz, Leyla Mis, Salih Çibuk;* ***Materials:*** *Leyla Mis, Halil Cumhur Yılmaz.*

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