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Antioxidant Contents and Oxidative Stress Markers in Pediatric Familial Mediterranean Fever

Pediatrik Ailesel Akdeniz Ateşinde Antioksidan İçerikleri ve Oksidatif Stres Belirteci

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ABSTRACT

Objective: Familial Mediterranean fever (FMF) is a non-genomic latent pathosis delineated by iterative attacks of fever with serositis. Variants of the FMF gene (MEFV) have been detected predominantly in patients from Mediterranean inhabitants. This study contemplates demonstrating the activity of antioxidants and oxidative stress in children diagnosed with FMF.
Material and Method: The study material comprised a range of 0-18 years of age of 35 individuals diagnosed with Familial Mediterranean Fever compared to 35 healthy participants. The study was conducted between 2016-2017. The samples were taken after the approval of Van Yüzüncü Yıl University, Medical Faculty of Research, education and Training Hospital, Department of Pediatric Health and Diseases Clinic and Research Laboratory Center. The studied enzymatic antioxidant activities such as in (GSH, GPx, and SOD) and the malondialdehyde (MDA) level, which represents the end-product of the lipid peroxidation process, the differences were revealed in the serum samples collected in distinction to patients diagnosed with FMF. The entirety of the analyses was conducted utilizing the SPSS statistics software package.
Results: In the estimation activity of GSH for the sera of patients, insignificant divergence was noticed at the time contrasted with comparator groups. The patient groups exhibited SOD activity that was revealed to be notably lower versus the healthy control group, showing statistical significance ($p<0.001$). Besides, no significant difference in serum GPx activity was discerned relative to the control group. The serum malondialdehyde (MDA) concentration was significantly elevated compared to the control groups. The distinction in the averages of GSH and GPx enzymes was found to be statistically insignificant, whereas the variance of MDA and SOD averages between the patient and control groups was found to be statistically significant ($p<0.05$). Hence, levels of MDA were elevated among the patients who endured Familial Mediterranean Fever disturbance. While, at the outset, the function of antioxidant enzymes such as SOD and GSH has shown a decline.
Conclusion: As a result of these grounds, alternative methods ought to be demonstrated in clinical applications for FMF patients, antioxidant enzymes might alter the underlying causes of the disease and its etiopathogenesis. Consequently, from our findings, we inferred that the reason for the progress and advancement of Familial Mediterranean Fever (FMF) disease might be the outcome of disruption and Inequity among the levels of antioxidants and oxidative stress (OS).

Keywords: *Familial Mediterranean Fever, GSH, GPx, SOD and MDA*

ÖZET

Giriş: Ailesel Akdeniz Ateşi (FMF), tekrarlayan ateş atakları ve serozit ile tanımlanan genetik olmayan bir patolojidir. FMF geninin (MEFV) varyantları ağırlıklı olarak Akdeniz bölgesinde yaşayan hastalarda tespit edilmiştir. Bu çalışma, FMF tanısı konan çocuklarda antioksidanların ve oksidatif stresin aktivitesini göstermeyi amaçlamaktadır.
Materyal ve Metot: Çalışma materyali, Ailesel Akdeniz Ateşi tanısı konan 0-18 yaş aralığındaki 35 hasta ve 35 sağlıklı katılımcıdan oluşuyordu. Çalışma 2016-2017 yılları arasında gerçekleştirilmiştir. Örnekler, Van Yüzüncü Yıl Üniversitesi Tıp Fakültesi Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği ve Araştırma Laboratuvarı Merkezi'nin onayından sonra alınmıştır. FMF tanısı konan hastalardan alınan serum örneklerinde enzimatik antioksidan aktiviteler (GSH, GPx ve SOD) ve lipid peroksidasyonunun son ürününü temsil eden malondialdehit (MDA) seviyesi ortaya konmuştur. Analizlerin tamamı SPSS istatistik yazılım paketi kullanılarak yapılmıştır.
Bulgular: Hastaların serumlarındaki tahmini GSH aktivitesinde, karşılaştırma gruplarıyla karşılaştırıldığında önemsiz bir sapma fark edildi. Hasta grupları, sağlıklı kontrol grubuna göre belirgin şekilde daha düşük ve istatistiksel anlamlılık gösteren SOD aktivitesi sergiledi ($p<0.001$). Ayrıca, serum GPx aktivitesinde kontrol grubuna göre anlamlı bir fark saptanmadı. Serum malondialdehit (MDA) konsantrasyonu kontrol gruplarına göre anlamlı olarak yükseldi. GSH ve GPx ortalamalarındaki farkın istatistiksel olarak önemsiz olduğu, ancak MDA ve SOD ortalamalarının hasta ve kontrol grupları arasındaki varyansının istatistiksel olarak anlamlı olduğu bulundu ($p<0.05$). Bu nedenle, Ailesel Akdeniz Ateşi bozukluğuna maruz kalan hastalarda MDA seviyeleri yükselmiştir. Başlangıçta, SOD ve GSH gibi antioksidan enzimlerin aktivitesi azalmıştır.
Sonuç: Bu gerekçelerin bir sonucu olarak, FMF hastaları için klinik uygulamalarda alternatif yöntemler gösterilmelidir. Antioksidan enzimler, hastalığın altında yatan nedenleri ve etiyopatogenezini değiştirebilir. Sonuç olarak, bulgularımızdan, Ailesel Akdeniz Ateşi (FMF) ilerlemesinin nedeninin, antioksidanlar ve oksidatif stres (OS) seviyeleri arasındaki bozulma ve dengesizliğin sonucu olabileceği sonucuna vardık.

Anahtar kelimeler: *Ailesel Akdeniz Ateşi, GSH, GPx, SOD ve MDA*

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INTRODUCTION

Free radicals are active compounds and proactive chemicals in the outermost orbital in the context of unshared electrons (Poljsak et al., 2013). Within the biological entity, the free radicals originate frequently from oxygen, nitrogen, and sulfur molecules. These particularly highly reactive molecules that are identified as free radicals are components within several groups of molecules that are known as Reactive Oxygen Species (ROS), Reactive Sulfur Species (RSS), and Reactive Nitrogen Species (RNS) (Lu et al., 2010). Reactive oxygen species have been implicated in the pathogenesis of numerous conditions. Both reactive oxygen species (ROS) and reactive nitrogen species (RNS) exhibit divergent characteristics, with detrimental and beneficial effects. (Valko, 2005).

ROS perceive both free radical and non-free radical oxygen-comprising molecules such as singlet oxygen (1/2 O_2), superoxide ($O_2{\cdot}-$), hydrogen peroxide (H_2O_2), and the hydroxyl radical (·OH). Besides, there exist reactive species involving nitrogen, copper sulfur, and iron (Poljsak et al., 2013). The reactive nitrogen species (RNS) are produced from nitric oxide when it reacts with O_2•, resulting in the formation of $ONOO^-$•. In addition, RSS is effortlessly consolidated and thiols can generate reactive species by reacting with ROS (Lu et al., 2010). This resulted in attributing generation of high amounts of ROS with oxidative stress and mitigating the balance of redox (Poljsak et al., 2013). The dualistic role of ROS includes their function as secondary messengers in crucial intracellular signaling pathways, contributing to the development and propagation of cancerous traits in cancer cells. Additionally, ROS can trigger and induce cellular senescence and apoptosis, potentially acting as anti-tumor agents (Valko, 2005).

Both reactive oxygen & nitrogen species become visible as an outcome of the respiratory cycle and oxidative phosphorylation process that potentially affects biological macromolecules like cellular DNA, resulting in single-strand and double-strand breaks, and inducing ultimate triggers in mutagenic changes, cardiovascular diseases, cell aging, and cancerous tumor growth (Çekiç et al., 2013). ROS can directly induce oxidative damage to cells by harming nucleic acids, proteins, lipids, and cell membranes within tissues. Highly reactive free radicals are produced during cellular energy generation from food and oxygen. Additionally, exposure to factors such as microbial infections, intense exercise, and various pollutants or toxins like smoking emissions, Ionizing and UV rays, alcohol, biocides, and ozone can also trigger the formation of these conditions (Poljsak et al., 2013).

Each cell has complex antioxidant defense systems, consisting of both low- and high-molecular-weight components, to safeguard against reactive oxygen species (ROS). The defensive mechanisms encompass both endogenous (internally produced) and exogenous (acquired through diet) components (Çekiç et al., 2013). The accumulated replication of reactive oxygen species and reactive nitrogen species (ROS/RNS), whether originating from internal processes or external factors, is ascribed as oxidative stress (Valko, 2005).

In recent years, numerous studies have highlighted the association between oxidative stress, cellular senescence, and certain diseases. Conversely, in the modern world, our lifestyle tends to promote the overabundance of free radicals and reactive oxygen species (ROS) within our physiological systems and biological organs. This leads to an elevation in oxidative stress levels, coupled with a decrease in the antioxidant efficacy (Zamora et al., 2016). Sies first delineated oxidative imbalance as "an inconvenience in the prooxidant to antioxidant equilibrium in the beneficence of the former, affecting potential damage" (Poljsak et al., 2013). Eminently, oxidative stress aids in the progression of inflammatory diseases, cancer, cardiovascular conditions, Alzheimer's disease, cataracts, diabetes, autism, and the aging process (Lu et al., 2010).

The disease of Familial Mediterranean fever (FMF) stands as the most prevalent type of hereditary auto-inflammatory disorder, marked by recurring fever episodes accompanied by inflammation of serosal or synovial tissues, each episode lasting from 12 to 72 hours. Furthermore, untreated or inadequately managed patients suffering from Familial Mediterranean fever (FMF) face an elevated risk of developing secondary amyloidosis, which predominantly affects renal and vascular function. Colchicine, the current prevailing standard and conventional treatment for FMF patients, has been widely recognized as safe and effective. It proves successful in most patients, it lowers the occurrence of inflammatory episodes and diminishes the likelihood of amyloidosis development. Yet, presently there are no alternative treatments that are both effective and approved for Familial Mediterranean fever (FMF) patients who experience adverse reactions to colchicine. Additionally, reducing the dosage due to adverse effects may lead to reduced effectiveness. Furthermore, roughly 5-10% of FMF patients experience persistent inflammatory flare-ups, even when administered the maximum (1.5 to 2.0 mg/day) tolerable doses of colchicine. The majority of (FMF) Familial Mediterranean fever patients exhibit a genetic trait inherited in an autosomal recessive manner allied to mutations in the MEFV gene, responsible for encoding the protein called pyrin (Gül et al., 2015). Pyrin (also known as marenostrin), along with several proteins containing the pyrin domain, constitutes intracellular signaling modules associated with inflammation and is connected to autoinflammatory maladies. Alterations in the MEFV,

the gene responsible for encoding pyrin, result in Familial Mediterranean fever (FMF), marked by reiterative polyserositis in a recessive manner. These mutations are also linked, albeit to a minor degree, with diverse autoinflammatory afflictions. In the context of a Th1-associated autoimmune disease, possessing a mutation in MEFV may exacerbate the course of the disease, as evidenced by carriers observed among patients with non-Ashkenazi origin multiple sclerosis (Rabinovich, 2005).

MATERIAL and METHOD

For this study, samples of blood were gathered from a total of 70 individuals 35 healthy and 35 children diagnosed with Familial Mediterranean Fever (FMF), comprising both males and females. Each participant, whether healthy or diagnosed with FMF, contributed 4ml of blood obtained from the antecubital venous vein. This sample was evenly distributed, with 2 ml added to a biochemistry tube and the remaining 2 ml to an EDTA tube.

The entire study population included individuals ranging from 0 to 18 years of age, encompassing 35 patients diagnosed with Familial Mediterranean Fever and an additional 35 healthy individuals who served as the control group. Several biochemical parameters were evaluated utilizing serum samples. The ethical approval was attained from the ethical committee of Van Yüzüncü Yıl University, Educational Research and Training Hospital of Medical Faculty, specifically from the Department of Pediatric Health and Diseases Clinic and Research Center. Four milliliters of blood were smoothly withdrawn from both selected healthy and affected individuals as planned for the study. The gathered blood samples were subsequently centrifuged. at 5000 revolutions per minute for 10 minutes, after which the serum was isolated from the plasma. The isolated serums were employed to assess some antioxidant parameters like glutathione peroxidase (GPx), superoxide dismutase (SOD), reduced glutathione (GSH), and an assessment of the body's oxidative stress through malondialdehyde (MDA).

Analysis Methods

1. Assessment of superoxide dismutase (SOD) activity

Superoxide dismutase enzyme activation was dictated by the suggested technique employed by (Popov et al., 2003). The antioxidant SOD is a compound that disposes, scavenges, and suppresses the formation of free radicals and enhances the decomposition of hydrogen peroxide and molecular oxygen effectively mitigating the presence of superoxide radicals (O2-•) generated in the course of oxidative energy production. The indicated approach is entrenched in the optical density quantification obtained by utilizing xanthine and xanthine oxidase. This process involves the detection of superoxide radicals derived from the blue-colored formazan dye of the compound Nitro Blue Tetrazolium (N.B.T) This procedure includes identifying superoxide radicals produced from the blue formazan dye of Nitro Blue Tetrazolium (N.B.T) compound by measuring their absorbance at a wavelength of 560 nm. In the serum sample, the Superoxide dismutase that subsists hinders the interaction of formazan by eliminating O2-• (superoxide radicals) from the ambiance. During the trial circumstances and investigative parameters, one unit of SOD is defined as a 50% reduction in the rate of decline of the oxidant N.B.T.

% İnhibition = [(Blank OD – Sample OD) / Blank OD] x 100

2. Assessment of reduced glutathione (GSH) activity

In the erythrocyte destruction facilitated by EDTA, equipped with distilled water, the entire set of proteins that do not convey the sulfhydryl (SH) group is induced to settle with a precipitating solution. The measurement of reduced glutathione (GSH) was taken upon the reaction's conclusion, marking the attainment of the final product. That marked the formation and emergence of the yellow hue in the transparent fluid resulting from the sulfhydryl groups and DTNB (5',5'-(dithiobis 2-nitrobenzoic acid). The evaluation of the antioxidant reduced glutathione levels in EDTA blood was conducted by spectrophotometer at a wavelength of 412 nm, and the analysis was completed within 24 hours duration (Beutler et al., 1963).

Activity (mg / dl) = [(OD2 – OD1) / 13600 x E1 1.25] x 1000

OD1 = First absorbance prior to augmentation of DTNB.

OD2 = Second absorbance post augmentation of DTNB.

Both absorbances are read at a wavelength of 412 nm.

E1 = 1 as part of the analysis.

The molar absorptivity or extinction coefficient of the resulting yellow hue observed during the GSH and DTNB interaction is 13600.

3. Assessment of glutathione peroxidase (GPx) activity

The evaluation of Beutler's method approach was employed for determining the glutathione peroxidase enzyme activity. The underlying concept beyond this approach is rooted in the activity of the glutathione peroxidase that facilitates the oxidation of oxidized glutathione (glutathione: H2O2: oxidoreductase, EC 1.11.1.9) ensued arose as a result of the interaction and reaction of reduced glutathione and hydrogen peroxide wherein the enzyme Glutathione reductase (GSH-R) reduces oxidative glutathione (GSSG) to

GSH amidst NADPH and reduction in NADPH is observed and monitored at a wavelength of 340 nm.

Enzyme Activity (U/ml) = (ΔOD/t) * [(Vt) / 6.22*Vs)]

ΔOD = Absorbance changes consistent with time.

t = time

Vt= The overall volume of the reaction (ml).

Vs Sample volume (ml).

An optical density of 6.22 is observed for 1 mmol of NADPH in a light path of 1 cm.

4. Assessment of malondialdehyde level (MDA)

The interaction between fatty acids and free radicals leads to the production of malondialdehyde, representing lipid peroxidation's outcome. The assessment uses thiobarbituric acid that imparts a colored appearance (Gutteridge, 1995). 200 µl is required from the blood sample and should be transferred within one tube. The chemicals, Phosphate buffer (800 ml), BHT solution (25 ml), and %30 TCA (500 ml) were infused. The tubes were vortexed and kept in an ice bath for 2 hours. Next, they were centrifuged at a rate of 2000 rpm in 15 minutes. One milliliter of the supernatant was extracted and shifted to other tubes. Subsequently, 75 ml of EDTA plus 250 ml of TBA were appended. The tubes were vortexed and placed in a hot water bath within 15 minutes. Following that, permitted to equilibrate to 25 Celsius, and the absorbance was gauged utilizing a UV/Vis spectrophotometer at a wavelength of 532 nm.

C = F * 6.41 * A

C: Concentration.

F: Dilution factor.

A: Absorbance.

Statistical Analysis

The essential statistical information of the analyzed parameters was disclosed through the standard deviation. During pairwise comparisons between groups, the employed T-test achieves a normal deviation, whereas Mann-Whitney U statistics were implemented in cases where it was not achieved. A significance level of 5% was presumed, and all evaluations were conducted utilizing the SPSS statistical software package.

RESULTS

A substantial statistical relationship ($p<0.05$) was identified upon examining the enzyme SOD (superoxide dismutase) activity), as in (Table 1) between the levels of the control group (5.028 ± 2.198 U/L) and those of the patient group (1.876 ±1.400 U/L).

Upon the inspection of (GSH) reduced glutathione enzyme activity, the correlation amidst levels of the control group (0.018 ± 0.011 U/L) along with patient group levels (0.019 ± 0.009 U/L) were noted statistically ($p<0.001$) to lack a significant relationship.

When the activity of the glutathione peroxidase (GPx) enzyme was evaluated, the association among the levels of the control group (0.038 ± 0.040 U/L) and the patient group (0.047 ± 0.044 U/L) were revealed to exhibit a statistically ($p > 0.001$) non-significant relationship.

After determining the levels of MDA (malondialdehyde), a lipid peroxidation marker, a statistically significant correlation ($p<0.05$) was found among the control group levels (1.214 ± 0.214 U/L) and the patient group levels (1.521 ± 0.200 U/L).

Table 1. Evaluation as stated in the Reference group along with FMF patients.

Parameter	Control $\bar{X}$ ±SD (n= 35)	Patient $\bar{X}$ ±SD (n=35)
SOD (U/L)	5.028 ± 2.198 *	1.876 ± 1.400 *
GPx (U/L)	0.038 ± 0.040 ^	0.047 ± 0.044 ^
GSH (U/L)	0.018 ± 0.011 ^	0.019 ± 0.009 ^
MDA (µmol/L)	1.214 ± 0.214 *	1.521 ± 0.200 *

*: $p<0.05$ ^: $p>0.001$

The activity of (SOD, GPx, and GSH) of serums with (MDA) serum level of the study population.

Upon reviewing the yielded results during our assessment of the reduced glutathione (GSH) enzyme activity, as depicted in (Table 1), a comparison between the control group measurements (0.018 ± 0.011 U/L) as revealed in (Figure 1) besides the extent of the patient group (0.019 ± 0.009 U/L) revealed a statistically insignificant relationship ($p>0.001$).

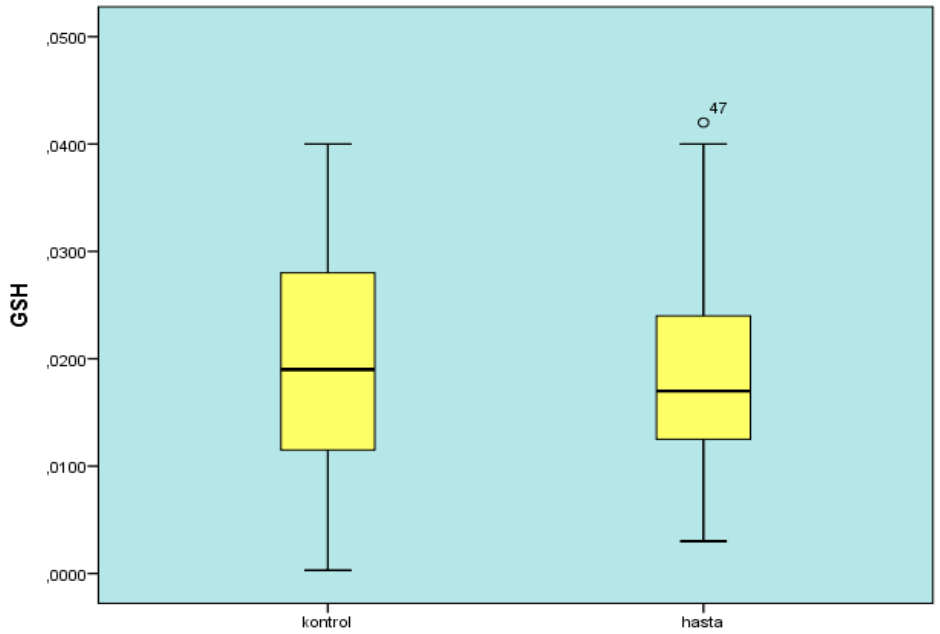

Figure 1. The activity level of GSH enzyme in both control participants and FMF patients

A significant statistical ($p<0.05$) relationship was observed in the evaluation of superoxide dismutase (SOD) enzyme activity, between the levels in the control group (5.028±2.198 U/L) and the patient group (1.876±1.400 U/L). Notably, the SOD enzyme activity as revealed in (Figure 2) in the patient group was comparatively below the SOD activity in the group that serves as the control.

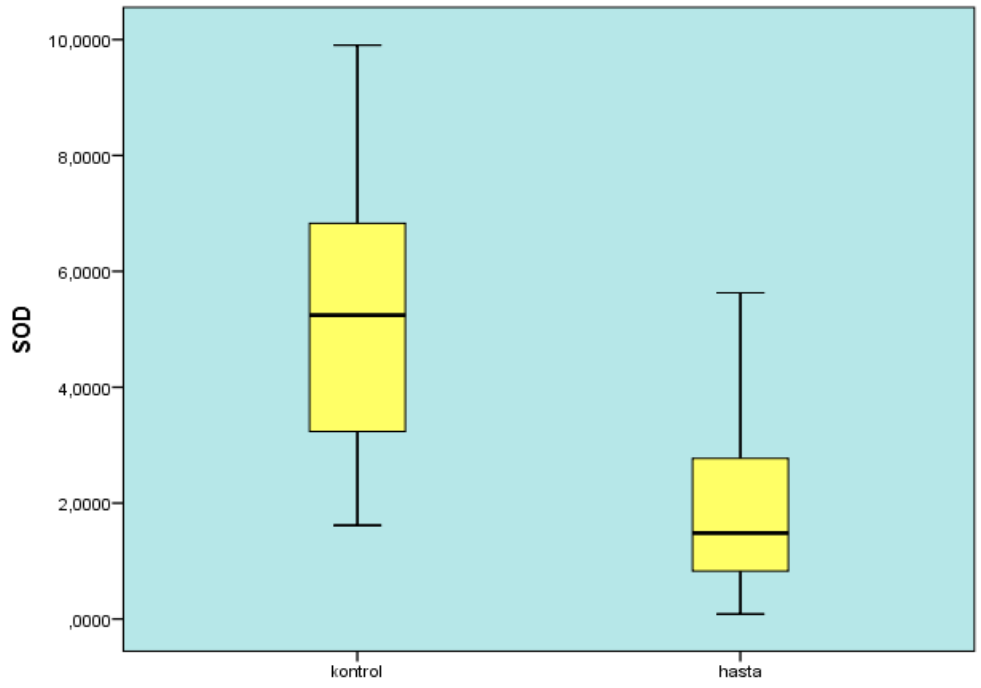

Figure 2. Activity of the SOD enzyme in both control participants and FMF patients

We assessed the enzyme activity of GPx (glutathione peroxidase) as shown in Table 1. Upon comparing the control group measures (0.038±0.040 U/L) besides the levels of patient groups (0.047 ± 0.044 U/L), a statistically insignificant relationship ($p>0.001$) was observed as revealed in (Figure 3).

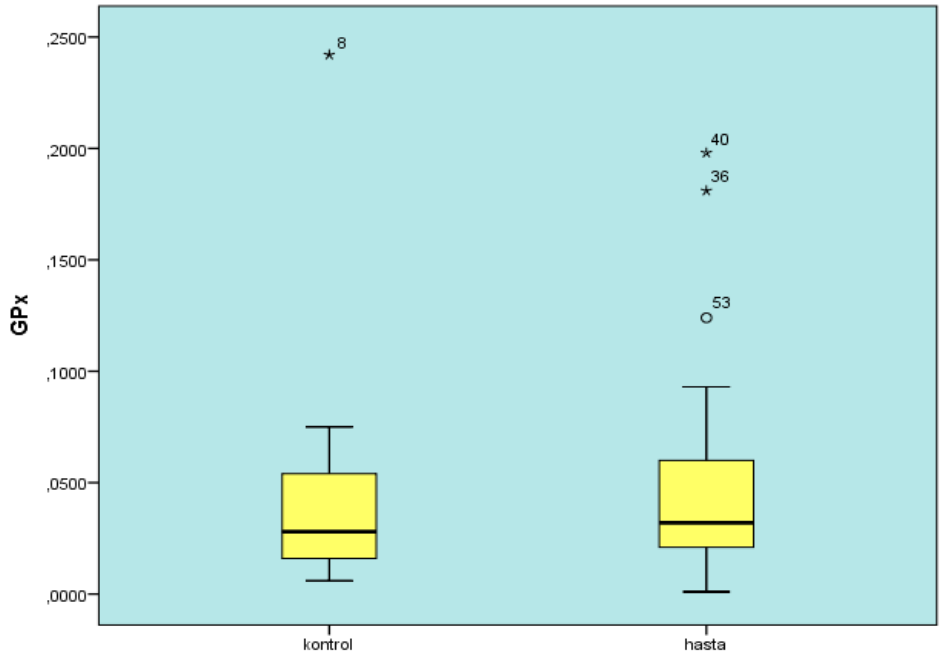

Figure 3. Activity level of GPx enzyme in both control participants and FMF patients

While investigating malondialdehyde (MDA) levels, a significant statistical ($p<0.05$) association was attained medially among the levels of the control group (1.214±0.214 U/L) and the patient group (1.521±0.200 U/L). As originated from (Table 1), the MDA level in the patient groups was relatively higher in comparison to the control groups, as evident revealed in (Figure 4).

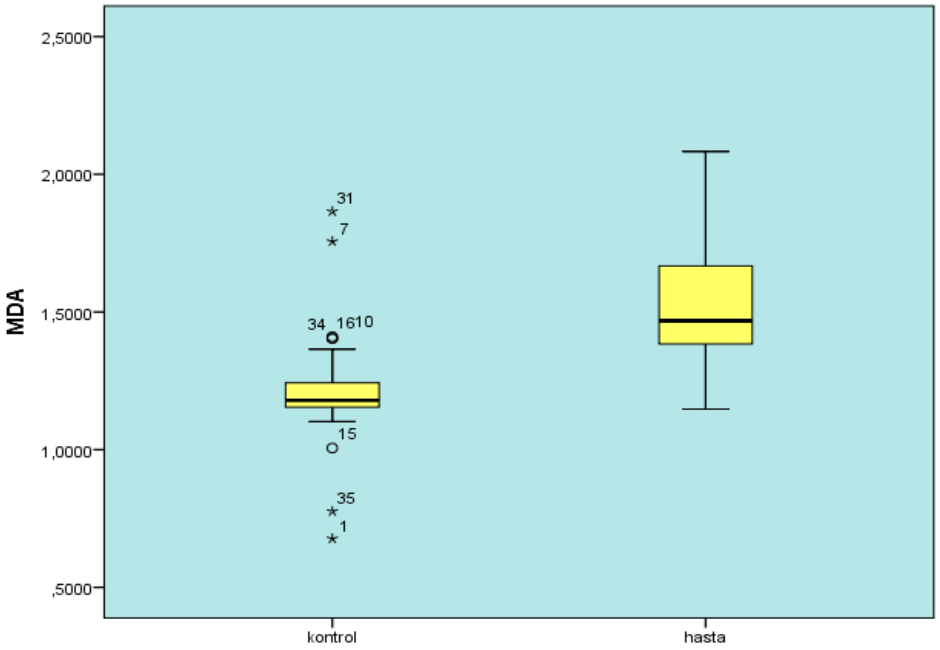

Figure 4. Levels of MDA in both control and FMF patients

DISCUSSION

This investigation analyzed and compared malondialdehyde levels in children, serving as an indicator of oxidative stress, among those diagnosed with familial Mediterranean fever disease, alongside alternative antioxidants like (GSH) reduced glutathione, (GPx) glutathione peroxidase, and (SOD) superoxide dismutase. Within biochemistry, sophisticated enzymology techniques play a pivotal and crucial role in curtailing and eradicating the detrimental effects of oxidants. This involves the utilization of various enzymes, both exogenous and endogenous antioxidants, characterized by their small molecular size. Ansari and Scheff established a strong association between diverse degenerative ailments and the extent of oxidative damage, encompassing markers like catalase, glutathione, SOD, thiobarbituric acid reactive compounds, protein carbonyl, acrolein, 4-hydroxynonenal & 3-nitrotyrosine (Ansari and Scheff, 2010). The current

study findings have not yet provided convincing evidence to ascertain the status of antioxidants in each organ when vulnerable to oxidative stress attacks. These attacks can potentially inflict harm and trigger participation and collaboration among genetic codes and protein-coding genes. Genetic alterations and molecular mechanisms specifically enable us to comprehend and highlight the free radical interactions. Additionally, they underscore the crucial role played by genomics, proteomics, and the progression of disease. Moreover, additional environmental factors, including oxygen tension and the transition metal concentrations, in terms of their oxidation-reduction status, will also play a crucial role in determining factors and resolution components (Rahal et al., 2014).

Glutathione peroxidases (GPxs) among eukaryotic organisms are recognized as the primary enzymatic defense in opposition to oxidative stress induced by hydroperoxides. Through harnessing the reducing capability offered by GSH, H2O2, and various organic hydroperoxides, like fatty acid hydroperoxides, undergo reduction to form the respective alcohols (Michiels et al., 1994). In certain studies, there has been a correlation between glucose intolerance and diabetes, where increased GPx activity was observed, while in others, a decrease in activity was noted. In a study, individuals suspected of having coronary disease and anticipated to have cardiovascular disorders exhibited low GPx activity (Morano et al., 2012). Nevertheless, their study found an insignificant association between (GPx) activity and cardiovascular disease. However, logically, the direction of the association aligned with previous studies. The cause of reduced (GPx) activity in cardiovascular disorders and its increase in the context of diabetes, which are often interconnected illnesses, remains ambiguous and uncertain. Studies conducted on animals demonstrate that the introduction of hydrogen peroxide initiates oxidative stress, resulting in the up-regulation of glutathione peroxidase (GPx). In cases of diabetes and persistent oxidative stress, one might anticipate increased activity of GPx due to this enzyme's upregulation. During myocardial infarction, characterized by acute oxidative stress, an excess production of free radicals might be noticed. Based on the obtained results, it is inferred that the activity of glutathione peroxidase (GPx) fluctuates with age and may be affected by particular diseases, as well as individual physical conditions (Espinoza et al., 2008).

FMF signifies an autoinflammatory disorder characterized by advancing inflammation levels. Inflammatory response functions predominantly in the advancement and atherosclerosis progression in certain rheumatic disorders. Throughout the inquiry, various measurements, including the MDA level, were employed to assess early indicators of atherosclerosis in FMF individuals. They found that MDA levels remained consistent among FMF patients in the interim of acute attacks and free periods. Among individuals with Familial Mediterranean Fever (FMF), irrespective of their oxidative stress status, the findings pointed towards an increased propensity for atherosclerosis over FMF alone. However, during this inquiry, we established a notable statistical correlation with a significance level ($p<0.05$) between both individuals when analyzing the MDA levels in healthy controls and FMF patients. Hence, the existence of additional inflammatory conditions among individuals suffering from FMF could modify their status of oxidative stress (Arıtürk et al., 2013). Our results align with recent literature. Consequently, elevated blood MDA levels can be regarded as a mitigating factor in studies assessing the risk of cancer.

Multiple studies have indicated that the acceleration of atherogenesis occurs significantly due to heightened autoimmune assaults and inflammation in inflammatory conditions characterized by elevated levels, as in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Recently, the correlation of atherogenesis with low-grade inflammatory conditions like ankylosing spondylitis as well as FMF has relatively surfaced, with ongoing studies progressively establishing this association. Yet, research exploring carotid atherosclerosis in individuals of FMF has identified a less aggressive atherogenesis progression than in high-grade inflammatory disorders. The researchers assessed various antioxidant marker levels for serum and whole blood during FMF-attack periods (AP) and FMF-attack-free periods (AFP). Additional researches are required to elucidate the lipoprotein (LDL and HDL) levels' impact on atherosclerosis in individuals experiencing FMF, considering the lipid-lowering effect of colchicine. Their findings exposed that FMF patients exhibit elevated oxidative stress levels during attack periods (Ediz et al., 2011). A study by Erden et al., demonstrated that colchicine that is employed in the regimen of knee osteoarthritis, elevates the capacity of the total antioxidants while reducing amounts of malondialdehyde. In vitro studies, particularly those conducted utilizing multidrug-resistant cell lines, have presented that colchicine elevates glutathione levels and GST activity (Erden et al., 2012). Hence, in many studies focusing on FMF, colchicine therapy seems to be associated with a less aggressive progression of atherogenesis. In this study, patient groups exhibited statistically significant elevations in LDL, ESR, and fibrinogen levels. No notable difference was observed between the groups referring to other biochemical parameters. The literature presents varying findings in FMF patients regarding levels of LDL and HDL (Gürbüz et al., 2016).

In a different study, scientists investigated the levels of oxidants and antioxidants in individuals with

familial Mediterranean fever (FMF) during both periods of attacks and attack-free intervals. They analyzed markers such as MDA, GSH, protein carbonyl (PC), and antioxidant vitamins (A, C, and E), as well as GPx and CAT activity in the serum and total blood of FMF patients. The concentrations of protein carbonyl (PC) and malondialdehyde (MDA) were notably higher ($P < 0.05$) in both the serum and total blood of FMF patients during attacks compared to attack-free periods. Additionally, the activities of GPx and CAT were notably reduced ($p<0.05$) during attacks in FMF patients compared to healthy individuals.

Moreover, no significant discrepancies were observed statistically within the levels of antioxidant vitamins between the healthy groups and patients. The ambiguous findings of the current study demonstrated increased oxidative stress levels during the attack period in patients suffering from FMF (Ediz et al., 2011).

An investigation addressing arthritis and rheumatoid arthritis (RA), both categorized under inflammatory disorders, highlighted those individuals with arthritis and rheumatoid arthritis experience oxidative stress, as indicated by significantly higher MDA levels ($p<0.01$) in comparison to healthy controls. Moreover, additional research revealed reduced amounts of both ascorbate (vitamin C) and α-tocopherol (an isoform of vitamin E) in arthritis and rheumatoid arthritis patients. Additionally, this implies a negative correlation between antioxidant levels and the inflammation present in the serum of these individuals (Sharma et al., 2014).

A widespread deficiency and considerably prevalent in children with FMF when compared to healthy individuals is vitamin D deficiency. Levels of 25(OH)D vitamin vary based on geographical location, skin complexion, sun exposure, and seasons. Certain investigators have suggested that low extents of Vitamin D might be an outcome of the inflammatory process, although this conclusion is not entirely definitive. However, this study provided clarification, indicating a negative correlation wherein Vitamin D levels decreased with increasing age. There were significantly fewer ($p<0.01$), levels of 25-hydroxy vitamin D observed among FMF patients and healthy controls with a higher prevalence among females (Onur et al., 2016).

The discrepancies in genetic mutations will impact the recognition given to FMF patients. In nearly the entire studies, the M694V mutation was recognized as the most prevalent. Additionally, serum amyloid A (SAA) levels upon entry were notably more elevated in individuals with homozygous M694V mutation as compared to those with heterozygous mutations or compound mutations. Additionally, it is indicated that fever, representing 97.3%, is the predominant symptom of FMF (Kilic et al., 2015).

Numerous findings have acknowledged the level of MDA as an indicator of the lipid peroxidation process. Patients with gastric cancer have shown elevated MDA levels in comparison to healthy individual groups. In a research investigation that examined levels of IL-18 in addition to MDA in patients suffering from renal cell carcinoma before surgery and following surgical intervention. The study found that the inflammatory mediator, IL-18, significantly increased after the surgery, alongside raised levels of MDA. Gender-based analysis revealed higher IL-18 concentrations and lower levels of MDA after surgery in the male group. Although IL-18 levels were elevated in the female group, there was no notable variation in MDA levels, while CAT activity showed an increase. Ultimately, the activity of the SOD enzyme showed an increase after surgery in both groups. This indicates that oxidative stress is not solely confined to cancerous cells besides extends to the entire organism (Didžiapetrienė et al., 2014).

The FMF prognosis is established after identifying the distinctive attributes and ruling out additional potential causes of periodic fever. Hence, diagnosing patients becomes challenging, particularly when the symptoms are less severe or present atypical manifestations of the infection. Within the clinical context of FMF, the existence of two mutations on separate alleles—whether homozygous or heterozygous may confirm the diagnosis. However, the diagnosis persists and remains inconclusive when a peerless mutation is detected. Per findings from a study aimed at identifying the fundamental genotypic distribution and diverse presentations clinically in FMF patients, as well as assessing the impact of colchicine therapy on these groups over one year. The disease's severity was evaluated according to the Severity Score of Tel Hashomer. Around one-third of FMF patients possess a single mutation on one allele. Conversely, in a single allele mutation situation, there might be an additional gene not yet fully identified responsible for the disease. The reasons leading to a lack of colchicine response may be elucidated by recognizing that colchicine should traverse different phases to modulate inflammation along its course, potentially influencing its efficacy at multiple points. Several factors, such as grapefruit juice, erythromycin, clarithromycin, simvastatin, lovastatin, cyclosporin, and others, can impact the effectiveness of colchicine by affecting its metabolism at the cytochrome 3A4 level.

Recent findings from a study involving 70 FMF patients primarily exhibited fever, abdominal pain, and arthritis, confirming these as the prevailing symptoms among homozygous, heterozygous, and undefined cases. The mutations E148Q, M680I, and V726A were identified as the most prevalent among the heterozygous group. The mean colchicine dosage necessary for the attack management was notably lower, and heterozygous group individuals displayed

a significantly more effective response to colchicine therapy than homozygous group individuals (Talaat et al., 2012). In the last years, a Turkish research group (Yalçınkaya-Özen) proposed novel parameters and guidelines used to diagnose FMF in children. The group determined that the pediatric criteria were more effective in identifying FMF symptoms in children during early years compared to Tel Hashomer and the Livneh criteria. The pediatric criteria yielded results more accurate and sensitive for diagnosing FMF among children (Demirkaya et al., 2013).

Regarding the metabolic impacts of colchicine, despite its ancient origins and historical use for gout treatment. Scholars note that it has been tested in numerous acute inflammatory contexts such as rheumatoid arthritis (RA) and during FMF acute episodes, despite its limited impact. Colchicine, an extracted portion derived from the colchicum autumnale plant, was recognized for treating acute gout in the sixth century and has been continually prescribed since then. Its impact might not be robust in small doses, yet its effectiveness relies on its interaction with different stages within the inflammatory response. Ultimately, the group of Tel Hashomer in Israel identified and endorsed colchicine as the preferred medication for managing and mitigating FMF following their investigation involving a cohort of 350 patients (Schwabe et al., 1977). Moreover, substantial colchicine usage at elevated doses resulted in notable adverse impacts. Exceeding a daily dosage of 1.8 mg of colchicine might induce fat malabsorption, D-xylose, and Vitamin B12. Furthermore, at higher doses, it may inhibit intestinal enzymes and potentially pose toxicity to the gastrointestinal mucosa, lungs, kidneys, bone marrow, and cardiovascular system. The safe recommended daily dosage, emphasized across various studies, typically ranges from 1 to 1.8 mg (Peters et al., 1983).

During a study involving 20 patients in the acute phase of FMF, a comparison was made against a group of 15 healthy controls. Indicators of the acute-phase reaction included fibrinogen, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and leukocyte levels. Markers of lipid peroxidation were evaluated through measurements of conjugated diene, thiobarbituric acid reactive substances (TBARS), and lipid hydroperoxide concentrations. To assess the oxidation of DNA, the study evaluated 8-hydroxy-2-deoxyguanosine (8-OHdG). Additionally, the study analyzed thiol (T-SH) levels and carbonyl groups to indicate protein oxidative damage. Conversely, markers of antioxidant status such as (GSH) reduced glutathione level, (GPx) glutathione peroxidase, CuZn superoxide dismutase as well as the catalase activities were recognized and quantified. The levels of conjugated diene and carbonyl group were significantly surpassing ($p<0.001$) in individuals with FMF in comparison to healthy controls. Additionally, GPx activity revealed a significant decline ($p<0.01$) in FMF patients when compared to the group of individuals in good health. In the course of an attack, FMF patients exhibited substantially greater levels ($p < 0.001$) of ESR, CRP, leukocytes, and fibrinogen in comparison to those within the course of the attack-free period. FMF patients exhibited significantly reduced Cu-Zn SOD activity ($p < 0.05$) during the attack period. with higher T-SH levels ($p < 0.05$). Hence, the findings indicated an elevation in the acute phase response (APR) and elevated measurements of (OS) oxidative stress in FMF patients as related to healthy controls and individuals during the period of the attack (Guzel et al., 2012). Furthermore, this study highlights the discrepancy in SOD and Cu-Zn SOD behaviors. Contrary to previous findings where SOD levels were more elevated than controls, the assessments conducted during periods of the attack and attack-free, exhibited distinct outcomes. Therefore, more comprehensive studies will elucidate the conclusive outcomes. Oxidative stress levels escalate during the painful episodes of this disorder. The cause of this stress, whether it stems from FMF symptoms or other unidentified factors, isn't entirely clear. However, enhancing antioxidant defenses might help alleviate the symptoms. Furthermore, some available evidence suggests that boosting tissue antioxidant levels through dietary α-tocopherol supplementation can help prevent lipid peroxidation. Dietary supplementation with α-tocopherol has shown potential benefits in FMF treatment, hence prompting the need for further investigations (Karaguezyan et al., 1996).

There's an emerging body of evidence suggesting that genetic changes might heighten susceptibility to oxidative stress, and conversely, oxidative stress could potentially cause genetic alterations. The correlation between gene alterations and oxidative stress holds particular significance within various chronic conditions like neurodegenerative ailments, cancer, and cardiovascular diseases. The tumor suppressor gene p53 is a prime example of susceptibility to oxidative stress. It holds a critical role in controlling cell growth to inhibit cancer development, and it's notably impacted by oxidative stress. Exactly, high levels of oxidative stress can induce alterations or mutations in p53, potentially contributing to the onset of cancer.

Genetic alterations can indeed impact inherited immunity and the regulation of oxidative stress, contributing to various health conditions. Certainly, the partial penetration or varying expressivity of the R202Q mutation might impact the manifestation of the autoinflammatory disease across different ethnic populations (Milenković et al., 2016). Similar outcomes were observed when comparing patients of M694V homozygous in conjunction with another homozygous individual or the combination of the

remaining three mutations in a heterozygous state. Patients homozygous for M694V experienced an increased frequency of attacks within a month ($P<0.001$) and a notably higher ($p<0.015$) occurrence of arthritis (Brik et al., 1999). Research conducted in Iran reported and revealed by the FMF registration center that mutations of M694V-M694V were the most prevalent and frequently observed mutations among patients over ten years. Additionally, during the last ten years, the V726A-M694V mutation combination was frequently observed in those presenting with the disease. Younger patients predominantly exhibit the homozygous mutation M694V, presenting with primary symptoms like abdominal pain and joint involvement. This genotype shares similarities with those found in Arab and Armenian populations (Salehzadeh, 2015).

A recent study highlighted FMF as the primary cause of amyloidosis in Turkish patients. It was reported that the highest occurrence of FMF (1 in 123 individuals) was identified in the Tokat region of Turkey. Abdominal pain can vary in intensity, ranging from dull discomfort to severe, mimicking symptoms of an acute abdomen. Furthermore, it's often misdiagnosed as appendicitis, resulting in unnecessary appendectomies. Patients exhibiting the observable characteristics and identified mutations associated with Familial Mediterranean Fever (FMF) are categorized as phenotype I, while those in phenotype II develop amyloidosis without preceding distinct FMF attacks (Yilmaz and Ozer, 2010). Studies suggest that the triggers for recurrent disease attacks remain uncertain and could stem from physiological, emotional, or physical stress, menstrual cycles, dietary changes, and other ambiguous factors. In a recent study utilizing a case-crossover design, researchers identified an affirmative and significant association statistically between stressful incidences and the occurrences of attacks of FMF (Ktsoyan et al., 2013).

Research suggests that patients of FMF face an elevated susceptibility to cardiovascular disease in comparison to the broader community. The study focuses on assessing the significance of inflammation in FMF patients and individuals following standard intervention and comparing it to dialysis patients, who are presumed to be at higher risk of developing cardiovascular disorders. Additionally, they elucidated the link between the pathophysiological impacts of acute phase proteins and inflammation, a crucial aspect for complications arising from Familial Mediterranean Fever (FMF) ailment management (Akalin et al., 2015).

Given the potential for amyloidosis despite mild inflammation, several analyses have aimed to identify subclinical infection-signaling inflammation in FMF patients, seeking new indicators for this purpose.

At a level of inflammation individuals with Familial Mediterranean Fever (FMF) not exhibiting overt clinical symptoms increase onset complications such as heart disease, anemia, decreased bone mineral density, splenomegaly, and notably amyloidosis, which can pose life-threatening risks. Inflammation typically arises from the release of pro-inflammatory cytokines via macrophages and monocytes. α-TNF, IL-1, IL-6, and sIL-2r exhibit significant involvement during acute FMF episodes. Contrastingly, in interludes devoid of attacks, there is an elevation in the levels of IL-1b among individuals diagnosed with Familial Mediterranean Fever (FMF), correlating with levels of CRP. Moreover, IL-1b levels might serve as a significant indicator of subtle inflammation observed during periods devoid of attacks. within FMF patients. Among patients with Familial Mediterranean Fever (FMF) who are in attack-free phases, measurements of interleukins (IL-6, IL-8) and α-TNF were also detected. The study highlighted the neutrophil/lymphocyte ratio (NLR) as a dependable indicator of inflammation in FMF. The NLR exhibited a significant elevation statistically in individuals with chronic renal failure compared to individuals of good health. Additionally, the quantities were observed to increase concerning the severity of chronic renal failure. NLR serves as a useful indicator to identify inflammation undergoing hemodialysis or peritoneal dialysis in patients, those with cardiac issues particularly myocardial infarction, type 2 diabetes mellitus, and endometriosis, much like in the case of final-stage renal disease. This marker, derived from a complete blood count (CBC), offers a straightforward way to detect subclinical inflammation without incurring additional costs (Özer et al., 2015).

When conducting my literature review, I didn't encounter any studies identical to mine. Besides, a near investigation was found. The study encompassed individuals aged 20 to 40, aiming to delineate the oxidant and antioxidant statuses among FMF patients within courses of both attack period (AP) and attack-free periods (AFP) intervals. The MDA activity was significantly ($p <0.05$) elevated in both samples of serum and total blood obtained from the FMF individuals during the attack period in contrast to the other groups. CAT and GPx activities during the attack-free period, the levels in the FMF individuals revealed a decline ($p < 0.05$) in comparison to the healthy control group. Nevertheless, no significant variations were observed statistically in the amounts of antioxidant vitamins among the groups. So, it could be inferred that the influence and significance of antioxidant levels are greater in children than in adults (Ediz et al., 2011).

Conclusion

Consequently, patients with familial Mediterranean fever displayed elevated MDA levels. Initially, a decline was observed in the action of antioxidant enzymes, like superoxide dismutase (SOD) and reduced glutathione (GSH). Novel clinical approaches should be demonstrated for patients suffering from Familial Mediterranean Fever (FMF), due to these reasons and considering the potential impact of antioxidant enzymes on the disease's etiopathogenesis. Additionally, the clinical assessment of increased MDA levels, a byproduct of lipid peroxidation and indicative of oxidative stress, should prompt further studies for potential treatment approaches. We anticipate that this study will illuminate future research endeavors.

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