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Investigation of the Oxidative Process by Measuring Total Antioxidant Capacity and Total Oxidant Capacity in Patients with Mucopolysaccharidosis: Cross-Sectional Prospective Study

Mukopolisakkaridoz Hastalarında Total Antioksidan Kapasite ve Total Oksidan Kapasite Ölçümleri Yapılarak Oksidatif Sürecin Araştırılması: Kesitsel Prospektif Çalışma

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ABSTRACT Objective: To compare the oxidative stress status between the patients with mucopolysaccharidosis who received and did not receive enzyme replacement therapy and healthy control group. **Material and Methods:** A retrospective study of mucopolysaccharidosis patients with analysis of the total oxidant and antioxidant capacity levels. **Results:** We included 29 mucopolysaccharidosis patients aged between 1-18 years and 50 healthy children. Total antioxidant capacity and total oxidant capacity parameters between this patients and healthy control group were compared. The median age of the patients who were included in the study was 9.0 years and the median age of the cases included in the control group was 8.0 years. Total antioxidant capacity, total oxidant capacity and Oxidative Stress Index (OSI) values did not differ significantly in patients receiving enzyme replacement therapy compared to patients who did not receive enzyme replacement therapy. A comparison of the oxidant and antioxidant system parameters between the patient and control groups revealed a distinct difference, with the control group exhibiting a considerably higher total antioxidant capacity than mucopolysaccharidosis patients, and the patient group showing a significantly higher total oxidant capacity and OSI. **Conclusion:** In this study, it was observed that the antioxidant defence system decreased in patients with mucopolysaccharidoses. It is thought that, in addition to standard treatments, the administration of antioxidant treatments and supporting nutrition in mucopolysaccharidosis patients will increase the quality of life of the patients. Regular sleep, eating healthy foods and doing regular exercise would also increase the effectiveness of these supplements.

Keywords: Mucopolysaccharidoses; oxidative stress; oxidants; antioxidants

ÖZET Amaç: Bu çalışmanın amacı, enzim replasman tedavisi alan ve almayan mukopolisakkaridozlu hastalar ile sağlıklı kontrol grubu arasındaki oksidatif stres durumunu karşılaştırmaktır. **Gereç ve Yöntemler:** Total oksidan kapasite ve total antioksidan kapasite düzeylerinin analizi ile mukopolisakkaridoz hastalarının oksidatif stres seviyelerinin retrospektif incelenmesi. **Bulgular:** Çalışmaya 1-18 yaş arası 29 mukopolisakkaridoz hastası ve aynı yaş grubunda 50 sağlıklı çocuk dâhil edildi. Bu hastalar ile sağlıklı kontrol grubu arasındaki toplam antioksidan kapasite ve toplam oksidan kapasite parametreleri karşılaştırıldı. Çalışmaya alınan hastaların yaş ortalaması 9,0 iken, kontrol grubuna alınan olguların yaş ortalaması 8,0 yaş idi. Enzim replasman tedavisi alan hastalarda total antioksidan kapasite, total oksidan kapasite ve Oksidatif Stres İndeksi (OSİ) değerleri, enzim replasman tedavisi almayan hastalara göre anlamlı farklılık göstermedi. Hasta grubu ve kontrol grubu değerleri oksidan ve antioksidan sistem parametreleri açısından karşılaştırıldığında, kontrol grubunun total antioksidan kapasite değeri mukopolisakkaridoz hastalarına göre anlamlı olarak yüksek olmasına rağmen total oksidan kapasite ve OSİ değerleri hasta grubunda anlamlı olarak yüksek bulundu. **Sonuç:** Bu çalışmada, mukopolisakkaridozlu hastalarda antioksidan savunma sisteminin azaldığı gözlendi. Mukopolisakkaridoz hastalarında standart tedavilere ek olarak antioksidan tedaviler ve beslenmeyi destekleyici uygulamaları hastaların yaşam kalitelerini artırabilir. Düzenli uyku, sağlıklı besinler yemek ve düzenli egzersiz yapmak da bu takviyelerin etkinliğini artırabilir.

Anahtar Kelimeler: Mukopolisakkaridozlar; oksidatif stres; oksidanlar; antioksidanlar

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Mucopolysaccharidosis (MPS) is among the progressive genetic metabolism disorders characterized by multi-system involvement depending on the lack of acid hydrolases that break down glycosaminoglycans (GAG), which are the structural compounds of the connective tissue, in the lysosome.[1] In general, MPS frequency is between 3.4 and 4.5/100,000.[2] Except for MPS II, they are inherited autosomal-recessively. MPS II, on the other hand, is a recessively inherited disease depending on chromosome X.

These are chronic and progressive diseases. This group of diseases, most of which proceed with multisystemic involvement, is characterized by coarse face appearance, organomegaly, dysostosis multiplex, and some with mental retardation. Although the age at which symptoms start and the clinical course of the disease vary, most patients are normal at birth, and clinical findings begin to appear in time.[3] Patients with serious MPS I, MPS II, MPS III and MPS VII (Sly) forms have progressive mental retardation. However, in patients with MPS IV (Morquio) and MPS VI, although somatic findings are very pronounced, there is no mental retardation. The most obvious and common clinical characteristics in all MPS types are being normal at birth, progressive and slow progression, multisystem involvement, mental and motor retardation, coarse face appearance, short stature, growth and developmental retardation, hepatosplenomegaly, dysostosis multiplex, hearing loss, visual impairment, limitation in joint movements, and loss of function in the respiratory and cardiovascular systems.[4]

The diagnosis of MPS is made with laboratory results that are examined in urine GAG analyses and enzyme activity tests. An abnormal enzyme activity is diagnostic for MPS disorder, and the presence of disease-specific GAG's makes the physician consider sub-types of MPS and guide towards appropriate enzyme analysis. Urinary GAG testing is usually the first step for diagnosis.[5] After urinary GAG analysis, confirmation is made by enzyme activity measured in leukocytes or cultured fibroblasts (skin biopsy). Molecular tests, on the other hand, provide limited benefit in initial screening due to the high genetic heterogeneity when considering all MPS types.

The accumulation of GAG's causes destruction in tissues by causing inflammatory response. Excessive 2-O-sulfation of heparan sulfate in MPS I patients exacerbates inflammation by affecting leukocyte and immune cell migration. Apart from this, it is known that by activating TLR-4's, GAG's increase the expression and release of proinflammatory cytokines, and as a result of its accumulation in lysosomes, it causes disintegration of lysosomal membranes. Thus, oxidative stress, apoptosis and necrosis occur in tissues.[6]

It is possible to measure serum concentrations of different oxidant types separately; however, these measurements are time-consuming, labor-intensive and high-cost techniques. Since this is not practical, total oxidant capacity (TOC) measurement was brought to the agenda. One of the most frequently used methods to evaluate oxidant-antioxidant balance in biological systems is determining total antioxidant capacity (TAC). Various measurement methods were developed for TOC and TAC. The most common methods used currently are the colorimetric, fluorescence and chemiluminescence.[7]

In the present study, the purpose was to make TOC and TAC measurements in patients followed-up with MPS diagnosis in the pediatric metabolism clinic of our hospital, compare oxidative stress with healthy individuals, and determine whether there is a statistically significant difference. In addition, it was also aimed in the study to examine the effect of enzyme replacement therapy (ERT) on oxidative stress by performing TOC and TAC measurements in groups who received and who did not receive ERT. With the results obtained, we believe that antioxidant substances can be included in the treatment of MPS patients if oxidative stress parameters show a significant difference, and that mortality and morbidity can be reduced by removing oxidant substances from the macro and micronutrients of patients.

MATERIAL AND METHODS

A total of 29 patients were diagnosed with MPS, 14 of them were female and 15 were male, with ages ranging between 1-18 years. The age, gender, history, vital and physical examination findings were

recorded at the time of application for all patients; the patients who received or who did not receive ERT were noted; hemoglobin, white blood cell, platelet values, and serum liver and kidney function tests, and serum electrolytes levels were examined. The blood samples were taken for total oxidant and antioxidant capacity levels.

A total of 50 children 25 of whom were girls and 25 of whom were boys, who referred to our hospital for routine screening purposes, with no signs of chronic systemic disease, no signs of local or systemic infection, were included as the control group. The blood samples of these children were also received to determine the total oxidant and antioxidant capacity levels, and biochemical parameters. There was no smoking exposure or any other additional chronic disease that could increase oxidative stress in the patient and control groups.

For TAC and TOC tests, blood samples were collected in yellow-capped gel biochemistry tubes and allowed to stand for 30 minutes, then centrifuged at 3,000 rpm for 5 minutes. After the centrifugation process, the serum separated from the blood was placed in eppendorf tubes and stored at -80°C for a maximum of 9 months. TAC and TOC measurements were worked in a fully automatic "Rel Assay Diagnostics" laboratory using the method developed by Dr. Erel with "Rel Assay Selectra E" device.[8] The rate of TOC to TAC was considered as the Oxidative Stress Index (OSI). The resulting TAC unit was converted into μmol/L for calculation, and the OSI value was calculated according to the following formula: OSI=TOC (μmol H2O2 Equiv./L)/TAC (μmol Trolox Equiv./L).

All statistics were performed using the program IBM SPSS Statistics for Windows, Version 22.0 (Armonk, NY: IBM Corp.). The distribution of variables was evaluated with the Kolmogorov-Smirnov test. The Mann-Whitney U test was used for comparing means values of age, TAC, TOC, OSI, and all biochemical parameters. Chi-square test was used in the analysis of qualitative independent data. All data are expressed as mean±standard deviation. Statistical significance was set at $p<0.05$. The study was approved by the University of Health Sciences Ankara Child Health and Diseases Hematology Oncology Training and Research Hospital Clinical Research Ethics Committee (date: March 25, 2019; 2019-025) and made in accordance with the Declaration of Helsinki. The patients included in the study agreed to collection and sharing of their data for scientific purposes.

RESULTS

Twenty-nine patients diagnosed with MPS and 50 healthy children were included in the study. Fifteen of the patient group were male (51.7%), and 14 (48.3%) were girls. The control group consisted of 25 (50%) girls and 25 (50%) boys. The ages of the patients included in the study ranged between 1 and 17 (mean 8.6±4.8) years, and the ages of the cases included in the control group varied between 1 and 16 years. No statistically significant differences were detected between the case and control groups in terms of age and gender.

Five of the patients included in the study were followed up due to MPS I, 6 due to MPS II, 10 due to MPS III, 5 due to MPS IV, and 3 due to MPS VI. During the admittance, 8 (27.6%) of patients had mild mental retardation, 2 (6.9%) had moderate mental retardation, 11 (37.9%) had severe mental retardation, and 8 were mentally normal (27.6%). Nine of the 10 MPS III patients had severe mental retardation.

No significant differences were detected between the serum hemoglobin, white blood cell, platelet values, liver and kidney function tests and serum electrolyte levels of the patient and control group. The TAC, TOC and OSI values did not differ significantly in patients receiving ERT compared to patients who did not receive ERT.

When the values of the case group and control group were compared in terms of oxidant and antioxidant system parameters, a significant difference was detected in TAC, TOC and OSI values. Although the TAC value of the control group was significantly higher, TOC and OSI values were significantly higher in the patient group ($p<0.05$) (Table 1) (distributions of TAC, TOC and OSI values are shown in Figure 1, Figure 2, Figure 3).

The TAC, TOC and OSI parameters did not differ at significant levels ($p>0.05$) in groups receiving and not receiving ERT (Table 2).

TABLE 1: Comparison of the TAC, TOC and OSI parameters of the patient and control groups.

	Study group		Control group		
	X̄±SD	Median	X̄±SD	Median	p value
TAC (mmol/L)	1.15±0.21	1.15	1.27±0.19	1.25	0.020
TOC (µmol/L)	26.75±17.45	22.59	9.80±4.79	8.37	0.000
OSI	2.45±1.77	1.74	0.78±0.38	0.70	0.000

TAC: Total antioxidant capacity; TOC: Total oxidant capacity; OSI: Oxidative Stress Index; SD: Standard deviation.

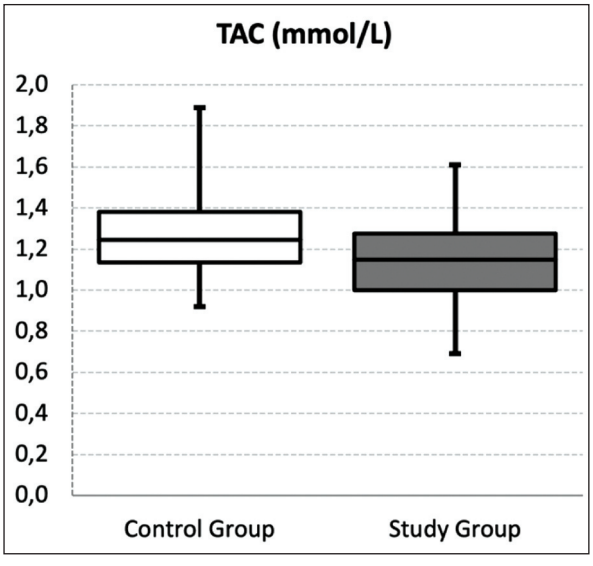

FIGURE 1: Distribution of TAC values in patients and control groups (p<0.05). TAC: Total antioxidant capacity.

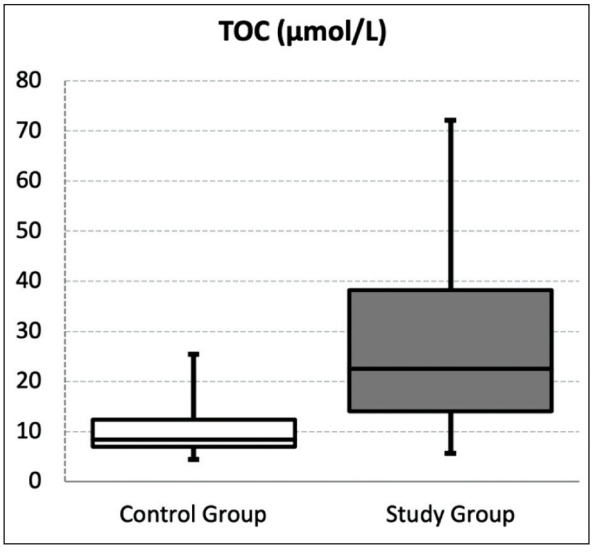

FIGURE 2: Distribution of TOC values in patients and control groups (p<0.05). TOC: Total oxidant capacity.

DISCUSSION

Numerous studies have been conducted to demonstrate the role of oxidative stress in the pathogenesis of inborn errors of metabolic disorders. The main reason for the increase in free radical formation in inborn errors of metabolic disorders is the accumulation of toxic metabolites. It is known that in lysosomal storage diseases, especially in MPS, keeping the production and removal of reactive species in balance is important in preventing lysosomal overload. Lysosomes can be easily affected by oxidative stress, and damaged lysosomal membranes leads to the release of metabolites into the cytosol, resulting in apoptosis and necrosis. The release of lysosomal components can also cause mitochondrial damage through the production of superoxide radicals and hydrogen peroxide, suggesting that lysosomal damage increases oxidative stress.[9]

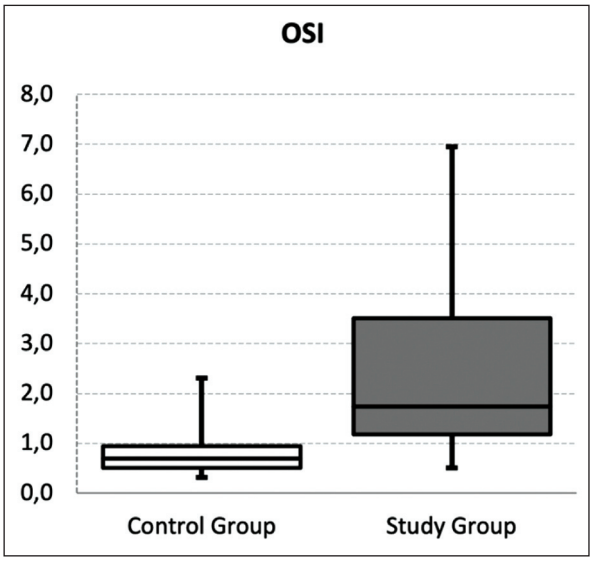

FIGURE 3: Distribution of OSI values in patients and control groups (p<0.05).

One of the possible hypotheses put forward to explain cellular damage in mucopolysaccharidoses is

TABLE 2: Comparison of the TAC, TOC and OSI parameters in groups receiving and not receiving ERT.

	Receiving ERT		Not Receiving ERT		
	X̄±SD	Median	X̄±SD	Median	p value
TAC (mmol/L)	1.14±0.29	1.10	1.16±0.12	1.18	0.662
TOC (µmol/L)	29.73±19.07	23.16	23.96±15.95	21.70	0.407
OSI	2.77±1.99	2.09	2.15±1.54	1.74	0.359

TAC: Total antioxidant capacity; TOC: Total oxidant capacity; OSI: Oxidative Stress Index; ERT: Enzyme replacement therapy; SD: Standard deviation.

that the degradation products of GAG's are structurally similar to lipopolysaccharides, the endotoxin of gram-negative bacteria. These degradation products bind and activate TLR-4 similarly to lipopolysaccharides. With activation of TLR-4, dendritic cells increase phagocytosis, migrate to lymph nodes, process and present phagocytosed antigens, resulting in elevated expression of adhesive and costimulatory proteins that help activate T cells. Thus, the innate immune system response is induced.[10] Animal models of MPS VI and VII have demonstrated elevated nitric oxide and proinflammatory cytokine.

In the literature, there are many articles on the relation between MPS and oxidative stress and antioxidant system. In a study conducted by Donida et al., it was shown that there was an increase in urine 15-F2t-isoprostane and 8-hydroxydeoxyguanosine levels, which showed lipid peroxidation and oxidative damage, compared to the control group in Morquio A patients.[11] In some studies, increased lipid and protein oxidation was determined in the cerebellum of young mice with MPS IIIB; and MPS II had an accumulation of a recent lipoperoxidation product in human brain tissue.[12,13] Simonaro et al analyzed MPS VI and VII animal models; and found that synovial fluid and fibroblasts had a large number of inflammatory molecules and cytokine expression that were secondary to GAG accumulation.[14,15]

Filippon et al. verified that in relation to antioxidant enzymes, both superoxide dismutase (SOD) and catalase activities during ERT, when compared to the control group, was increased only in the first six months.[16] On the other hand, TAC measurement in MPS II patients reached similar values to the control group after six months of ERT. These results show that nonenzymatic antioxidant mechanisms are restored in a shorter time after ERT compared to enzymatic antioxidant mechanisms. Although ERT can lead to a decrease in oxidative stress, it is not sufficient alone. Since ERT cannot fully reach all tissues, different alternatives are needed to increase antioxidant capacity. Pereira et al. confirmed that different ERT processes caused some changes in SOD and catalase activity, which are erythrocyte antioxidant enzymes in MPS I patients. As in a similar study with Gaucher disease patients, a decrease in SOD activity and an increase in catalase activity were observed at different periods of ERT compared to the healthy group.[17] Catalase and SOD activities not only regulated after ERT but also by the presence of reactive oxygen species (ROS); for example, hydrogen peroxide increases catalase and inhibits SOD activity. The effects of ERT on oxidative stress were also investigated in MPS IVA patients by Aguilar Delgado et al., through the analysis of oxidative/nitrative stress indicators in urine and plasma samples.[18] This research reveals that patients with MPS IVA who underwent long-term ERT did not exhibit any DNA/RNA oxidative damage, and there was no significant difference in the production of pro-inflammatory cytokines between the patient and control groups. Similar to other studies, it was found in our study that oxidative stress increased in children with MPS, and the antioxidant defense system decreased. Although it was not found to be statistically significant, the TAC level in patients who received ERT was higher than the patients who did not receive ERT. Since there were not enough MPS subgroups, we did not include data on oxidative stress changes in the subgroups before and after ERT. Therefore, our results in this regard are not reliable.

Some studies were conducted on whether antioxidant treatments had an oxidative stress-reducing effect in MPS and lysosomal storage diseases. In the

study conducted by Oliveira-Silva et al. in 30 patients, it was found that selenium supplementation improved plasma selenium levels; and the rates of serum total glutathione, reduced glutathione oxidation rate and glutathione peroxidase concentrations decreased.[19]

Matalonga et al. conducted a study and showed that coenzyme Q10 levels decreased in fibroblasts of Sanfilippo A patients whose basal coenzyme Q10 was measured.[20] The findings of a study suggest that genistein may be effective in correcting the cell cycle irregularities in MPS II cells.[21] The study carried out by Delgado et al. revealed that genistein has the potential to be utilized as an additional therapeutic approach for addressing the elevated levels of ROS resulting from the accumulation of GAGs in individuals with MPS II.[22] The data from this study did not demonstrate any effects of coenzyme Q10 on SOD and catalase activities or ROS production. Jacques et al. showed that both genistein and coenzyme Q10 have a significant protective effect in vitro against oxidative damage by reducing SOD enzyme activity.[23]

It was shown in our study as well in several previous studies that oxidative stress increased in patients with MPS. How can we increase antioxidant capacity? It has been shown in some studies that the antioxidant system is supported by medical and herbal treatments, nutrition regulation and lifestyle changes. Coenzyme Q, selenium, magnesium, vitamin C, vitamin A supplements are known to reduce oxidant stress. Although getting these vitamins and minerals from natural food sources is a priority, supportive treatment should be started when necessary. Melatonin and genistein are also supplements that have been shown to reduce oxidative stress. In a study, it was shown that Medicago sativa (alfalfa) plant managed to reduce the GAG levels in MPS III patient skin fibroblasts, with its antioxidant and chelating properties of iron ions. Dried clover leaves are widely used as a dietary supplement in capsule or powder form. Resveratrol, one of the grape compounds, has been shown to contribute to the attenuation of neuromuscular degeneration and the restoration of normal motor function in MPS VII studies. Resveratrol is found in high levels in grapes especially in grape seeds, hazelnuts, peanuts, mulberries, blueberries, and cranberries. Regular sleep, eating healthy foods and doing regular exercise also increase the effectiveness of these supplements.

CONCLUSION

In this study, in which the oxidative stress and antioxidant capacity in children with MPS was evaluated, it was observed that the antioxidant defense system decreased in patients. Although more comprehensive studies are needed, this result of our study may be guided in applying antioxidant treatment in MPS patients as a supportive treatment.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

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: *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş;* ***Design:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş;* ***Control/Supervision:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş;* ***Data Collection and/or Processing:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş, Özlem Ünal Uzun, Mehmet Gündüz;* ***Analysis and/or Interpretation:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş, Özlem Ünal Uzun, Mehmet Gündüz;* ***Literature Review:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş, Özlem Ünal Uzun, Mehmet Gündüz;* ***Writing the Article:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş;* ***Critical Review:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş, Özlem Ünal Uzun, Mehmet Gündüz;* ***References and Fundings:*** *Eylem Şerife Kalkan, Aynur Küçükçongar Yavaş, Özlem Ünal Uzun, Mehmet Gündüz;* ***Materials:*** *Eylem Şerife Kalkan.*

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