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Analysis of the Relation Between the Systemic and Ocular Oxidative Stress in Pediatric Patients with Idiopathic Congenital Cataracts: A Cross-Sectional Study

İdiyopatik Konjenital Kataraktı Olan Pediatrik Hastalarda Sistemik ve Oküler Oksidatif Stres Arasındaki İlişkinin İncelenmesi: Kesitsel Çalışma

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ABSTRACT Objective: To investigate the systemic and ocular oxidant-antioxidant status of pediatric patients with idiopathic congenital cataracts. **Material and Methods:** This study investigated the serum and aqueous humor samples of 18 cases with idiopathic congenital cataract and the serum samples of 20 age-and sex-matched healthy cases. Total antioxidant status (TAS), total oxidant status (TOS), oxidative stress index (OSI), total thiol (T-SH), and thiobarbituric acid reactive substances (TBARS) levels in serum and aqueous humor samples were evaluated using spectrophotometric and spectrofluorometric methods. The weight, height, and body mass index parameters were recorded. **Results:** Study groups had statistically similar serum TAS, TOS, OSI, T-SH, and TBARS levels (p>0.05). Statistically significant correlations between oxidant-antioxidant status in serum and aqueous humor were not detected in the patient group (p>0.05). There was a statistically significant positive correlation was observed between the axial length and aqueous humor T-SH levels (r=0.651, p=0.042). Additionally, statistically significant positive correlation was observed between the age and serum TBARS levels in the patient group (r=0.422, p=0.008). **Conclusion:** In terms of oxidant-antioxidant status, this study did not find a correlation between serum and aqueous humor samples in pediatric patients with idiopathic congenital cataract and no difference in serum samples between study groups. This study suggests that oxidative stress may not be a part of idiopathic cataract development in the pediatric population.

Keywords: Antioxidant; aqueous humor; cataract; oxidant

ÖZET Amaç: İdiyopatik konjenital kataraktı olan pediatrik hastalarda, sistemik ve oküler oksidan-antioksidan seviyelerinin incelenmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bu çalışmada, idiyopatik konjenital kataraktı olan 18 olgunun serum ve hümor aköz örnekleri ile yaş ve cinsiyet uyumlu 20 sağlıklı olgunun serum örnekleri incelenmiştir. Serum ve hümor aköz örneklerindeki total antioksidan seviye (TAS), total oksidan seviye (TOS), oksidatif stres indeksi (OSI), total tiyol (T-SH) ve tiyobarbitürik asit reaktif maddeleri [thiobarbituric acid reactive substances (TBARS)] düzeyleri spektrofotometrik ve spektroflorimetrik yöntemler kullanılarak ölçüldü. Boy, kilo ve vücut kitle endeksi değerleri kaydedildi. **Bulgular:** Çalışma grupları arasında, istatistiksel olarak benzer serum TAS, TOS, OSI, T-SH ve TBARS düzeyleri saptandı (p>0,05). Hasta grubunda, serum ve hümor aköz oksidan-antioksidan seviyeleri arasında istatistiksel olarak anlamlı herhangi bir korelasyon saptanmadı (p>0,05). Aksiyel uzunluk ve hümor aköz T-SH düzeyleri arasında istatistiksel olarak anlamlı pozitif korelasyon izlendi (r=0,651, p=0,042). Ayrıca hasta grubunda serum TBARS düzeyleri ile yaş arasında istatistiksel olarak anlamlı pozitif korelasyon saptandı (r=0,422, p=0,008). **Sonuç:** Bu çalışmada, idiyopatik konjenital kataraktı olan pediatrik hastalardaki serum ve hümor aköz oksidan-antioksidan seviyeleri için herhangi bir korelasyon saptanmadı. Ayrıca çalışma grupları arasında, serum oksidan-antioksidan seviyeleri açısından herhangi bir farklılık görülmedi. Bu çalışma, pediatrik popülasyonda oksidatif stresin idiyopatik katarakt gelişimi için önemli bir etkisi olmayabileceğini düşündürmektedir.

Anahtar Kelimeler: Antioksidan; hümor aköz; katarakt; oksidan

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A transparent crystalline lens is essential for clear vision, and cataract formation leading to reduced lenticular transparency is one of the most common causes of decreased visual acuity, especially in the aging population. In the pediatric population, detection of cataract formation is more important than in adults, due to possible complications such as blindness and amblyopia. Approximately 10 million children are affected annually by congenital cataracts, which account for 14% of causes of childhood blindness.[1] Children who are visually affected by congenital cataracts experience lifelong social or educational problems; therefore, understanding the exact reasons for congenital cataracts is important to avoid possible complications and to find correct treatment approaches.[2,3] The etiologies of congenital cataract formation, which are detectable only in a small number of patients, include heredity, metabolic disorders, intrauterine infections, and isolated ocular disorders.[3] Regardless of unilateral or bilateral involvement, congenital cataract formation is mostly idiopathic, and the exact cause is unclear.[2,3]

Reactive oxygen species (ROS) are produced in metabolic and physiological processes and cause denaturation of basic intracellular molecules by disrupting antioxidant defense mechanisms.[4,5] Oxidative stress plays a role in the pathogenesis of many systemic or ocular diseases such as diabetic nephropathy, cardiovascular disease, cancer, age-related macular degeneration, and cataract.[6,7] Ocular oxidative-antioxidative imbalance, which occurs as a result of the breakdown of the oxygen radical scavenging system with aging, is one of the most important factors leading to age-related cataract formation.[8-10] Moreover, higher serum oxidant levels may be associated with increased levels of aqueous humor (AH) oxidants in patients with senile cataracts.[11]

Investigation of serum and AH oxidant-antioxidant status may be useful in determining whether the effect of systemic oxidant status on ocular oxidant status leads to cataract formation. While oxidative parameters in patients with senile cataracts have been reported, no investigations in pediatric patients with congenital cataracts have been performed. Therefore, the aim of this study was to explain the effect of systemic oxidative status on cataract development by evaluating the oxidant-antioxidant levels in serum and AH and detecting possible correlations between the serum and AH oxidant-antioxidant parameters in patients with idiopathic congenital cataracts.

MATERIAL AND METHODS

STUDY DESIGN AND PARTICIPANTS

This prospective study was performed at the pediatric ophthalmology and medical biochemistry departments of tertiary hospitals. The study was approved by the Ethics Committee of Ankara Training and Research Hospital (date: August 27, 2020, no: E-20-203) and conducted in accordance with the ethical principles of the Declaration of Helsinki. Written informed consent was obtained from all the participants. This study investigated a total of 18 (9 girl, 9 boy) pediatric patients who were diagnosed as having idiopathic congenital cataracts and operated upon in our clinic between the ages of 4 and 15 (mean=8.6±4.5 years), and 20 (8 girl, 12 boy) healthy children with clinically clear crystalline lens between the ages of 4 and 12 (mean=6.6±2.5 years).

Pediatric cataract was diagnosed by a single, experienced pediatric ophthalmologist based on detailed ophthalmologic examination. All patients underwent anterior segment examinations with slit-lamp biomicroscopy, intraocular pressure (IOP) measurements with noncontact tonometry, and dilated fundus examinations. Lenstar LS 900 (Haag-Streit AG, Switzerland) was used to measure the axial length (AL) of the eye. Additionally, height and weight measurements of all individuals were recorded. In order to exclude hereditary transmission, a detailed ocular history was taken from the parent(s) of each participants, and these parents were examined with slit-lamp biomicroscopy. Routine pediatric examinations were performed to exclude systemic diseases that led to secondary cataract.

Exclusionary criteria included any systemic disease leading to secondary cataract or affect oxidant status; any systemic drug use; poor cooperation during ocular examination; Toxoplasmosis, other agents, *Rubella*, *Cytomegalovirus*, and Herpes Simplex (TORCH) infection in pregnancy; white blood cells count >11,000 per microliter; C-reactive protein >5

mg/L, body temperature >37.0˚C; any physical symptoms indicating infection, such as cough, sneeze, debility, diarrhea, and painful urination; AL>26 mm; IOP>21 mmHg; and a history of ocular trauma, uveitis, glaucoma, retinopathy of prematurity, persistent fetal vasculature, ocular surgery, or laser treatment. Other cases than the patients with idiopathic sporadic cataracts were not included in this study.

The patient group consisted of cases with lamellar cataracts, and samples belonging to a limited number of patients with other cataract types were not included in this study in order to achieve homogeneity in the patient group (Figure 1). The unilateral cataract formation was observed in 12 (right eye in 7 cases and left eye in 5 cases) cases and bilateral cataract formation was observed in the remaining 6 patients. To avoid duplication, only the right eyes were included in patients with bilateral cataracts.

SURGERY AND COLLECTING SAMPLES

All patients underwent lens extraction with phacoemulsification under general anesthesia by the same experienced surgeon. Ten percent povidone-iodine was used to clean the surgical area. After local antisepsis, the eye was covered with a disposable drape. The corneal incision was performed with a 1.1 mm microvitreoretinal blade; then, approximately 0.1-0.2 cc AH was taken with a 26-gauge insulin injector. AH samples were transferred into the Eppendorf® (Eppendorf, Germany) microcentrifuge tube and stored at -80°C immediately. Following sample collection, routine cataract surgery, including lens extraction with phacoemulsification and intraocular lens implantation, was performed. Topical eye drops such as steroids were not administered before surgery.

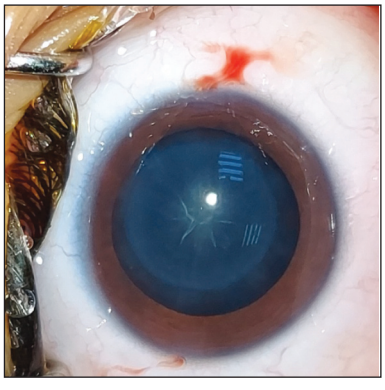

FIGURE 1: The anterior segment photography of the lamellar cataract formation in a 5-year-old male pediatric patient.

Blood samples were collected into the serum separator tube (SST®, BD Vacutainer, USA) during the surgical preparation procedure by establishing vascular access before general anesthesia was performed. These samples were separated from the cells by centrifugation at 2,500 revolutions per minute (rpm) for 15 minutes; then, serum samples were collected, placed into the Eppendorf® microcentrifuge tube, and stored at -80°C without delay.

MEASURING THE OXIDATIVE AND ANTIOXIDATIVE PARAMETERS

In this study, to determine the oxidant and antioxidant conditions, total oxidant status (TOS) and thiobarbituric acid reactive substances (TBARS) levels with total antioxidant status (TAS) and total thiol (T-SH) levels were measured. The oxidative stress index (OSI) (arbitrary unit) was determined by the TOS (μmol H_2O_2 Eq/L)/TAS (mmol Trolox Eq/L) ratio.

TOS and TAS were measured by spectrophotometric method (Rel Assay Diagnostics®) described by Erel using Cobas 501 Autoanalyser (Roche Diagnostics, Mannheim, Germany).[5,12] TBARS level was measured with a spectrofluorometric method, defined by Wasowicz et al., based on measurement of the fluorescent product resulting from the reaction of lipid peroxides with thiobarbituric acid using Hitachi F-2500 Fluorescence Spectrophotometer (Hitachi High Tech America, USA).[13] Ellman's Reagent (5,5'-dithio-bis-[2-nitrobenzoic acid] [DTNB]) is used to estimate sulfhydryl groups (-SH) in a sample by comparing to a standard curve of a sulfhydryl-containing compound. The reaction between -SH and DTNB produces a yellow-colored product measured spectrophotometrically at 412 nm, and T-SH concentration was measured by this method using Shimadzu CL-770 Spectrophotometer (Shimadzu Scientific Instruments, USA).[14] Intra-assay coefficient variations (CV) have been reported as 3.3%, 3.9%, <5%, and <5% for TAS, TOS, TBARS, and T-SH; respectively.

STATISTICAL ANALYSIS

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS version 24.0; IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the distribution pattern of the variables. A student *t*-test was used to compare study groups showing normally distributed data (presented as mean±standard deviation), while the Mann-Whitney U test was used for non-normally distributed data [presented as median (minimum-maximum)]. A χ^2 test was used to analyze gender data. The correlations between parameters were tested by Pearson correlation coefficient for normally distributed data and Spearman's rho correlation coefficient for non-normally distributed data. Statistical significance was considered as $p<0.05$.

RESULTS

Demographic and clinical characteristics between the study groups are shown in Table 1. There were no differences in age or gender characteristics of the 2 (p=0.096 and p=0.536, respectively) groups. Additionally, both study groups had similar body mass index values (p=0.737; Table 1).

Mean IOP and AL measurements were 13.6±3.3 mmHg (range, 9-20) and 21.7±2.3 mm (range, 18.3-26.0) in the patient group, 14.7±4.2 mmHg (range, 8-21) and 21.1±2.5 (range, 17.4-25.5) in the control group, respectively. There were no differences in IOP and AL parameters between the study groups (p=0.462 and p=0.479, respectively).

Table 2 shows serum oxidant-antioxidant status in study groups. Both groups had similar serum TAS, TOS, OSI, T-SH, and TBARS levels (p>0.05; Table 2, Figure 2). For the patient group, AH levels of TAS, TOS, OSI, T-SH, and TBARS were 4.1±0.3 mmol Trolox Eq/L, 27.9 (12.5-32.7) umol H_2O_2 Eq/L, 6.3±1.6, 377.2±71.3 umol/L, and 28.5±9.0 nmol/L, respectively. Additionally, statistically significant correlations between oxidant-antioxidant status in serum and AH TAS, TOS, OSI, T-SH, and TBARS levels were not detected (r=0.351, p=0.183; r=0.013, p=0.961; r=0.073, p=0.789; r=0.441, p=202; r=0.089, p=0.744; respectively).

TABLE 1: Comparison of demographic and clinical characteristics between study groups.

	Patient group (n=18)	Control group (n=20)	p value
Age, years median (minimum-maximum)	6.5 (4-15)	5.5 (4-12)	0.314*
Gender, *n*			
Girl	9	8	0.770**
Boy	9	12	
Height, *m* median (minimum-maximum)	1.4 (0.9-1.7)	1.2 (1.0-1.5)	0.084*
Weight, *kg* median (minimum-maximum)	34.0 (20.0-80.0)	29.0 (17.0-55.0)	0.146*
BMI, kg/m^2 median (minimum-maximum)	19.5 (14.7-29.3)	19.4 (14.0-24.7)	0.737*

*Mann-Whitney U test, **χ^2 test; m: Meter; kg: Kilogram; BMI: Body mass index.

TABLE 2: Comparison of demographic and clinical characteristics between study groups.

	Patient group (n=18)	Control group (n=20)	p* value
TAS, *mmol Trolox Eq/L* median (minimum-maximum)	0.7 (0.1-1.7)	0.7 (0.1-1.4)	0.828
TOS, umol H_2O_2 Eq/L median (minimum-maximum)	12.0 (6.5-32.9)	23.4 (1.6-32.4)	0.331
OSI, *arbitrary unit* median (minimum-maximum)	16.5 (5.3-157.0)	27.1 (6.5-116.3)	0.784
T-SH, *umol/L* median (minimum-maximum)	588.5 (280.0-953.0)	630.0 (398.0-924.0)	0.515
TBARS, *nmol/L* median (minimum-maximum)	75.8 (53.7-125.4)	75.8 (58.3-107.2)	0.784

Non-normally distributed variables are presented as median (minimum-maximum); *Mann-Whitney U test; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; T-SH: Total thiol; TBARS: Thiobarbituric acid reactive substances.

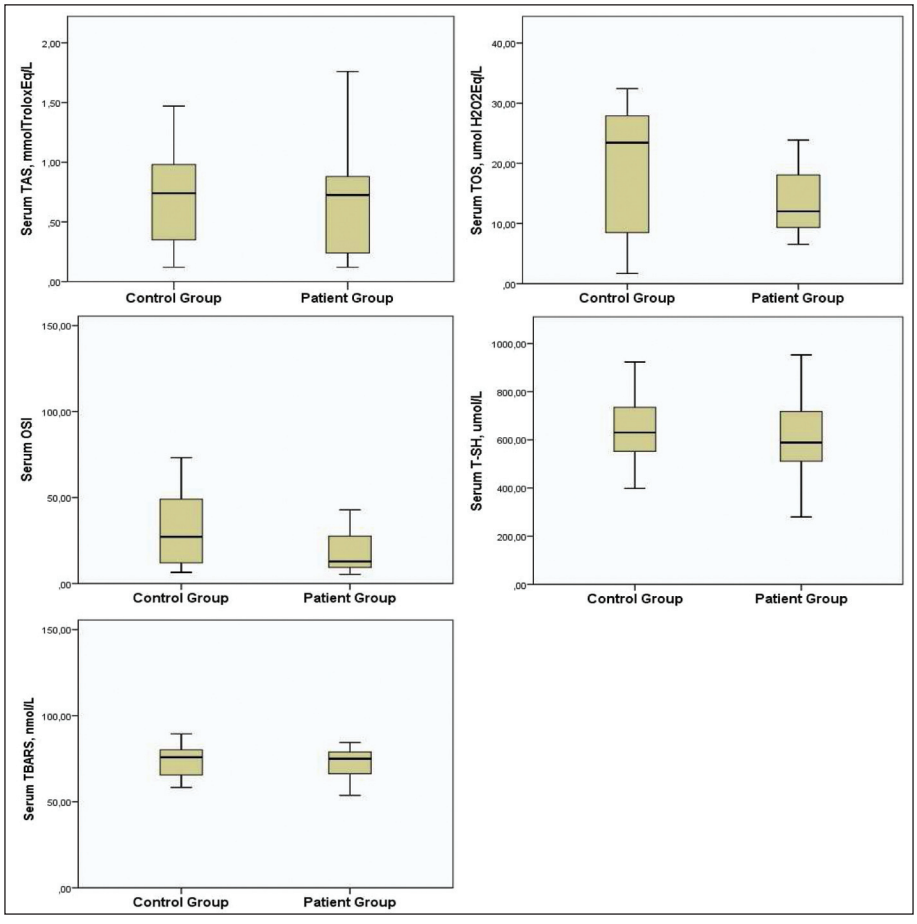

FIGURE 2: Comparison of the serum TAS, TOS, OSI, T-SH, and TBARS levels between the pediatric patients with idiopathic congenital cataract and healthy subjects. TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index; T-SH: Total thiol; TBARS: Thiobarbituric acid reactive substances.

A significant moderate positive correlation between the AL and AH T-SH levels was observed (r=0.651, p=0.042). Additionally, a statistically significant positive correlation was also observed between the age and serum TBARS levels in the patient group (r=0.422, p=0.008).

DISCUSSION

The balance between oxidant molecules, such as ROS, MDA, and nitric oxide (NO), and antioxidant molecules, such as vitamin C, glutathione (GSH), and superoxide dismutase (SOD), is essential to maintain normal cellular functions.[15] Oxidative stress, which shows harmful effects on basic cellular structures, including nucleic acids, proteins, and lipids, occurs by decreased oxidant clearance or increased oxidant levels. The detrimental effects of oxidative stress on the human body may be responsible for the onset and progression of many systemic diseases (e.g., cardiovascular diseases, cancer, and diabetes).[15,16]

This oxidative balance is also important to maintain normal functions of the ocular system. Disruption of normal oxidant-antioxidant status leads to many ocular diseases such as age-related macular degeneration (ARMD), glaucoma, dry eye syndrome, and cataract.[17,18] The crystalline lens whose nutrition and metabolic waste removal are provided by AH is susceptible to oxidative stress due to intense sunlight exposure. The oxidant-antioxidant status in AH may indirectly reflect whether the crystalline lens has oxidative stability due to the close anatomical and metabolic relationship of AH with the lens. In this study, we evaluated the TAS, TOS, OSI, T-SH, and TBARS in the AH and serum of pediatric patients with idio-

pathic congenital cataracts to explain the possible effects of systemic oxidative stress on cataract development.

The quantitative analysis of oxidative stress in several ocular diseases has been investigated in previous studies. Higher TOS levels with lower TAS levels in both the serum and AH samples of patients with pseudoexfoliation syndrome were detected compared to the healthy subjects.[19] Rokicki et al. analyzed the blood samples of patients with glaucoma, and they found a decrease in total SOD activity and an increase in MDA and TOS levels in these patients compared to those without glaucoma.[18] Because of their high metabolic rate and ultraviolet (UV) radiation exposure, retinal tissues are prone to oxidative damage; and retinal disorders such as ARMD and retinal vein occlusion may result in increased oxidative stress in the ocular system.[20,21] As a result, oxidative stress imbalance may be seen in many ocular diseases.

Another disorder in which oxidative stress can play a role in the pathophysiology is cataract formation. With aging, the human lens loses the normal function of its oxygen-radical-scavenger system and cannot protect itself from the harmful effects of oxidative stress.[22,23] Additionally, the relationship between the age-related nuclear cataract and insufficient GSH levels in the lens nucleus has been determined.[24] Following these studies, Elmazar et al. reported that patients with senile cataract (mean age=68.0±6.1 years) had higher levels of serum MDA and lower levels of serum catalase and SOD activity than healthy subjects.[11] They also detected a significant positive correlation between serum ischemia-modified albumin and AH MDA levels in the patient group.

In contrast to these studies, there were no significant differences in serum oxidant-antioxidant parameters between the study groups. Additionally, significant correlations between serum and AH oxidant-antioxidant parameters in children with congenital cataracts were not observed. This study suggests that these results might indicate two different hypotheses. The first view is that the systemic oxidant-antioxidant imbalance may not have begun because protection against oxidative damage at a younger age is sufficient.[22] The second one is that systemic oxidative stress may not be an important contributing factor to cataract development in the pediatric population. Similar to this view, Kao et al. examined AH samples taken from patients of different ages and found lower NO levels in patients with juvenile cataracts (mean age=5.1±2.6 years) than those with senile cataracts (mean age=69.1±10.8 years).[25] Furthermore, they detected a significant moderate positive correlation between age and NO levels in the age-related cataract group.[25] In accord with this study, we found a statistically significant positive correlation between the age and serum TBARS levels in the patient group. In conclusion, it is thought that aging leads to cataract formation with destroying the oxidant-antioxidant balance.

In addition to senile changes, the type of cataract formation and ocular features may affect ocular oxidant status. In diabetic patients, cataract development can be affected by osmotic stress in addition to the oxidative stress generated by polyol pathway activity.[26,27] UV exposure, which impacts oxidative stress in the ocular system, has a more significant impact on the development of cortical cataracts than nuclear cataracts.[28] In accordance with this, Elmazar et al. showed the differences in oxidant-antioxidant levels in patients with cortical and nuclear cataracts.[11] Furthermore, higher AH NO levels were determined by Kao et al. in patients with mature cataracts than patients with nuclear, cortical, and posterior subcapsular cataracts.[25] Since cataract types affect the oxidant-antioxidant status, this study minimized this effect by investigating only patients with lamellar cataracts and focused on the part of oxidative stress in congenital cataract formation, regardless of the cataract type. Ocular anatomical characteristics may also affect the ocular oxidative status. Kim et al. found a lower level of cellular oxidative biomarkers and their correlations with AL (negative) in patients with high myopia.[29] Similarly, the present study detected a positive correlation between the AL and AH T-SH levels. Therefore, it may be stated that reduced metabolic activity in myopia can be related to reduced oxidative stress.[29]

While there is no consensus on the efficacy of systemic antioxidant treatments to prevent cataract

development, a review of previous studies showed that ocular oxidative status can be changed with systemic antioxidant treatment in older patients. Hah et al. determined that the concentration of ascorbic acid in AH is higher in patients treated with systemic vitamin C than in controls.[30] In addition, the concentration of vitamin C in AH of patients with senile cataracts decreases with aging, suggesting that this decrease may play a role in the susceptibility to cataract progression in the elderly population.[31] Less progression of cataract opacities can be observed in eyes treated with vitamin C however the clinical effect of treatment with vitamin C is still controversial.[32,33] On the other hand, certain antioxidants such as N-acetylcarnosine have not been found to be clinically effective in preventing cataract progression, despite its known biochemical antioxidant effect.[34] Since there was no difference in systemic oxidative status between the study groups and no correlation between the systemic and ocular oxidative status of pediatric patients with cataracts, this study suggests that systemic antioxidant treatments may not be useful to prevent cataract formation for children. As a result, systemic or local antioxidant treatments to prevent cataract formation are still being under investigation and further studies are needed to know whether antioxidant treatments are effective for pediatric patients with cataracts.

There were some limitations in the current study, such as a relatively small sample size. Therefore, these results must be explored by further studies to obtain more accurate data. Further, there was no control group with which to compare AH results in this study, as it is not ethically possible. Although the exclusion of the other types of cataracts than lamellar can improve the accuracy of correlation results, this study was not able to investigate systemic oxidant status in patients without lamellar cataracts. Additionally, systemic oxidative stress is not the only factor influencing ocular oxidant status; however, this study tried to decrease other factors using exclusion criteria. Finally, the results of the biochemical analysis can vary depending on measurement techniques and calibration or standardization of the instruments.

CONCLUSION

In conclusion, when this study evaluated the oxidant-antioxidant status in pediatric patients with idiopathic congenital cataracts, no significant differences in serum samples compared to healthy subjects with no significant correlations between serum and AH samples were observed. Therefore, it might be thought that systemic oxidant-antioxidant imbalance may not contribute significantly to the pathophysiology of idiopathic congenital cataract formation, and systemic antioxidant treatment may not prevent pediatric cataract formation; however, further investigation is required to obtain more accurate results

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: *Ali Mert Koçer, Zeynep Adıyaman Koçer;* ***Design:*** *Ali Mert Koçer, Mehmet Şeneş,* ***Control/Supervision:*** *Çiğdem Ülkü Can, Sibel Polat;* ***Data Collection and/or Processing:*** *Gizem Yılmaz Çalık, Eyüpcan Şensoy;* ***Analysis and/or Interpretation:*** *Ali Mert Koçer, Mehmet Şeneş;* ***Literature Review:*** *Ali Mert Koçer;* ***Writing the Article:*** *Ali Mert Koçer, Zeynep Adıyaman Koçer;* ***Critical Review:*** *Mehmet Şeneş, Çiğdem Ülkü Can;* ***Materials:*** *Çiğdem Ülkü Can, Sibel Polat.*

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