Dynamic Thiol-Disulphide Homeostasis and Serum Ischemia Modified Albumin Levels in Patients with Age-Related Cataract

Yaşlılığa Bağlı Katarakt Hastalarında Dinamik Tiyol-Disüfit Dengesi ve Serum İskemi Modifiye Albumin Seviyesi

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ABSTRACT

Purpose: We aimed to determine the alterations in thiol/disulphide homeostasis and ischemia-modified albumin (IMA) levels in patients with different subtypes of age-related cataract by comparing these values with control cases.

Material and Method: Totally 198 eyes of 99 consecutive patients diagnosed with age-related cataract and 188 eyes of 94 control cases were included in the study. In cataract group disease subtypes were recorded as nuclear cataract, cortical cataract, posterior subcapsular cataract or mixed cataract.

Results: Native thiol and total thiol levels were significantly lower in cataract group while disulphide, disulphide/native thiol and disulphide/total thiol ratios were significantly higher. IMA and adjusted IMA levels were also significantly higher in cataract group. When patients with different subtypes of cataract were analyzed; there was not any significant difference between patients with different subtypes of cataract regarding the thiol/disulphide homeostasis parameters or adjusted IMA levels.

Conclusion: Serum dynamic thiol/disulphide homeostasis is altered in age-related cataract patients in the favor of oxidative stress and there was a significant increase in serum IMA and adjusted IMA levels in cataract patients. However, we did not determine any significant difference in dynamic thiol/disulphide homeostasis parameters or IMA levels between patients with different subtypes of cataract. Since age-related cataract is a common disease that can only be treated with surgery; to prevent or slow down its development is critical. The parameters of dynamic thiol/disulphide homeostasis or IMA may be regarded as new targets for the new treatment modalities in cataract.

Key Words: Cataract, Thiol, Disulphide, Ischemia modified albumin, Oxidative stress.

ÖZ

Amaç: Bu çalışmada yaşa bağlı katarakt hastalığının farklı alt tiplerinde tiyol/disülfit dengesi ve iskemi modifiye albumin (IMA) seviyelerini kontrol grubu ile karşılaştırmayı amaçladık.

Gereç ve Yöntem: Çalışmaya yaşlılığa bağlı katarakt tanısı konulan 99 hastanın 198 gözü ve kontrol grubundaki 94 hastanın 188 gözü dahil edildi. Katarakt grubundaki hastalar nükleer katarakt, kortikal katarakt, arka subkapsüler katarakt ve karışık katarakt olmak üzere alt gruplara ayrıldı.

Bulgular: Katarakt grubunda natif tiyol ve total tiyol seviyeleri anlamlı olarak düşük bulunurken, disülfit seviyesi ve disülfit/natif tiyol, disülfit/total tiyol oranları anlamlı olarak yüksek saptandı. Ayrıca IMA ve düzeltilmiş IMA seviyeleri katarakt hastalarında anlamlı olarak yüksek bulundu. Katarakt hastalarının alt grupları arasında tiyol/disülfit dengesi ve düzeltilmiş IMA seviyelerinde anlamlı bir fark bulunmamıştır.

Sonuç: Yaşlılığa bağlı katarakt hastalarında kandaki dinamik tiyol/disülfit dengesi oksidatif stres lehine değişmiş saptanırken, serum IMA ve düzeltilmiş IMA seviyeleri anlamlı yüksek saptanmıştır. Bununla birlikte alt gruplarda tiyol/disülfit dengesi veya düzeltilmiş IMA seviyelerinde anlamlı fark saptanmamıştır. Yaşlılığa bağlı katarakt sadece cerrahi tedavi ile tedavi edilebilen yaygın bir hastalık olduğundan gelişimini önlemek veya yavaşlatmak önemlidir. Dinamik tiyol/disülfit dengesi veya düzeltilmiş IMA parametreleri katarakt hastalığında yeni tedavi modaliteleri için yeni hedefler olarak kabul edilebilir.

Anahtar Kelimeler: Katarakt, Tiyol, Disülfit, İskemi modifiye albumin, Oksidatif stres.

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INTRODUCTION

Age-related cataract is one of the most common causes of visual impairment of elderly population worldwide.[1] The role of oxidative stress, defined as an imbalance between the formation and removal of free radicals in the eye, in pathogenesis of cataract has been reported before.[2-4] In especially age-related cataract, the increased susceptibility of lens nucleus to oxidation and decreased ability to repair oxidative damage has been shown.[5]

Thiol is an organic compound that is well known with its anti-oxidant effects in the cells. Oxidation of thiols results in the formation of reversible disulphide bonds and this thiol disulphide balance has a critical importance for the organisms.[6] Abnormalities in thiol-disulphide balance were reported in many diseases such as malignancies, diabetes mellitus, cardiovascular diseases, and psoriasis before.[7-10]

In pathological conditions such as hypoxia or acidosis, the heavy metals binding capacity of the terminal end of amino acids in albumin was shown to be decreased.[11] This altered form of albumin was named as "ischemia-modified albumin (IMA)" and has been studied in many pathological conditions mainly associated with ischemia.[11-13]

To the best of our knowledge, the data about the relationship between parameters of thiol/disulphide homeostasis and IMA levels with cataract is limited. In this study, we aimed to determine the alterations in thiol/disulphide homeostasis and IMA levels in patients with age-related cataract by comparing these values with control cases and we also aimed to define the alterations in these parameters in patients with different subtypes of cataract.

MATERIAL AND METHOD

Totally 198 eyes of 99 consecutive patients (52 Female, 47 Male) diagnosed with cataract and 188 eyes of 94 control cases (54 Female, 40 Male) were included in the study. The study was performed in Erzincan Mengücek Gazi Education and Research Hospital between April 2017 and April 2018. This study was approved by local ethics committee and informed consent was obtained from all study participants. Serum IMA measurements were carried out within the scope of The Scientific and Technological Research Council of Turkey (TUBITAK) project numbered 117S455.

Patients with concurrent systemic disorders such as rheumatologic diseases, chronic inflammatory diseases, diabetes mellitus, cardiovascular diseases, malignancy, liver and kidney dysfunction, thyroid dysfunction, smokers, alcoholics, patients with a body mass index (BMI) greater than 30.0 kg/m^2, patients with secondary cataract due to steroid administration, diabetes, trauma or any other reason, patients with any ocular disease or ocular surgery and patients denied to incorporate into the study, pregnant and breastfeeding women were excluded from the study.

In patients with cataract the disease period and disease subtype were recorded as nuclear cataract, cortical cataract, posterior subcapsular cataract or mixed cataract. All study participants underwent a complete ophthalmic evaluation. Best-corrected distance visual acuity (BCDVA) based on the logMAR chart were recorded. Venous blood samples were obtained for serum thiol-disulphide and IMA measurements in the early morning after 8 hours of fasting. The samples were centrifuged at 3600 rpm for 10 minutes and the obtained sera were kept at −80°C until analysis.

The parameters of thiol-disulphide homeostasis were measured by using a novel automatic measurement method (Roche Hitachi Cobas c501 automatic analyzer. Roche Diagnostics. USA). In this method, by using NaBH4, the dynamic disulfide bonds (-S-S-) were reduced to functional thiol groups (-SH) and the residual NaBH4 materials were removed from the environment with formaldehyde. The amount of total thiol in the sample was determined with Ellman's reagent. The dynamic disulfide content was calculated as (total thiol - native thiol)/2 and the ratios were calculated in all study participants.[6]

Ischemia-modified albumin levels were determined by measuring the albumin bound cobalt level in serum samples as defined by the Bar-Or et al.[11] Albumin-adjusted IMA (Adj-IMA) levels were calculated by the formula suggested by Lippi et al as:[14]

Individual serum albumin concentration/ median albumin concentration of the population x IMA value

Statistical Analyses

Statistical analysis of the data was performed with SPSS for Windows Version 21.0 (SPSS. Inc. Chicago, IL, USA) software. The distribution of data was analyzed with Kolmogorov-Smirnov normality test. Continuous variables were expressed as mean± standard deviation; while categorical data were reported as number of cases and percentages. Comparisons between two groups were carried out using chi-square test for categorical variables and independent-samples t-test for normally distributed continuous variables. Comparison of data between more than two groups was performed with one way ANOVA test. The correlation of adjusted IMA and thiol/disulphide homeostasis parameters with disease duration or visual acuity of patients with cataract was evaluated using the Pearson or Spearman correlation test. A p value <0.05 was accepted as statistically significant.

RESULTS

Totally 198 eyes of 99 consecutive patients (52 Female,

47 Male; mean age: 68.12± 7.87 years) diagnosed with cataract and 188 eyes of 94 control cases (54 Female, 40 Male; mean age: 66.42 ± 7.64 years) were included in the study. Age (p:0.09) and gender (p:0.07) distribution of study participants were similar between two groups. Visual acuity was significantly better in control group (p:0.001).

In analysis of thiol/disulphide parameters; native thiol and total thiol levels were significantly lower in cataract group (p:0.001) while disulphide, disulphide/native thiol and disulphide/total thiol ratios were significantly higher (p:0.001) (Table 1). IMA (p: 0.02) and adjusted IMA levels (p: 0.005) were also significantly higher in cataract group compared with the control cases.

When patients with different subtypes of cataract were analyzed; patients with posterior subcapsular cataract were determined to be younger than other groups (Table 2). In that group, visual acuity was worse than other groups while disease duration was significantly shorter. However, there was not any significant difference between patients with different subtypes of cataract regarding the thiol/disulphide homeostasis parameters or adjusted IMA levels.

In correlation analysis performed between the thiol/disulphide homeostasis parameters and adjusted IMA levels with disease duration or visual acuity of patients with cataract (Table 3); there was a positive correlation between native thiol and total thiol levels and visual acuity (p:0.001); while there was a negative correlation between disulphide levels and visual acuity (p:0.001).

Table 1. *General characteristics and laboratory findings of study participants.*

	Cataract patients (n: 99)	Control (n:94)	P
Age (years)	68.12± 7.87	66.42 ± 7.64	0.09
Gender (M/F)	47/52	40/54	0.12
Visual Acuity	0.55±0.16	0.006±0.02	**0.001**
Native thiol (µmol/L)	353.95±49.53	398.72±40.24	**0.001**
Total thiol (µmol/L)	392.40±50.97	442.32±41.44	**0.001**
Native/Total thiol	90.11±2.56	90.46±2.48	0.72
Disulphide (µmol/L)	22.12 ± 4.82	19.22 ± 4.84	**0.001**
Disulphide/Native thiol	5.53±1.64	4.36±1.43	**0.001**
Disulphide/Total thiol	4.94±1.28	3.89±1.14	**0.001**
Albumin	3.99 ± 0.18	4.01±0.14	0.28
IMA	0.79± 0.07	0.71± 0.07	**0.02**
Adjusted IMA	0.78± 0.07	0.71± 0.07	**0.005**

M: Male. **F:** Female. **IMA:** ischemia modified albumin, **p:** comparison between cataract and control groups

Table 2. *General characteristics. ocular findings and laboratory data in different types of cataract.*

	Nuclear cataract (n:56)	Cortical cataract (n:46)	Posterior subcapsular cataract (n:34)	Mixed cataract (n:62)	P
Age (years)	66.19± 5.30	70.84±5.92	56.88± 5.94	73.61±4.44	**0.01**
Gender (M/F)	32/24	17/29	16/18	30/32	0.24
Visual Acuity	0.54±0.14	0.54 ±0.10	0.39±0.08	0.64±0.17	**0.01**
Disease Duration (years)	5.92± 2.16	6.45 ±1.79	3.41± 1.04	8.29±2.34	**0.01**
Native thiol (µmol/L)	347.16± 47.98	347.68 ±46.12	360.09± 39.43	361.36±57.35	0.29
Total thiol (µmol/L)	385.70± 47.72	384.83±48.41	398.74± 41.03	400.60±59.35	0.25
Native/Total thiol (%)	89.86± 2.93	90.29±2.09	90.26± 2.33	90.11±2.69	0.79
Disulphide (µmol/L)	19.26± 4.88	18.57 ±4.30	19.32± 4.68	19.61±5.32	0.74
Disulphide/Native thiol (%)	5.70± 1.94	5.40 ±1.30	5.42± 1.42	5.53±1.70	0.83
Disulphide/Total thiol (%)	5.06± 1.46	4.85 ±1.04	4.86± 1.16	4.94±1.34	0.83
Albumin	4.02± 0.15	3.92 ±0.14	4.01± 0.25	4.01±0.19	0.11
IMA	0.77±0.05	0.77 ± 0.07	0.76± 0.06	0.75± 0.09	0.11
Adjusted IMA	0.78± 0.05	0.76± 0.06	0.75± 0.06	0.75±0.08	0.12

M: Male. **F:** Female. **IMA:** ischemia modified albumin, **p:** comparison between four subgroups of cataract

Table 3. *Results of Correlation Analysis.*

	Disease Duration		Visual Acuity	
	r	p	r	p
Native thiol	-0.016	0.824	**-0.359**	**0.001**
Total thiol	-0.019	0.788	**-0.390**	**0.001**
Native/Total thiol (%)	0.001	0.987	-0.023	0.697
Disulphide	-0.019	0.785	**0.238**	**0.001**
Disulphide/Native thiol (%)	-0.003	0.969	-0.026	0.657
Disulphide/Total thiol (%)	0.003	0.962	0.027	0.652
IMA	-0.087	0.223	0.119	0.082
Adjusted IMA	-0.126	0.076	0.107	0.071

DISCUSSION

In this study, we determined a significant alteration in thiol/disulphide homeostasis in the favor of oxidative stress in patients with age-related cataract and we determined a significant increase in IMA levels in cataract patients. However, we did not determine any differences in thiol/disulphide homeostasis or IMA levels in patients with different subtypes of cataract. In cataract group, visual acuity was positively correlated with native thiol and total thiol levels; and negatively correlated with disulphide levels.

Age related cataract is a common health problem among elderly patients that may cause blindness and with an increase in life expectancy; age-related cataract is predicted to increase dramatically in near future. Since the only treatment of cataract is via intraocular surgery leading to a major medical cost and burden for both the patients and health care systems; prevention of this disease gains more important. On the other hand, surgical treatment of cataract may also have many complications.

We determined decreased native and total thiol levels with an increase in disulphide levels. Similar with our results; Elbay et al[15] reported that, both in serum and aqueous humor, thiol/disulfide homeostasis was altered in the favor of oxidative stress in patients with cataracts compared with the healthy controls. Although the data about the dynamic thiol/disulphide homeostasis in cataract is limited, there are many studies in literature evaluating the role of oxidative stress in cataract pathogenesis. Kaur et al[16] reported that the pro-oxidant levels were increased while the levels of enzymatic anti-oxidants were decreased in the cataract patients. Chang et al[17] defined oxidative stress as an important risk factor in the development of age-related cataract. Katta et al (18) demonstrated an enhanced lipid peroxidation with a decrease in total antioxidant levels both in the sera and the lenses of the cataract patients. They further subdivided the cataract patients as having nuclear, cortical and diabetic cataract; and reported the worst results in diabetic group while the best results in cortical cataract patients. Miric et al[19] reported that aqueous humor lipid peroxidation markers and antioxidants may significantly depend on the cataract maturity stage. Recently, Shahinfar et al[20] reported that, despite the high level of oxidative stress in cataract patients, the activity rates of serum anti-oxidant enzymes were also increased. In this study, we determined that, there was a significant decrease in serum total and native thiol levels, while there was a significant increase in disulphide levels showing the presence of an augmented oxidative stress in cataract patients. However, to the best of our knowledge, for the first time in literature, we investigated the alterations in serum dynamic thiol/disulphide homeostasis in different subtypes of cataract and we did not determine any significant difference between patients with nuclear cataract, cortical cataract, posterior subcapsular cataract or mixed cataract.

The data about the changes in IMA levels in age-related cataract patients is also limited. In a prospective study, Elmazar et al[21] reported that patients with cortical cataracts were having higher level of serum IMA levels compared with the patients with nuclear cataracts. In our study, we determined significantly higher IMA and adjusted IMA levels in cataract patients compared with the healthy controls; but we did not establish any significant differences between patients with different subtypes of cataract. This elevated IMA levels also demonstrate an augmented oxidative stress in cataract patients.

In correlation analysis, with an increase in oxidative stress parameters, visual acuity was getting worse. This is an important finding and we suggest that; decreasing oxidative stress may slow down the loss of visual acuity in patients with cataract. On the same way, in an experimental study, Manikandan et al reported that, two anti-oxidant agents, curcumin and aminoguanidine prevent selenium-induced cataractogenesis in vitro.[22] However, in a recent review, convincing evidence could not be found regarding the protective effects of –N- acetylcarnosine drops on cataract.[23] This topic also requires further investigations.

There are some limitations of this study that should be mentioned. We analyzed the oxidative stress parameters in serum samples but combining these findings with the findings of aqueous humor would also be more efficient since eye is isolated from the systemic circulation by the blood-retina, blood-vitreous and blood-aqueous barriers. Secondly, in this prospective study, evaluating oxidative stress parameters in different time periods and evaluating the alterations in these parameters in time during maturation of the cataract would also give more data about the role of these parameters in cataract development. And lastly, we did not determine any significant differences regarding oxidative stress parameters in different subtypes of cataract, although the proposed mechanism of development of different types of cataract was different.

In conclusion, in this study we determined that; serum dynamic thiol/disulphide homeostasis is altered in cataract patients in the favor of oxidative stress and there was a significant increase in serum IMA and adjusted IMA levels in cataract patients. However, we did not determine any alterations in dynamic thiol/disulphide homeostasis parameters or IMA levels in patients with different subtypes of cataract. Since cataract is a common disease that can only be treated with surgery; to prevent or slow down its development is critical. The parameters of dynamic thiol/disulphide homeostasis or IMA may be regarded as new targets for the novel treatment modalities in cataract.

Declaration of interest:

The authors declare no conflict of interest

REFERENCES / KAYNAKLAR

1. Quigley HA, Broman AT. The number of people with glaucoma 1. Klein R, Klein BEK. The prevalence of age-related eye disease and visual impairment in aging: Current estimates. Investig. Ophthalmol. Vis. Sci. 2013;54:ORSF5–ORSF13.
2. Thiagarajan R, Manikandan R.Antioxidants and cataract. Free Radic Res. 2013;47(5):337-45.
3. Tinaztepe O.E., Ay M., Eser E. Nuclear and mithocondrial DNA of age-related cataract patients are susceptible to oxidative damage. Curr. Eye Res. 2017;42:583–8.
4. Wang S, Guo C, Yu M, Ning X, Yan B, Zhao J, Yang A, Yan H. Identification of H_2O_2 induced oxidative stress associated microRNAs in HLE-B3 cells and their clinical relevance to the progression of age-related nuclear cataract. BMC Ophthalmol. 2018;18(1):93.
5. Beebe DC, Holekamp NM, Shui YB.Oxidative damage and the prevention of age-related cataracts.Ophthalmic Res. 2010;44(3):155-65.
6. Erel O, Neselioglu S. A novel and automated assay for thiol/disulphide homeostasis. Clin Biochem. 2014;47:326–32.
7. Sönmez MG, Kozanhan B, Deniz CD, Göger YE, Kilinc MT, Neşelioglu S, Ere O. Is oxidative stress measured by thiol/disulphide homeostasis status associated with prostate adenocarcinoma?Cent Eur J Immunol. 2018;43(2):174-9.
8. Tola EN, Köroğlu N, Ergin M, Oral HB, Turgut A, Erel Ö. The Role of Follicular Fluid Thiol/Disulphide Homeostasis in Polycystic Ovary Syndrome Balkan Med J. 2018;35(4):306-10.
9. Sivri S, Kasapkara HA, Polat M, Alsancak Y, Durmaz T, Erel Ö, Bozkurt E. Dynamic thiol/disulphide homeostasis and its prognostic value in patients with non-ST elevation-acute coronary syndromes.Kardiol Pol. 2018;76(2):426-32.
10. Kilic A, Yorulmaz A, Erdogan S, Cakmak SK, Guney E, Sen O, Erel O. An evaluation of thiol/disulphide homeostasis in patients with psoriasis. Postepy Dermatol Alergol. 2017;34(5):464-7.
11. Bar-Or D, Lau E, Winkler JV. A novel assay for cobaltalbumin binding and its potential as a marker for myocardial ischemia-a preliminary report. J Emerg Med. 2000;19(4):311-5.
12. Dogru M, Akoglu H, Kilinckaya MF, Ulfer G. Ischemia-modified albumin levels in children with asthma: a pilot study.Arch Argent Pediatr. 2018;116(4):e522-e528.
13. Wahab MAKA. Ischemia modified albumin (IMA) in acute coronary syndrome (ACS) and left bundle branch block (LBBB). Does it make the difference? Egypt Heart J. 2017;69(3):183-90.
14. Lippi G, Montagnana M, Salvagno GL, Guidi GC (2007). Standardization of ischaemia modified albumin testing: adjustment for serum albumin. Clin Chem Lab Med, 45, 261-2.
15. Elbay A, Ozer OF, Altinisik M, Elbay AE, Sezer T, Bayraktar H, Ozdemir H. A novel tool reflecting the role of oxidative stress in the cataracts: thiol/disulfide homeostasis. Scand J Clin Lab Invest. 2017;77(3):223-7.
16. Kaur J, Kukreja S, Kaur A, Malhotra N, Kaur R. The oxidative stress in cataract patients. J Clin Diagn Res. 2012;6(10):1629-32.
17. Chang D, Zhang X, Rong S, Sha Q, Liu P, Han T, Pan H. Serum antioxidative enzymes levels and oxidative stress products in age-related cataract patients.Oxid Med Cell Longev. 2013;2013:587826.
18. Katta AV, Katkam RV, Geetha H. Lipid peroxidation and the total antioxidant status in the pathogenesis of age related and diabetic cataracts: a study on the lens and blood.J Clin Diagn Res. 2013;7(6):978-81.
19. Miric DJ, Kisic BM, Zoric LD, Miric BM, Mirkovic M, Mitic R. Influence of cataract maturity on aqueous humor lipid peroxidation markers and antioxidant enzymes.Eye (Lond). 2014;28(1):72-7
20. Shahinfar J, Keshavarzi Z, Ahmadi M, Barzegar S, Asieh G, Abbaspour A. Serum Oxidative Stress Markers in Patients with Senile Cataract and Healthy Controls.J Coll Physicians Surg Pak. 2018;28(6):448-51.
21. Elmazar HM, Elmadbouh I, Mandour SS, Al Ariny GM, Ibrahim AM.Association between cataract progression and ischemia-modified albumin in relation to oxidant-antioxidant profiles in the serum, aqueous humor, and lens. J Cataract Refract Surg. 2018;44(2):134-9.
22. Manikandan R, Thiagarajan R, Beulaja S, Chindhu S, Mariammal K, Sudhandiran G, Arumugam M. Anti-cataractogenic effect of curcumin and aminoguanidine against selenium-induced oxidative stress in the eye lens of Wistar rat pups: An in vitro study using isolated lens. Chem Biol Interact. 2009;181(2):202-9.
23. Dubois VD, Bastawrous A. N-acetylcarnosine (NAC) drops for age-related cataract.Cochrane Database Syst Rev. 2017;2:CD009493.