Role of Anti-Oxidant System and Lipid Peroxidation in the Development of Age-Related and Diabetic Cataract

Yaşa Bağlı ve Diabetik Katarakt Gelişiminde Anti-Oksidan Sistem ve Lipid Peroksidasyonunun Rolü

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ABSTRACT

Purpose: To investigate the possible relationship of age-related nuclear and diabetic cataract development with antioxidant system, lipid peroxidation and sialic acid levels in serum and aqueous humour.

Materials and Methods: Blood and humour aqueous samples of 25 patients with age-related cataract (Group 1), 25 patients with diabetic cataract (Group 2), and 24 age-matched controls (Group 3) without cataract were included. Sialic acid (SA) and malondialdehyde (MDA) concentrations, and catalase (CAT) and superoxide dismutase (SOD) activities were detected in serum samples. Aqueous samples were analysed to detect only SA levels and CAT activity.

Results: Group 2 patients had significantly higher serum SA and MDA concentrations as compared to group 1 ($p<0.001$ for both) and group 3 ($p<0.0001$, and $p<0.001$ respectively) and lower serum CAT and SOD activities than group 3 ($p<0.001$ and $p<0.01$ respectively). Serum CAT activity was also significantly lower in group 2 than group 1 ($p<0.01$), and SOD activities were not different between the groups 2 and 1 ($p>0.05$).

In case of aqueous samples, group 2 patients had higher mean concentration of SA, and lower levels of CAT activity as compared to group 1 ($p<0.001$ for both) .Group 1 patients also had significantly decreased CAT activity when compared to group 3 ($p<0.01$). But SA levels were not different between groups 1 and 3 ($p>0.05$).

Conclusions: Increased oxidative stress and decreased antioxidant enzyme activities may have a role in the development of age-related and diabetic cataract. Increased sialic acid levels seem to be associated with cataract development in diabetics.

Key Words: Anti-oxidant system, cataract, diabetes mellitus, oxidative stress, sialic acid.

ÖZ

Amaç: Çalışmanın amacı yaşa bağlı ve diabetik katarakt gelişiminde muhtemel antioksidan sistem, lipid peroksidasyonu ve sialik asit ilişkisini araştırmak.

Gereç ve Yöntem: Çalışmaya kan ve ön kamara sıvısı alınan 25 yaşa bağlı kataraktlı (grup 1), 25 diabetik kataraktlı (grup 2) hasta ve 24 eş yaşta sağlıklı kontrol grubu alınmıştır (grup 3). Serumda, sialik asit (SA), malondialdehit (MDA) konsantrasyonları, Katalaz (CAT) ve superoksit dismutaz (SOD) aktiviteleri, ön kamara sıvısında ise SA ve CAT aktiviteleri bakılmıştır.

Bulgular: Grup 2 hastalarında serum SA ve MDA konsantrasyonları grup 1 ($p<0.001$ heriki parametre için)ve grup 3 (sırasıyla $p<0.0001$ ve $p<0.001$) ile karşılaştırıldığında anlamlı yüksek tespit edilmiştir. Ayrıca grup 2 serum CAT ve SOD aktivitesi grup 3 ile karşılaşrırıldığında anlamlı düşük izlenmiştir. Grup 2 Serum CAT aktivitesi Grup 1 ile karşılaştırıldığında anlamlı düşük bulunurken ($p<0.01$), SOD aktivitesi iki grup arasında anlamlı farklı bulunmamıştır ($p>0.01$). Ön kamara örneklerinde ise grup 2 hastalarında grup 1 ile karşılaştırıldığında yüksek ortalama SA konsantrasyonu ve düşük CAT aktivitesi tespit edilmiştir ($p<0.001$ her iki değer için). Grup 1 hastaları grup 3 hastaları ile karşılaştırıldığında ise düşük CAT aktivitesi bulunmuştur ($p<0.01$). Buna rağmen SA seviyeleri grup 1 ve grup 3 arasında anlamlı farlı bulunmamıştır ($p>0.01$).

Tartışma: Artmış oksidatif stres ve azalmış antioksidan enzim aktivitesinin yaşa bağlı ve diabetik katarakt gelişiminde rol oynadığını düşünmekteyiz.Artmış sialik asit seviyeleri ise katarakt gelişimi ile ilgili gözükmektedir.

Anahtar Kelimeler: Antioksidan sistem, katarakt, diabet, oksidatif stress, sialik asit.

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INTRODUCTION

Cataract is the leading cause of blindness in the world, responsible for 48% of blindness worldwide. Multiple forms of cataracts exist and the pathophysiology of cataract formation is not completely understood, but a putative cause for age-related nuclear cataracts is oxidative stress.[1]

The lens depends on a balanced redox state for maintaining its transparency. The endogenous high level of glutathione and some other enzymes plays a vital role as the first line of defense against exogenous and endogenous reactive oxygen species (ROS) and keeps lens proteins in a reduced state.[2] It is widely believed that a rise in the intracellular levels of ROS will damage various cell components, interrupt physiological functions and lead to aging and various oxidative-stress-associated diseases, such as cancer, cardiovascular diseases, nerve degenerations, macular degeneration and cataracts.[3] Cellular defense mechanisms protecting against the toxic effects of oxidative insult must therefore play an important role in defense against cataractogenesis. Superoxide dismutase (SOD) and catalase (CAT) are two major anti-oxidant enzymes, which protect lens proteins against ROS mediated oxidative damage.[4]

ROS mediated lipid peroxidation (LPO) also plays a role in cataract development[5]. Lipid peroxidation due to oxidative stress occurs in human cataract and lens opacity has been found to correlate with the level of LPO degradation products accumulated in the lens.[6] LPO is implicated in human cataractogenesis because the toxic peroxidation products induce fragmentation of soluble lens proteins and damage vital membrane structures, correlating with an increase in lens opacity and changes in the refractive properties of the lens.[7-9] One of the most frequently used biomarkers providing an indication of the overall lipid peroxidation level is the plasma concentration of malondialdehyde (P-MDA), one of several byproducts of lipid peroxidation processes.[10]

There is strong evidence to show that diabetes is associated with increased oxidative stress, which is thought to play an important role in the pathogenesis of various diabetic complications. The powerful arguments indicate that oxidative stress is increased in diabetes due to overproduction of ROS and decreased efficiency of antioxidant defences, a process that starts very early and worsens over the course of the disease. During the development of diabetes, oxidation of lipids, proteins and DNA increase with time. However, the source of the hyperglycemia-induced oxidative stress is not clear. It was found that the polyol pathway is the major contributor to oxidative stress in the lenses diabetic mice.[11-13]

Sialic acid -a family of acetylated or glycosylated derivatives of neuraminic acid- occupy the terminal position of glycoproteins and glycolipids. Most studies on sialic acid have focused primarily on cell protection, cell differentiation, cell adhesion, immunology, inflammation, fertilization, and tumors. Serum SA levels were reported to be elevated in type-2 diabetic patients, and increased level of sialic acid in blood has been claimed to be associated with the increased risk of chronic complications of diabetes including atherosclerosis and nephropathy.[14-16]

In the current study, we tried to detect the serum and aqueous humour activities of two important antioxidant enzymes, SOD and CAT, and the levels of MDA, an important biomarker of LPO process, in normals without cataract, in diabetic patients with cataract and in patients with age-related cataract. We also measured the levels of sialic acid to evaluate its role in the development of cataract.

MATERIALS AND METHODS

This case-control study included a total of 25 patients with age-related nuclear cataract (Group 1), 25 patients with diabetic cataract (Group 2) and 24 controls (Group 3) without cataract who underwent pneumatic retinopexy for retinal detachment. The patients and controls were selected consecutively. Participants in the study had no clinical evidence of any disease state which might effect the antioxidant capacity except for group 2 patients who

Table 1: Serum SA and MDA levels and CAT and SOD activities (mean±SD and range).

	Group 1	Group 2	Group 3	P		
				Groups 1/ 3	Groups 2 / 3	Groups 1/ 2
SA (mg/dL) Range	73.02±4.09 65.80-79.80	82.69±3.66 77.1-90.10	73.88±6.94 54.80-82.10	>0.05	<0.0001	<0.001
MDA (nmol/mL) Range	3.50±0.54 2.77-4.22	4.83±0.60 3.88-6.31	2.52±1.69 1.98-3.37	<0.001	<0.001	<0.001
CAT (kU/L) Range	33.00±4.04 25.31-41.78	19.74±4.04 12.17-25.23	38.52±6.11 28.12-52.24	<0.001	<0.001	<0.01
SOD (U/mL) Range	21.52±3.09 17.11-28.11	20.84±2.34 17.55-25.82	25.35±1.69 21.28-28.04	<0.01	<0.01	>0.05

P value demostrated statistical differences between each two groups. SA: Sialic Acid. MDA: Malondialdehyde, CAT: Catalase, SOD: Superoxide Dismutase.

Table 2: Aqueous humor SA levels and CAT activities (mean±SD and range).

	Group 1	Group 2	Group 3	P		
				Groups 1/ 3	Groups 2 / 3	Groups 1/ 2
SA (mg/dL) Range	1.93±0.29 1.35-2.50	3.35±0.85 1.95-4.65	2.03±0.18 1.75-2.43	>0.05	<0.0001	<0.001
CAT (ku/L) Range	8.99±1.62 5.35-12.37	5.08±1.57 1.27-7.50	11.09±2.15 7.42-14.47	<0.01	<0.0001	<0.001

P value demostrated statistical differences between each two groups. SA: Sialic acid. MDA: Malondialdehyde, CAT: Catalase, SOD: Superoxide dismutase

had diabetes mellitus (DM). All subjects were selected as nonsmokers. The research followed the tenets of the Declaration of Helsinki. Informed consent was obtained from all subjects after explanation of the nature of the study. The study was approved by the local ethics committee.

Groups 1 and 2 patients had a significant vision loss (best-corrected visual acuity lower than 0.3) and an age-related or diabetic cataract respectively in at least one eye. Any patients with a secondary cataract were excluded: for example, those due to trauma, drug use, uveitis, and other known causes. Group 3 consisted of age- and sex-matched patients who had clear lenses and underwent pneumatic retinopexy for retinal detachment.

8 cc venous blood samples and 100 μl aqueous humor samples were collected. Serum was obtained by centrifugation at 3000g for 10 min. Aqueous samples of group 1 and 2 patients were obtained with a syringe through a side port incision created with a MVR blade at the beginning of the cataract surgery. In group 3, aqueous humor samples were obtained by paracenthesis during the retinopexy procedure. All samples were stored immediately at -80°C until analysis.

Serum total SA level was assayed using thiobarbituric acid assay.[17] CAT and Cu-Zn SOD activities were measured by Aebi spectrophotometeric method[18] and the method described by Sun et al respectively.[19] MDA levels were estimated by the modified thiobarbituric acid method described by Buege and Aust.[20]

The data were presented as mean±SD and range. Differences among all groups for SA and oxidant/ antioxidant parameters were evaluated by Kruskal-Wallis variance analysis. When the p-value of the Kruskal-Wallis test was statistically significant, Bonferroni corrected Mann-Whitney U-test was used to know which groups differ from which others. The limit of statistical significance was set at $p<0.0167$.

RESULTS

There was no statistically significant difference between the mean age values among the 3 groups; 65.32 ± 7.74 years for Group 1, 65.92 ± 6.18 years for Group 2, and 63.32 ± 4.20 years for controls ($p>0.01$).

Differences among all three groups for serum parameters of SA, MDA, CAT and SOD were statistically significant ($p<0.01$). Serum parameters of the patients and controls were shown on Table 1. When the serum parameters of groups 1 and 2 were compared, SA and MDA levels were found to be increased in group 2 ($p<0.001$ for both); CAT activity was lower in group 2 ($p<0.01$) and SOD activities were not different between the groups ($p>0.01$).

When groups 2 and 3 were compared, group 2 patients had significantly higher serum SA and MDA levels ($p<0.0001$), and lower serum CAT ($p<0.001$) and SOD ($p<0.01$) activities.

When groups 1 and 3 were compared, mean serum MDA concentration was significantly higher in group 1 ($p<0.01$), and CAT and SOD activities were significantly higher in group 3 ($p<0.01$). SA levels were not different ($p>0.01$).

Quantity of aqueous samples was not enough for detection of SOD activity and MDA levels and only CAT activity and SA levels could be detected (Table 2). Differences among all groups for aqueous parameters of SA and CAT were statistically significant ($p<0.01$). Group 2 patients had higher mean concentration of SA, and lower levels of CAT activity as compared to group 1 ($p<0.001$ for both) and group 3 ($p<0.0001$ for both). Group 1 patients also had significantly increased aqueous decreased CAT activity when compared to group 3 ($p<0.001$). SA levels were not different between groups 1 and 3 ($p>0.01$).

DISCUSSION

Oxidative stress is the result of an imbalance of antioxidants and pro-oxidants. Since oxygen is a strong oxidant, it is not possible to avoid secondary oxidations that are involved in ordinary metabolism. Oxidative stress is involved in many ocular diseases such as age-related macular degeneration, retinopathy of prematurity, retinal light damage, and age-related cataract. The mechanism of cataractogenesis in diabetes also seems to be associated with oxidative stress and osmotic stress as well.[8,10,11]

The oxidative stress associated with diabetes mellitus may play an important role in the initiation and progression of diabetic complications. It has been

suggested that free oxygen radicals trigger cataract, one of the degenerative manifestations of diabetes. The toxic effects of the reactive oxygen species are neutralized in the lens by the enzymatic and nonenzymatic antioxidants. The enzymatic (superoxide dismutase, glutathione peroxidase, catalase) and nonenzymatic (ascorbate, glutathione, cysteine) antioxidant system activities are decreased in the lens and aqueous humor during aging and are implicated in the development of senile cataract.[21]

In the current study we evaluated the oxidative stress markers both in aqueous humor and serum since in senile cataract and especially in diabetics the oxidative insult seems to be systemic and not only at the lens level. We found that serum CAT and SOD activities were lowest in diabetic cataract patients. Aqueous samples also showed the lowest CAT activity in diabetics. Control patients had the highest antioxidant enzyme activities. Also, malondialdehyde, one of the important LPO products, was significantly higher in serum samples of diabetics and age-related cataract patients than controls. These results support the hypothesis that diabetic and age-related cataract development were associated with decreased antioxidant enzyme activities and increased oxidative stress markers.[22-25]

The increased concentrations of primary molecular LPO products were detected in the lipid moiety of the aqueous humor samples obtained from patients with cataract as compared to normals.[26] The aqueous humor normally contains superoxide anion and hydrogen peroxide (H_2O_2), a compound capable of generating reactive oxygen species, which has been reported to be increased in aqueous humour of the cataract patients as compared to controls.[3] These molecules may flow into the lens and thus predispose the lens centre to oxidation.[27] So, antioxidant defence supplied by aqueous humor may have importance to remove oxidants released into immediate environment of the avascular lens tissue.

Although the other parameters of oxidative stress in aqueous humour have been evaluated before in cataract patients[28-31], the current study is the first to analyse CAT activity in aqueous humour of cataract patients. We found decreased activity in senile and diabetic cataract patients, and this finding was parallel with systemic decrease. Many other studies detecting SOD and CAT activities in cataract patients were limited only to plasma[32-34] or cataractous lens tissues itself[21,35] and all of them reported decreased enzyme activities. Maurya et al reported that the serum levels of these anti-oxidant enzymes decrease, which lead to early cataract formation in diabetic patients.[34] Ozmen et al reported that the antioxidant capacity in the diabetic cataractous lens tissues were decreased and suggested a role of antioxidant enzymes in the genesis of diabetic cataracts.[21] Studies analyzing these parameters in aqueous humour were performed mainly in glaucoma patients.[36,37] Glaucoma is also an oxidative stress related disease and reported to be associated with decreased antioxidant enzyme activities in aqueous humour.

One of the most important findings in the current study is that increased serum and aqueous SA levels seems to be associated with cataract development in diabetic patients. To our knowledge, this study is the first to detect SA levels to explore any association with cataract development. Previous studies investigating the SA levels in anterior chamber have been performed in diseases other than cataract such as Behçet's disease.[38,39]

Sialic acid is an acidic sugar that is commonly found at the ends of the glycan chains of cell-surface glycoproteins and glycolipids. They are negatively charged under physiological conditions, contribute to biophysical characteristics of cell surfaces and can be recognized by many receptors of endogenous and exogenous origin. It was reported to be associated with coronary atherosclerosis, hypercholesterolemia and myocardial infarction[15]. Increased levels of sialic acids in senile cataractous lenses[40-42] and serum[43] have been shown in patients with senile cataract. Although not statistically significant we also found high levels of SA in serum and aqueous samples of age-related cataract patients than controls.

In the current study, diabetic cataract patients had the highest levels of SA in serum and aqueous as compared to senile cataract patients and controls. Serum SA levels are reported to be elevated in type-2 diabetic patients, and increased level of sialic acid in blood has been claimed to be associated with the increased risk of many microvascular complications of DM and may be a possible useful marker for diabetic microangiopathy.[14-16,44] Increased levels of SA in diabetics have been also explored to detect its relationship with diabetic retinopathy.[45] A recently published study showed that significant increases in the levels of SOD activity and total protein correlated with the severity of the cataract and no significant age-associated difference in antioxidant enzyme levels was detected.[46] Notwithstanding, this paper also suggested that progressed cataract is associated with molecules leaking from the lens capsule. However our results show that SA levels may have an association with cataract development in diabetics.

In conclusion, our results show that increased oxidative stress and decreased antioxidant enzyme activities may have a role in the development of age-related and diabetic cataract. Diabetes seems to deepen the age-related antioxidant function decrease. Also, elevated serum and aqueous sialic acid levels seem to be associated with cataract development in diabetic patients.

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