



OPEN Increased oxidative stress biomarkers in central serous chorioretinopathy

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Current data suggest that oxidative stress may play an important role in the occurrence of acute central serous chorioretinopathy (CSC), as chorioretinal integrity may be affected by disruption of the patient's metabolic redox balance, indicating the need for biomarkers. In addition to oxidative stress, high-density lipoprotein (HDL) dysfunction due to dyslipidemia can also lead to many types of physical discomfort. However, little is known about the pathophysiology of the disease resulting from oxidative stress and HDL dysfunction in CSC. The aim of this study was to investigate whether serum oxidative stress and HDL functionality markers have an impact on CSC disease. The case series of this study included 33 consecutive patients with treatment-naïve acute CSC. Thirty-five healthy volunteers of similar age were included in this study as non-CSC controls. Serum samples of the participants were taken and routine lipid values, serum Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidized Low Density Lipoprotein (ox-LDL), and Paraoxonase (PON1) levels were measured quantitatively. Serum oxidative stress index (OSI) was then calculated. Serum Ox-LDL, TOS and OSI levels in the acute CSC group, consisting of patients who had never been treated before and had no other disease, were statistically significantly higher than the control group. Conversely, serum PON1 and TAS levels were lower in CSC than in the control group. The relationship between CSC and deterioration in serum redox balance and decrease in PON1 activity, an important marker of HDL functionality, was demonstrated for the first time through this study. According to the literature, serum levels of these biomarkers, which identify acute/chronic inflammation and oxidative stress, have not been measured before in CSC disease. Finally, it is conceivable that redox balance and HDL functionality may be important in the diagnosis and treatment of the acute phase of CSC.

Keywords Central serous chorioretinopathy, Dyslipidemia, High density lipoprotein, Redox balance, Oxidative stress, Paraoxonase

Central serous chorioretinopathy (CSC), which has become increasingly common in today's world, was first defined as "Ueber Centrale recidivirende retinitis" by Von Graefe in 1866. The use of the term "Retinitis" in naming the disease describes the inflammatory process. However, over time, it became clear that the main pathology in CSC was focal fluid leakage from the retinal pigment epithelium of the choroidal interstitial fluid of the eye. In 1967, Gass stated that both the retina and the choroid were responsible for the pathology of CSC disease and defined it as "idiopathic central serous chorioretinopathy"^{1,2}.

Central serous chorioretinopathy (CSC) is among the most common causes of vision loss from non-surgical retinopathy worldwide and ranks 4th after senile macular degeneration, diabetic retinopathy and retinal vein occlusion³. CSC accounts for 5% of patients who come to retinal clinics. While CSC is becoming increasingly widespread in the world, at present, the exact molecular mechanisms leading to the occurrence of CSC disease remain unclear, and there are still relatively few studies on CSC in the literature⁴.

CSC disease is seen more often in men than in women, and usually affects people between the ages of 20 and 50. When evaluated clinically, risk factors for CSC disease include high corticosteroid level, mineralocorticosteroid receptor activation, obstructive sleep apnea, type A personality, pregnancy, abnormal coagulation and platelet aggregation, smoking, hypertension, and H.pylori infection⁵. However, because glucocorticoids used in the treatment exacerbate CSC, potential disease mechanisms may be quite different⁶. One of the main pathomechanisms in CSC has been reported to be disruption of the microvasculature of the choriocapillaris and subsequent hyperpermeability of the choroidal circulation⁷. Increased oxidative stress due to the production of

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high reactive oxygen species (ROS) may be a possible common mechanism both in association with risk factors and in the development of CSC disease.

Clinical association with CSC disease as well as other diseases characterized by increased systemic oxidative stress, such as atherosclerotic diseases, may make systemic redox imbalance a risk factor. However, there is still limited information in the literature regarding oxidative stress levels in CSC. In some studies, biomarkers of systemic oxidative stress have been presented as complementary information in clinical diagnosis and decision-making in the treatment of patients with CSC or pre-CSC^{7,8}. In addition, changes in lipid metabolism, which are involved in the basic formation of many eye diseases, may also be a factor in the formation of CSC. For example, HDL-cholesterol (HDL-C) function may play an important role in the development of CSC disease^{9,10}. Functional HDL may have a stronger impact on the formation of the mineralocorticoids than previously thought¹¹. Although many common predisposing factors have been observed for eye diseases and atherosclerosis in general, the basic molecular mechanisms of the relationship between these two diseases have not been confirmed¹².

When assessing oxidative stress, total oxidant status (TOS) is used as the sum of lipid peroxidation levels caused by ROS and total antioxidant status (TAS) is used as an indicator of antioxidant activity in the environment. TOS and TAS measurements provide information on the overall serum oxidative stress index (OSI) of the individual. These reliable and sensitive parameters are generally used to determine the current oxidative status^{13,14}.

Oxidized low-density lipoprotein (ox-LDL) is produced after LDL is exposed to ROS in the vessel wall and is a major causative factor in the development of atherosclerosis. It is one of the most widely used biomarkers of systemic oxidative stress¹⁵.

Serum paraoxonase (PON1) enzyme activity is associated with HDL functionality and is responsible for the antioxidant properties of HDL. It provides protection against ROS at lipoprotein level¹⁶. Reduced PON1 activities have been reported in patients with cardiovascular disease and other pathologies (dyslipidemia, inflammatory processes, diabetes, and certain neuropathies) that increase the risk of vascular disorders under increased oxidative stress¹⁷.

The aim of this preliminary study was to demonstrate the possible relationship between oxidative stress markers and CSC. It was also aimed to investigate whether serum ox-LDL levels and HDL functionality markers play a role in CSC disease. To our knowledge, this is the first study to evaluate HDL-related PON1 enzyme, atherosclerotic lipoprotein ox-LDL, systemic redox balance parameters, TAS, and TOS levels in CSC patients.

Results

The mean age of the patient group was 46.63 ± 10.07 years, and the mean age of the control group was 43.43 ± 9.16 years. As shown in Table 1, there was no statistical difference between the mean age of the patient and control groups (*p* = 0.553). Out of all the patients, 75.7% (*n* = 25) were male and 24.3% (*n* = 8) were female. And in the control group, 82.8% (*n* = 29) were male and 17.2% (*n* = 6) were female. The routine lipid levels did not differ significantly between the patient and control groups (Table 1). Table 2 shows the parameters that were investigated as primary variables in the patient and healthy groups. In the patient group, ox-LDL was found to be significantly higher than in the control patients (*p* = 0.020). Conversely, in accordance with our hypothesis, PON1 enzyme activity was found to be significantly lower in the patient group when compared to the healthy controls (*p* = 0.020). Due to increased systemic oxidative stress, blood TOS and OSI values were found to be significantly higher (*p* = 0.001, *p* = 0.001, respectively). On the contrary, TAS, which measures systemic antioxidant capacity, was significantly lower in the patient group than in healthy controls (*p* = 0.001).

Discussion

One of the most important findings of this study was the demonstration of impaired systemic oxidative balance in CSC patients, as serum OSI value and accordingly serum TOS level in CSC patients included in our study were statistically significantly higher than healthy control patients. On the other hand, serum TAS level, which indicates antioxidant balance, saw a statistically significant decrease in CSC patients compared to control patients. Another important finding was the statistically significant decrease in serum antioxidant enzyme PON1 enzyme

Parameters	CSC (n = 33)	Control (n = 35)	<i>p</i>
Age	46.63 ± 10.07	43.43 ± 9.16	0.553 [†]
TC (mg/dL)	206.24 ± 37.54	198.97 ± 25.58	0.352 [†]
HDL-C (mg/dL)	50.88 ± 10.41	50.49 ± 7.88	0.861 [†]
LDL-C (mg/dL)	124.42 ± 32.6	121.4 ± 23.12	0.659 [†]
VLDL (mg/dL)	27 (23–38)	29 (23–31)	0.667 [‡]
TG (mg/dL)	99 (88–109)	100.5 (99–106.5)	0.303 [‡]

Table 1. Blood lipid levels and age in patients and healthy controls. CSC Central serous chorioretinopathy, TC Total cholesterol, HDL-C High density lipoprotein-cholesterol, LDL-C Low density lipoprotein-cholesterol, VLDL Very low-density lipoprotein, TG Triglyceride. [†]Independent Samples T test, Mean ± SD. [‡]Mann Whitney U test, Med(IQR).

Parameters	CSC Patients (n = 33)	Control (n = 35)	p
ox-LDL (ug/L)	16.882 (10.882–39.774)	28.701 (17.588–128.273)	0.020[#]
PON1 (U/L)	209 (162–475)	625 (366–750)	0.020[#]
TOS (μmol H ₂ O ₂ Equiv./L)	5.56 (4.16–6.69)	3.71 (3.06–4.81)	0.001[†]
TAS (nmol Troloks/L)	1.48 ± 0.21	1.67 ± 0.17	0.001[#]
OSI (AU)	4.54 ± 2.62	2.67 ± 0.87	0.001[#]

Table 2. Patients and healthy controls data of oxidative stress biomarkers. Significant values are in bold. *ox-LDL* Oxidized low density lipoprotein, *PON1* Paraoxonase, *TOS* Total oxidant status, *TAS* Total antioxidant status, *OSI* Oxidative stress index. [†]Independent Samples T test, *Mean* ± *SD*. [#]Mann Whitney U test, *Med(IQR)*.

activity, which is involved in the functional structure of HDL in CSC patients. Additionally, it was noted that proatherogenic ox-LDL levels were higher in CSC patients than in control patients (Table 2).

In CSC, serous retinal detachment develops in the neurosensory retina along with focal retinal pigment epithelium (RPE) and circulatory choroidal changes, although it usually resolves itself within six months. Recent advanced imaging techniques have demonstrated abnormal perfusion, especially at the choroidal level, and multiple areas of choroidal vascular hyperpermeability¹⁸. However, under normal physiological conditions, RPE cells keep the retina dehydrated by pumping fluid from the subretinal space to the choroid. Consequently, the pumping is reversed with loss of electrical polarity due to oxidative stress in CSC or changes in mineralocorticoids and other factors. The fluid is directed into the subretinal space. Unfortunately, the lack of perfusion mechanism in the choriocapillaries may cause the venous channels to expand and increase the hydrostatic pressure. According to the literature, one of the main cellular mechanisms in the development of CSC is the deterioration of the robustness of the microvascular structure of the choriocapillary. In addition, excessive permeability of the excess endothelium of the colloidal circulation may play a role in the development of CSC^{19–21}. In CSC disease, oxidative stress and inflammatory processes that may cause disruption of the integrity of the endothelial layer in the eye can occur with similar mechanisms. Important factors in the damage to the lipid barrier of the endothelial layer of the eye are perhaps the increase in ox-LDL and the decrease in PON1 enzyme levels^{22–24}. The fact that the retina is the organ with the highest oxygen consumption per volume in the body may also contribute to the vicious cycle of endothelial and oxidant damage until oxidative balance is achieved with systemic enzymatic and non-enzymatic antioxidants^{19–24}. And limitation of CSC disease over time is perhaps the result of balancing the oxidative damage due to stimulus in anti-oxidative defense mechanisms.

The main finding of this study may be the disruption of the oxidant/antioxidant balance in serum in CSC. Thanks to these data and by measuring serum oxidative stress markers, it is now possible to identify new pathways and molecules that affect the pathophysiology of CSC. These results suggest that the formation of systemic oxidative balance in favor of oxidants may assist the pathogenesis of CSC. The concept of oxidative stress was first described approximately 40 years ago for research in redox biology and medicine²⁵. Hundreds of thousands of studies were then conducted on oxidative stress in a relatively short time. Despite this, there are only a few articles on the relationship between oxidative stress and CSC disease.

Daruich et al. compared the oxidative stress biomarker malondialdehyde (MDA) between CSC and healthy control groups and found that it was higher in the patient group²⁶. Similarly, Urfalıoğlu et al. evaluated the oxidant-antioxidant balance and found that oxidant MDA was high and antioxidant catalase (CAT) was low in the patient group²⁷. Türkoğlu et al. found in chronic CSC patients, and Altinkaynak et al. discovered in acute CSC patients, that there was significantly higher thiol/disulfide homeostasis when compared to the healthy control group^{28,29}. Similar to our study, Türkücü et al. compared TAS, TOS and serum DHEA-S and found that they were at particularly low levels in patients with acute CSC. They suggested that the antioxidant defense system is inadequate or corrupted in patients with CSC³⁰. There are also data in the literature on the use of antioxidants in CSC patients. Some studies showing that antioxidant vitamin derivatives (e.g. vitamin D and Beta Carotene) have a positive effect on CSC^{31,32}. Similarly, in a multicenter study, Shinojima et al. found a statistically significant decrease in subfoveal fluid and increase in BCVA in the group with CSC treated with antioxidant supplementation containing lutein³³. In our study, TOS and OSI were high, while TAS was low in patients with CSC, indicating increased oxidative stress and supporting the limited literature.

Today, it may be important to measure the functional proteins and enzymes in the structure of the complex HDL molecule rather than the amount of HDL-C. PON1 enzyme is present in HDL-C and helps indicate its functionality. PON1 activity decreases in parallel with the reduction in antioxidant mechanisms with aging. It may help prevent the formation of ox-LDL^{34,35}. The enzyme reduces lipid hydroperoxides to hydroxides and breaks down hydrogen peroxide (H₂O₂), one of the ROS produced under oxidative stress, by exhibiting peroxidase activity³⁶. Increased ROS production and relatively reduced total antioxidant capacity (TAS) resulting from additional metabolic activity, as well as decreased PON1 enzyme, may help exacerbate the endothelial damage of the disease³⁷. Decreased PON1 activity is associated particularly with cardiovascular diseases and atherosclerosis. Decreased PON1 activity has also been reported in patients with diabetes, chronic renal failure, nephrotic syndrome, chronic hepatitis B and H. pylori³⁸. However, decreased PON1 enzyme activity has been previously reported in eye diseases such as Behçet’s disease, age-related macular degeneration, central retinal vein occlusion, diabetic retinopathy, pseudoexfoliation glaucoma and cataract^{23,39}. Serum ox-LDL levels, a proatherogenic lipoprotein, are usually assessed together with PON1. Cellular cholesterol accumulation contributes significantly to the development of atherosclerosis through inflammation and thrombosis⁴⁰. In addition to cardiovascular diseases, an association has been demonstrated between oxidative stress-mediated association and diseases such as endothelial dysfunction and gout^{40,41}. The only study in the literature on the relationship between ox-LDL and

eye diseases is Javadzadeh et al.'s work on exudative age-related macular degeneration (AMD)⁴². They reported that plasma ox-LDL elevation and ox-LDL as an oxidant agent in the patient group may indicate the presence or risk of AMD more precisely.

There are few studies in the literature on PON1 enzyme and ox-LDL and eye diseases; and to our knowledge, there is no study on CSC. In our study, there were no demographic differences in regards to age, gender, or lipid profile between the groups. Furthermore, patients with any additional disease that might affect the oxidative stress evaluation were excluded to maintain optimal conditions aligning with the overall objective. Low levels of PON1 enzyme and high levels of ox-LDL were discovered in the CSC group. Our present results both supported the hypothesis of CSC-related oxidative stress and showed that new molecules that can directly damage the endothelium can factor into this hypothesis.

The relationship between CSC and systemic cardiovascular diseases has been reported in various studies^{43,44}. Tsai et al. concluded that the increased incidence of stroke in CSC patients was independently connected to other confounding factors⁴⁵. Caccavale et al. showed that systemic aspirin use was effective in the treatment of CSC⁴⁶. Additionally, a type A personality, which is common in cardiovascular patients, is a common predisposing factor for both diseases. Therefore, the presence of CSC can be considered a potential risk factor for atherosclerosis in men considering the 5-year cumulative incidence of coronary heart disease in patients with CSC is approximately twice as high as it is in patients without CSC^{12,47}. Similarly, another study reported a significantly higher risk of CSC in patients with end-stage renal disease compared to controls. As with kidney disease, patients with CSC can be expected to have increased cardiovascular risk due in part to low HDL levels combined with proatherogenic inflammatory dyslipidemia⁴⁸. Unfortunately, CSC patients, despite their improved lipid profile and increased HDL levels, still have a high risk of cardiovascular morbidity even when treated for a long time^{48,49}. HDL-C functions and CSC disease have also not been sufficiently investigated. For these reasons, oxidative stress may be a potential common pathway in explaining the association of CSC disease with cardiovascular diseases and its relationship with defined risk factors that may cause the development of CSC disease. Our study results do seem to indicate that PON1 depletion and ox-LDL elevation have an active role to play in this pathway.

Our study has some important limitations, the first of these being the low number of patients included in the current study. These findings need to be supported by future studies with a larger sample size. Secondly, there are few studies evaluating oxidative stress in CSC disease, with a particularly notable lack of research done on PON1 and ox-LDL. This means that we cannot compare our results with any previous findings.

This research clearly demonstrated the relationship between TAS, TOS oxidative stress-related parameters and lipid parameters such as PON1 and ox-LDL in CSC. Statistically significant increases in oxidative stress and the presence of proatherogenic molecules in patients with CSC were identified. Data supporting the oxidative stress pathway among the possible pathogenesis mechanisms of the disease were also obtained throughout the course of this study. Moreover, molecules such as PON1 and ox-LDL were evaluated for the first time, and new assessments were made regarding both their contribution to oxidative stress and the association with risk factors for CSC.

Methods

Samples and measurements

This prospective study included 33 acute CSC patients admitted to hospital ophthalmology clinics. As a healthy control group, volunteers over 30 years of age, without any additional systemic and ocular diseases, who applied to the ophthalmological outpatient clinics of the same hospital for routine ophthalmological examinations were randomly selected and included in the study. Patients with evidence of age-related macular degeneration, choroidal neovascularization such as pathological myopia, or other ocular disease that could lead to macular exudation such as polypoid choroidal vasculopathy were excluded. In addition, people who had undergone intraocular surgery in the last 6 months, used antioxidant supplements and/or supplements, vitamins, had obesity and/or diabetes, or used lipid-lowering drugs were unable to participate. This study was given the approval of University of Health Sciences, Antalya Training and Research Hospital ethics committee number 21/17. It was conducted and performed in compliance with the ethical standards set out in the Declaration of Helsinki. Written informed consent was obtained from each participant.

Blood samples from the patients and healthy controls included in the study were clotted at room temperature for half an hour and then centrifuged at 4100 rpm for 10 min to separate their serum.

Serum samples were transferred to plastic-capped Eppendorf tubes and stored at -80°C until the day of analysis, although those with hemolysis were excluded entirely from the research. Routine biochemistry values (Triglyceride [TG], Total cholesterol [TC], HDL, Low-density lipoprotein [LDL] and Very-low-density lipoprotein [VLDL]) of the patients included in the study were obtained from the laboratory information system (LIS) of the hospitals on the same day. In routine tests, a Beckman AU 5800 (Beckman Coulter Diagnostics, USA) biochemistry autoanalyzer and commercial reagent kits of the same brand were used for TG, HDL, LDL, VLDL, TC parameters. Since the serum fasting TG levels of all participants were $<400\text{ mg/dl}$, the Friedewald formula was used to calculate $\text{LDL} = \text{TC} - (\text{VLDL} + \text{HDL})$, ($\text{VLDL} = \text{TG}/5$). Then, Total Antioxidant Status (TAS), Total Oxidant Status (TOS), Oxidized low density lipoprotein (ox-LDL), Paraoxonase (PON1) measurements were made from all stored serum samples on the same day and the values were recorded.

Serum TAS level was measured with a Rel Assay® Total Antioxidant Level Test Kit (MegaTip, Turkey) and a Selectra autoanalyzer (Netherlands). Similarly, a serum TOS level Rel Assay® Total Oxidant Level test kit (MegaTip, Turkey) and Selectra autoanalyzer (Netherlands) were utilized. Oxidative stress index (OSI) and the TOS values of the samples proportionate to the TAS values in percent and the OSI values were calculated. The OSI unit is AU (Arbitrary Unit) = $(\text{TOS}, \mu\text{mol H}_2\text{O}_2 \text{ eq/L}) / (\text{TAS}, \mu\text{mol Trolox eq/L})$.

PON1 enzyme activity measurement is a fully automatic method. Rel Assay® PON1 test kit (Mega Tip, Turkey) and Selectra autoanalyzer (Netherlands) were used for PON1 enzyme activity measurement. The absorbance of

p-nitrophenol, which is formed from the enzymatic hydrolysis of paroxone (diethyl-p-nitrophenylphosphate) used as a substrate in the PON1 measurement method, at 37°C and 412 nm in the environment with and without salt (NaCl) was measured by the kinetic method. The salt-added, i.e., stimulated value is calculated from the basal activity. Its unit is U/L.

For the measurement of ox-LDL, quantitative ELISA (Enzyme-Linked Immunoabsorbent Assay) immuno-analytical method and YL Biont® (Shangai YL Biotech Ltd. China) brand and manual diagnostic kits were used. Experiment result Optical density measurement ELX 800 BioTek® (BioTek, ELX 800, USA) was performed with an ELISA reader. Intraassay CV is < 8%, interassay CV is < 10%.

Statistical analysis

The data was analyzed with IBM SPSS Statistics 25 © Copyright SPSS Inc. 1989, 2017 software. As it was not normally distributed according to the correlation analysis of continuous variables, Spearman correlation analysis was used. Independent Samples t test was employed for the data that was normally distributed in the analysis of two independent groups while Mann Whitney U test was applied for the data that was not normally distributed in the analysis. $p < 0.05$ was considered as statistically significant in the study.

Data availability

The raw data are provided by the corresponding author upon reasonable request.

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E.E.A. Conceptualization, E.E.A. methodology and E.Y. investigation, E.E.A., E.Y., and M.A. resources, E.E.A. and M.A. data curation, E.E.A., E.Y., and N.Y. writing—original draft preparation, E.E.A., E.Y., N.Y., and M.A. writing—review and editing, E.E.A. and M.A. supervision, E.E.A., E.Y., and N.Y. project administration, E.E.A. and M.A.. All authors have read and agreed to the published version of the manuscript.

Competing interests

The authors declare no competing interests.

Additional information

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