



Vitreous albumin redox state in open-angle glaucoma patients and controls: a pilot study

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Abstract

Purpose Numerous studies suggest that reactive oxygen species play a crucial role in the development of glaucoma. Since glaucoma patients exhibit posterior vitreous detachment earlier than controls, it has been suggested that reactive oxygen species—increased in glaucoma—also affect the vitreous. In the present study we evaluated the influence of open-angle glaucoma oxidative stress on the redox state of vitreous albumin.

Methods Albumin redox states of the vitreous and plasma were evaluated in 22 subjects—11 open-angle glaucoma patients and 11 controls—matched for age, gender, and vitreous state. According to the redox state of cysteine-34, albumin can be separated into: human mercaptalbumin (the thiol form), human nonmercaptalbumin1 (a reversible modification due to mild oxidation), and human nonmercaptalbumin2 (an irreversible modification due to severe oxidation).

Results Albumin of both, the open-angle glaucoma group and the control group, was more oxidized in the

vitreous compared to plasma. Furthermore, significantly higher human nonmercaptalbumin1 fractions were found in the vitreous of open-angle glaucoma patients compared to controls. No significant differences were found in the plasma albumin fractions between the groups.

Conclusion Our results support the hypothesis that oxidative stress plays a crucial role in open-angle glaucoma and that reactive oxygen species in glaucomatous eyes may also affect the vitreous.

Keywords Glaucoma · Open-angle glaucoma · Vitreous · Albumin · Free radicals

Background

Glaucoma—the leading cause of irreversible blindness worldwide—is a multifactorial disease among which oxidative stress may play a major pathophysiological role [1, 2].

Several studies demonstrated increased levels of oxidative stress markers in aqueous humor, serum, and retina of glaucoma patients [3–9]. In particular, primary open-angle (POAG) and pseudoexfoliation (PEX) glaucoma have been associated with higher levels of oxidative stress [4]. In this regard, oxidative stress and thus reactive oxygen species (ROS) seem to have a major impact on aqueous humor outflow

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pathway as they damage structures of the human trabecular meshwork (HTM) and especially induce DNA damage in HTM cells [10–13]. Thereby, aqueous humor outflow resistance and increased intraocular pressure (IOP) increase, facilitating the clinical onset of glaucoma and supporting the hypothesis that oxidative stress is an important factor in open-angle glaucoma [10, 14]. Recently, the observation that glaucoma is linked to premature posterior vitreous detachment (PVD) has led to the hypothesis that ROS, which appear increased in glaucoma, might also lead to changes of the vitreous [15]. However, the impact of glaucomatous oxidative stress on the vitreous has not been investigated yet. This issue seems to be of special interest because the presence of oxidative stress markers in the vitreous could explain the pathophysiology behind premature glaucomatous PVD—which might be a valuable hint in glaucoma screening. Furthermore, these investigations could provide new insights into the role of oxidative stress in glaucoma since the vitreous is a reservoir for metabolic products including high levels of antioxidants (e.g., ascorbic acid or glutathione).

Albumin, the main serum protein, is also found—albeit at much lower concentrations—in the vitreous. Besides its function as transport protein, albumin exhibits various forms of antioxidant capacity. In this context albumin's cysteine-34 deserves particular attention: this amino acid contains a free thiol group which is able to reduce (and thereby detoxify) ROS. Regarding on the redox state of this thiol group, albumin can be separated into three fractions: (1) human mercaptalbumin (HMA), the unmodified, reduced form with a free thiol group on cysteine-34; (2) human nonmercaptalbumin1 (HNA1), a reversible modification, with, e.g., cysteine or homocysteine bound by a disulfide bond; and (3) human nonmercaptalbumin2 (HNA2), with cysteine-34 oxidized to sulfinic or sulfonic acid, an irreversible modification due to stronger oxidation, e.g., by hydrogen peroxide (H₂O₂). HMA and HNA1 are in a dynamic exchange with small thiol-containing compounds and disulfides like cysteine/cystine or glutathione (GSH)/glutathione disulfide (GSSG), respectively. An increase in HNA1 rather indicates an increased activity of the antioxidant system than severe oxidative stress. Rising levels of HNA2 are seen in conditions of high ROS formations and/or reduced ability to detoxify these species [16–18].

With its cysteine-34, albumin serves as a thiol/disulfide pool and the redox state of albumin reflects the redox balance of the respective body compartment. In this way albumin redox state is a novel indicator enabling both quantitative and qualitative investigation of oxidative modification [16, 18]. Therefore, this biomarker seems to be highly appropriate to measure oxidative modifications in the vitreous and plasma of open-angle glaucoma patients which is the aim of this study.

Methods

Patients

We evaluated vitreous albumin redox state in an open-angle glaucoma group ($n = 11$) and compared the results with a control group ($n = 11$) matched for age, gender, and vitreous state. Vitreous state was evaluated intraoperatively and staged as: detached in all eyes. Vitreous samples were obtained during uneventful vitrectomy for idiopathic epiretinal membrane peeling. For both groups inclusion criteria were: age above 18 years, capacity of consent, planned vitrectomy for removal of an epiretinal membrane. Exclusion criteria were: previous intraocular surgery (including cataract, glaucoma, and laser surgeries), diabetes, intraocular bleedings, evidence or history of vessel occlusion as well as intraocular inflammatory diseases. All included patients stated not to smoke.

Open-angle glaucoma was already known and treated prior vitrectomy with eye pressure-lowering eye drops containing one active substance or a combination of max. 3 active substances of different drug classes (prostaglandins, beta blockers, carbonic anhydrase inhibitors). Open-angle glaucoma was (re-)evaluated by a glaucoma expert and defined by the presence of optic disk notching, thinning of the neuroretinal rim, or increased cup/disk ratio (in relation to the optic disk size).

After obtaining informed consent, blood and vitreous samples were taken from each patient.

Sample collection and pre-analytical procedures

Plasma samples

In total, 2.5 mL of blood was drawn from each patient shortly (within 3 h) before the patient underwent surgery. Blood samples were centrifuged immediately at 4 °C at the in-house laboratory of the Department of Ophthalmology in order to separate plasma. The plasma was then transferred into Eppendorf safe-lock tubes for albumin redox state analysis and stored on crushed ice. The remaining blood samples were used for quantitative plasma albumin analysis at the Unit of Physiological Chemistry, Otto-Loewi Research Center, Medical University of Graz.

Vitreous humor samples

Between 300 and 500 µL vitreous (core) humor samples were taken at the beginning of the vitrectomy under air exchange. Samples were aspirated through a 5-mL syringe from the waste gate port of the vitrectomy system. Special care was taken to gain air bubble free vitreous. The syringe was sealed air-tight and put on crushed ice. Vitreous and plasma samples were then brought—both stored on crushed ice—to the Unit of Physiological Chemistry, Otto-Loewi Research Center, Medical University of Graz, where all samples were analyzed within 2 h after sample collection.

The time window of 2 h and the vitreous sample storage on crushed ice in an air bubble free, sealed syringe were identified as reliable conditions in preliminary experiments.

Analytical methods

To determine the redox state of albumin in plasma and vitreous humor, albumin was split into its different fractions (HMA, HNA1, and HNA2) by high-performance liquid chromatography (HPLC) as described by Hayashi et al. [19]. In brief, plasma samples were diluted 1:100 and vitreous samples 1:4 with 0.1 M sodium phosphate, 0.3 M sodium chloride, pH 6.87, and filtered through a Whatman 0.45-µm nylon filter (Bartelt Labor- & Datentechnik, Graz, Austria). In total, 20 µL of the respective diluted sample was injected into the HPLC system. Separation was performed using a Shodex Asahipak ES-502 N 7C

anion exchange column with 50 mM sodium acetate, 400 mM sodium sulfate, pH 4.85, as mobile phase. For elution, a gradient of 0 to 6% ethanol and a flow rate of 1 mL/min were used. The column was kept at 35 °C. Detection was carried out by fluorescence at 280/340 nm. Quantification was based on the heights of the individual peaks as determined by EZ Chrome Elite chromatography software (VWR, Vienna, Austria).

Statistical analysis

Categorically coded variables are presented as frequencies and percentages and continuous variables as means ± standard deviations or medians and ranges. Intergroup differences of normally distributed data were assessed by Student's *t* tests and those of non-normally distributed data by Mann–Whitney *U* tests. *P* < 0.05 was considered to indicate statistical significance. Data were stored in a Microsoft Excel data sheet, and explorative data analysis was performed using SPSS v18 (Chicago, IL, USA).

Results

In this study we evaluated vitreous albumin redox state in 11 open-angle glaucoma patients and 11 controls matched for age, gender (male *n* = 5; female *n* = 6), and vitreous state. All patients underwent uneventful vitrectomy for epiretinal membrane peeling of the macula. The vitreous state was evaluated preoperatively (due slit-lamp examination) and intraoperatively and judged as detached in all patients. The open-angle glaucoma group consisted of 6 POAG and 5 PEX glaucoma patients. Further characteristics of the groups are given in Table 1.

The redox state of plasma and vitreous albumin was evaluated in all patients. No significant differences between plasma and vitreous were found for HMA and HNA1 in the control group. In the open-angle glaucoma group, HMA fractions were lower in the vitreous and HNA1 fractions significantly higher compared to plasma albumin. Significantly higher vitreous HNA2 fractions compared to plasma were found in the open-angle glaucoma as well as in the control group. Detailed data are given in Fig. 1a.

None of the plasma albumin fractions revealed significant differences between the open-angle

Table 1 Demographic data of controls and glaucoma patients

	Controls	Open-angle glaucoma	Open-angle glaucoma versus controls	
			<i>P</i> value	Significance
Sex (m/f)	5/6	5/6		
Age (years)				
Mean ± SD	75.3 ± 5.5	75.1 ± 6.3	0.898 [†]	Ns
Intraocular pressure (mmHg)				
Mean ± SD	14.3 ± 2.8	16.8 ± 5.0	0.193 [†]	Ns
Optic disk excavation				
Median (range)	0.3 (0.1 – 0.8)	0.7 (0.4 – 0.9)	0.003 [‡]	**

SD standard deviation; Ns not significant

***p* < 0.01; [†]unpaired Student's *t* test; [‡]Mann–Whitney *U* test

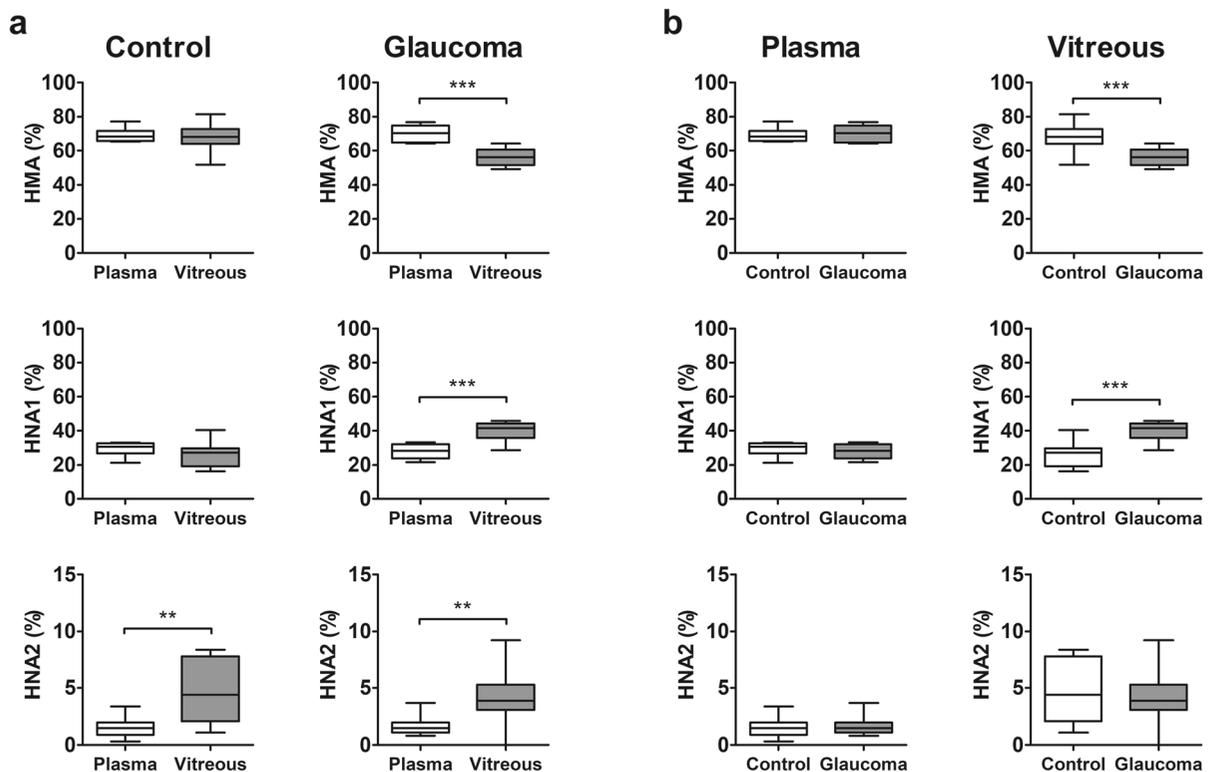


Fig. 1 Redox state of albumin in plasma and vitreous of controls and open-angle glaucoma patients. Boxplots of **a** control (left panel) and open-angle glaucoma patients (right panel) comparing plasma (white boxes) and vitreous albumin fractions (gray boxes) and **b** plasma (left panel) and vitreous

albumin fractions (right panel) comparing controls (white boxes) and open-angle glaucoma patients (gray boxes). SD, standard deviation; ***p* < 0.01; ****p* < 0.001 by unpaired Student's *t* test

glaucoma and the control group (HMA: *p* = 0.478; HNA1: *p* = 0.432; HNA2: *p* = 0.848). Regarding vitreous albumin fractions, significantly higher HNA1 (*p* = 0.0002) and significantly lower HMA

fractions (*p* = 0.0003) were found in the vitreous of open-angle glaucoma patients compared to controls. HNA2 did not differ between the groups (*p* = 0.655). No significant differences were found within the open-

angle glaucoma group comparing PEX and POAG in vitreous albumin fractions (HMA: $p = 0.614$; HNA1: $p = 0.175$; HNA2: $p = 0.745$). Plasma and vitreous albumin fractions with regard to the presence of open-angle glaucoma are given as boxplots in Fig. 1b.

Discussion

Numerous studies strongly indicate that an increased occurrence of ROS plays a crucial role in glaucomatous eyes in both the anterior and the posterior pole [3–7, 10, 20]. Malondialdehyde—an end product of lipid peroxidation—was found at higher concentrations in the aqueous humor, retina, and even in the plasma of glaucoma patients compared with controls [4].

The finding that glaucoma is linked to PVD has led to the hypothesis that ROS in these patients might also affect the vitreous [15]. However, the impact of increasingly occurring oxidative stress on the vitreous during the development of glaucoma was not yet investigated properly. Therefore, we measured the redox state of albumin in the vitreous of open-angle glaucoma patients and a control group as an indicator for oxidative modification.

Vitreous samples were collected during a vitrectomy for epiretinal membrane peeling. No other underlying diseases for vitrectomy were included in order to avoid possible bias.

Furthermore, we only included patients with a detached vitreous. High levels of ascorbate—a potent antioxidant—can be found in the vitreous humor. However, vitreous ascorbate concentrations decrease after PVD [21]. To avoid bias due to different ascorbate levels, we only included patients with a detached vitreous to gain homogenous groups.

It is well known that oxidative damages of biomolecules accumulate with age and albumin fractions are shifted to more HNA1 during aging [22]. Therefore, the groups were matched for age. Gender has no influence on distribution of plasma albumin fractions, but we assessed significant differences in vitreous HMA between men and women [23], which was also considered by matching the groups for gender. Also other factors, e.g., previous intraocular surgery, diabetes, intraocular bleedings, evidence or history of vessel occlusion, and intraocular

inflammatory diseases, can alter albumin redox state. Therefore, these factors were defined as exclusion criteria.

Albumin is synthesized in the liver and circulates in the blood flow—its redox state has been shown as very appropriate biomarker in order to gain insights into redox reactions in humans [16–18, 22]. Via ultrafiltration albumin is brought into the eye by the ciliary body. In all patients plasma and vitreous samples were analyzed. While we found a marked increase in HNA2 in vitreous albumin compared to plasma albumin in both groups, a shift of HMA to HNA1 in the vitreous compared to plasma was observed only in the open-angle glaucoma group. However, the broad variation of vitreous HNA2 fractions in both groups should be noted. Despite high HNA2, HNA1 showed no difference between plasma and vitreous in the controls.

Glaucoma refers a heterogenic group of eye diseases, leading to a uniformly loss of optic nerve fibers resulting in an irreversible loss of vision. Oxidative stress plays a major role in the pathogenesis of glaucoma—especially in POAG and PEX. Despite different pathologies, oxidative stress markers are elevated under both conditions but are not described to differ significantly [4, 24, 25]. We included both PEX and POAG to compare the redox status of albumin between these two groups. Importantly, oxidative stress levels were higher in both forms, but no differences in vitreous albumin fractions were found within the open-angle glaucoma group comparing POAG and PEX. However, we cannot rule out that group samples were too small to assess differences in the redox status of albumin.

We did not find significant differences in the redox state of plasma albumin between the groups. Furthermore, no correlations between plasma and vitreous albumin fractions were found, suggesting that vitreous albumin is modified (i.e., oxidized) locally within the eye.

HMA and HNA1 are in a dynamic exchange with small thiols and disulfides like GSH and its oxidized form GSSG. Along this way increasing levels of GSSG lead to increasing levels of HNA1, while GSH favors the formation of HMA. GSH and GSSG have both been found at high concentrations in the vitreous [4, 26, 27]. GSH serves as an antioxidant by itself and also as a substrate for antioxidant enzymes (e.g., glutathione peroxidase)—resulting in the formation of GSSG.

Interestingly, increased activities of glutathione peroxidase and superoxide dismutase (another antioxidant enzyme) have been found in retinas and aqueous humor of glaucomatous eyes [4]. The increase in these two antioxidant enzymes is seen as an upregulated protective response of the eye to oxidative irritation. The synergistically catalyzed reactions in the detoxification of ROS as well as the direct reaction of ROS with GSH lead to increasing GSSG levels and consequently result in a shift from HMA to HNA1 (Fig. 2).

In this context it is interesting to mention that a decrease in systemic GSH levels has been demonstrated in glaucoma patients [4]. The alterations of the antioxidant defense system in open-angle glaucoma result in higher GSSG levels and consequently in a shift from HMA to HNA1 (Fig. 2). In accordance with these findings, in aqueous humor of cataract patients extremely low fractions of HMA and high fractions of HNA1 have been reported [19].

The higher levels of HNA1 in the vitreous of open-angle glaucoma patients indicate a higher activity of an upregulated antioxidant system due to increased ROS formation. Increased HNA2 indicates generally high ROS formation in both the open-angle glaucoma and the nonglaucoma group. We found significantly higher fractions of HNA2 in the vitreous compared to plasma in both groups. Neither plasma nor vitreous HNA2 differed between the groups. This is remarkable because this finding suggests that in both glaucomatous and nonglaucomatous eyes locally oxidizing processes may occur, leading to an increase in HNA2. One possible explanation is that a certain amount of H_2O_2 —a strongly oxidizing intermediate product of oxygen lowering reactions in the vitreous—

reacts with HMA to give HNA2. This finding merits further investigation in order to evaluate the suggested role of oxygen and ascorbate in the formation of H_2O_2 , especially against the background that high ascorbate doses are regularly prescribed to certain patients suffering from age-related macular degeneration: high doses of ascorbate might actually lead to increasing H_2O_2 formation in the vitreous.

Recently it has been shown that glaucoma patients exhibit PVD earlier than controls [15]. It has been suggested that increased formation of ROS in glaucomatous eyes promotes vitreous liquefaction (due to the depolymerization of hyaluronic acid) and consequently leads to PVD. Our findings of elevated fractions of oxidized albumin in the vitreous of open-angle glaucomatous eyes support this hypothesis.

The fact that we did not examine vitreous samples of “truly” healthy patients with and without open-angle glaucoma is one obvious limitation of our study. However, for ethical reasons it is impossible to collect vitreous samples from “healthy” eyes. It has to be mentioned that vitreous samples from “healthy” cadaver eyes were no option because shortly after death the production of ROS exceeds.

It would also have been of interest to correlate albumin fractions with open-angle glaucoma stage/severity. Unfortunately, the presence of an epiretinal membrane influences both factors which could be used for glaucoma staging: visual field mean deviation and peripapillary retinal nerve fiber thickness (measured by optical coherence tomography).

Certainly, a larger study population would provide stronger evidence. However, we think that our study strongly gains good reliability from accurate and

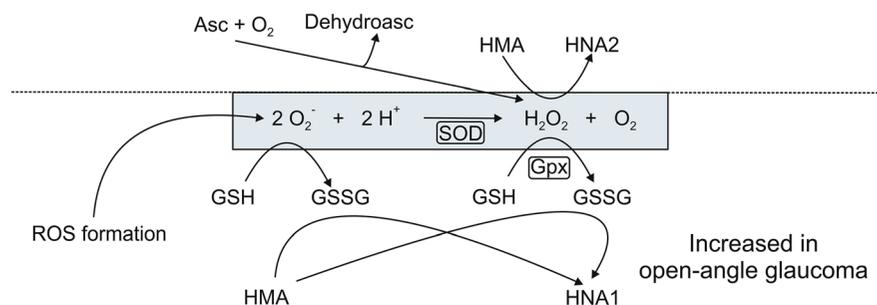


Fig. 2 Biochemical mechanisms leading to increases in HNA1 (glaucoma) and HNA2 (open-angle glaucoma and nonglaucoma) in the vitreous. SOD, superoxide dismutase; GPx,

glutathione peroxidase; Asc, ascorbic acid; ROS, reactive oxygen species; HMA, human mercaptalbumin; HNA1, human nonmercaptalbumin1; HNA2, human nonmercaptalbumin2

conscientious group matching of several factors (which on the other hand made it difficult to gain a larger study population).

Another limitation is that all open-angle glaucoma patients were previously treated. Although glaucoma therapy is proven to prevent further glaucomatous damage, we can only speculate about its influence on the antioxidant system. Whereas many eye pressure-lowering drugs rather exhibit antioxidant effects, added preservatives induce the opposite [28–31]. Moreover, prostaglandins may affect the results of the study as they increase permeability of the blood-ocular barriers and facilitate leukocyte migration [32]. In a recent study ROS production was measured in cultured human corneal epithelial cells treated with different anti-glaucoma prostaglandin ophthalmic solutions. The results reveal that ROS production does not correlate with the concentration of prostaglandins within the formulation but is dependent on the used preservatives [33]. Therefore, the effects of prostaglandins as well as preservatives on ROS production in open-angle glaucoma remain to be further elucidated. These issues merit further investigation, for instance in a longitudinal and prospective setting which could be realized in an animal model.

In summary, our results support the hypothesis that open-angle glaucoma is associated with higher oxidative stress and that oxidative stress in open-angle glaucomatous eyes also affects the vitreous. Furthermore, we were able to demonstrate that the redox state of vitreous albumin is a valuable marker to investigate the redox situation in the vitreous.

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Authors' contributions Christoph Schwab and Karl Oetl were responsible for conception and design of the work, data acquisition, data analysis and interpretation, drafting the article, and critically revising the article; Margret Paar for conception and design of the work, data acquisition, data analysis and interpretation, drafting the article, critically revising the article, and final approval of the version to be published; Vera Heike Fengler contributed to data acquisition, data analysis and interpretation, drafting the article, and critically revising the article; and Ewald Lindner, Anton Haas, Domagoj Ivastinovic, Gerald Seidel, Martin Weger, and Andreas Wedrich acquired the data and critically revised the article.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in this study were in accordance with the ethical standards of the institutional and national research committee (registered at the Office for Human Research Protections of the US Departments of Health and Human Services: IRB00002556) and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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