Original Article

Linear association between aging and decreased blood thiol antioxidant activity in patients with cataract

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We comprehensively assessed the roles of systemic redox markers by including both prooxidant and antioxidant markers in 121 Japanese subjects (mean ± SD age, 70 ± 11 years; 38 men) with no ocular pathology except age-related cataract. Serum levels of lipid peroxides, ferric-reducing activity, and thiol antioxidant activity were measured using the diacron reactive oxygen metabolite (dROM), biologic antioxidant potential (BAP), and sulfhydryl (SH) tests, respectively, using a free-radical analyzer. Univariate analyses suggested that older age, higher pulse rate, worse best-corrected visual acuity (BCVA), higher intraocular pressure, and higher cataract grade were associated with a lower SH level. Scatterplots revealed virtually linear associations between age and the SH level (estimate, –4.4 μM/year). Multivariate analyses suggested that older age, higher systolic blood pressure, and worse BCVA were associated with a lower SH level. Neither the univariate nor multivariate analyses, except between female sex and higher dROM level, were associated with the dROM or BAP level. A lower serum SH level was the driver of aging itself and age-related decline in VA due to cataract. The serum SH level may be an excellent predictor of aging status in each subject.

***Key Words*:** **age-related cataract, glutathione, redox, visual acuity, systemic oxidative stress, visual field**

Age-related cataract (ARC) is a major cause of severe visual loss and blindness in older adults in developed and developing countries.[1,2] Worldwide, among 237.1 million individuals with moderate/severe visual impairment, almost 25%, i.e., 57.1 million had cataracts by 2020. The blind population numbered 38.5 million, and of those, 13.4 million were blind as a result of cataracts.[3] Changes in water content and abnormal protein aggregation cause the normal crystalline lens to become opaque as a result of exposure to ultraviolet and x-ray radiations, steroids and other chemicals/medications, and local/systemic diseases, e.g., diabetes, cigarette smoking, and poor nutrition.[4] Defense systems that include small-molecule antioxidants (e.g., vitamins C and E and carotenoids) and antioxidant enzyme systems [e.g., superoxide dismutase (SOD), catalase, and the glutathione enzyme systems including glutathione peroxidase (GPX), glutathione reductase (GR), and glucose-6-phosphate dehydrogenase (G6PD)] generally can control the damaged proteins in young lenses.[5] This was demonstrated by the antioxidant protective effect of the lens cell membrane against oxidative stress that prevented Na+-K+-ATPase-dependent pump deterioration caused by oxyradical-dependent oxidation of its proteins and lipids.[6]

Formation of multiple reactive oxygen species that initiate and propagate free radicals generally induces oxidative stress. The net oxidative burden between the prooxidant and antioxidant systems is the oxidative stress that damages cellular and tissue macromolecules, i.e., lipids, proteins, and nucleic acids, and causes cellular/tissue dysfunction and apoptosis.[7] Progressively increasing prooxidant and generalized decreasing antioxidant defenses are associated with aging and age-related degenerative diseases including ARC.[8] Simultaneous modulation of advanced glycation end products and oxidative stress can be beneficial in preventing cataract genesis.[9] Cysteine thiols are key factors in the proper functioning of enzymes, receptors, ion channels, transporters, and transcription factors,[8] but are the targets of oxidation.

In the current study, by including both prooxidant and antioxidant markers, the systemic redox status was assessed comprehensively in subjects with ARC. As a result, among the markers attested, decreased total thiol levels in serum were found to be the determinant of aging and ARC severity in our subjects.

Materials and Methods

Subjects. The study was conducted according to the tenets of the Declaration of Helsinki, and the Ethical Guidelines for Medical and Health Research Involving Human Subjects in Japan. The institutional review board (IRB) of Shimane University Hospital reviewed and approved the research (IRB No. 20091119-1; August 26, 2019). All subjects provided written informed consent. A total of 121 Japanese subjects without any remarkable ocular pathology or ARC were selected from a dataset of 531 subjects.[7,10,11] The subjects' diagnoses and demographic data were reported previously.[7] With the exception of cataract, no subject reported glaucomatous optic neuropathy or a history of intraocular pressure (IOP) of 21 mmHg or higher; ocular pathologies including clinically detectable ocular inflammation, infection, neuropathies, retinopathies, or maculopathies; or severe systemic diseases. Patients were excluded who had acute brain infarction and hemorrhage, systemic neurologic diseases, cardiac diseases requiring catheter placement or surgery, cardiac failure and other systemic diseases affecting physical activity, lung diseases associated with dyspnea, chronic and acute hepatitis requiring interferon, liver cirrhosis, renal failure requiring hemodialysis, autoimmune diseases requiring systemic steroids and other immunosuppressive therapies, severe anemia requiring blood transfusions, major visceral surgery,

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malignancies, severe hypertension causing cardiac and kidney failure, and severe diabetes requiring insulin therapy.

Clinical parameters and laboratory tests. To adjust for any confounding effects of background factors,[12–14] we recorded the presence/absence of diabetes, current smoking, systolic blood pressure (SBP) and diastolic blood pressures (DBP), and pulse rate (PR) before obtaining serum samples. The best-corrected visual acuity (BCVA) was measured using a Landolt ring chart in decimal notation and converted to the logarithm of the minimal angle of resolution (logMAR) for statistical analyses. The Emery-Little classification (grades 0–5) was used to record the cataract grades.[15] Goldmann applanation tonometry was used to measure IOP. The eye of each patient with the better BCVA was included in the analyses. Venous blood specimens were collected from the antecubital vein into evacuated tubes. During all handling procedures, the temperature was maintained at 4°C. Serum samples obtained by centrifugation of the collected venous blood were stored at 4°C until oxidative stress measurements were performed.

Redox parameters. A free-radical analyzer system (FREE Carpe Diem, Wismerll Company Ltd., Tokyo, Japan) was used for all blood analyses.[7] All analyses were performed within 48 h after the specimens were collected to prevent falsely high or low results, according to the manufacturer's recommendation the diacron reactive oxygen metabolite (dROM), biologic antioxidant potential (BAP), and sulfhydryl (SH) tests were performed, respectively, to analyze the serum levels of reactive oxygen metabolites, the antioxidant capacity, and thiol-antioxidant capacity. The dROM test results are expressed in arbitrary units (U.Carr); each unit corresponds to 0.8 mg/L of hydrogen peroxide;[12,16] the BAP test results are expressed in μM of the reduced ferric ions; the SH test results are expressed as the μM of the SH groups. The dROM test reflects the amount of organic hydroperoxides that is related to the free radicals from which they are formed. When the samples are dissolved in an acidic buffer, the hydroperoxides react with the transition metal (mainly iron) ions liberated from the proteins in the acidic medium and are converted to alkoxy and peroxy radicals. These newly formed radicals oxidize an additive aromatic amine (*N,N*-diethyl-*para*-phenylen-diamine) and cause formation of a relatively stable colored cation radical that is spectrophotometrically detectable at 505 nm.[12,16] The BAP test provides an estimate of the global antioxidant capacity of blood plasma, measured as its reducing potential against ferric ions. When the sample is added to the colored solution obtained by mixing a ferric chloride solution with a thiocyanate derivative solution, decoloration results. The intensity of the decoloration is spectrophotometrically detectable at 505 nm and is proportional to the ability of plasma to reduce ferric ions.[13,17] The SH test provides an estimate of the total thiol groups in the biologic samples, using a modified Ellman method.[18,19] When the sample is added to the solution, SH groups in the sample react with 5,5-dithiobis-2-nitrobenzoic acid, which is followed by development of a stained complex that is spectrophotometrically detectable at 405 nm and is proportional to their concentration according to the Beer-Lambert law.[13,16] To standardize the measurement kit by the manufacturer, L-cysteine was used as the standard. The measured levels of oxidative stress between the non-glaucomatous and glaucomatous groups were compared previously.[7]

Statistical analyses. Linear regression analyses by the Pearson's correlation coefficient for continuous variables and the unpaired *t* test for categorical variables were used to identify possible correlations between each redox parameter and other parameters. Possible associations between serum redox parameters and various parameters were tested further using multiple regression analyses to adjust for parametric differences among groups. All statistical analyses were performed using the JMP Pro statistical software ver. 15.2 (SAS Institute, Inc., Cary, NC). The data are expressed as the means ± SD for continuous variables and in numbers and percentage for categorical variables. *P* values <0.05 were considered statistically significant.

Results

The demographic subject data and measured results of serum redox parameters are summarized in Table 1. The subjects were mean age of 70 ± 11 years, and included 38 (31%) men. Cataract grade were distributed to 20% in Grade 0, 34% in Grade 1, 24% in Grade 2 or 3, and 22% in IOL implanted eyes. Mean levels of serum dROM, BAP, and SH were 348 ± 56 U.Carr, 2,022 ± 240 μM, and 621 ± 98 μM, respectively. By linear regression analysis, correlation among each pair of serum redox parameters was not significant; $r = 0.12$ and $p = 0.19$ between dROM and BAP, $r = -0.07$ and $p = 0.47$ for dROM and SH, and $r = -0.15$ and $p = 0.11$ for BAP and SH.

Possible associations among demographic parameters and each serum redox parameter were assessed by univariate analyses. Among continuous parameters (Table 2), older age (estimate = −4.4/year, $p<0.0001$), higher PR (estimate = 2.1/cpm, $p = 0.004$), worse BCVA (estimate = −342/logMAR, $p = 0.0002$), and higher IOP (estimate = 6.1/mmHg, $p = 0.04$) were associated significantly with lower serum SH levels, while none assessed were associated with the dROM or BAP levels. As shown in the scatterplot, age and serum SH level were linearly correlated with each other ($r = -4.4$, $p = 0.04$) (Fig. 1).

Among categorical parameters (Table 3), female (357 ± 55 U.Carr) rather than male (329 ± 53 U.Carr) sex was associated significantly with higher serum dROM levels ($p = 0.01$), and cataract grade ≥1 or IOL (611 ± 101 μM) rather than cataract grade of 0 (663 ± 75 μM) was associated significantly with lower serum SH levels ($p = 0.02$), while none of the assessed parameters were associated with the serum BAP level. The serum SH level decreased significantly in association with the increased cataract grade ($p = 0.04$) (Fig. 2).

We further assessed the possible associations among demographic parameters and each serum redox parameter by multivariate analyses. For dROM, female sex (estimate = 14/male, $p = 0.02$) was associated significantly with a higher serum dROM level (Table 4). None of the parameters assessed were

Table 1. Demographic subject data and serum redox parameters

Parameter	Mean ± SD or *n* (%)	95% CI or *n* (%)
Age, years	70 ± 11	68, 72
Sex	Men, 38 (31)	Women, 83 (69)
SBP (mmHg)	137 ± 19	133, 140
DBP (mmHg)	75 ± 12	73, 77
PR (cpm)	73 ± 12	71, 76
Diabetes	Yes, 18 (15)	No, 103 (85)
Smoking	Yes, 12 (10)	No, 109 (90)
BCVA, logMAR	0.02 ± 0.10	0.01, 0.04
IOP (mmHg)	13.8 ± 3.0	13.3, 14.4
Cataract surgery	Yes, 27 (22)	No, 94 (78)
Cataract grade	Grade 0, 24 (20)	Grade 1, 41 (34)
	Grade 2 or 3, 29 (24)	IOL, 27 (22)
dROM (U.Carr)	348 ± 56	338, 358
BAP (μmol/L)	2,022 ± 240	1,979, 2,065
SH (μmol/L)	621 ± 98	604, 639

CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; cpm, count per minute; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum an-gle of resolution; IOP, intraocular pressure; IOL, intraocular lens; dROM, diacron reactive oxygen metabolite; BAP, biologic antioxidant potential; SH, sulfhydryl.

Table 2. Possible associations among serum redox parameters and various continuous parameters calculated by univariate analyses

Parameter	dROM			BAP			SH		
	Estimate	95% CI	*p* value	Estimate	95% CI	*p* value	Estimate	95% CI	*p* value
Age (years)	0.5	−0.5, 1.4	0.35	1	−3.1, 5.1	0.64	−4.4	−5.9, −2.9	<0.0001*
SBP (mmHg)	−0.3	−0.8, 0.3	0.34	0.9	−1.4, 3.1	0.45	0.6	−0.3. 1.5	0.21
DBP (mmHg)	0.1	−0.8, 0.9	0.91	2.5	−1.1, 6.1	0.18	1.1	−0.3, 2.6	0.13
PR (cpm)	0.2	−0.7, 1.0	0.72	2.4	−1.2, 6.0	0.19	2.1	0.7, 3.6	0.004*
BCVA (logMAR)	29	−75, 134	0.58	−221	−671, 230	0.33	−342	−517, −167	0.0002*
IOP (mmHg)	−2.5	−5.9, 0.8	0.13	9.6	−4.7, 23.9	0.19	6.1	0.3, 11.9	0.04*

The correlation is calculated with Pearson's correlation coefficient. *p<0.05. SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; cpm, count per minute; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; dROM, diacron reactive oxygen metabolite; BAP, biologic antioxidant potential; SH, sulfhydryl; CI, confidence interval.

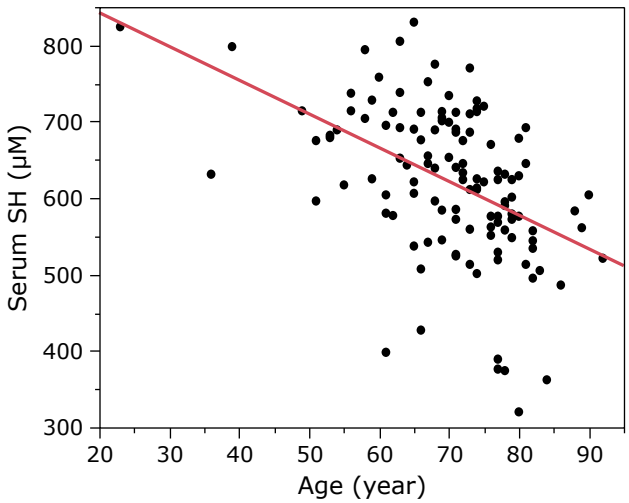

Fig. 1. Scatter plot graph of serum SH levels and age in subjects. $r = -4.4$ and $p = 0.04$ calculated by linear regression analysis. SH, sulfhydryl.

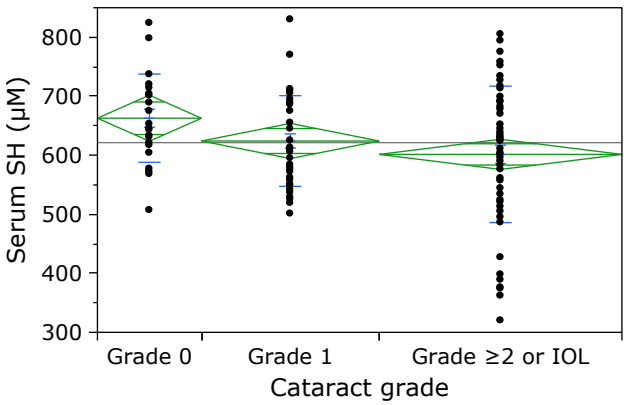

Fig. 2. Serum SH levels in subjects having eyes with different cataract grades. $p = 0.04$ calculated using one-way analysis of variance among groups. The green lines indicate the mean ± 95% confidence intervals. SH, sulfhydryl; IOL, intraocular lens.

Table 3. Possible associations among serum redox parameters and various categorical parameters calculated by univariate analyses

Parameter	Mean ± SD	Mean ± SD	*p* value
dROM (U.Carr)			
Sex	Male, 329 ± 53	Female, 357 ± 55	0.01*
Diabetes	No, 348 ± 50	Yes, 346 ± 82	0.86
Smoking	No, 349 ± 55	Yes, 343 ± 62	0.76
Cataract surgery	No, 351 ± 56	Yes, 337 ± 54	0.26
Cataract grade	Grade 0, 336 ± 50	Grade ≥1 or IOL, 351 ± 57	0.25
BAP (μmol/L)			
Sex	Male, 2,019 ± 260	Female, 2,023 ± 232	0.92
Diabetes	No, 2,019 ± 240	Yes, 2,037 ± 245	0.78
Smoking	No, 2,015 ± 243	Yes, 2,087 ± 202	0.33
Cataract surgery	No, 2,027 ± 216	Yes, 2,003 ± 313	0.64
Cataract grade	Grade 0, 2,043 ± 231	Grade ≥1 or IOL, 2,017 ± 243	0.63
SH (μmol/L)			
Sex	Male, 638 ± 109	Female, 614 ± 93	0.2
Diabetes	No, 624 ± 96	Yes, 608 ± 115	0.54
Smoking	No, 616 ± 98	Yes, 666 ± 96	0.1
Cataract surgery	No, 625 ± 87	Yes, 607 ± 130	0.39
Cataract grade	Grade 0, 663 ± 75	Grade ≥1 or IOL, 611 ± 101	0.02*

P values are calculated using the unpaired *t* test. *p<0.05. IOL, intraocular lens; dROM, diacron reactive oxygen metabolite; BAP, biologic antioxidant potential; SH, sulfhydryl.

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Table 4. Possible associations among serum dROM and various parameters analyzed by a multiple regression model

Parameter	Estimate	95% CI	*p* value	Standard β
Age (years)	0.2	–1.0, 1.5	0.71	0.05
Sex (female/male)	14	2.1, 27	0.02*	0.24
SBP (mmHg)	–0.4	–1.1, 0.3	0.26	–0.13
DBP (mmHg)	1	–0.2, 2.2	0.11	0.21
PR (cpm)	0.1	–0.8, 1.1	0.75	0.03
Diabetes (yes/no)	–0.9	–16, 14	0.9	–0.01
Smoking (yes/no)	8.1	–11, 27	0.4	0.09
BCVA (logMAR)	–12	–128, 105	0.85	–0.02
IOP (mmHg)	–2.7	–6.5, 1.0	0.15	–0.15
Cataract surgery (yes/no)	–12	–25, 0.9	0.07	–0.18
Cataract grade (grade ≥1 or IOL/grade 0)	15	–15, 44	0.33	0.1

P values are calculated using a multiple regression model. *$p<0.05$. CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; cpm, count per minute; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; dROM, diacron reactive oxygen metabolite; IOL, intraocular lens.

Table 5. Possible associations among serum BAP and various parameters analyzed by a multiple regression model

Parameter	Estimate	95% CI	*p* value	Standard β
Age (years)	5.4	–0.2, 11	0.06	0.24
Sex (female/male)	28	–26, 83	0.31	0.11
SBP (mmHg)	–0.4	–3.5, 2.6	0.78	–0.03
DBP (mmHg)	3.4	–1.9, 8.7	0.2	0.17
PR (cpm)	1.1	–2.9, 5.2	0.58	0.06
Diabetes (yes/no)	13	–52, 77	0.7	0.04
Smoking (yes/no)	56	–28, 140	0.19	0.14
BCVA (logMAR)	–296	–810, 217	0.26	–0.12
IOP (mmHg)	9.9	–6.5, 26	0.23	0.12
Cataract surgery (yes/no)	–7.8	–66, 50	0.79	–0.03
Cataract grade (grade ≥1 or IOL/grade 0)	–47	–178, 84	0.48	–0.08

P values are calculated using a multiple regression model. CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; cpm, count per minute; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; BAP, biologic antioxidant potential; IOL, intraocular lens.

Table 6. Possible associations among serm SH and various parameters analyzed by a multiple regression model

Parameter	Estimate	95% CI	*p* value	Standard β
Age (years)	–4.3	–6.3, –2.3	<0.0001*	–0.46
Sex (female/male)	4.7	–15, 24	0.63	0.04
SBP (mmHg)	1.1	0.0, 2.2	0.04*	0.22
DBP (mmHg)	–1.6	–3.5, 0.3	0.09	–0.2
PR (cpm)	1.3	–0.2, 2.7	0.08	0.26
Diabetes (yes/no)	10	–13, 33	0.37	0.08
Smoking (yes/no)	1.6	–28, 31	0.91	0.01
BCVA (logMAR)	–190	–373, –7.1	0.04*	–0.19
IOP (mmHg)	–0.1	–5.9, 5.8	0.98	0
Cataract surgery (yes/no)	–7.9	–29, 13	0.45	–0.07
Cataract grade (grade ≥1 or IOL/grade 0)	13	–33, 60	0.57	0.05

P values are calculated using a multiple regression model. *$p<0.05$. CI, confidence interval; SBP, systolic blood pressure; DBP, diastolic blood pressure; PR, pulse rate; cpm, count per minute; BCVA, best-corrected visual acuity; logMAR, logarithm of the minimum angle of resolution; IOP, intraocular pressure; SH, sulfhydryl; IOL, intraocular lens.

associated with the serum BAP level (Table 5). For SH, older age (estimate = −4.3/year, $p<0.0001$), higher SBP (estimate = 1.1/mmHg, $p = 0.04$), and worse BCVA (estimate = −190/logMAR, $p = 0.04$) were associated significantly with a lower serum SH level (Table 6).

Discussion

The current results indicated that a lower serum SH level, a measure of the total amount of reduced thiols, was associated significantly with a higher nuclear cataract grade in univariate

analysis (Table 3, Fig. 2). A hospital-based case-control study showed that lower levels of an antioxidant index based on the levels of red blood cells of GPX and G6PD and plasma levels of vitamins C and E were associated with an increased risk of development of ARC.[20] In a case-control study conducted in India, the thiobarbituric acid reactive substance (TBARS) level was higher, and SOD and GPX levels were lower in a cataract group compared with controls.[21] In a case control study in China, serum malondialdehyde, 4-hydroxynonenal, and conjugated dienes levels were higher, and serum SOD, catalase and GPX activities were lower in a cataract group compared with controls.[22] The SH serum level did not differ significantly between different types of cataracts (nuclear, cortical, and posterior subcapsular cataracts).[23] Accordingly, our results further added evidence that the level of systemic SH can reflect the severity of ARC in humans (Fig. 2). No association between the cataract grade and serum SH levels was seen in multivariate analysis (Table 6), while worse BCVA was associated with lower SH levels in both univariate and multivariate analyses (Table 2 and 3). Confounding effect derived from a strong direct association between cataract grade and BCVA likely explains the non-significant role of cataract grade on serum SH levels in the multivariate analysis.

The major thiol-mediated redox systems in humans are the glutathione and thioredoxin systems, although the plasma glutathione level is 100 to 1,000 times higher than that of thioredoxin.[24,25] Reduced cysteine and its oxidized form (i.e., cystine) constitute the predominant low-molecular-weight thiol-disulfide pool in plasma;[26] in humans, the plasma cysteine concentration was 4.5 times higher than that of reduced glutathione.[8] Thus, the SH level in the current study primarily might reflect the level of free cysteine, but that remains to be clarified. In an experimental model, inhibition of glutathione synthesis with L-buthionine (S, R)-sulphoximine induced cataracts in newborn rats[27] and depletion of reduced glutathione with diethylmaleate induced TBARS formation and lens opacity in isolated lenses.[28] A low glutathione content in lenses also was associated with cataractogenesis induced by steroids,[29] sugar,[30] and ultraviolet radiation[31] in rats. Glutathione precursor *N*-acetylcysteine inhibited cataractogenesis induced by naphthalene[32] and acetaminophen[33] in mice. Depleted glutathione levels resulted in significantly increased susceptibility to H_2O_2-induced apoptosis in human lens epithelial cells.[34] Thus, oxidative stress associated with cataractogenesis can be reduced by thiol-dependent reactions. Decreased levels of glutathione in the serum of type 2 diabetic patients[35] and in red blood cells of type 2 diabetic patients[36] were reported. Given that the diabetes is a well-known risk factor of cataractgenesis, impaired glucose tolerance reflected by reduced serum thiols might be involved in the mechanism of negative association between serum SH level and cataract grade in this study.

Our results clearly demonstrated the negative association between age and systemic SH level (Table 2 and 6, Fig. 1). Previously, a negative correlation was reported between age and total glutathione level in red blood cells.[37] In individuals between 19 and 85 years, cysteine/cystine redox was linearly oxidized while glutathione/glutathione disulfide redox was not oxidized before 45 years and started to oxidize linearly after 45 years.[8] Considering the age distribution of our subjects, the current results coincided well with the previous observations. An age-related decrease in GPX, GR, and G6PD activities but no age-related change in SOD activity in lenses from rats for up to 24 months of age were reported.[38] Reduced glutathione content based on age also was reported; while chronic administration of vitamin E but not sodium ascorbate resulted in restoration of the glutathione levels to those of younger rats. Together with the previous results, the current study suggests the possible modulation of cataract formation and/or age-dependent decline in VA via modulation of the serum SH level,[39] and this remains to be proven. Univariate analysis showed that a lower serum SH level was associated with lower IOP (Table 2), while the association became nonsignificant after adjustment of other parameters including age (Table 6). In our previous studies in general populations, an age-dependent decline of IOP was observed.[40,41] The balance between aqueous humor inflow and outflow determines the IOP. Aging causes decreased aqueous humor production[42] and increased trabecular meshwork resistance;[43] thus, SH might affect the IOP via the effects of age.

For BAP, a reflection of the small-molecule antioxidants such as vitamin C and polyphenols, none of the parameters assessed was significantly associated. In our previous studies of glaucoma subjects, lower BAP was associated with glaucoma risk,[7] higher IOP,[10] more severe visual field damage,[11] and narrower retinal vessel diameters[44] in glaucoma, while neither dROM nor SH levels were associated with them. Thus, the results suggested the specific roles of systemic thiols on crystalline lens integrity rather than other eye diseases such as glaucoma. Modification of thiol levels may be associated with cataract prevention more effective than the modification of small molecule antioxidants levels, but remains to be elucidated.

For dROM, female gender was the only significant determinant in both univariate (Table 3) and multivariate (Table 4) analyses, while dROM was not associated with cataract grade. A higher dROM level in females than males agreed with our previous study in glaucoma subjects[7] as well as previous observations regarding a gender difference in systemic oxidative stress.[45,46] Generally, cataract formation is more prevalent in women than men.[47] Previous studies have shown the possible increment of systemic oxidation in cataract patients;[48,49] thus, the difference in the male/female ratio between the current and previous studies might explain the discrepancy. The mechanism of gender roles on the systemic pro-oxidant level was not determined in this study.

We reported previously that the serum BAP level was well correlated with the intraocular oxidative stress assessed by SOD levels in the aqueous humor.[50] However, the GR or GPX activities in the lens epithelium and the same enzymatic activity in erythrocytes or the type/cataract severity were not correlated.[51] Accordingly, the association between the serum SH level and intraocular thiol level still remains to be elucidated. Although the manufacturer's information suggested that maintaining serum samples at 4°C facilitates the ability to obtain stable data for up to 48 h, since prooxidants and antioxidants can be unstable, a relatively long duration between the serum collection and measurements might affect the results. In this study, the timing of blood sampling differed among subjects, and the samples were not the fasting blood. Previous study suggested the presence of diurnal variation in plasma glutathione and cysteine levels and roles of duration after meal on plasma glutathione and cysteine levels.[52] Instead of fasting before the blood collection, we recorded the duration after the last meal;[7,10,11] although the duration was not different among the cataract grade groups (4.2 ± 3.2 h for grade 0, and 4.0 ± 2.9 h for grade ≥1 or IOL; $p = 0.76$), these factors might affect the results also. Another possible limitation of the current study was that the use of antioxidants and other supplements was not stipulated in the inclusion/exclusion criteria. Our study included both phakic and pseudophakic subjects; thus, a history of cataract surgery might weaken the statistical power for detecting the association between BCVA/cataract grade and redox parameters.

This comprehensive study indicated that a lower serum SH level was a determinant of aging itself and an age-related decline in VA due to cataract.

Author Contributions

Conceptualization, MT; methodology, MT and SK; formal

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analysis, MT; investigation, MT, YTakayanagi, AI, SI, YTakai, and SK; data curation, MT and SK; writing–original draft preparation, MT; writing–review and editing, YTakayanagi, YTakai, and SK. All authors have read and agreed to the published version of the manuscript.

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Conflict of Interest

No potential conflicts of interest were disclosed.

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