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Serum selenium levels are associated with age-related cataract

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Abstract

Objective. The aim of the study is to analyse correlations between age-related cataract (ARC), serum selenium levels and glutathione peroxidase gene 1 and 4 (GPX-1 and GPX-4).

Materials and method. A total sample of 275 participants were enrolled into the study: group A, 94 subjects elligible for ARC surgery, and group B, 181 volunteers without ocular symptoms, gender-, age-, and smoking- status and volume-matched at 1:2 with subjects in group A. All participants (n=275) were divided according to the Lens Opacities Classification System III (LOCS III) into: 1) study group (subjects with clinically significant cataract; N≥3 or C≥3 or P≥2), 2) control group (controls with clinically non-significant cataract; N<3 and C<3 and P<2). The single nucleotide polymorphisms of GPX-1 and GPX-4 were assessed using Real Time PCR. Serum selenium levels were assayed using Inductively Coupled Plasma Mass Spectrometry.

Results. Low selenium levels significantly predicted any age-related cataract (OR 7.969; p<.01), nuclear cataract (OR 12.823; p<.01) and cortical cataract (OR 3.31; p<.01). There was no significant effect of gender, age, SNP GPX-1 and SNP GPX-4 on the prevalence of age-related nuclear, cortical and posterior sub-capsular cataract. Serum selenium levels of 75–85 μg/L were associated with the lowest prevalence of ARC.

Conclusions. Due to a confirmed association between serum selenium levels and age-related cataract, low serum selenium levels may constitute a potential risk factor of age-related cataract.

Key words

selenium, age-related cataract, single nucleotide polymorphism, LOCS III, glutathione peroxidase, SNP

INTRODUCTION

According to the World Health Organisation (WHO, 2016), age-related cataract (ARC) is a cause of moderate or severe vision impairment in 50 million people worldwide [1]. Currently, the only effective treatment involves surgical cataract extraction with intraocular lens implantation. In the USA, cataract surgery is the most common type of surgery with 3 million procedures performed each year [2], and the annual cost of ARC treatment is approximately USD 3.5 billion [2]. ARC surgery rates in the US are high, over 8,000 procedures/1 million inhabitants, although in the developing countries it can be only 50 procedures/1 million inhabitants [3]. According to the WHOs estimates, in order to fully meet the growing need for treatment, the number of cataract surgery procedures worldwide would have to triple in 2000–2020 [3]. Considering population growth and ageing in developed countries and high costs of surgery, widely-available and effective cataract treatment still seems an unmet need. Therefore, alternative, non-surgical methods are being sought to inhibit lens opacity. The etiology of ARC has been studied extensively within the last 20 years, with particular focus on slowing the progression/delaying the onset of ARC [4–7]. However, the attempts so far have been unsuccessful.

Lens ageing and ARC are associated with a number of biochemical changes to the crystalline lens. These are primarily affected by oxidative stress, due to the presence of reactive oxygen species (ROS) [8, 9]. Glutathione/glutathione peroxidase 1 and 4 (GSH/GPX1/GPX-4) is the key enzyme system involved in protecting the lens against ROS-induced damage [10, 11]. Glutathione peroxidase 1 and 4 are known as selenoproteins which, owing to their selenocysteine content, their enzymatic effect is 1,000-fold stronger than their cysteine homologues [12]. A number of studies in humans and animals have confirmed a decreased activity of GPX and glutathione in a opacified lens [13–17]. Furthermore, an increased level of hydrogen peroxide H_2O_2 (which is reduced by GPX) was shown in the aqueous humour of patients with cataracts [18–20]. The role of GPX activity in cataract formation (especially nuclear cataract) has been well established [13, 18, 21, 22]. Lens opacity, especially within the nucleus, developed significantly faster in GPX knockout mice [21, 22].

The GPX activity is selenium-dependent. The suggested serum Se levels in humans, optimum for GPX and other selenoprotein function range between 78.9 μg/L and 94.7 μg/L (1.00–1.20 mmol/L) [23–25]. Knowledge of serum Se levels in patients with ARC may provide essential data relative to lens metabolism and human health. There are many reports suggesting that suboptimum Se levels may increase the risk of

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cancers (i.e. laryngeal), as well as cardiovascular, pulmonary, and inflammatory diseases [10, 22, 23, 28]. Moreover, single reports suggest that suboptimum Se levels may adversely affect lens metabolism, increasing its opacity [21]. This appears to be particularly relevant in the Polish population, with the low mean serum Se level of 70 μg/l, while in North America the average reported Se concentration ranges from 122.4–151.8 μg/l [26–28]. Serum selenium levels may differ among populations, depending on a number of factors, including but not limited to concentration of selenium in food, water (groundwater in Poland Se=0.05 μg/L), soil [26–28]. More than 77% of the area of Poland is characterized by a decreased level of Se in soil, the lowest in the eastern regions – 0.06 – 0.4 mg/kg, the highest in northwestern regions – 2.3 – 4.2 mg/kg. At the same time, Se level in soil in the USA is 6 – 15mg/kg. The concentration of selenium is also dependent on the industrialization of the region (USA – 30 ng/m^3, South Pole – 0.004 – 0.008 ng/m^3). These data confirm the thesis that the selenium concentration is strongly dependent on both environmental factors and pollution.

Single nucleotide polymorphism (SNP) is a variation in the DNA sequence, involving a single nucleotide (A,T,C or G) change between the corresponding chromosomes of a given individual. In GPX-1 and GPX-4 genes, polymorphisms involving thymine (T) and cytosine (C) changes are of key functional importance. These may present as CC/CT/TT genotypes [30–32]. However, the SNP GPX have not been assessed in ophthalmology. The current study is the first analysis of SNP GPX-1 (rs1050450) and SNP GPX-4 (rs713041) in patients with ARC. Detailed characteristics of genes and single nucleotide polymorphisms (SNP) of GPX 1 and GPX 4 are shown in Table 1.

Research supports the crucial role of GPX-1 and GPX-4 in lens metabolism and pathophysiology of ARC. There are single reports suggesting the role of selenium in regulating the enzymes in question. A detailed analysis of the above may significantly contribute to our understanding of cataract prevention. This is particularly important in the context of increasing ARC prevalence in the general population, and the related treatment needs and costs.

Table 1. Characteristics of glutathione peroxidase genes 1 and 4

Chromosome/ gene	Function	SNA	Position	SNP locus	Allele
3p21/ GPX-1	GPX-1 enzyme detoxifies H_2O_2 and lipid hydroperoxides	rs1050450	49357401	Pro198Leu (exon 198)	C/T
19p13/ GPX-4	GPX-4 enzyme, reduces H_2O_2 and phospholipid hydroperoxides	rs713041	1106616	3-UTR	C/T

GPX – 1 glutathione peroxidase 1; GPX-4 – glutathione peroxidase 4; H_2O_2 – hydrogen peroxide; SNP – single nucleotide polymorphism; Pro – praline; Leu – leucine; C – cytosine; T – thymine; 3-UTR – untranslated region.

MATERIALS AND METHOD

Participants. A total sample of 275 individuals (103 men, 172 women) were enrolled, including:
A) 94 patients eligible for age-related cataract surgery at the Ophthalmology Outpatient Clinic who were intended as the core of the study group. The mean age in this subgroup was 72.4 years ± 7.25 (range: 56–89 years). B) 181 volunteers without ocular symptoms, matched at 1:2 to the patients from group A, the core of the control group. The controls were matched to patients based on: year of birth (± 3 years), gender, number of packet-years ± 20% (packet-years defined as the number of cigarette packets smoked daily, multiplied by the number of years an individual has been a smoker). Group B was recruited from the Genetic Oncology Outpatient Clinic. Pedigree and clinical characteristics of hereditary malignancies were equally present in groups A and B. High-risk mutation carriers were excluded. The mean age in this subgroup was 70.9 years ± 7.36 (range: 53–88 years).

In order to control for the confounding variables, strict inclusion/exclusion criteria were applied. Exclusion criteria included taking prescription medications, the presence of diseases known to effect the lens, as well as eye diseases other than age-related cataract. Thus, an individual with diabetes and fasting hyperglycaemia was excluded in order to minimise the role of glycation products and sorbitol in cataract development in the study sample. Furthermore, individuals taking micro-/macroelement and/or vitamin-based supplements were excluded, along with those on a reduction or therapeutic diet. Medical history ascertained such factors as excessive exposure to UV or IR radiation in, e.g. the high-risk professions of a steel worker or a welder.

All participants (n=275) were classified into the study group according to the Lens Opacities Classification Scale III (LOCS III) – subjects with clinically significant cataract, or the control group – controls with clinically non-significant cataract (Tab. 2). The division between clinically significant and non-significant cataract was determined as in previous research [33–35], despite which there is still no formal cataract classification into those clinically significant and non-significant.

The rs1050450 genotype of GPX-1 and rs713041 genotype of GPX-4 were assessed in 275 enrolled participants. The CT and TT genotypes were jointly referred to as non-CC, on the grounds of similarities in their function. The CC GPX-1 genotype constituted 46.18% of all GPX-1 polymorphisms and the non-CC genotype was shown in 148 participants (53.82%). The CC GPX-4 genotype (rs713041) constituted 35.64% of all GPX-4 polymorphisms, and the non-CC genotype was shown in 64.36% of all participants.

All participants gave their informed consent to participate in the study. The study protocol, designed in accordance with the Declaration of Helsinki, was approved by the Internal Review Board at the Pomeranian Medical University in Szczecin.

Selenium level assay in biological samples. Venous blood samples of all patients were obtained in the morning (fasting) and frozen at -80C within 2hrs following collection. Selenium levels were assayed in serum, which is used the most often for selenium level measurements in research [26, 27]. Selenium in serum determination was carried out using the Inductively Coupled Plasma-Mass Spectrometer (ICP-MS). Serum specimens were initially centrifuged at 3,000 G for 10 minutes. Next, the supernatant volume was diluted 100-fold with 0.65% nitric acid solution SUPRAPUR (Merck, Germany). The processed sample was then used for selenium

Table 2. Study group classification by cataract grading (LOCS III)

Opacity	Controls (with clinically non-significant cataract as per LOCS III)				Subjects (with clinically significant cataract as per LOCS III)			
	LOCS III	Group A	Group B	Total	LOCS III	Group A	Group B	Total
nuclear*	N<3	n=7	n=168	n=175	N≥3	n=87	n=13	n=100
cortical	C<3	n=16	n=136	n=152	C≥3	n=78	n=45	n=123
posterior subcapsular	P<2	n=42	n=150	n=192	P≥2	n=52	n=31	n=83
Any age-related cataract	N<3 and C<3 and P<2	n=0	n=106	n=106	N≥3 or C≥3 or P≥2	n=94	n=75	n=169

*N determined as a mean of NO (nuclear opalescence) and NC (nuclear colour)

determination using ICP-MS (Elan DRC-e, PerkinElmer, USA). The quantitative assay required a calibration curve. Therefore, a multi-element calibration standard was created using dilution (Multi-Element Calibration Standard 3; PerkinElmer, USA), with the endpoint concentrations of calibration standards of 0.1µg/L, 1µg/L, 5µg/L and 10µg/L, respectively. Serum control with the verified selenium content (ClinChek® Serum Control, RECIPE, Germany) was used as the reference sample. The ICPMS method used in the sample-processing laboratory was validated by international reference centres.

Selenoprotein gene variant determination. The real-time PCR (LightCycler 480 II, Roche Diagnostics GmbH, Germany) was used for gene quantification. Functional DNA fragments with high polymorphism were selected for analyses. The following genes were analysed: GPX-1 (RS1050450) and GPX-4 (RS713041).

Statistical analysis. A sample of 275 participants was divided into quartiles (n=68, 69) according to their serum selenium levels, with the 1st quartile presenting with the lowest (31.64–67.73 µg/L) and 4th quartile – with the highest (81.29–163.54 µg/L) levels. The 3rd quartile (75.18–81.28 µg/L) was a reference group, as their lens opacity as per LOCS III was the lowest; therefore, they were the most representative of the general population. Cataract was graded as per LOCS III (Tab. 2).

Multiple logistic regression was used in order to identify factors significantly predicting increased prevalence of ARC in the study sample. This included all ARC subtypes. The analysed variables included: age, gender, serum selenium level, as well as the polymorphism (CC vs. non-CC) of GPX-1 and GPX-4. The confidence interval ranged between 2.5% – 97.5%, with p <.05 considered statistically significant. Each type of ARC was assessed as an independent variable, just as performed in some other studies in this field [34, 35].

RESULTS

All participants had an intraocular pressure (IOP) of 8–21 mmHg and normal fundus morphology. The best distance corrected visual acuity (BDCVA) fell within the range of.02 –.1 (logMAR). The results of multiple logistic regression are shown in Tables 3–6. The 3rd quartile of Se levels was not included as a reference range. Low serum selenium levels (within the 1st quartile range) significantly predicted any cataract (Tab. 3), and – in particular – nuclear (Tab. 4) and cortical (Tab. 5) cataract in the study sample. The incidence of any age-related cataract was 8-fold higher than in the general population, with serum selenium levels within the 1st quartile (range: 31.64 – 67.73 µg/L): OR 7.969, CI 95% 3.391–20.672; p<.01 (Tab. 3). The lowest incidence of ARC was observed in the subgroup of participants with serum Se levels ranging between 75 µg/L – 85 µg/L, which broadly corresponds with the 3rd quartile Se levels. There was no significant association between gender or age and age-related cataract prevalence (Tab. 3). There was no effect of SNP of GPX-1 or GPX-4 on the incidence of ARC. The statistics relative to the CC-genotype are shown in Tables 3–6. As none of these values was statistically significant, it can be assumed that the CC-genotype does not affect the incidence of ARC.

Table 3. Factors associated with increased incidence of any age-related cataract – multiple logistic regression

Assessed factor	OR	2.5 %	97.5 %	p
Se 1st quartile (Se levels range of 31.64–67.73 µg/L)	7.969	3.391	20.672	<.01
Se 2nd quartile (Se levels range of 67.74–75.17 µg/L)	1.465	0.742	2.918	.273
Se 4th quartile (Se levels range of 81.29–163.54 µg/L)	1.117	0.567	2.211	.749
age	1.019	0.981	1.059	.325
Gender (male)	1.188	0.686	2.076	.541
CC genotype of GPX-1	1.499	0.888	2.552	.132
CC genotype of GPX-4	0.785	0.456	1.349	.38

The results of multiple logistic regression for nuclear and cortical cataract are shown in Tables 4 and 5, respectively. Subjects with the lowest Se levels (1st quartile) had a 12-fold higher occurrence of nuclear opacity: OR 12.823; CI 95% 5.672–30.972; p<.01. The prevalence of cortical cataract was lower, yet significant: OR 3.31; CI 95% 1.635–6.866; p<.01. There was no significant effect of SNP GPX-1 and SNP GPX-4, gender or age. The results of multiple logistic regression for posterior sub-capsular cataract are shown in Table 6. There was no effect of selenium levels, gender, age, SNP GPX-1 or SNP GPX-4 on the incidence of this type of cataract.

Table 4. Factors associated with increased incidence of nuclear cataract – multiple logistic regression

Assessed factor	OR	2.5 %	97.5 %	p
Se level in the 1st quartile (range of 31.64–67.73 µg/L)	12.823	5.672	30.972	<.01
Se level in the 2nd quartile (range of 67.74–75.17 µg/L)	1.709	0.753	3.979	.204
Se level in the 4th quartile (range of 81.29–163.54 µg/L)	1.745	0.766	4.082	.19
age	1.044	1.002	1.089	.043
sex (male)	1.605	0.874	2.979	.129
CC genotype of GPX-1	1.445	0.819	2.571	.206
CC genotype of GPX-4	0.646	0.351	1.172	.155

Table 5. Factors associated with increased incidence of cortical cataract – multiple logistic regression

Assessed factor	OR	2.5 %	97.5 %	p
Se levels in the 1st quartile (range of 31.64–67.73 µg/L)	3.31	1.635	6.866	<.01
Se levels in the 2nd quartile (range of 67.74–75.17 µg/L)	1.317	0.66	2.642	.435
Se levels in the 4th quartile (range of 81.29–163.54 µg/L)	1.036	0.513	2.093	.921
age	1	0.965	1.037	.992
gender (male)	1.365	0.809	2.315	.245
CC genotype of GPX-1	1.115	0.679	1.834	.667
CC genotype of GPX-4	0.973	0.579	1.63	.916

Table 6. Factors associated with increased incidence of posterior subcapsular cataract – multiple logistic regression

Assessed factor	OR	2.5 %	97.5 %	P
Se levels in the 1st quartile (range of 31.64–67.73 µg/L)	2.02	0.96	4.36	.07
Se levels in the 2nd quartile (range of 67.74–75.17 µg/L)	1.72	0.82	3.68	.15
Se levels in the 4th quartile (range of 81.29–163.54 µg/L)	0.91	0.40	2.02	.81
age	1.01	0.97	1.05	.51
gender (male)	1.48	0.85	2.60	.17
CC genotype of GPX-1	1.16	0.68	1.98	.58
CC genotype of GPX-4	0.76	0.43	1.32	.33

DISCUSSION

Selenium is a micronutrient with a complex metabolism with multi-factorial regulation of its activity. Its concentration in the body depends on bioavailability, diet, level of Se in the soil and drinking water. Selenium is supplied to the body with food in an organic form (selenomethionine, selenocysteine) and inorganic (selenine). Selenomethionine is provided in animal and vegetable diet, its bioavailability is up to 90% [23–25]. Selenomethionine covers half of the daily requirement for Se. Selenocysteine is also characterized by 90% bioavailability and is present in plant food [23–25]. Selenium in inorganic form has lower bioavailability – 50% [23–25]. Recommended daily dose in diet for selenium ranges from 40 – 70 µg/day [25]. In Poland, the average daily intake is 27.8 µg/day, while in Japan – 82.7 µg/day and USA – 95.9 µg/day [26]. As mentioned in the Introduction, there are reports suggesting that suboptimum Se levels may adversely affect human health, including lens metabolism [10, 22, 23].

Role of selenium and glutathione peroxidase in pathogenesis of ARC. As mentioned before, glutathione peroxidase is the key enzyme for protecting the lens against oxidative stress and ARC development. Selenium (Se) presence in a form of selenocysteine in a GPX molecule additionally enhances its enzymatic activity by almost 1,000-fold, compared to cysteine homologues [12]. A number of studies support the hypothesis that a lower serum selenium level is associated with decreased GPX activity in various tissues: blood [36, 37], kidneys [37], and liver, up to 99% [38]. Furthermore, the study in rats by Cai indicates that decreased serum Se level decreases GPX activity in the lens, thus increasing the prevalence of cataracts [21]. The results of the current study also suggest that the increased prevalence of ARC (nuclear and cortical, Tabs. 4 – 5) may be secondary to the decreased serum selenium levels.

The fact that GPX knockout [18, 22, 39, 40] or its GPX inhibition [13, 21] is associated with increased prevalence of cataract seems confirmation of the GPX role in ARC pathogenesis. According to Reddy, GPX-1 knockout resulted in damage to the cellular membranes of lens fibres and progressive nuclear opacity. However, no damage to lens epithelium or cortex has been shown, which can be explained by higher levels of glutathione in these structures, which has an established antioxidant effect [41, 42]. Another study showed an increased epithelial resistance to the cytotoxic effect of H_2O_2 in transgenic animals with increased GPX activity, compared to non-transgenic animals [43]. It should be noted, however, that cells composing the lens nucleus or cortex do not have their own organelles. They therefore depend on their environment and adjacent lens epithelium which shows normal enzymatic activity. Considering the distance from the epithelium, the lens nucleus may be more susceptible to oxidative stress than the lens cortex. This corresponds to the current findings, that decreased serum Se levels correlated with the prevalence of nuclear cataract increased 4-fold, compared to the prevalence of cortical cataract (nuclear ARC vs. cortical ARC: OR 12.8 vs. 3.3).

The current study is the first to assess polymorphisms of glutathione peroxidase gene 1 (rs1050450) and 4 (rs713041) in ophthalmology. As shown above, statistical analysis did not confirm an association between LOCS III and SNP GPX-1 or GPX-4 (Tabs. 6 – 9). Mao (2016) did not show an association between Se and SNP GPX-1 or GPX-4 [44], which is in line with Donadio (2016), although the latter study only assessed SNP GPX-1 [32]. Obviously, the absence of correlations between ARC and assessed SNPs does not imply that there is no potential effect of other SNP GPX-1 or GPX-4 on glutathione peroxidase enzymes.

Association between selenium levels and prevalence of ARC. A number of correlational animal and clinical studies have been carried out to-date to determine the association between selenium levels and prevalence of ARC [21, 29, 45, 46]. In the opinion of the authors of the current study, they all have significant methodology-related limitations, which preclude reliable interpretation of results. The current study is the first to use LOCS III for cataract classification, which enabled statistical analysis of different ARC subtypes. Furthermore, the current study assumed the strictest sample selection criteria, which helped minimize the effect of artifacts seen in other studies.

The results of this study confirm a significant ($p<.01$) correlation between low selenium levels and ARC prevalence. In subjects with the lowest Se levels (1st quartile: Se 31.64–67.73 µg/L), the prevalence of nuclear cataract was increased 12-fold, of cortical cataract – 3-fold, and of any ARC – 8-fold, compared to the reference group. These findings are in line with results reported by other authors [21, 29]. In the study by Dawczyński [29], the study sample consisted of patients with mature cataract undergoing extracapsular cataract extraction (ECCE) only. This sample might have not been representative of the general population, especially if LOCS III was not applied. Furthermore, Se levels were determined

in the study by using atomic absorption spectrometry (AAS), the accuracy of which is inferior to ICPMS. In a study carried out in the Finnish population in 1997, Knekt did not confirm the association between serum Se levels and ARC prevalence [45]. However, unlike the current study, the one by Knekt had a number of significant limitations: patients treated with diuretics were not excluded, LOCS III grading was not assessed, and Se levels were determined using atomic absorption spectrometry (AAS). The study group consisted of patients undergoing surgery due to mature cataract. The controls were volunteers who did not report cataract. However, their lens opacity was not assessed and they did not undergo an eye exam. Furthermore, fasting blood samples were not ensured and patients with diabetes were not excluded. Therefore, Se levels might have been masked by metabolic changes, medications, diabetic diet, as well as occult or manifest nephropathy. All the above could have decreased the reliability of Se assays and further statistical analyses. On the other hand, the study by Jacques found an association between Se levels of > 100 μg/L and increased prevalence of ARC. However, the results were on the verge of significance with p >.05 and <.1 [46]. Finally, methodology limitations of that study were the same as in Knekt's research [46]. The presented findings do not support the hypothesis that higher Se levels increase the prevalence of ARC (Tabs. 3 – 6). Subjects in the 4th quartile (i.e. with the highest serum Se levels) had increased OR for n uclear (OR=1,745; Tab. 4) and cortical cataract (OR=1.036; Tab. 5), although the findings were not significant (p >.05). The OR in patients with posterior subcapsular cataract and highest Se levels was.91 (Tab. 6); however, the result was not significant. Jacques' findings have also not been confirmed in research performed in the Chinese population [47]. The Chinese study was carried out in a population inhabiting an industrial area with high pollution and high soil and water concentration of selenium. The authors reported no association between higher selenium concentrations and ARC prevalence. The prevalence of nuclear (23.7%), cortical (22.4%), and posterior sub-capsular (5.2%) opacity in the study sample was comparable to the general Chinese population. These results, however, cannot be compared with those of the presented study, as the study by Li was based on LOCS II classification, and different criteria of clinical significance were applied to cataracts: ≥N1, ≥C1, ≥P1 [47].

Posterior sub-capsular cataract, which differs clinically and histologically from cortical or nuclear opacities, requires a separate comment. It can be induced by steroids and trauma, or develop secondarily to diabetes. However, there are cases of posterior sub-capsular cataract without an obvious cause. Histologically, there is no crystalline aggregation in posterior sub-capsular cataract, which is commonly seen in cortical and nuclear cataract. Vision impairment observed in patients with posterior sub-capsular cataract is primarily due to light scattered by the epithelial cell organelles which have migrated to the posterior pole of the lens. Epithelial cells show the highest enzymatic activity and the highest concentration of antioxidants, i.e. glutathione, among all lens structures. Therefore, oxidative stress seems to play a relatively minor role in posterior sub-capsular cataract. The above is consistent with the current findings, as is the lack of correlation between blood selenium levels and sub-capsular opacity grading as per LOCS III (Tab. 6).

CONCLUSIONS

Due to the confirmed association between serum selenium levels and age-related cataract, low serum selenium levels may constitute a potential risk factor for age-related cataract.

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