The Effect of Dietary Antioxidant Supplementation in Patients with Cataract and Glaucoma

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Research

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Abstract

Background: Oxidative stress may be a key risk factor for cataract and glaucoma, and many previous reports have suggested that antioxidants could be a promising treatment. Here, we investigated the effects of a novel supplement containing three food-derived antioxidants (hesperidin, crocetin, and tamarindus indica) on markers of oxidative stress in patients with these conditions.

Methods: This study had a prospective, single arm design. Fifty Japanese subjects with cataract and glaucoma were recruited and asked to refrain from the use of vitamin or carotenoid supplements for 2 weeks before the study. The subjects took 4 tablets together with ample water twice a day for 8 weeks, stopped the treatment, and were then followed for an additional 8 weeks. The subjects were examined at four-week intervals, for a total of 5 examinations. We measured biological antioxidant potential (BAP) with a free radical analyzer. Clinical laboratory data, including malondialdehyde (MDA) and superoxide dismutase (SOD), were measured in venous blood samples. Clinical parameters were also recorded. The Mann-Whitney U test and Fisher's exact test were used to determine the significance of differences between groups. Other comparisons used a one-way analysis of variance (ANOVA) followed by the Student's t-test or Dunnett's test.

Results: BAP was significantly elevated at weeks 8, 12, and 16 ($P = 0.007$, $P = 0.035$, $P = 0.015$). The MDA level was significantly reduced at week 8 ($P = 0.019$). BAP changes were recorded by subtracting the value at week 8 from week 0. Multiple regression analysis revealed that SOD, total bilirubin and diabetes were independent contributing factors to the change in BAP ($P = 0.039$, $P = 0.019$, $P = 0.013$). There were no supplement-related adverse events or abnormal results in blood testing in any of the patients.

Conclusion: Our study found that an 8-week oral course of antioxidant supplementation was effective in patients with a low antioxidative stress level. Dietary supplementation holds promise in the treatment of systemic oxidative stress-related diseases.

Trial registration: UMIN-CTR UMIN 000032050

Background

Oxidative stress in the body is normally managed by balancing the production of reactive oxygen species (ROS) with the activation of a variety of antioxidative cellular mechanisms. The efficacy of these mechanisms is critical, because if they are impaired, oxidative damage can continue, even when overall oxidative stress is within normal levels. Oxidative damage to proteins, DNA, and lipids contributes to many age-related neurodegenerative diseases, and contributes to age-related macular degeneration, diabetic retinopathy, cataract, and glaucoma [1–5]. The World Health Organization estimates that among the 37 million people with blindness worldwide, 60% have lost their sight due to diseases associated with oxidative stress: 48% due to cataract and 12% due to glaucoma [6]

Several reports have revealed that ROS have a key role in the pathogenesis and progression of cataracts. ROS directly cause oxidation of the lens and also lower the capacity of the lens to remove oxidants created by ultraviolet radiation and aging. Sawada et al. revealed that cataract severity was correlated with significantly increased superoxide dismutase (SOD) activity [7]. Kaur et al. revealed that cataract patients had a higher serum malondialdehyde (MDA) level [1]. Cataract patients have also been shown to have a lower level of plasma thiobarbituric acid reactive substances when the plasma level of vitamin C is increased [8]. Ravindran et al. found that a lower level of vitamin C was strongly associated with cataract [9]. Such findings have inspired past efforts to develop dietary supplements containing anti-oxidants to treat ocular diseases, including cataract [10, 11].

Treatment for glaucoma most commonly involves therapy to reduce intraocular pressure (IOP). However, disease progression persists in some patients even after IOP is successfully reduced. This has led to past investigations of possible non-IOP risk factors for glaucoma and its key underlying pathomechanism, retinal ganglion cell (RGC) degeneration. Previously reported risk factors include genetics [12], vascular dysregulation [13], mitochondrial dysfunction [14], and in particular, oxidative stress [2]. Oxidative stress has three key effects in glaucoma. First, it raises IOP by altering the trabecular meshwork and impairing aqueous humor outflow [15, 16]. Second, it disrupts autoregulation of blood flow to the optic nerve by altering the vessels that feed it [17, 18]. Finally, patients with a low antioxidant level in the eye are susceptible to systemic oxidative stress, which can induce RGC death, as we have previously reported [19, 20]. Harris et al. revealed that one month of oral supplementation with an antioxidant increased blood flow biomarkers in the eyes of patients with open-angle glaucoma (OAG) [21]. Park et al. found that a four-week course of daily administration of 160 mg of gingko biloba extract led to a significant improvement in retinal blood flow volume and velocity in 15 patients with normal-tension glaucoma (NTG).

Here, we gave a daily dietary antioxidant supplement over 8 weeks to patients with cataract and glaucoma. The supplement was developed and first reported by Maekawa et al., who identified the components of the supplement through screening, and found that it had a neuroprotective effect in a mouse glaucoma model [22]. We believe that the findings reported here will shed light on the potential of new treatments for cataract and glaucoma based on antioxidant supplementation.

Methods

Study design

This study had a prospective, single arm design. Japanese patients with previously diagnosed NTG or cataracts were recruited at Tohoku University Hospital between March 2018 and October 2019; all patients were followed for 16 weeks.

Participants

Inclusion criteria for participation were as follows: overall good health, age between 30 and 75 years; NTG confirmed in one or both eyes by a glaucoma specialist; a biological antioxidant potential (BAP) level between 1600 to 2200 nmol/L; a diacron-reactive oxygen metabolite (dROM) level not less than 300 Carrelli units (U. Carr), body mass index less than 26 kg/m^2. Exclusion criteria were as follows: hyperopia (above + 3D); high myopia (below − 8D); any type of secondary glaucoma; high IOP (> 16 mmHg) despite glaucoma medication; and severe systemic disease, including cancer, hyperthyroidism, and autoimmune disease. No patients used exogenous hormones. Pregnant women, or women planning pregnancy during the study period, were also excluded. Candidates were asked to refrain from the use of vitamin or carotenoid supplements for 2 weeks before the study. If a patient had diabetes, hyperlipidemia, hypertension, or a current smoking habit, it was recorded. Cataract patients were recruited from the Tohoku University Hospital eye clinic.

Figure 1 shows an overview of the study design. Participants were examined 5 times, at four-week intervals. At the examination, we measured clinical parameters, confirmed compliance with the study protocol of twice-daily use of the supplement, and recorded any adverse events.

Study intervention

Maekawa et al. previously reported 12 candidate neuroprotective compounds [22]. Based on these results, we developed the novel supplement used in this study, which contained the following ingredients in each daily dose of 4 tablets: hesperidin (50 mg/4 tablets), crocetin (7.5 mg/4 tablets), and tamarindus indica (25 mg/4 tablets). The supplement was manufactured and supplied by Wakamoto Pharmaceutical Co. Ltd (Tokyo, Japan). The candidates took 2 tablets with ample water twice a day (i.e., 4 tablets/day) for 8 weeks, and no supplementation for 8 weeks. Any unused supplements were returned for a pill count at the 8-week visit.

Measurements

A complete ophthalmic examination of all patients was performed by a glaucoma and cataract specialist. This comprised measurement of best-corrected visual acuity, recorded as the logarithm of the minimal angle of resolution, examinations with slit-lamp biomicroscopy and funduscopy, and evaluation of the optic disc with a 90-diopter lens. The patients with glaucoma and cataract also underwent measurement of mean deviation (MD) with the Humphrey field analyzer (HFA). If both eyes had glaucoma, the analysis included the worse-MD eye. Similarly, for cataract subjects, the analysis included the better-VA eye.

Clinical laboratory measurements

Samples of blood were stored in containers with EDTA at weeks 0 and 8. We confirmed the supplement safety with clinical laboratory measurements. Plasma samples were stored at -80 °C for later biochemical analysis. Serum samples from the screening visit were sent to LSI Medience Co. (Tokyo, Japan), analyzed for AST, ALT, γ-GTP, total bilirubin, total protein, albumin, high-density lipoprotein cholesterol, low-density

lipoprotein cholesterol, total cholesterol, triglycerides, creatinine, blood urea nitrogen, uric acid, glucose, $HbA1_C$, white and red blood cell count, platelet count, hematocrit, and hemoglobin.

Measurement of MDA and SOD

Venous blood samples were collected in a tube with no anticoagulant and centrifuged at 3280 rpm for 20 min. The supernatant was moved to another tube, and the samples were subsequently shipped in dry ice to Wakamoto Pharmaceutical Co. Ltd (Kanagawa, Japan). All samples were frozen at -20 °C for storage and thawed only once, before they were analyzed.

Blood sampling and oxidative stress measurement

Serum samples were evaluated for oxidative stress levels and anti-oxidative potential with a free radical analyzer system (Free Carpe Diem, Wismerll Company Ltd., Tokyo, Japan). Blood samples were collected more than 3 hours after a subject ate. The samples were also evaluated for dROMs, which represent the total oxidant capacity of a serum sample towards N, N-diethyl-para-phenylendiamine, used as an indicator. The results are expressed in U. Carr. Total plasma antioxidant capacity in the samples was measured with the BAP test, which is based on the ability of a sample to reduce iron from its ferric (Fe3+) to its ferrous (Fe2+) state. The analyses were performed as previously reported [19, 20].

Urinary sampling

Urinary levels of 8-hydroxy-2'-deoxyguanosine (8-OHdG), oxidative stress marker, were measured with a commercially available ELISA kit (LSI Medience Co., Tokyo, Japan). Creatinine levels were also measured in urine samples. Urine samples were stored at -4° C.

Statistical analysis

The significance of differences between groups was determined with the Mann-Whitney U test and Fisher's exact test. Comparisons of groups used one-way analysis of variance (ANOVA) and the Student's t-test or Dunnett's test. All numerical findings are mean ± SD. Statistical significance was set at $P < 0.05$. SPSS version 23.0 (SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Subjects

This study enrolled 50 patients with NTG and cataract. Table 1 shows the demographic characteristics of the subjects. There was no supplement-related adverse events for patients including blood tests (data not shown).

Table 1
Characteristics of cataract and glaucoma patients

Demographics	All
Number	50
Age (years)	60.72 ± 8.51
Sex (male: female)	21:29
Visual acuity (logMAR)	0.08 ± 0.32
IOP (mmHg)	12.46 ± 2.98
Men deviation (dB)	-5.12 ± 6.19
BMI (kg/m2)	22.35 ± 2.16
Diabetes (%)	1 (2.00)
Hypertension (%)	10 (20.00)
Current smoker (%)	4 (8.00)
Hyperlipidemia (%)	6 (12.00)

logMAR = logarithm of minimum angle of resolution, IOP = intraocular pressure, BMI = body mass index, Unmarked P values: Mann-Whitney U test

Oxidative stress

BAP was significantly elevated at weeks 8, 12, and 16 (P = 0.007, P = 0.035, P = 0.015, respectively; Table 2, Fig. 2A). MDA level was significantly reduced at week 8 (P = 0.019, Table 2, Fig. 2B). There were reductions in the 8OHdG level, but these did not reach statistical significance at any of the five time points (Table 2, Fig. 2C). There were no significant differences in dROMs and SOD after supplementation.

Table 2
Changes in serum parameter levels from baseline to week 16

	Treatment			After treatment	
	Week 0	Week 4	Week 8	Week 12	Week 16
BAP (mmol/L)	2003.68 ± 143.77	2056.72 ± 192.32	2099.98 ± 223.00	2083.24 ± 203.68	2092.38 ± 264.49
dROM (U.CARR)	383.08 ± 45.98	382.14 ± 50.16	386.66 ± 47.54	390.08 ± 54.02	393.80 ± 52.85
MDA (pmol/mL)	102.40 ± 134.35	88.30 ± 102.69	82.96 ± 90.41	89.58 ± 113.01	100.34 ± 108.11
8OHdG (ng/mL creatinine)	7.46 ± 3.91	7.14 ± 4.47	6.31 ± 3.28	8.65 ± 3.82	8.35 ± 4.50
SOD (Unit/mL)	68.94 ± 37.25		76.38 ± 40.55		
Albumin (g/dL)	4.29 ± 0.24	-	4.26 ± 0.20	-	-
Total bilirubine (mg/dL)	0.75 ± 0.24	-	0.71 ± 0.22	-	-

dROM = diacron reactive oxygen metabolites, BAP = biological antioxidant potential, U. Carr = Carrelli units, MDA = malondialdehyde, SOD = superoxide dismutase

Multiple regression analysis

BAP changes were recorded by subtracting the value at weeks 8 from weeks 0. A univariable regression analysis revealed that SOD, total bilirubin and diabetes independently contributed to the change in BAP (P = 0.023, P = 0.013, P = 0.007, respectively; Table 3). Thus, we selected these three variables and analyzed them with a multiple regression analysis. This revealed that SOD, total bilirubin, and diabetes remained independent contributing factors to the change in BAP (P = 0.039, P = 0.019, P = 0.013, respectively; Table 3).

Table 3
Factors independently contributing to BAP change in patients

Variable	Univariable model			Multivariable model		
	β	(95% CI)	P value	β	(95% CI)	P value
Sex (male:female)	0.01	-125.48 to 135.78	0.937			
Age (yrs)	0.02	-7.03 to 8.27	0.871			
dROM (U. Carr)	-0.13	-2.05 to 0.76	0.364			
MDA (pmol/mL)	-0.07	-0.60 to 0.37	0.630			
SOD (unit/mL)	-0.32	-3.59 to -0.28	0.023	-1.58	-3.08 to -0.08	0.039
8OHdG (ng/mL creatinine)	-0.09	-21.93 to 11.28	0.522			
Albumin (g/dL)	0.10	-175.01 to 368.39	0.478			
Total bilirubin (mg/dL)	-0.35	-581.67 to -73.58	0.013	-280.53	-512.46 to -48.61	0.019
BMI (kg/m^2)	-0.11	-41.06 to 18.98	0.463			
Hypertention (%)	-0.14	-238.91 to 80.16	0.322			
Diabetes (%)	0.38	171.02 to 1024.29	0.007	509.71	114.94 to 904.48	0.013
Hyperlipidemia (%)	0.15	-81.14 to 250.87	0.309			
Current smoker (%)	0.14	-88.76 to 259.48	0.329			
MD (dB)	0.06	-8.38 to 12.63	0.686			
VA (LogMAR)	0.10	-130.63 to 269.81	0.488			
IOP (mmHg)	-0.17	-34.42 to 9.33	0.254			

IOP = intraocular pressure, BMI = body mass index, dROM = diacron reactive oxygen metabolites, BAP = biological antioxidant potential, U. Carr = Carrelli units, MDA = malondialdehyde, SOD = superoxide dismutase, β = standard partial regression coefficient

Discussion

Our study found that patients with glaucoma and cataract who took a daily antioxidant supplement showed an increase in BAP, a biomarker of the antioxidant capacity of the body. This may be an important finding, because the development and progression of cataracts are known to be promoted by oxidative damage to the proteins comprising the lens. Oxidative stress may also play an important role in glaucoma, which is an age-related chronic neurodegenerative disease. Our results are particularly interesting for patients with a low antioxidant level and suggest that antioxidant supplementation may be effective in treating them.

BAP was significantly higher than baseline at weeks 8, 12, and 16, while MDA level was significantly reduced at week 8. MDA is an end product of free radical reactions in membrane fatty acids [23]. A variety of antioxidant molecules can be found in human plasma, with the following compounds being most common: α-tocopherol, β-carotene, albumin, ascorbic acid, bilirubin, catalase, ceruloplasmin, ferritin, glutathione peroxidase, lycopene, reduced glutathione, SOD, and uric acid [24]. All these compounds can catalytically remove reactive species such as free radicals. After taking our novel supplement, the antioxidative level increased in the subjects in this study. The higher the level of antioxidative activity, the lower the level of oxidative stress.

A multiple regression analysis showed that SOD, total bilirubin, and diabetes were independent contributing factors to changes in antioxidative potential after supplementation in both the cataract and glaucoma groups. This means that our supplement was effective in patients with a low antioxidative stress level. This is especially interesting for glaucoma, which can sometimes progress even with successful IOP-lowering treatment. There is extensive clinical evidence that systemic oxidative stress contributes to glaucomatous optic neuropathy. Moreover, antioxidant therapy has shown promising results in animal- and human-based research. Antioxidant treatment can decrease the activation of NF-κβ and decrease the production of cytokines in the optic nerve and retina [25]. In a rat glaucoma model, overexpression of thioredoxins can protect the RGCs [26]. Higher green leafy vegetable intake is associated with a lower primary OAG risk [27]. Lee et al. found that ginkgo biloba extract protected against the effects of glaucoma in some patients [28]. These results suggest that insufficient serum antioxidant proteins underlie the contribution of oxidative stress to glaucoma, suggesting that antioxidants should have a neuroprotective effect. Our past research also showed that visual field damage was strongly correlated with systemic antioxidant levels in young, male patients with OAG [19]. Antioxidant treatments might therefore be a useful therapeutic option to delay or prevent disease progression.

Previously, Maekawa et al. reported that three food-derived compounds, hesperidin, tamarindus indica, and crocetin, had a protective effect in a primary culture of retinal cells under oxidative stress. Hesperidin is effective in reducing apoptosis, oxidative stress and inflammation. Maekawa confirmed that hesperidin was effective *in vivo* in mice, reducing oxidative stress and preventing RGC death caused by NMDA-induced excitotoxicity [22]. Tamarindus indica is indigenous to tropical Africa. It is high in tartaric acid, B vitamins, and minerals. It has antioxidant [29, 30], anti-inflammatory [31], anti-diabetic [32], and anti-atherosclerotic effects [33]. Crocetin is a natural apocartenoid dicarboxylic acid that is found in the

crocus flower and in Gardenia jasminoides. Crocetin has various effects, acting as an antioxidant [34] and anti-inflammatory [35], and can inhibit the caspase pathway, preventing retinal damage induced by N-methyl-D-aspartate (NMDA) [36]. These results suggest that these three food-derived compounds, used as a dietary supplement, might help reduce RGC degeneration in retinal disease.

Systemic oxidative stress may be a key factor in the development of cataracts [37, 38]. Past findings support the idea that antioxidant therapy is effective for cataract patients. Nuclear opacities have been reported to be associated with nutrients (folate, α-carotene, and dietary fiber) from the intake of foods, particularly vegetables [39]. Chylack et al. found that an oral antioxidant slightly slowed cataract progression [40]. Another study found that subjects who received multivitamin/mineral supplementation had a 36% lower prevalence of nuclear cataracts [41]. Hayashi et al. compared the total amount of hydroperoxides in the aqueous humor before and after supplementation with an antioxidant, Ocuvite Lutein [42], and found that hydroperoxides decreased in female, but not in male, subjects. That study suggested that it might be possible to inhibit oxidative stress in the aqueous humor and the lens epithelium. Lutein has been investigated by several *in vitro* studies, and has been reported to lower the intracellular accumulation of H_2O_2 by scavenging both H_2O_2 and superoxides [43]. Lutein supplementation of lens epithelial cells has also been reported to decrease protein oxidation, lipid peroxidation and DNA damage induced by H_2O_2 [44]. Based on these data, we consider that a decreased general oxidative stress level after supplementation may result in a reduced oxidative stress level in the aqueous humor, potentially delaying cataract progression.

Our study has some limitations. First, it lacked a placebo arm, which is needed to prove the efficacy of any supplement. Thus, we plan to conduct further studies with a randomized, doubled-blind, placebo-controlled design. Second, while we observed significant differences in BAP before and after supplementation, we did not make a similar finding for dROMs. Nevertheless, the improvement in BAP after supplementation for eight weeks was significant. This discrepancy might have been due to an increase in oxidative stress after supplementation, causing increased endogenous antioxidant activity. Finally, we could not include a control group, because all potential candidates already had cataracts, due to their advanced age. We were also limited in our ability to detect relatively modest associations, making longer follow-up of the subjects necessary in a future study.

Our study indicates that patients with a low systemic antioxidant level may have increased susceptibility to oxidative stress, thereby accelerating the progression of cataract and glaucoma. This raises the possibility that antioxidant supplementation may be a viable option to delay or prevent age-related cataracts and glaucoma progression.

Conclusion

Oxidative stress may be a key non-IOP risk factor for age-related cataracts and glaucoma. Our study revealed that antioxidant supplementation was effective in patients with a low antioxidative stress level,

suggesting that such supplementation may be a novel way of combating diseases induced by systemic oxidative stress, and could contribute to individualized treatment for these diseases.

Abbreviations

ROS
reactive oxygen species; SOD:superoxide dismutase; MDA:malondialdehyde; IOP:intraocular pressure; RGC:retinal ganglion cell; OAG:open-angle glaucoma; NTG:normal-tension glaucoma; BAP:biological antioxidant potential; dROM:diacron-reactive oxygen metabolite; U.Carr:Carrelli units; MD:mean deviation; HFA
Humphrey field analyzer; 8-OHdG
8-hydroxy-2’-deoxyguanosine.

Declarations

Ethics approval and consent to participate

This study adhered to the Declaration of Helsinki and Clinical Trials Act was approved by the Clinical Research Review Board of Tohoku University (study 2019-6-068), which is certified by the Japanese Ministry of Health, Labor and Welfare. The trial was registered with the UMIN clinical trial registry, number 000032050. Written informed consent was obtained from all subjects before the start of the study.

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on reasonable request.

Competing interests

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Authors’ contribution

NH: contributed to the interpretation of the data; drafted the work. MY, YS, ST, KO, HK: contributed to revising this critically for important intellectual content. TN: contributed to the conception and design of the work and revised it critically for important intellectual content.

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References

1. Kaur J, Kukreja S, Kaur A, Malhotra N, Kaur R: The oxidative stress in cataract patients. *J Clin Diagn Res* 2012, 6:1629–1632.
2. Himori N, Kunikata H, Shiga Y, Omodaka K, Maruyama K, Takahashi H, Nakazawa T: The association between systemic oxidative stress and ocular blood flow in patients with normal-tension glaucoma. *Graefes Arch Clin Exp Ophthalmol* 2016, 254:333–341.
3. Cecilia OM, Jose Alberto CG, Jose NP, Ernesto German CM, Ana Karen LC, Luis Miguel RP, Ricardo Raul RR, Adolfo Daniel RC: Oxidative Stress as the Main Target in Diabetic Retinopathy Pathophysiology. *J Diabetes Res* 2019, 2019:8562408.
4. Pawlowska E, Szczepanska J, Koskela A, Kaarniranta K, Blasiak J: Dietary Polyphenols in Age-Related Macular Degeneration: Protection against Oxidative Stress and Beyond. *Oxid Med Cell Longev* 2019, 2019:9682318.

5. Tezel G: Oxidative stress in glaucomatous neurodegeneration: mechanisms and consequences. *Prog Retin Eye Res* 2006, 25:490–513.
6. Foster A, Resnikoff S: The impact of Vision 2020 on global blindness. *Eye (Lond)* 2005, 19:1133–1135.
7. Sawada H, Fukuchi T, Abe H: Oxidative stress markers in aqueous humor of patients with senile cataracts. *Curr Eye Res* 2009, 34:36–41.
8. Tarwadi KV, Chiplonkar SA, Agte V: Dietary and nutritional biomarkers of lens degeneration, oxidative stress and micronutrient inadequacies in Indian cataract patients. *Clin Nutr* 2008, 27:464–472.
9. Ravindran RD, Vashist P, Gupta SK, Young IS, Maraini G, Camparini M, Jayanthi R, John N, Fitzpatrick KE, Chakravarthy U, et al: **Inverse association of vitamin C with cataract in older people in India**. *Ophthalmology* 2011, **118**:1958–1965.e1952.
10. Wei L, Liang G, Cai C, Lv J: Association of vitamin C with the risk of age-related cataract: a meta-analysis. *Acta Ophthalmol* 2016, 94:e170-176.
11. Wang A, Han J, Jiang Y, Zhang D: Association of vitamin A and beta-carotene with risk for age-related cataract: a meta-analysis. *Nutrition* 2014, 30:1113–1121.
12. Guo Y, Chen X, Zhang H, Li N, Yang X, Cheng W, Zhao K: Association of OPA1 polymorphisms with NTG and HTG: a meta-analysis. *PLoS One* 2012, 7:e42387.
13. Shiga Y, Kunikata H, Aizawa N, Kiyota N, Maiya Y, Yokoyama Y, Omodaka K, Takahashi H, Yasui T, Kato K, et al: Optic Nerve Head Blood Flow, as Measured by Laser Speckle Flowgraphy, Is Significantly Reduced in Preperimetric Glaucoma. *Curr Eye Res* 2016:1–7.
14. Inoue-Yanagimachi M, Himori N, Sato K, Kokubun T, Asano T, Shiga Y, Tsuda S, Kunikata H, Nakazawa T: Association between mitochondrial DNA damage and ocular blood flow in patients with glaucoma. *Br J Ophthalmol* 2018.
15. Ferreira SM, Lerner SF, Brunzini R, Evelson PA, Llesuy SF: Oxidative stress markers in aqueous humor of glaucoma patients. *Am J Ophthalmol* 2004, 137:62–69.
16. Sacca SC, Pascotto A, Camicione P, Capris P, Izzotti A: Oxidative DNA damage in the human trabecular meshwork: clinical correlation in patients with primary open-angle glaucoma. *Arch Ophthalmol* 2005, 123:458–463.
17. Feilchenfeld Z, Yucel YH, Gupta N: Oxidative injury to blood vessels and glia of the pre-laminar optic nerve head in human glaucoma. *Exp Eye Res* 2008, 87:409–414.
18. Nakazawa T: Ocular Blood Flow and Influencing Factors for Glaucoma. *Asia Pac J Ophthalmol (Phila)* 2016, 5:38–44.
19. Asano Y, Himori N, Kunikata H, Yamazaki M, Shiga Y, Omodaka K, Takahashi H, Nakazawa T: Age- and sex-dependency of the association between systemic antioxidant potential and glaucomatous damage. *Sci Rep* 2017, 7:8032.
20. Uchida K, Himori N, Hashimoto K, Shiga Y, Tsuda S, Omodaka K, Nakazawa T: The association between oxidative stress and corneal hysteresis in patients with glaucoma. *Sci Rep* 2020, 10:545.

21. Harris A, Gross J, Moore N, Do T, Huang A, Gama W, Siesky B: The effects of antioxidants on ocular blood flow in patients with glaucoma. *Acta Ophthalmol* 2018, 96:e237-e241.
22. Maekawa S, Sato K, Fujita K, Daigaku R, Tawarayama H, Murayama N, Moritoh S, Yabana T, Shiga Y, Omodaka K, et al: The neuroprotective effect of hesperidin in NMDA-induced retinal injury acts by suppressing oxidative stress and excessive calpain activation. *Sci Rep* 2017, 7:6885.
23. Donma O, Yorulmaz E, Pekel H, Suyugul N: Blood and lens lipid peroxidation and antioxidant status in normal individuals, senile and diabetic cataractous patients. *Curr Eye Res* 2002, 25:9–16.
24. Seifried HEAD, Milner JA, Greenwald P: **Reactive oxygen speicies and dietary antioxidants:double-edged swords?** In *New developments in antioxidant research.* Edited by H P: Nova Science Publishers Inc; 2006: 1–25.
25. Yang X, Hondur G, Tezel G: Antioxidant Treatment Limits Neuroinflammation in Experimental Glaucoma. *Invest Ophthalmol Vis Sci* 2016, 57:2344–2354.
26. Caprioli J, Munemasa Y, Kwong JM, Piri N: Overexpression of thioredoxins 1 and 2 increases retinal ganglion cell survival after pharmacologically induced oxidative stress, optic nerve transection, and in experimental glaucoma. *Trans Am Ophthalmol Soc* 2009, 107:161–165.
27. Kang JH, Willett WC, Rosner BA, Buys E, Wiggs JL, Pasquale LR: Association of Dietary Nitrate Intake With Primary Open-Angle Glaucoma: A Prospective Analysis From the Nurses' Health Study and Health Professionals Follow-up Study. *JAMA Ophthalmol* 2016, 134:294–303.
28. Lee J, Sohn SW, Kee C: Effect of Ginkgo biloba extract on visual field progression in normal tension glaucoma. *J Glaucoma* 2013, 22:780–784.
29. Escalona-Arranz JC, Perez-Roses R, Rodriguez-Amado J, Morris-Quevedo HJ, Mwasi LB, Cabrera-Sotomayor O, Machado-Garcia R, Fong-Lorez O, Alfonso-Castillo A, Puente-Zapata E: Antioxidant and toxicological evaluation of a Tamarindus indica L. leaf fluid extract. *Nat Prod Res* 2016, 30:456–459.
30. Natukunda S, Muyonga JH, Mukisa IM: Effect of tamarind (Tamarindus indica L.) seed on antioxidant activity, phytocompounds, physicochemical characteristics, and sensory acceptability of enriched cookies and mango juice. *Food Sci Nutr* 2016, 4:494–507.
31. Komutarin T, Azadi S, Butterworth L, Keil D, Chitsomboon B, Suttajit M, Meade BJ: Extract of the seed coat of Tamarindus indica inhibits nitric oxide production by murine macrophages in vitro and in vivo. *Food Chem Toxicol* 2004, 42:649–658.
32. Agnihotri A, Singh V: Effect of Tamarindus indica Linn. and Cassia fistula Linn. stem bark extracts on oxidative stress and diabetic conditions. *Acta Pol Pharm* 2013, 70:1011–1019.
33. Martinello F, Soares SM, Franco JJ, Santos AC, Sugohara A, Garcia SB, Curti C, Uyemura SA: Hypolipemic and antioxidant activities from Tamarindus indica L. pulp fruit extract in hypercholesterolemic hamsters. *Food Chem Toxicol* 2006, 44:810–818.
34. Ohba T, Ishisaka M, Tsujii S, Tsuruma K, Shimazawa M, Kubo K, Umigai N, Iwawaki T, Hara H: Crocetin protects ultraviolet A-induced oxidative stress and cell death in skin in vitro and in vivo. *Eur J Pharmacol* 2016, 789:244–253.

35. Nam KN, Park YM, Jung HJ, Lee JY, Min BD, Park SU, Jung WS, Cho KH, Park JH, Kang I, et al: Anti-inflammatory effects of crocin and crocetin in rat brain microglial cells. *Eur J Pharmacol* 2010, 648:110–116.
36. Ohno Y, Nakanishi T, Umigai N, Tsuruma K, Shimazawa M, Hara H: Oral administration of crocetin prevents inner retinal damage induced by N-methyl-D-aspartate in mice. *Eur J Pharmacol* 2012, 690:84–89.
37. Li L, Duker JS, Yoshida Y, Niki E, Rasmussen H, Russell RM, Yeum KJ: Oxidative stress and antioxidant status in older adults with early cataract. *Eye (Lond)* 2009, 23:1464–1468.
38. Weikel KA, Garber C, Baburins A, Taylor A: Nutritional modulation of cataract. *Nutr Rev* 2014, 72:30–47.
39. Mares-Perlman JA, Brady WE, Klein BE, Klein R, Haus GJ, Palta M, Ritter LL, Shoff SM: Diet and nuclear lens opacities. *Am J Epidemiol* 1995, 141:322–334.
40. Chylack LT, Jr., Brown NP, Bron A, Hurst M, Kopcke W, Thien U, Schalch W: The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. *Ophthalmic Epidemiol* 2002, 9:49–80.
41. Maraini G, Williams SL, Sperduto RD, Ferris F, Milton RC, Clemons TE, Rosmini F, Ferrigno L: A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities. Clinical trial of nutritional supplements and age-related cataract report no. 3. *Ophthalmology* 2008, 115:599–607.e591.
42. Hayashi R, Hayashi S, Arai K, Sakai M, Okamoto H, Chikuda M: The gender-differentiated antioxidant effects of a lutein-containing supplement in the aqueous humor of patients with senile cataracts. *Exp Eye Res* 2014, 129:5–12.
43. Kim JH, Na HJ, Kim CK, Kim JY, Ha KS, Lee H, Chung HT, Kwon HJ, Kwon YG, Kim YM: The non-provitamin A carotenoid, lutein, inhibits NF-kappaB-dependent gene expression through redox-based regulation of the phosphatidylinositol 3-kinase/PTEN/Akt and NF-kappaB-inducing kinase pathways: role of H(2)O(2) in NF-kappaB activation. *Free Radic Biol Med* 2008, 45:885–896.
44. Gao S, Qin T, Liu Z, Caceres MA, Ronchi CF, Chen CY, Yeum KJ, Taylor A, Blumberg JB, Liu Y, Shang F: Lutein and zeaxanthin supplementation reduces H2O2-induced oxidative damage in human lens epithelial cells. *Mol Vis* 2011, 17:3180–3190.

Figures

Fig 1

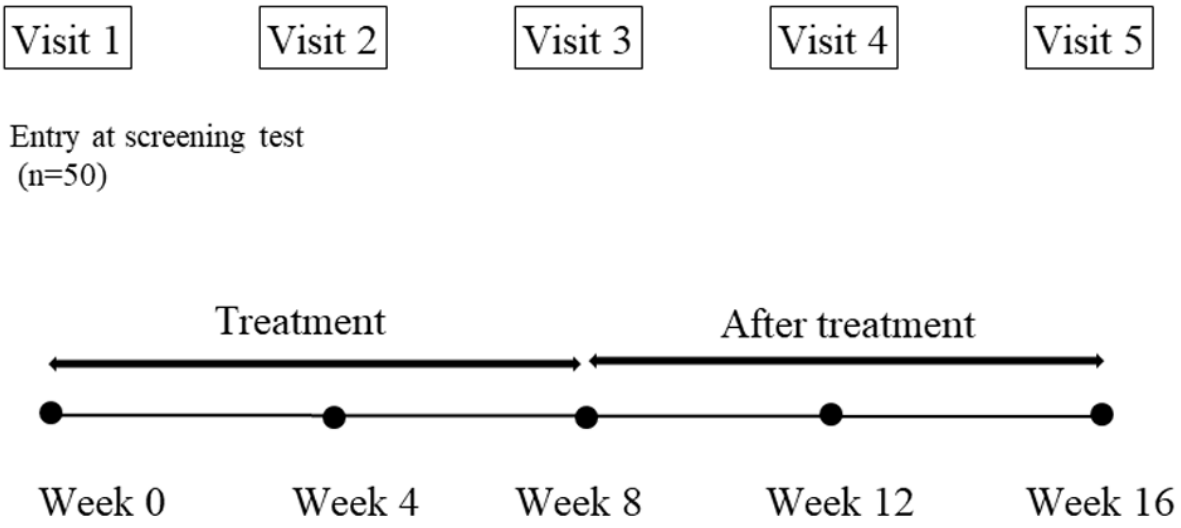

Figure 1

Overview of the study design

Fig 2

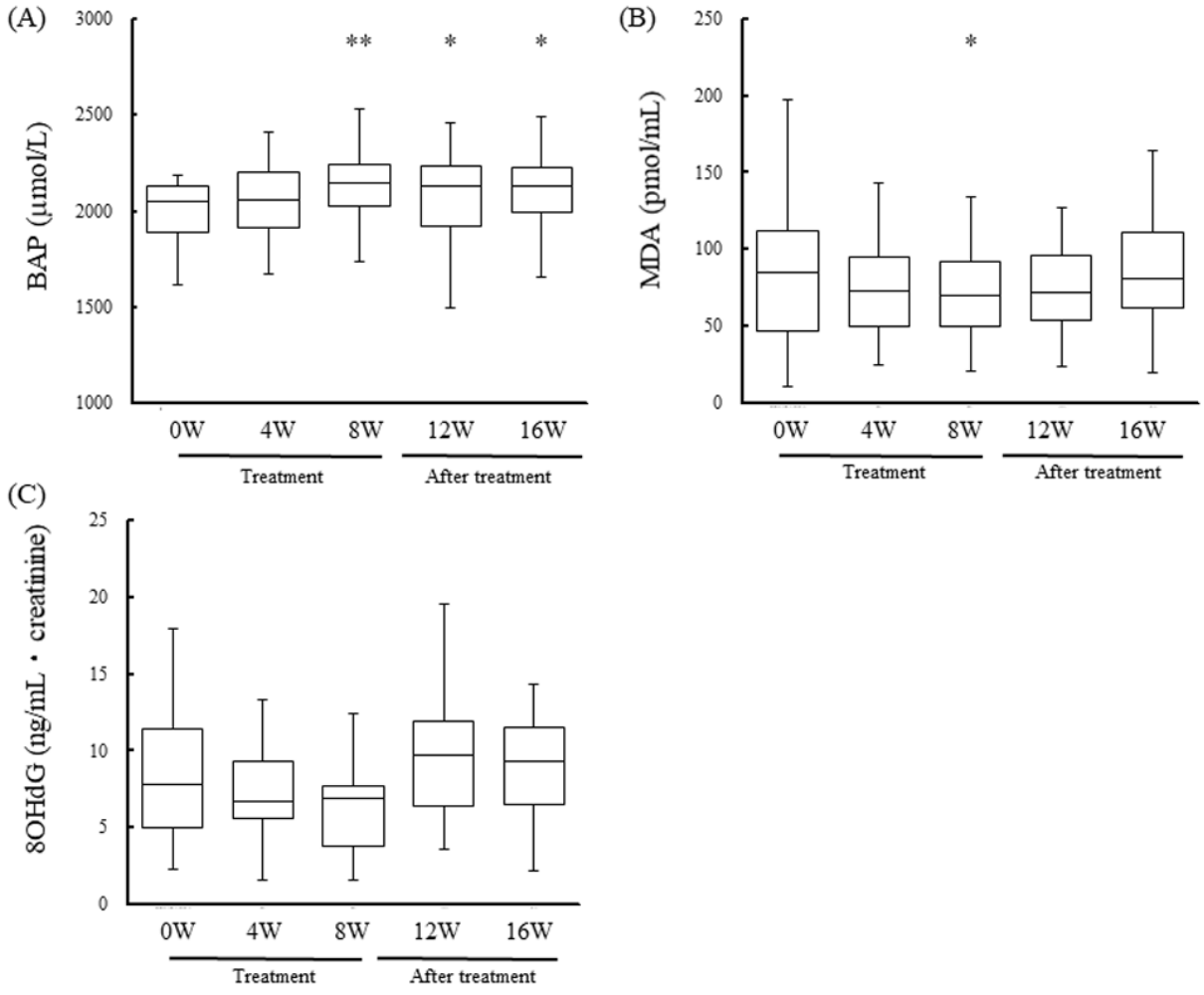

Figure 2

Comparison before and after antioxidant treatment in patients with glaucoma and cataract. (A) BAP level significantly increased at weeks 8, 12, and 16. (B) MDA level significantly increased at week 8. (C) 8OHdG level did not significantly increase. *p < 0.05, **p < 0.01