Original Article

Serum antioxidants and age-related macular degeneration among older Japanese

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From the perspective of human nutrition, the prevention of age-related macular degeneration (AMD) through diet control is feasible and desirable. We investigated the relationship between serum antioxidants and AMD in the community-dwelling older Japanese eating a typical Japanese diet. In this study, 722 subjects aged 65 years or older (297 males and 425 females) who had gradable fundus photographs were included. The subjects were divided into three groups of early or late AMD or non-maculopathy. Serum antioxidants (alpha-, gamma-tocopherols, retinol, beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, and lutein and zeaxanthin) were measured with high-performance liquid chromatography. To clarify the combined effect as the group of the antioxidants, we defined the carotene family (alpha-, beta-carotenes and lycopene) and carotenoid family (beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, lutein and zeaxanthin). Tertiles of each serum antioxidant were obtained and the prevalence of early or late AMD was compared with univariate or multivariate analysis. The overall prevalence of early AMD was 4.4% (95% confidence interval: 3.1-6.2) and late AMD was 1.1% (0.5-2.2). Only alpha-tocopherol and beta-cryptoxanthin were related to late AMD as single antioxidants. On the other hand, the carotene and carotenoid families as a combination of antioxidants were protectively associated with late AMD. No relationship was found between serum antioxidants and early AMD. Our findings support the hypothesis that a combination of serum antioxidants obtained from the traditional Japanese diet is protective for late AMD, but not for early AMD.

Key Words: serum antioxidants, Age-related Macular Degeneration (AMD), diet, aged, Japan

INTRODUCTION

Age-related macular degeneration (AMD) is a major cause of severe visual impairment and adult blindness among aged people in Western countries.[1,2] Extensive efforts have been made to develop new therapeutic measures, but effective therapies have not been established sufficiently. Therefore, primary prevention and measures to slow the progression of the disease remain crucial.[3]

Earlier studies have revealed that oxidative stress can trigger onset of the disease,[4,5] and several epidemiological studies have suggested that dietary factors play a key role in reducing the incidence and progression of AMD[6-8] as well as other chronic diseases. Both supplementation and diet control have been focused on as possible preventive measures. The results of the Age-Related Eye Disease Study (AREDS) showed that use of supplementation with antioxidants plus zinc significantly reduced the risk of developing advanced AMD in the higher-risk groups such as those with extensive intermediate size drusen.[6] However, investigation on the efficacy and effectiveness of intervention with supplementation were not sufficient. Moreover, adding vegetables and fruits to the daily diet costs less than supplement use,[7] and high-dose supplementation is potentially harmful.[9] From the perspective of human nutrition, diet control is more feasible and desirable. Evidence of the role of dietary antioxidants as a primary preventive measure for AMD also remains controversial. The usage of objective, precise evaluation of antioxidant levels, e.g. direct measurement in serum, rather than food frequency questionnaires is needed.

It is widely accepted that a traditional Japanese diet is the major reason for the lower incidence of heart disease among the Japanese than among many Western populations. It is well known that the traditional Japanese diet contains a lot of vegetables, fruits and fish, and only a little meat and poultry,[10,11] and it has been reported that the serum antioxidant levels of the Japanese tend to be higher than those of the Westerners.[12] We carried out a population-based study of community-dwelling older Japanese eating a typical Japanese diet to

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elucidate the relationship between serum antioxidants and AMD with expectation that we would find further evidence for the preventive role of antioxidants taken from the diet.

MATERIALS AND METHODS

Study Population

The target population was the older residents, aged 65 years or older, in Kurabuchi Town of Takasaki City, Gunma Prefecture, which is a rural area approximately 100 km north of Tokyo. Between April 2005 and July 2006, a home-visit health survey was conducted by trained public health nurses and local welfare commissioners using a structured questionnaire. We defined eligible population as all residents in this town excluding those hospitalised or institutionalised persons and identified 1,446 eligible subjects aged 65 years or older. In the present study, we included the subjects who had undergone detailed health assessment at eight town community centres and for whom readable fundus photographs were available, and excluded the secondary choroidal neovascularization or chorioretinal atrophy as seen in degenerative myopia using the findings of fundus photographs. Of the 1,446, 722 participants (297 males and 425 females, approximately 50% of those eligible) were subjected to analysis. The response proportion was 55.7% in the 65 to 74 years group and 44.5% in the 75 years or older group. Of these, 46.3% of eligible males and 53.5% of females participated in this study. The prevalence of difficulty reading a newspaper were not different between the participants in the detailed health assessment and non-participants (9.1% vs 12.3%, age and gender adjusted p = 0.305).

The study was approved by the Ethics Committee of Keio University's School of Medicine, and all the subjects gave their written informed consents without financial remuneration.

Ophthalmologic Examination

Stereoscopic 45° fundus photographs centred on the disc and macula were taken for both right and left eyes by clinical laboratory technicians using a non-mydriatic fundus camera (Canon Inc., Tokyo, Japan). Due to the community-setting, it was difficult to perform the ophthalmologic examinations by eye specialists and pupil dilatation was not allowed for safety reasons. To obtain high-quality photographs, the procedures were standardised and a training session was held for the examiners. A ophthalmologist (SI) assessed all photographs under masked conditions in terms of participant information. The definition for AMD was based on that of the International ARM Epidemiologic Study Group's grading protocol:[13] late AMD was characterised by either choroidal neovascularization (wet type) or geographic atrophy (dry type), and early AMD was defined by the presence of soft drusen or retinal pigment epithelial abnormalities without signs of late AMD. The subjects were classified as having early or late AMD according to the status in the worse eye.

Measurement of Antioxidants

Serum samples of non-fasting venous blood were collected, immediately frozen and stored at −80℃ until measurement. Serum antioxidants including alpha-, gamma-tocopherols, retinol (only half sample), beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, and lutein and zeaxanthin (as the sum of both forms) were measured with high-performance liquid chromatography. Moreover, to clarify the combined effect of the group of antioxidants, we defined two antioxidant families: the carotene family (alpha-, beta-carotenes and lycopene) and the carotenoid family (beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, and lutein and zeaxanthin).[14]

Covariates

Demographic information and risk factors for AMD were collected. The body mass index (BMI) was calculated from height and body weight. Total cholesterol (TC) and hemoglobin A1c (HbA1c) were measured at a national clinical laboratory by standard methods under an internal/external quality control program. Information on education, smoking status, alcohol drinking habits, the current or recent history of hypertension, history of cataract surgery and outdoor activity was obtained from a self-administered questionnaire. Reported current or recent history of hypertension was determined by asking participants whether they had ever been told of these conditions by physician. Outdoor activities were categorised as "Yes" (very long/long) or "No" (medium/short/very short).

Statistical Analysis

A crude comparison of the distribution of the risk factors between the non-maculopathy group and the early or late AMD groups was done with the chi-square test or the Fisher's exact test. For serum antioxidants, a similar comparison was made by ANOVA with Dunnet's method after logarithmical transformation to obtain normal distribution.

As the serum antioxidant levels differed widely according to age and gender, age- (65–69, 70–79, 80– years old) and gender-specific tertiles (low, middle and high as categories) of each serum antioxidant were obtained, and the prevalence of early and late AMD was calculated. To divide antioxidant families into categories, we assigned each person a category score (1 = low, 2 = middle, 3 = high) for each antioxidant based on the age- and gender-specific tertiles. Then, the sum of category scores of contained antioxidants, ranging from 3 to 9 for the carotene family (alpha-, beta-carotenes and lycopene) and from 6 to 18 for the carotenoid family (beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, and lutein and zeaxanthin) was counted. Using these scores, the subjects were automatically divided into tertiles (low, middle and high) of each antioxidant family by statistical software. Prevalence of early and late AMD was compared with the Fisher's exact test and crude odds ratio (OR) and 95% confidence interval (CI) of early or late AMD for one-category increase in antioxidant tertiles was calculated by logistic regression. In the adjusted model, we added age, gender, smoking status (none, ex, current), alcohol drinking habits (none, ex, current), education (elementary or junior high, high school or higher), hypertension (no, yes), BMI (<25.0 kg/m^2, ≥25.0 kg/m^2), TC (<5.7 mmol/L, ≥ 5.7 mmol/L), HbA_{1c} (≤ 5.8%, > 5.8%), cataract surgery (no, yes) and

Table 1. The distribution of demographic and risk factors among the non-maculopathy, early and late AMD groups

		Non-maculopathy† (n = 682‡)	Early AMD (n = 32‡)	Late AMD (n = 8‡)
		Number (%)	Number (%)	Number (%)
Age (years)	65–69	180 (26.4)	6 (18.8)	1 (12.5)
	70–79	348 (51.0)	16 (50.0)	5 (62.5)
	80–	154 (22.6)	10 (31.2)	2 (25.0)
Gender	Male	282 (41.4)	9 (28.1)	6 (75.0)
	Female	400 (58.6)	23 (71.9)	2 (25.0)
Smoking status	None	529 (81.1)	27 (84.4)	4 (50.0)
	Ex	51 (7.8)	0 (0.0)	2 (25.0)
	Current	72 (11.1)	5 (15.6)	2 (25.0)
Alcohol drinking habits	None	422 (65.6)	23 (71.9)	2 (25.0)
	Ex	22 (3.4)	0 (0.0)	2 (25.0)
	Current	199 (31.0)	9 (28.1)	4 (50.0)*
Education	Elementary or Junior high	490 (76.1)	23 (71.9)	6 (75.0)
	High school or higher	154 (23.9)	9 (28.1)	2 (25.0)
Hypertension	No	400 (63.3)	22 (68.7)	3 (37.5)
	Yes	232 (36.7)	10 (31.3)	5 (62.5)
Body mass index (kg/m^2)	< 25.0	506 (74.3)	28 (87.5)	6 (75.0)
	≥ 25.0	175 (25.7)	4 (12.5)	2 (25.0)
Total cholesterol (mmol/L)	< 5.7	473 (69.4)	24 (75.0)	6 (75.0)
	≥ 5.7	209 (30.6)	8 (25.0)	2 (25.0)
Hemoglobin A_{1c} (%)	≤ 5.8	579 (84.9)	29 (90.6)	8 (100)
	> 5.8	103 (15.1)	3 (9.4)	0 (0.0)
Cataract surgery	No	586 (86.0)	25 (78.1)	5 (62.5)
	Yes	95 (14.0)	7 (21.9)	3 (37.5)
Outdoor activity	No	408 (60.0)	24 (75.0)	2 (25.0)
	Yes	272 (40.0)	8 (25.0)	6 (75.0)*

* $p < 0.05$ by the chi-square test or the Fisher's exact test, the early or late AMD groups versus the non-maculopathy group.
† Non-maculopathy was defined as the absence of signs of early or late AMD.
‡ Because of missing values, number of subjects does not always add up to this figure.

Table 2. Comparison of serum antioxidant levels (μmol/L) among the non-maculopathy, early and late AMD groups

	Non-maculopathy† (n = 682)	Early AMD (n = 32)	Late AMD (n = 8)
	Geometric mean (Geometric standard deviation)	Geometric mean (Geometric standard deviation)	Geometric mean (Geometric standard deviation)
alpha-Tocopherol	26.0 (1.42)	30.1 (1.52)	19.6 (1.11)**
gamma-Tocopherol	2.55 (1.79)	2.38 (1.80)	2.22 (2.08)
Retinol	2.08 (1.42)	2.07 (1.34)	2.15 (1.26)
beta-Cryptoxanthin	0.19 (2.08)	0.19 (1.98)	0.08 (1.87)*
alpha-Carotene	0.10 (1.97)	0.11 (1.85)	0.07 (1.51)
beta-Carotene	0.77 (2.11)	0.80 (2.10)	0.41 (1.93)*
Lycopene	0.20 (2.21)	0.26 (2.13)	0.15 (2.26)
Lutein and zeaxanthin	0.48 (1.67)	0.47 (1.94)	0.36 (1.70)

* $p < 0.05$ by ANOVA with Dunnet's method, the early or late AMD groups versus the non-maculopathy group.
** $p = 0.056$ by ANOVA with Dunnet's method, the early or late AMD groups versus the non-maculopathy group.
† Non-maculopathy was defined as the absence of signs of early or late AMD.

outdoor activity (no, yes). No significant interactions between the variables were noted in the multivariate analysis. The analysis included each antioxidant concentration as a continuous variable was also done. All statistical analysis was done with the Statistical Package of Social Sciences (SPSS) version 14.0 (SPSS Japan Inc., Tokyo, Japan).

RESULTS

In this study population, thirty-two had early AMD and eight had late AMD, thus the overall prevalence of early and late AMD was 4.4% (95% CI: 3.1-6.2) and 1.1% (95% CI: 0.5-2.2), respectively. Of the 8 late AMD cases, 2 were of the wet type and 6 were of the dry type. Males (2.0%, 95% CI: 0.7-4.3) were more likely to suffer from late AMD than females (0.5%, 95% CI: 0.1-1.7) (p = 0.05 by the Fisher's exact test). The prevalence of early AMD did not significantly differ according to gender.

Table 1 shows the distribution of various demographic and risk factors among the non-maculopathy, early and late AMD groups. The serum antioxidant concentrations were also compared among these three groups (Table 2). Serum antioxidants levels in the early AMD group did not differ when compared with those in the non-maculopathy group. Conversely, serum levels for alpha-tocopherol, beta-cryptoxanthin and beta-carotene were lower in the late AMD group than in the non-maculopathy group. To further examine the association between serum antioxidants and late AMD, the prevalence of late AMD was

Table 3. Association between serum antioxidant levels and late AMD

Serum antioxidants	Category†	Prevalence (%)	Odds ratio for one-category increase‡	
			Crude odds ratio (95% CI)	Multi-adjusted odds ratio§ (95% CI)
alpha-Tocopherol	Low	6/213 (2.8)		
	Middle	2/238 (0.8)		
	High	0/239 (0.0)*	0.20 (0.05−0.78)**	0.13 (0.03−0.66)**
gamma-Tocopherol	Low	3/231 (1.3)		
	Middle	3/228 (1.3)		
	High	2/231 (0.9)	1.00 (0.43−2.34)	0.92 (0.35−2.39)
Retinol	Low	0/ 97 (0.0)		
	Middle	4/111 (3.6)		
	High	1/107 (0.9)	1.31 (0.43−4.03)	3.53 (0.52−23.82)
beta-Cryptoxanthin	Low	6/217 (2.8)		
	Middle	2/229 (0.9)		
	High	0/244 (0.0)*	0.20 (0.05−0.79)**	0.14 (0.03−0.68)**
alpha-Carotene	Low	4/222 (1.8)		
	Middle	3/233 (1.3)		
	High	1/235 (0.4)	0.53 (0.21−1.35)	0.57 (0.18−1.78)
beta-Carotene	Low	4/222 (1.8)		
	Middle	3/232 (1.3)		
	High	1/236 (0.4)	0.53 (0.21−1.34)	0.39 (0.12−1.24)
Lycopene	Low	3/227 (1.3)		
	Middle	3/233 (1.3)		
	High	2/230 (0.9)	0.82 (0.35−1.95)	0.78 (0.29−2.07)
Lutein and zeaxanthin	Low	3/224 (1.3)		
	Middle	5/240 (2.1)		
	High	0/226 (0.0)	0.54 (0.21−1.38)	0.29 (0.08−1.03)
Carotene family¶	Low	4/167 (2.4)		
	Middle	4/350 (1.1)		
	High	0/173 (0.0)*	0.32 (0.10−1.00)**	0.21 (0.05−0.95)**
Carotenoid family††	Low	4/161 (2.5)		
	Middle	4/347 (1.2)		
	High	0/182 (0.0)*	0.31 (0.10−0.96)**	0.19 (0.04−0.86)**

* $p < 0.05$ by the Fisher's exact test when compared with the low category.
** Odds ratios for one-category increase in antioxidant tertiles were statistically significant ($p < 0.05$).
† Age- and gender-specific tertiles of each serum antioxidant were used.
‡ For the trend analysis, we performed logistic regression using category as an integral value.
§ Adjusted for age, gender, smoking status (none, ex, current), alcohol drinking habits (none, ex, current), education (elementary or junior high, high school or higher), hypertension (no, yes), body mass index (< 25.0 kg/m^2, ≥ 25.0 kg/m^2), total cholesterol (< 5.7 mmol/L, ≥ 5.7 mmol/L), hemoglobin A_{1c} (≤ 5.8%, > 5.8%), cataract surgery (no, yes) and outdoor activity (no, yes).
¶ Carotene family contained alpha-, beta-carotenes and lycopene.
†† Carotenoid family contained beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, and lutein and zeaxanthi

estimated with relation to age- and gender-specific tertiles of serum antioxidant levels (Table 3). As single antioxidants, high tertile category of alpha-tocopherol and beta-cryptoxanthin was related with decreased prevalence of late AMD. Crude- and multivariate-adjusted ORs for one-category increase in antioxidant tertiles also revealed that protective association of alpha-tocopherol and beta-cryptoxanthin with late AMD. Even when including as a continuous variable in the model, these two remained statistically significant individually.

On the other hand, carotene family as a combination of alpha-, beta-carotenes and lycopene was protectively associated with late AMD, though alpha-, beta-carotenes and lycopene individually showed no statistically significant relationship with late AMD. The carotenoid family (beta-cryptoxanthin, alpha-, beta-carotenes, lycopene, and lutein and zeaxanthin) was also related to late AMD.

The prevalence of early AMD was also calculated by age- and gender-specific tertiles. However, as no difference in serum antioxidant levels between early AMD and non-maculopathy groups was observed, all antioxidants and antioxidant families did not show any relationships with early AMD (data not shown).

DISCUSSION

The study results revealed that increased serum antioxidant levels were associated with a decreased prevalence of late AMD, but not with early AMD, in a older Japanese population. This may provide further support for the role of antioxidants mainly on AMD progression but not in primary prevention, in keeping with the randomised control trial evidence from the AREDS.[6] The findings may have two implications. First, a traditional Japanese diet can play an important role in preventing the development of AMD, because the majority in our study population have been consuming the traditional Japanese diet thorough their lifetime; 80% of the study subjects have lived in the town for their whole life and have implemented a typical Japanese lifestyle; only 5% of those have ever used any supplements (from the subsample of 247 persons

in our subjects). Second, the antioxidants can still be an important factor for late AMD even in a Japanese population whose serum levels of antioxidants are generally high.[12]

There is general consensus that cumulative oxidative damage is responsible for ageing, and may, therefore, play an important role in the pathogenesis of AMD. A recent experimental study strongly supported this hypothesis by showing that mice deficient in Cu, Zn-superoxide dismutase (SOD1), an oxidative stress scavenger, had features typical of AMD in humans, such as drusen, thickened Bruch's membrane and choroidal neovascularization.[15] To combat oxidative stress, the synergistic action of carotenoids and other antioxidants has been proposed. Several studies have revealed interactions between beta-carotene and alpha-tocopherol in preventing radical reactions.[16,17] Another in vitro study has shown that combinations of carotenoids are more effective than single compounds in preventing oxidative damage.[18,19] Synergistic antioxidant efficacy was also found when a carotenoid mixture was modified with alpha-tocopherol. Along with an observational study in Rotterdam,[7] the results of our study indicate that the benefit of various antioxidants in combination are greater than those of single compounds, which is in good agreement with the concept of potential synergistic action. A report of the Blue Mountains Eye Study[8] suggested that high intake of vegetables including many kinds of antioxidants was protective for AMD also supports our findings. The results of intervention studies with supplements add weight to this hypothesis. Supplementation with multi antioxidants was shown in the AREDS to lower the risk for and slow the progression of AMD, whereas supplementation with 1 or 2 antioxidants in other clinical trials did not.[6, 20-22]

No association between serum antioxidant levels and early AMD was observed in our study, which is in agreement with other epidemiological studies[23-25] including the AREDS.[6] The latest systematic review by Chong et al also showed that antioxidants had little effect in the primary prevention of early AMD.[26] In contrast, West et al and Delcourt et al found that an increased serum level of alpha-tocopherol was associated with a decreased prevalence of early AMD.[27, 28] There is not enough evidences, to date, on this association of serum antioxidants with the prevention of early AMD, suggesting a need for further investigation.

One of the potential limitations in this study is that the response rate to the study (50%) was not excellent. However, we conducted a home-visit health survey to compare with the health information between the participants in the detailed health assessment and non-participants. There was no difference in visual difficulty between the two groups. Additionally, the overall prevalence of late AMD (1.1%) in this study was compatible with the prevalence in the Japanese population-based reports of the Hisayama Study[29] (1.1% at aged 60 years or older) and the Funagata Study[30] (1.0% at aged 65 years or older) when adjusted for the age and sex distribution. Another potential limitation is the limited number of late AMD cases due to the low prevalence of AMD in Japan. We might underestimate the association between serum antioxidants and late AMD, and this limited us to explore further analysis such as stratification by AMD type; wet and dry. Thirdly, misclassification of AMD may have occurred due to lack of other supportive method such as fundus fluorescein angiography, because this is not a hospital-based study. Likewise, misclassification of serum antioxidant levels could be possible. However, such misclassification would likely occur non-differentially and lead to null association between serum antioxidants and AMD if any.

In conclusion, we have demonstrated that increased serum antioxidant levels obtained from a traditional Japanese diet were associated with a decreased prevalence of late AMD in one community-dwelling older Japanese population. It seems likely that antioxidants are effective against late AMD in combination rather than individually. Considering the nature of a cross-sectional design, the observed association should be confirmed in studies with a longitudinal design.

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AUTHOR DISCLOSURES

None

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Original Article

Serum antioxidants and age-related macular degeneration among older Japanese

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日本老人血清中抗氧化物質與老年黃斑病變之關係

在人類營養之前瞻性研究中發現，透過飲食控制老年黃斑病變（AMD）是可行且受期望的。我們調查居住社區且攝食傳統飲食之日本老人，其血清中抗氧化物質與 AMD 之關係。本研究共有 722 位受試者（297 位男性與 425 位女性），年齡為 65 歲以上，都已做眼基底攝像。將受試者分為三組，分別為早期 AMD、晚期 AMD 及未有黃斑病變組。血清中抗氧化物質（α-生育醇、γ-生育醇、維生素 A、β-隱黃質、α-胡蘿蔔素、β-胡蘿蔔素、茄紅素、葉黃素及玉米黃質）利用高性能液相色層分析測量。為闡明抗氧化物質的結合性效用，定義胡蘿蔔素家族有 α-胡蘿蔔素、β-胡蘿蔔素及茄紅素；類胡蘿蔔素家族包括 β-隱黃質、α-胡蘿蔔素、β-胡蘿蔔素、茄紅素、葉黃素及玉米黃質。將血清抗氧化物質濃度分為三分位，利用單變項及多變項分析，比較早期 AMD 及晚期 AMD 之盛行率。早期 AMD 之盛行率為 4.4%（95%信賴區間為 3.1-6.2），而晚期 AMD 盛行率為 1.1%（95%信賴區間為 0.5-2.2）。只有 α-生育醇及 β- 隱黃質有單獨效應，與晚期 AMD 相關。另一方面，胡蘿蔔素及類胡蘿蔔素家族有整體性效用，對晚期 AMD 有保護性。然而血清中抗氧化物質與早期 AMD 無關聯。本研究發現可支持作者之假說，即從傳統日本飲食中獲得的血清中抗氧化物質，可共同作用保護晚期 AMD，但於早期 AMD 中未發現相同之結果。

關鍵字：血清抗氧化物質、老年黃斑病變、飲食、年長者、日本