Macular Pigment Optical Density in Central Serous Chorioretinopathy

Yuzuru Sasamoto,¹ Fumi Gomi,¹ Miki Sawa,¹ Motokazu Tsujikawa,¹ and Toshimitsu Hamasaki²

PURPOSE. To evaluate macular pigment optical density (MPOD) in patients with central serous chorioretinopathy (CSC) and in normal subjects.

METHODS. MPOD was measured by autofluorescence spectrometry by using a two-wavelength method. Central retinal thickness (CRT) was measured with optical coherence tomography. Statistical analyses were performed to determine factors associated with MPOD.

RESULTS. Ninety-four eyes of 94 normal control subjects, 123 eyes of 70 patients with chronic CSC, and 74 eyes of 41 patients with acute CSC were included. The mean MPOD was 0.548 density unit (DU; 95% confidence interval [CI]; 0.516–0.580) in the control group. Stepwise regression analysis of the control group showed that CRT was associated positively with MPOD (P = 0.0079). The mean MPOD was 0.386 DU (95% CI, 0.352–0.420) in the eyes with chronic CSC, 0.443 DU (95% CI, 0.401–0.484) in fellow eyes with chronic CSC, 0.542 DU (95% CI, 0.493–0.590) in affected eyes with acute CSC, and 0.528 DU (95% CI, 0.475–0.582) in fellow eyes with acute CSC. Stepwise regression analysis showed a significant association between eyes with a lower MPOD and affected eyes with chronic CSC (P = 0.0116) and fellow eyes with chronic CSC (P = 0.0023) and a thinner central retina (P = 0.0016).

CONCLUSIONS. MPOD may decrease in eyes with chronic CSC and in the fellow eyes. Low MPOD may indicate a risk of chronic CSC, and a decrease in MPOD may be accelerated by thinning of the central retina. (Invest Ophthalmol Vis Sci. 2010;51:5219–5225) DOI:10.1167/iovs.09-4881

Macular pigment is composed of three carotenoids (i.e., lutein, zeaxanthin, and meso-zeaxanthin). Lutein and zeaxanthin can be obtained only from food, and meso-zeaxanthin is synthesized mainly from retinal lutein.¹⁻⁶ Macular pigment is distributed primarily in the layer of the fibers of Henle in the fovea and the inner nuclear layer at the parafoveal site.⁷ Macular pigment has light-absorbing properties, with the maximum absorption at approximately 460 nm; macular pigment is thought to filter blue light, which is toxic to the photoreceptors.⁸⁻¹² In addition, macular pigment itself has an antioxidant effect. It quenches excited triplet states, reacts with singlet oxygen and free radicals, and inhibits peroxidation of long-chain polyunsaturated fatty acids.⁶¹³⁻¹⁷ Thus, it helps retard some destructive processes in the retina and the retinal pigment epithelium (RPE), which may lead to macular diseases such as age-related macular degeneration (AMD).

Some investigators have tried to determine the amount of macular pigment and elucidate factors affecting macular pigment. Differences in the amount and distribution of macular pigment associated with ethnicity have been reported.¹⁸⁻¹⁹ However, whether macular pigment optical density (MPOD) is affected by aging,¹⁹⁻²⁰⁻²⁶ sex,¹⁹⁻²¹,²³,²⁵,²⁷ and smoking¹⁹,²⁰,²³,²⁵ is still controversial. In those studies, several clinical methods of measuring MPOD were used, including heterochromatic flickering photometry, motion detection photometry, fundus reflectance spectroscopy, Raman spectrometry, and autofluorescence spectrometry.²⁶ Among them, autofluorescence spectroscopy using a two-wavelength method is independent of the psychophysical methods and is considered to have the highest reproducibility.²²⁻²⁴⁻⁵¹

Some research groups have investigated the relationship between AMD and the amount of macular pigment.¹²⁻⁷,²⁴⁻⁵⁴ Obana et al.³² reported that Japanese patients with AMD have low MPOD. Central serous chorioretinopathy (CSC) is characterized by serous detachment of the neural retina, which also may affect the macula and develop bilaterally.³⁶⁻³⁷ Associations with a type A personality, the use of corticosteroids, and pregnancy have been suggested, but the pathogenesis is still unknown.³⁸⁻⁴¹

To the best of our knowledge, MPOD in eyes with CSC has not been evaluated. In the present study, we measured MPOD and compared results in Japanese patients with CSC with those in normal subjects. To estimate the factors affecting MPOD in Japanese patients, we performed regression analysis and evaluated the contribution of CSC.

METHODS

Study Population

We conducted a cross-sectional observational study at Osaka University Hospital from July 2007 to November 2008. The institutional review board approved the study.

Patients with CSC who met the following criteria in at least one eye were recruited: current or previous episode of serous retinal detachment (SRD) at the macula detected by fundus examination and/or optical coherence tomography (OCT) performed in another institution or our hospital and symptoms of blurred vision, metamorphopsia, micropsia, dyschromatopsia, hypermetroptopia, or central scotoma in the affected eye. Eyes with other retinal disorders such as rhegmatogenous retinal detachment, choroidal neovascularization, polypoidal choroidal vasculopathy, retinal vein occlusion, macroaneurysms, diabetic retinopathy, and inflammatory eye diseases such as Vogt-Koyanagi-Harada disease were excluded by detailed fundus examina-

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Disclosure: Y. Sasamoto, None; F. Gomi, Bausch & Lomb Japan, Ltd. (F); M. Sawa, None; M. Tsujikawa, None; T. Hamasaki, None.

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tion and both fluorescein angiography (FA) and indocyanine green angiography (ICGA). Eyes with autofluorescence abnormalities within the area of an annulus with retinal eccentricity of 0.5° also were excluded.

Persistent CSC is sometimes categorized as chronic CSC, but there is no criterion to define it.42,43 In the present study, we classified eyes with CSC into chronic and acute cases according to the following definition: We defined chronic CSC as that in eyes with episodes of persistent or recurrent SRD during a period of 6 months or more and in which the latest episode of SRD was confirmed within 5 years; acute CSC was defined as that in eyes with current or previous SRD over a period of less than 6 months and that had occurred within 1 year. In all eyes with acute CSC, FA was performed, and the active dye leakage was confirmed. The duration of an SRD was estimated by OCT, fundus photography, or the clinical records at our hospital or the clinics where the patients had been treated.

If both eyes of a patient met the criteria, both eyes were examined as affected eyes, and when one eye did not have apparent abnormalities and no symptoms of CSC, it was examined as a fellow eye.

Subjects without retinal disorders in at least one eye, including healthy volunteers, were recruited for the control group after they agreed to participate in the study. We allowed subjects to participate who had the following retinal diseases in the contralateral eyes: macular hole, idiopathic epiretinal membrane, or rhegmatogenous retinal detachment. The right eye was selected in healthy volunteers in whom the patients had been treated.

Subjects sat in front of a table and fixated on an external light source with the fellow eye. If the fellow eye did not have adequate visual acuity (VA) for fixation, the subjects were asked to look straight as much as possible. The modified HRA was aligned with the subject’s eye, movies were taken with the 488- and 514-nm excitation wavelengths (scan size; 30°), computed mean autofluorescence images were obtained at each wavelength, and the two images were subtracted to calculate MPOD (expressed as density unit [DU]). The mean MPOD, averaged along the area of an annulus with retinal eccentricity of 0.5° (1° circle at the fovea), was recorded. We examined both eyes if possible.

Eyes were excluded if there was a decrease in the number of effective pixels (≥150/225 pixels), mainly due to poor fixation and failure to detect the fovea with the find-fovea mode. We measured MPOD two or three times at each visit in each eye and then selected the data that varied the least.

### Ophthalmic Examinations

The clinical examinations included measurement the best-corrected VA (BCVA) with a Landolt C chart, slit lamp biomicroscopy with a 90-D

![Figure 1](image-url)

**Figure 1.** MPOD in the control group and the CSC subgroups. The MPOD in the affected eyes and fellow eyes with chronic CSC was significantly lower than in the control eyes (*P < 0.0001 and **P = 0.0005, by the Dunnett test). However, the MPOD in the affected eyes and fellow eyes with acute CSC group did not differ significantly from that in the control eyes.
precorneal lens, digital fundus photography, and OCT (Stratus or Cirrus; Carl Zeiss Meditec, Inc., Dublin, CA), to ascertain the presence of an SRD. When images were obtained with Cirrus OCT, we measured the CRT, defined as the distance between the surface of the inner limiting membrane and the bottom of the sensory retina. Subretinal precipitates were not included in the CRT. FA and ICGA were performed in all eyes with acute CSC and in eyes with persistent SRD in chronic CSC. The presence of RPE damage involving the macula, except for the 1° circle at the fovea, was assessed by examining color fundus photographs, FA, or both. If the size of the areas with RPE damage was 5 disc areas or more, those eyes were defined as having diffuse RPE damage. In eyes with a current SRD, we measured the size of the SRD area from the fundus photograph.

Statistical Analysis

Since the standard deviation of MPOD when including both affected eyes did not differ significantly from data from the unilateral eye of patients with bilateral involvement, all eyes in which MPOD was measured were included in the analysis, even if both eyes of a patient were affected. The baseline characteristics of age, the size of the SRD, CRT, and the time from the onset of the latest event are expressed as the mean ± SD. The mean MPOD and CRT were compared between groups, and the 95% CI was calculated. The two-sided Dunnett t test was used to evaluate the difference in MPOD between groups, after we performed stepwise regression analysis to determine the covariates that significantly affect the CRT. Analysis of covariance (ANCOVA) and the Dunnett test were performed. P < 0.05 was considered significant (SAS software ver. 9.1; SAS Institute, Cary, NC).

RESULTS

A total of 291 eyes of 201 subjects were included (94 eyes of 94 subjects in the control group; 123 eyes of 70 patients in the chronic CSC group; 74 eyes of 41 patients in the acute CSC group). Seventeen patients were affected bilaterally; 13 had bilateral chronic CSC, and 4 had chronic CSC in one eye and acute CSC in the other eye. In the chronic CSC group, 76 eyes were affected and 47 fellow eyes had no apparent abnormalities. In the acute CSC group, 38 eyes were affected and 36 were fellow eyes. The baseline characteristics of all eyes are shown in Table 1.

MPOD in Control and CSC Eyes

The mean MPOD was 0.548 DU (95% CI, 0.516–0.580) in the control group and 0.386 DU (95% CI, 0.352–0.420) in the affected eyes with chronic CSC, 0.443 DU (95% CI, 0.401–0.484) in the fellow eyes with chronic CSC, 0.542 DU (95% CI, 0.493–0.590) in the affected eyes with acute CSC, and 0.528 DU (95% CI, 0.475–0.582) in the fellow eyes with acute CSC. The Dunnett test indicated that MPOD in the affected and fellow eyes with chronic CSC was significantly lower than in the control eyes (P < 0.0001 and P = 0.0005, respectively; Fig 1). MPOD in the affected and fellow eyes with acute CSC did not differ significantly from that in the control group (P = 0.9990 and P = 0.9306, respectively).

Factors Affecting MPOD in the Control Group

The overall mean MPOD ± SD was 0.548 ± 0.157 DU (n = 94): 0.547 ± 0.141 DU in men (n = 44) and 0.549 ± 0.172 DU in women (n = 50). The mean ± SD was 0.562 ± 0.149 DU in the subjects who smoked and 0.540 ± 0.163 DU in the nonsmokers. The stepwise regression analysis model, which included sex, age, smoking, and CRT as explanatory covariates and MPOD as a response, showed that CRT was the most important covariate associated with MPOD (P = 0.0079). The other covariates were not associated significantly with MPOD. Although the mean ± SD baseline ages in the subgroups were the same (Table 1), stepwise regression analysis did not identify

<table>
<thead>
<tr>
<th>Male/female</th>
<th>MPOD</th>
<th>P</th>
</tr>
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<tbody>
<tr>
<td>0.387 (0.350–0.424) (n = 65)</td>
<td>0.380 (0.283–0.477) (n = 11)</td>
<td>0.8849</td>
</tr>
<tr>
<td>0.385 (0.343–0.427) (n = 52)</td>
<td>0.388 (0.322–0.455) (n = 23)</td>
<td>0.9313</td>
</tr>
<tr>
<td>0.364 (0.314–0.413) (n = 33)</td>
<td>0.403 (0.356–0.451) (n = 43)</td>
<td>0.2515</td>
</tr>
<tr>
<td>0.385 (0.308–0.462) (n = 15)</td>
<td>0.386 (0.348–0.425) (n = 61)</td>
<td>0.9681</td>
</tr>
<tr>
<td>0.380 (0.333–0.426) (n = 40)</td>
<td>0.393 (0.341–0.445) (n = 36)</td>
<td>0.6992</td>
</tr>
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<table>
<thead>
<tr>
<th>Correlation Coefficient</th>
<th>P</th>
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<tr>
<td>Age (n = 76)</td>
<td>−0.14</td>
</tr>
<tr>
<td>Size of SRD (n = 40)</td>
<td>0.05</td>
</tr>
<tr>
<td>CRT (n = 68)</td>
<td>0.28</td>
</tr>
<tr>
<td>Duration (n = 76)</td>
<td>−0.34</td>
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MPOD data are expressed as the mean DU (95% CI).
age as an important covariate. Figure 2 shows the correlation between CRT and MPOD. MPOD rose significantly with increases in CRT (r = 0.40; 95% CI, 0.11–0.62).

Factors Affecting MPOD in All Eyes

The relationship between MPOD in the affected eyes with acute and chronic CSC and the covariates (i.e., age, sex, smoking, RPE damage, the presence or absence of an SRD, the size of the SRD, and the time from the onset of the latest event), are shown in Tables 2 and 3, respectively. MPOD correlated significantly with CRT (r = 0.28, P = 0.0210) and the time from the onset of the latest event (r = −0.34, P = 0.0026) in the affected eyes with chronic CSC. The other covariates did not correlate significantly with MPOD. To determine the major factors associated with MPOD, we performed stepwise regression analyses in all eyes, including the control group and the CSC subgroups (Table 4). RPE damage, SRD, and the CSC subgroups were included as explanatory covariates along with sex, age, smoking, and CRT. Because the duration was directly associated with the definition of chronic or acute and correlated strongly with CRT (r = −0.31, P = 0.0017), it was not included in this analysis. Stepwise regression analysis showed that CRT and the affected eyes and fellow eyes with chronic CSC were the important covariates associated with MPOD (P = 0.0016, P = 0.0126, and P = 0.0023, respectively). The smokers also tended to have a lower MPOD than did the nonsmokers (P = 0.1320). The other covariates had little effect on MPOD.

The results of stepwise regression analysis showed that CRT and CSC affected MPOD independently. To confirm the relationship between CRT and CSC, we used stepwise regression analysis and ANCOVA to analyze the factors that affected CRT.

CRT in the CSC eyes ranged from 44 to 289 μm (mean ± SD, 168.0 ± 49.3). Because stepwise regression analysis identified RPE damage, SRD, and the CSC subgroups as significant covariates associated with CRT among the sex, age, smoking, RPE damage, SRD, and CSC subgroups, we performed ANCOVA and the Dunnett test to compare CRT among the CSC subgroups. The adjusted mean CRT was 181.9 μm (95% CI, 168.3–195.4) in the control group, 138.4 μm (95% CI, 130.5–146.2) in the affected eyes with chronic CSC, 176.7 μm (95% CI, 162.4–190.9) in the fellow eyes with chronic CSC, 159.2 μm (95% CI, 147.2–171.3) in the affected eyes with acute CSC, and 179.2 μm (95% CI, 162.7–195.8) in the fellow eyes with acute CSC (Fig. 3). The Dunnett test showed that the central retinas in the affected eyes with chronic and acute CSC were thinner than those in the control group (P < 0.0001 and P = 0.0487, respectively). However, no significant differences were found in the CRT in the fellow eyes with chronic and acute CSC (P = 0.9019 and P = 0.9945, respectively).

DISCUSSION

We used autofluorescence spectrometry to evaluate MPOD in a control group and in two groups of patients with CSC. Among the several methods of estimating MPOD, this one is considered to have the highest reproducibility.22–28,31 Autofluorescence spectrometry has shown ethnic differences in the level and distribution of macular pigments; however, only one study reported MPODs in a Japanese population in which resonance Raman spectroscopy was used. Therefore, in the present study, we were the first to examine MPOD in both normal and CSC eyes in the Japanese, by using autofluorescence spectrometry.

In the study, MPOD at an eccentricity of 0.5° was 0.548 ± 0.157 DU in normal subjects. Previously, Liew et al.17 and Trieschmann et al.48 reported that the mean MPOD ± SD in normal subjects was 0.41 ± 0.15 and 0.50 ± 0.19 DU, respectively. Compared with those reports, the present study showed that the SD of MPOD was almost the same and the mean MPOD was significantly higher. Wolf-Schnurrbusch et al.18 reported that individuals of African descent had significantly higher MPOD than white non-Hispanics. The current data also sug-

### Table 3. Relationship between the MPOD Level and Covariates in the Affected Eyes with Acute CSC

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Coefficient (95% CI)</th>
<th>𝑃</th>
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<tbody>
<tr>
<td>Male/female</td>
<td>0.553 (0.499–0.607)</td>
<td>0.4343</td>
</tr>
<tr>
<td>Smoking, yes/no</td>
<td>0.525 (0.463–0.587)</td>
<td>0.3458</td>
</tr>
<tr>
<td>RPE damage, yes/no</td>
<td>0.587 (0.469–0.704)</td>
<td>0.2965</td>
</tr>
<tr>
<td>Diffuse RPE damage, yes/no</td>
<td>0.542 (0.493–0.590)</td>
<td>—</td>
</tr>
<tr>
<td>SRD, yes/no</td>
<td>0.530 (0.478–0.582)</td>
<td>0.3389</td>
</tr>
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</table>

### Table 4. Selected Covariates in all Eyes Affecting Macular Pigment Optical Density

<table>
<thead>
<tr>
<th>Selected Variable</th>
<th>Regression Coefficient (95% CI)</th>
<th>𝑡</th>
<th>𝑃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>0.344 (0.190 to 0.498)</td>
<td>5.03</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Smoking, yes</td>
<td>−0.055 (−0.082 to 0.016)</td>
<td>−1.51</td>
<td>0.1520</td>
</tr>
<tr>
<td>CRT</td>
<td>0.001 (0.000 to 0.002)</td>
<td>3.21</td>
<td>0.0016</td>
</tr>
<tr>
<td>Chronic CSC, affected eye</td>
<td>−0.095 (−0.176 to −0.010)</td>
<td>−2.52</td>
<td>0.0126</td>
</tr>
<tr>
<td>Chronic CSC, fellow eye</td>
<td>−0.105 (−0.181 to −0.028)</td>
<td>−3.08</td>
<td>0.0023</td>
</tr>
<tr>
<td>Acute CSC, affected eye</td>
<td>0.055 (−0.030 to 0.141)</td>
<td>1.47</td>
<td>0.1444</td>
</tr>
<tr>
<td>Acute CSC, fellow eye</td>
<td>−0.048 (−0.136 to 0.039)</td>
<td>−1.25</td>
<td>0.2145</td>
</tr>
</tbody>
</table>
The onset of the latest event, which may correlate inversely with chronic CSC, as seen in normal subjects. The time from the CRT correlated positively with MPOD in the affected eyes with MPOD in the affected eyes with chronic CSC. The duration of the SRD also was considered to be associated with lower MPOD, independent of the morphologic retinal changes in eyes with chronic CSC. The long-term persistence of subretinal fluid may disrupt the macular pigment supply from the RPE-choroid complex and cause a shortage in the retina. These possibilities suggest that the lower MPOD in CSC eyes is the result of the disease.

However, the results of regression analysis showed that the affected and fellow eyes with chronic CSC had significantly lower MPOD independent of CRT. This result suggests that eyes with low MPOD are likely to develop chronic CSC, but not as a result of persistent disease. This finding means that eyes with chronic CSC without thinning of the central retina had low MPOD, and the thinner central retina resulted in much lower MPOD. This hypothesis is supported by the finding of lower MPOD in fellow eyes with chronic CSC, although the CRT was maintained.

The possibility should be considered that the low MPOD in eyes with chronic CSC results from methodologic artifacts of autofluorescence spectrometry. The increased fundus autofluorescence (FAF) in eyes with CSC is well known. Eyes with autofluorescence abnormalities within the area of an annulus with retinal eccentricity of 0.5° were excluded from the present study, but if unknown substances reduce the absorption of FAF in the macular pigment at 488 nm or increase the absorption at 514 nm, autofluorescence spectrometry may measure lower MPOD.

In conclusion, low MPOD may be a risk factor for the development of chronic CSC, and a decrease in MPOD may be accelerated by a thinning central retina. A limitation of the present study was that MPOD in most eyes was measured once, not repeatedly, along with disease progression or persistence. We also could not exclude the possibility that a few asymptomatic eyes with CSC were included among the fellow eyes, despite detailed ophthalmic examinations including OCT. In addition, MPOD may vary interindividually, even when measured by autofluorescence spectrometry, probably because of difficulties in the standardization of individually different intensities and distributions of fundus autofluorescence. However, because we measured MPOD in a relatively large number of eyes, we believe that our data are meaningful. The exact relationship between low MPOD and development of chronic CSC is unknown; however, our data suggest the possibility that the supplementation of macular pigment suppresses the development or progression of chronic CSC, which causes substantial visual deterioration. Further studies are needed.

Acknowledgments

The authors are grateful for the immeasurable contribution of the late Yasuo Tano to this study.

References


