Relationships between macular pigment optical density and lacquer cracks in high myopia

Association entre la densité optique en pigment maculaire et la présence de rupture de la membrane de Bruch dans la myopie forte

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Summary

Purpose. — A low concentration of macular carotenoid pigment (lutein and zeaxanthin) is a significant risk factor for macular degeneration. The goal of this paper is to investigate the relationship between macular pigment optical density (MPOD) and lacquer cracks (LC) in high myopia.

Methods. — This is a prospective comparative observational study (NCT02205632) including high myopic patients with or without LC. High myopia was defined as a refractive error greater than 6 diopters of myopia or axial length greater than 26 mm. All patients underwent best-corrected visual acuity in logMAR, MPOD measurement, multicolor imaging, SD-OCT, autofluorescence and axial length measurement. MPOD was calculated using heterochromatic flicker photometry. Group 1 was defined as eyes without LC and group 2 as eyes with LC.

Results. — Forty-five eyes of 32 patients with a mean age of 51.3 years were included in group 1, and 15 eyes of 13 patients aged 54.1 in group 2 (P=0.56). Mean spherical equivalent was −10.11 diopters in group 1 and −15.11 in group 2 (P=0.0004). Mean visual acuity was

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+0.08 logMAR (0.8 in decimal notation) in group 1 and +0.11 logMAR (0.8 in decimal notation) in group 2 \( P = 0.061 \). Axial length was 27.8 mm in group 1 and 29.2 in group 2 \( P = 0.0052 \). Central macular thickness was lower in group 1 (295 \( \mu \)m) than in group 2 (305 \( \mu \)m) \( P = 0.0001 \), and macular choroidal thickness did not differ between the two groups \( P = 0.094 \). Mean MPD in group 2 was 0.52 and 0.63 in group 1 \( P = 0.042 \). Differences in axial length were not related to MPD measurements \( P = 0.74 \).

**Conclusion.** – A lower rate of MPD was observed in cases of LC in high myopia. Further studies are needed to investigate if dietary carotenoids could have a protective effect in reducing the risk of LC.

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**Introduction**

Myopia, the main cause of visual impairment worldwide, affects at least 30% of individuals over age 40 in Western Europe and United States [1]. High myopia, defined by a refractive error inferior to \( -6 \) D or axial length superior to 26 mm, is associated with retinal complications including lacquer cracks (LC), myopic choroidal neovascularization and choriotretilal atrophy [2]. LC, a complication related to the progressive mechanical elongation of the eyeball over time, can occur at different stages of myopic maculopathy and is an important risk factor of choroidal neovascularization and choriretital atrophy [3,4]. Macular xanthophyll pigment, containing carotenoids Lutein and Zeaxanthin, are provided by food intakes and are mainly concentrated in the internal plexiform and Henle layers of the macula where they are suggested to protect the retina and improve visual performance [5]. When focusing on the protective effects of the macular pigment (MP) a dual role of short wavelengths of blue light-filtering, and an antioxidant function have been described [6,7]. In age-related macular degeneration (AMD), a positive correlation exists between a high rate of macular pigments and a protective effect against AMD [8–10]. In myopia, LC has been associated with anatomical changes related to eyeball extension, including choroidal thinning and staphyloma. But other factors could

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be associated with the development of LC. In this context, we hypothesized that a decrease of xanthophyll MP concentration could be a risk factor of LC. The main objective of this study was to evaluate the relationship between LC in high myopic eyes and macular pigment optical density.

Methods

Experimental design

This is a prospective comparative open-label, non-randomized and monocentric study that included high myopic patients with refractive error of −6 D or less with or without LC, between February 2014 and November 2014.

Study patients

The study was approved by the local ethics committee, and adhered to the tenets of the Declaration of Helsinki. The study protocol is publicly available at the ClinicalTrials.gov registry (identifier No. NCT02205632).

Inclusion criteria were age of 18 years or more, refractive error of −6 diopters or less, presence or not of LC in Bruch’s membrane in one or both eyes. The main non-inclusion criteria were amblyopia in studied eye, corneal disease, dry eye or media opacities preventing reliable measurement of MPOD, vitreoretinal surgery in studied eye, other retinal diseases (diabetic retinopathy, age-related maculopathy, macular hole, epiretinal macular membrane, foveoschisis) in studied eye, extensive chorioretinal central atrophy in studied eye. High myopic eyes with macular LC were compared to high myopic eyes without LC. For each included patient, at least one eye was included in statistical analysis if all inclusion criteria were fulfilled. In cases of fulfillment of these criteria by the second eye, it was likewise included in the study, with a statistical correction provided during the analysis (see statistical part).

Each patient included in this study underwent best-corrected visual acuity assessment at 4 meters in LogMar scale, biomicroscopic and fundus examination, macular SD-OCT centered on the fovea (Spectral-Domain Optical Coherence Tomography, Spectralis Heidelberg Engineering®), multicolor retinography and autofluorescence retinography (Spectralis Heidelberg Engineering®) or color photographs (Topcon TRC), axial length measurement with an optical non-contact biometry (Lenstar LS900 Haag-Streit®) and the macular pigment optical density measurement provided with MPSII device heterochromatic flicker photometry technology (Horus Pharma®) as previously described [11]. Central retinal thickness was measured on the volume mode of SD-OCT scan after manual checking of the good position of the lines. Central foveal chorioidal thickness was measured manually by a senior ophthalmologist (NL) on the EDI mode of the OCT.

The primary outcome was the comparison between MPOD between patients with and without LC.

Statistical analysis

Statistical analysis was performed with SAS software, version 9.3 (SAS Institute Inc., Cary NC, USA). P < 0.05 was considered statistically significant. The sample size was computed to achieve 80% statistical power with alpha risk 5% in the comparison of macular pigment optical density with a difference of 35% (0.2 vs. 0.3) between two groups with unequal sample weights. The minimum number of subjects to be included was 39: at least 13 high myopic patients with LC and 26 patients without LC in the control group. Standard deviation of macular pigment optical density measure used as a reference was 0.1 [12]. Mean MPOD were compared between the two groups by mixed effects analysis of variance taking into account the correlation between measurements of one patient’s eyes. In this study, the correlation coefficient between the two eyes of the same patient was 0.75, which is a strong correlation. Logarithmic transformation was applied when necessary to achieve normal distribution. To investigate the relationships between MPOD and other variables, a mixed effects linear regression analysis was applied. Quantitative variables are presented as means and standard deviations.

Results

Demographic data

Thirty-nine patients with high myopia (n=60 eyes), 25 women and 14 men, (mean age 51.3 ± 15.1 years) were included in this study. Among them, 45 eyes (32 patients) had no LC and 15 eyes (13 patients) had LC. This point is more precisely presented in the flow chart (Fig. 1).

Mean spherical equivalent was −11.3 (± 4.7 D) in the study population, eyes without LC having a mean refractive error of −10.1 (± 3.9) and eyes with LC having a mean refractive error of −15.1 (± 4.9 D) (P=0.0004). Mean central macular thickness (CMT) was 297 μm (± 27) in the study group, and was respectively 305 μm (± 28) and 295 μm (± 26) in eyes with and without LC (P<0.0001). Mean central chorioidal thickness was 139 ± 79 μm in study population. There was no significant difference in central chorioidal thickness between eyes with LC and eyes without LC (P=0.094). Mean axial length in study population was 28.1 mm (± 1.7). In eyes without LC, mean axial length was significantly lower than in eyes with LC (P=0.0052). Mean MPOD in study population was 0.61 (± 0.21). In eyes with LC, mean MPOD was 0.52 (± 0.22) and in eyes without LC mean MPOD was 0.63 (± 0.21) (P=0.042). These results are developed in Table 1. Data related to MPOD distribution between the different groups are also presented on Fig. 2.

Relations between MPOD and other variables were also investigated. These results are developed in Table 2. Age and BCVA were correlated with MPOD with respective regression slope coefficients −0.0048 ± 0.0021 (P = 0.033) and −0.24 ± 0.09 (P = 0.014). These results are also presented on Figs. 3 and 4. The other variables, such as refractive error (P = 0.39), central macular thickness (P = 0.28), central chorioidal macular thickness (P = 0.18) and axial length (P = 0.74) were not found to be significantly related to MPOD.

Discussion

This study demonstrated a significant association between high myopic eyes with lacquer crack and lower MPOD lev-
Initial screening of 82 eyes from 41 patients

22 eyes excluded:
- Refractive error more than -6 D: 6 eyes
- Severe dry eye syndrome and bad fixation: 2 eyes
- Retinal serous detachment: 1 eye
- Extensive chorioretinal atrophy: 5 eyes
- Lamellar hole or epiretinal membrane: 3 eyes
- Retinal detachment: 4 eyes
- History of vitrectomy: 1 eye

Eligible cases
60 high myopic eyes included in the analysis
- 45 eyes without lacquer crack (from 32 patients)
- 15 eyes with lacquer crack (from 13 patients)

Figure 1. Study flow chart.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Comparison in mean values of age, spherical equivalent, BCVA, CMT, Choroidal macular thickness, AL, MPOD, between the two groups.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean values (standard deviation)</td>
<td>All eyes n = 60 eyes</td>
</tr>
<tr>
<td>Age in years (SD)</td>
<td>51.3 (15.1)</td>
</tr>
<tr>
<td>Spherical equivalent in diopters (SD)</td>
<td>–11.3 (4.7)</td>
</tr>
<tr>
<td>BCVA in logMAR (SD)</td>
<td>0.08 (0.29)</td>
</tr>
<tr>
<td>CMT in μ (SD)</td>
<td>297 (27)</td>
</tr>
<tr>
<td>Choroidal macular thickness CMT in μ (SD)</td>
<td>139 (79)</td>
</tr>
<tr>
<td>AL in mm (SD)</td>
<td>28.1 (1.7)</td>
</tr>
<tr>
<td>MPOD (SD)</td>
<td>0.61 (0.21)</td>
</tr>
</tbody>
</table>

BCVA: best-corrected visual acuity; CMT: central macular thickness; AL: axial length; MPOD: macular pigment optical density; SD: standard deviation.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Mixed linear regression slope estimates of macular pigment optical density (MPOD) in relation to age, spherical equivalent, best-corrected visual acuity (BCVA), central macular thickness (CMT), macular choroidal thickness (MCT), axial length (AL), determined from a linear regression model where $y = a + b_x$, with $y = MPOD$, $x$ = other variable, and $b$ = slope coefficient.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variables</td>
<td>Slope coefficient b ± standard error</td>
</tr>
<tr>
<td>Age</td>
<td>–0.0048 ± 0.0021</td>
</tr>
<tr>
<td>Spherical equivalent</td>
<td>+0.0051 ± 0.0058</td>
</tr>
<tr>
<td>BCVA in logMAR</td>
<td>–0.24 ± 0.094</td>
</tr>
<tr>
<td>CMT</td>
<td>+0.0011 ± 0.00098</td>
</tr>
<tr>
<td>MCT</td>
<td>+0.00044 ± 0.00032</td>
</tr>
<tr>
<td>AL</td>
<td>+0.046 ± 0.014</td>
</tr>
</tbody>
</table>

Investigating the relationship between LC and MPOD. The decrease of MPOD in eyes with LC may be explained by reduced choriocapillaris blood flow leading to a reduction of carotenoid intake through lipoprotein receptors [13] located on photoreceptors outer segments or on Henle’s fiber layer. Indeed, a reduction of choroidal thickness has been confirmed in the present study and has also been previously described among high myopic patients with LC [14]. On the other hand, it could also be suggested that the progressive retinal thinning induced by eyeball elongation may explain a reduction of MPOD. However, this hypothesis is not supported by the present study, because a higher central retinal thickness was observed in the eyes with LC compared to the other group. Other factors should be investigated in further studies to explain these results, including genetic factors recently associated with MPOD decrease. Indeed, recent evidence showed that gene variants rs11645428 of BCMO1 gene expressed in the RPE cells and involved in cleavage of beta-carotene and rs1929841 of ABCA1, a gene encoding a carotenoid and cholesterol membrane transport protein, are associated with lower MPOD [15,16]. An inverse correlation between MPOD and visual acuity was reported in the high myopic eyes without lacquer crack (P = 0.042). Furthermore, a negative significant correlation was established between MPOD decrease and age or lower visual acuity. This is to our knowledge the first study investigating the relationship between LC and MPOD.

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In this context, there is a need for further studies on similar population to confirm the positive correlation between MPD and visual acuity.

Different approaches have been used to analyze retinal macular pigments, including physical and psychological methods [24]. In physical methods, mainly represented by autofluorescence measurement and fundus reflectance, retinal excitation by an incident light is used and analysis of the reflected signal is then performed. These techniques allow rapid and objective measurement of spatial distribution of macular pigment and a density map image can be built after digital subtraction of the reflectance data. Psychophysical methods, namely heterochromatic flicker photometry and Raman spectroscopy, are the most commonly used because they represent easy, validated and relatively inexpensive methods to measure optical density of macular pigment in current practice [25]. The present study design used pigment heterochromatic flicker photometry (HFP), of which the whom concept has previously been described [26]. In HFP, a test and a reference lights, the blue wavelength being absorbed by the macular pigment while the green wavelength is not absorbed, are alternated in counterphase at medium or high frequencies (between 10 and 20 Hz) at 100% contrast while the observer adjusts the time-averaged luminance of one of the lights until the perception of flicker is minimized or absent. Finally, the luminance level of the test light obtained with the perception of minimum flicker for the observer is considered as the luminance level that is equal to the standard light luminance [27]. A limit, however, is related to a lack of reproducibility of measures because of the need for the patient’s cooperation [28]. However, if this limitation was not observed in our study, it was likely due to the exclusion criteria, to the relatively young age of the patients and to the myopic status, which is associated as so as to enhance near visual acuity.

The MPD was also found to significantly decrease with age, with a slope coefficient −0.0048 (P = 0.033). This result was not observed in the PIMAVOSA study, an observational study of healthy participants aged 20 to 60 years [12]. Indeed, there was no difference in terms of MPD between the 20–39 and the 40–60 groups in the PIMAVOSA study. However, the study population was different and the statistical approach, which was non-linear, differs from ours. Considering the scope of AMD, POLA study showed that high plasmatic levels of lutein and zeaxanthin were associated with a reduced risk of early AMD [29]. Furthermore, an in vitro study of the eyes of either healthy and AMD donors showed that eyes with high rates of lutein and zeaxanthin had reduced risk of AMD compared to eyes with lower rates of MP [OR = 0.18; 95% CI: 0.05–0.64] [11]. In LAST II, MPD measured by heterochromatic flicker photometry in atrophic AMD significantly increased to 0.3 (P = 0.017) in the group with lutein supplementation with MPD ≤ 0.3 at baseline [30]. The protective effect of lutein and zeaxanthin being demonstrated in AMD, it would be interesting to investigate the effect of dietary supplementation with lutein and zeaxanthin on the progression of myopic maculopathy. However, confirmation of these preliminary results is needed before organizing multicentric interventional prospective clinical trials aimed at demonstrating a potential protective effect on the progression of myopic maculopathy.

![Distribution of macular pigment optical density (MPD)](image)

**Figure 2.** Distribution of macular pigment optical density (MPD) in high myopic eyes; MPD in the whole population of high myopic eyes: 0.61 ± 0.21. a: MPD in eyes without lacquer crack: 0.63 ± 0.21; b: and MPD in eyes with lacquer crack: 0.52 ± 0.22 with P = 0.042.

The present study, with a slope coefficient of linear regression of −0.24 (P = 0.014). Different studies have investigated the putative beneficial role of carotenoids on improvement of visual performances, visual comfort, photostress recovery and disability glare [17–21]. This second property of macular pigments is mediated through attenuation of chromatic aberrations and light scattered through its short wave light-filtering properties [22]. We should acknowledge that other aspects of visual performance have not been investigated in our study, such as contrast sensitivity, color vision, glare disability, photostress recovery and critical flicker fusion frequency. Indeed, the primary objective of our study was to investigate the relationship between MPD and LC and not to investigate visual function and its relationship with MPD. Visual performance has been more widely prospectively investigated in a placebo-controlled, randomized, oral supplementation with a formulation containing lutein in normal subjects and negative results were obtained [23].
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**Figure 3.** Relationship between macular pigment optical density (MPOD) and age. A linear decrease of MPOD with age is observed with a slope coefficient $b \pm$ standard error: $b = -0.0048 \pm 0.0021 (P = 0.033)$.

**Figure 4.** Relationship between macular pigment optical density and visual acuity in LogMar. Slope coefficient $b \pm$ standard error $= -0.24 \pm 0.094 (P = 0.014)$.

**Conclusion**

In conclusion, this study focusing on MPOD in high myopic patients with or without lacquer crack showed that lower MPOD was more frequently observed in high myopic eyes with lacquer cracks. If duplicated, carotenoid pigment dietary supplementation could make sense as a means of reducing the risk of lacquer crack in high myopic patients.

**Disclosure of interest**

The authors declare that they have no competing interest.

**References**

Macular pigment optical density and lacquer crack in high myopia


