Effects of Lutein Supplementation on Macular Pigment Optical Density and Visual Acuity in Patients with Age-Related Macular Degeneration

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PURPOSE. There is evidence from several large-scale clinical trials that reduced intake of lutein, a major component of the macular pigment, is a risk factor for the development of AMD. In the present study (LISA; Lutein Intervention Study Austria) it was hypothesized that lutein supplementation increases macular pigment optical density (MPOD). In addition, an investigation was conducted into whether lutein supplementation improves visual acuity (VA) and macular function (mean differential light threshold; MDLT), as assessed with microperimetry.

METHODS. One hundred twenty-six patients with AMD (AREDS [Age-related Eye Disease Study] stages 2, 3, and 4) were included in this randomized (2:1), placebo-controlled, double-masked parallel group study. Lutein or placebo was administered for 6 months. MPOD was measured with a custom-built reflectometer. VA was assessed with ETDRS (Early Treatment Diabetic Retinopathy Study) charts, and MDLT was assessed with a microperimeter.

RESULTS. Lutein significantly increased MPOD by 27.9% ± 2.9% (P < 0.001 versus placebo). No significant effect of lutein supplementation on MDLT or VA was seen, although a tendency toward an increase was seen for both parameters (MDLT, P = 0.096 versus placebo; VA, P = 0.070 versus placebo). A significant correlation was found, however, between the increase in MPOD after 6 months and the increase in MDLT after 6 months (r = 0.25, P = 0.027), as well as between the increase in MPOD after 6 months and the increase in VA after 6 months (r = 0.27, P = 0.015).

CONCLUSIONS. The present study demonstrates that lutein supplementation increases MPOD, as assessed with an objective method. The correlation between the change in MPOD and the change in VA and MDLT indicates that patients who show a pronounced increase in MPOD also benefit in terms of visual function.

Genetic and environmental risk factors for age-related macular degeneration (AMD) have been identified.1–5 On the basis of the risk factor profile, oxidative stress has been implicated in the pathogenesis of the disease related to low-grade inflammation and hypoxia in the outer retina.5,6 This notion is compatible with the idea that low macular pigment optical density (MPOD) is a risk factor for the disease, because the natural components of the macular pigment, lutein and zeaxanthin, show potent antioxidative properties.7

Indeed, data from several large-scale studies, including the Carotenoids in Age-Related Eye Disease Study (CAREDS), the Blue Mountain Eye Study, and the Age-Related Eye Disease Study (AREDS), indicate that low dietary intake of the carotenoids lutein and zeaxanthin is related to the risk of AMD.8–10 On the other hand, the CAREDS study did not find a consistent cross-sectional association between MPOD and AMD.11 Measurement of MPOD is difficult, and up to now, no gold standard method for the objective measurement of MPOD has been developed.12 Most of the studies that investigated whether the intake of lutein and/or zeaxanthin increases MPOD were based on measurements using flicker photometry.15–16 Flicker photometry, however, is a subjective method and several limitations of this technique have been identified.17 Another study (Lutein Nutrition Effects Measured by Autofluorescence; LUNA) used an autofluorescence-based method for studying the effect of lutein/zeaxanthin on MPOD, but this was an open trial without placebo control.18

In the present study, we used a spectroscopic technique,19 to assess the effects of a 6-month lutein supplementation on MPOD in patients with AMD. We hypothesized in a double-masked, placebo-controlled, parallel-group trial that lutein supplementation for 6 months increases MPOD, as assessed with an objective method. In addition, we studied the effects on visual acuity (VA) measured with Early Treatment Diabetic Retinopathy Study (ETDRS) charts and on macular function determined by microperimetry.

MATERIALS AND METHODS

Subjects

One hundred twenty-six patients with AMD were included in the trial (LISA: Lutein Intervention Study Austria). Approval from the Ethics Committee of the Medical University of Vienna was obtained, and the study was performed in compliance with the tenets of the Declaration of Helsinki. The nature and possible consequences of the study were explained, and all subjects gave written informed consent to participate. Each subject passed a screening that included a full ophthalmic examination. Patients with either categories 2, 3, or 4, according to the AREDS criteria were included in the study.20 Further inclusion criteria were age between 50 and 90 years, clear nonlenticular ocular media,
and a VA > 0.4. All patients were naive to previous lutein and/or zeaxanthin administration. Exclusion criteria were primary retinal pigment epithelium atrophy >125 μm, moderate or severe nonproliferative diabetic retinopathy, proliferative diabetic retinopathy, participation in a clinical trial in the 3 weeks preceding the study, ocular surgery within the last 6 months, and a history of treatment with photosensitizing drugs.

A sample size calculation was performed before the study, assuming a dropout rate of a maximum of 20%. Accordingly, we assumed that at least 66 patients in the lutein group and 33 patients in the placebo group were going to finish the trial. The calculation was based on a priori assumptions of group were going to finish the trial. The calculation was based on a statistical power of 80% (type I error) and -1) to detect a 4% difference in MPOD between patients receiving lutein and those receiving placebo. Differences in MPOD smaller than 4% were considered clinically irrelevant.

**Study Protocol**

The study followed a randomized, double-masked, placebo-controlled, parallel-group design in patients with AMD. The randomization of lutein (Lutamax DUO; Pharmaselect, Vienna, Austria) versus placebo was 2:1, resulting in a total of 84 patients in the lutein group and 42 patients in the placebo group. The dosage in months 1 to 3 was 20 mg once daily and in months 4 to 6 was 10 mg once daily.

A screening day (visit 0) was scheduled a maximum of 4 weeks before inclusion in the study, but in most patients, a very short period passed between the screening visit and visit 1. All patients underwent a prestudy screening, including a physical examination and medical history, measurement of height and weight, blood pressure and pulse rate, and a full ophthalmic examination including optical coherence tomography (OCT). In each subject only one eye was selected for inclusion. If both eyes were eligible, one eye was selected randomly.

Baseline measurements of MPOD were performed on the first study day (visit 1). In addition, VA using ETDRS charts, intraocular pressure (IOP), and systemic blood pressure and pulse rate were assessed; microperimetry examination was performed; and a fundus photograph of the study eye centered on the macula was taken. On the morning of the next day, the subjects started the lutein or placebo intake. MPOD, VA, macular function, scanning laser scotometry, IOP, and systemic hemodynamic parameters were again measured 1, 3, and 6 months (visits 2–4) after the start of therapy. At the 6-month visit, fundus photographs were taken again.

All subjects were asked to bring their study medication to all visits, to allow compliance testing by tablet counting.

**Methods**

**AREDS Staging.** Staging was done as outlined in AREDS report 8. Only eyes with AREDS stages 2 to 4 with no choroidal neovascularization (CNV) in the study eye were included in the present trial. This staging was based on the fundus photographs taken at the baseline visits.

**Macular Pigment Optical Density.** Spectral fundus reflectance was measured with a custom-built densitometer, as described previously. For this purpose, an apparatus for measurement of foveal reflectance versus position on a horizontal section of the pupil plane was used. An illumination field of ~2° centered at the fovea was used. To obtain an estimate of MPOD, spectral reflectance was measured on the perpendicular and the oblique. An optic model of fovea reflection can be used to measure MPOD.

**Visual Function.** Microperimetry was performed (Microperimeter MP-1; Nidek Technologies, Padova, Italy) with a fundus-controlled device including an eye-tracking system that allows for fully automated assessment of central macular sensitivity. Furthermore, a delineation of absolute scotoma was performed. The stimulation pattern consisted of 41 stimulation loci covering the central area of 12° × 12°. The stimulus-size was Goldmann III, presented for a time-interval of 200 ms. The background color was white, and the background luminance was 1.27 cd/m². Differential threshold values were obtained with a 4-2-1 staircase strategy. A red 3° cross was used as the fixation mark. If the patient was unable to identify the 3° cross, the size was increased in 1° steps until stable fixation was achieved. A custom-developed software program was used to automatically transfer retinal sensitivity values for evaluation of mean retinal sensitivity (mean differential light threshold, MDLT).

**Blood Pressure and Pulse Rate.** Systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were measured on the upper arm by an automated oscillometric device (HP-CMS patient monitor; Hewlett Packard, Palo Alto, CA). PR was automatically recorded from a finger pulse oximeter (HP-CMS patient monitor; Hewlett Packard).

**Intraocular Pressure.** A slit-lamp–mounted Goldmann application tonometer was used to measure IOP. Before each measurement, 1 drop of 0.4% benoxinate hydrochloride combined with 0.25% fluorescein sodium was used for local anesthesia of the cornea.

### Table 1. Characteristics of the Patients at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>71.6 ± 8.6</td>
</tr>
<tr>
<td>Sex, male/female</td>
<td>50/66</td>
</tr>
<tr>
<td>AREDS staging, 2/3/4</td>
<td>50/25/43</td>
</tr>
<tr>
<td>MPOD</td>
<td>0.35 ± 0.10</td>
</tr>
<tr>
<td>MDLT, dB</td>
<td>71.6 ± 8.6</td>
</tr>
<tr>
<td>VA, %</td>
<td>83.9 ± 6.0</td>
</tr>
<tr>
<td>SBP, mm Hg</td>
<td>142.0 ± 16.8</td>
</tr>
<tr>
<td>DBP, mm Hg</td>
<td>70.3 ± 11.2</td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>94.1 ± 10.5.6</td>
</tr>
<tr>
<td>PR, beats/min</td>
<td>73.0 ± 11.8</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>14.0 ± 2.7</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.
follow-up in the placebo group the last observation was also carried forward. The tablet count showed that, in 99 patients, the remaining tablets were within ±10% of the expected number. In the remaining 17 patients, the count was between ±10% and ±20% of the expected number.

Figure 1 shows the effects of lutein or placebo on MPOD, MDLT, and visual acuity. The effect of lutein supplementation on MPOD was highly significant versus placebo (P < 0.001). After 6 months, MPOD increased by 27.9% ± 2.9% in the lutein group, whereas almost no change was seen in the placebo group (0.7% ± 5.9%). An increase in MPOD in the lutein group was already seen after 1 month of supplementation, although a continuous increase was observed until the end of the study period. Subgroup analysis revealed that the change in MPOD was equally seen in all AREDS subgroups (Fig. 2: P = 0.31).

The effect of lutein supplementation on MDLT was not significant, but a tendency toward an improvement was seen after 6 months of lutein supplementation (7.3% ± 13.2%; P = 0.096 versus placebo). The effect on VA was also not significant, although a tendency toward an increase was again seen in the lutein group (P = 0.07 versus placebo). The effect was small, however, with an increase of 2.1 ± 0.4 letters in the lutein group after 6 months. As shown in Table 2 neither lutein supplementation nor placebo had an effect on blood pressure, pulse rate, or IOP.

Given that placebo intake did not change MPOD, the correlation analysis was performed only for the patients in the lutein group. Figure 3 shows the association between the percentage of change in MPOD after 6 months and MPOD at baseline (r = −0.46, P < 0.001). It clearly reveals that the lower the MPOD at baseline, the greater the increase after 6 months of lutein intake. Figure 4 shows the association between the percentage of change in MPOD after 6 months and the change in MDLT after 6 months. A significant positive correlation was found, although it was weak (r = 0.25, P = 0.027). Figure 5 shows the association between the percentage of change in MPOD after 6 months and the change in VA after 6 months. Although we did not observe a significant increase in VA in the lutein group, there was a significant correlation between the percentage of change in MPOD after 6 months and the change in VA acuity after 6 months (r = 0.27, P = 0.013).

**RESULTS**

The baseline characteristics of the study population are shown in Table 1. In one subject, no measurements of MPOD could be obtained, and the data of this patient were not included in the analysis. Nine additional subjects appeared only at the baseline visit and were also not included in the analysis. In the lutein group five patients were lost to follow-up after the 1-month visit, and five patients were lost to follow-up after the 3-month visit. In two subjects, the withdrawal was due to serious adverse events. One subject had a myocardial infarction, and the other subject developed CNV in the study eye. In all 10 subjects, the last observation was carried forward. In the placebo group, two patients were lost to follow-up after the 1-month visit, and four patients were lost after 3 months. Of those patients, one developed CNV, which was again classified as a serious adverse event. In the six patients who were lost to

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**Table 2. Effects of Lutein Supplementation or Placebo on MAP, PR, and IOP**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1 Month</th>
<th>3 Months</th>
<th>6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lutein group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>93.0 ± 10.7</td>
<td>91.2 ± 9.4</td>
<td>91.5 ± 9.7</td>
<td>90.8 ± 9.2</td>
</tr>
<tr>
<td>PR, beats/min</td>
<td>72.2 ± 11.5</td>
<td>71.7 ± 12.1</td>
<td>71.8 ± 11.3</td>
<td>70.5 ± 12.5</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>13.8 ± 2.6</td>
<td>13.7 ± 2.6</td>
<td>13.7 ± 2.1</td>
<td>13.9 ± 3.1</td>
</tr>
<tr>
<td><strong>Placebo group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MAP, mm Hg</td>
<td>94.3 ± 10.3</td>
<td>91.5 ± 10.0</td>
<td>93.8 ± 12.9</td>
<td>93.3 ± 11.0</td>
</tr>
<tr>
<td>PR, beats/min</td>
<td>74.7 ± 12.5</td>
<td>71.5 ± 11.8</td>
<td>71.1 ± 12.3</td>
<td>75.6 ± 13.3</td>
</tr>
<tr>
<td>IOP, mm Hg</td>
<td>14.5 ± 2.8</td>
<td>14.5 ± 2.4</td>
<td>14.2 ± 2.2</td>
<td>14.4 ± 2.1</td>
</tr>
</tbody>
</table>

Data are presented as means ± SD.
level of significance. Nevertheless, a significant association between the change in MPOD and the change in both VA and MDLT was found. This result indicates that patients with a pronounced increase in MPOD also improved in their visual function.

In recent years, evidence has accumulated that AMD patients have reduced MPOD, although not all studies have found a significant difference between patients and healthy controls. In the AREDS it was shown that low dietary intake of lutein and zeaxanthin is associated with an increased likelihood of having large or extensive intermediate drusen, neovascular AMD, and geographic atrophy. In addition, reduced MPOD has been linked to several risk factors for AMD, including increased age, smoking, family history of AMD, light iris color, and obesity. No study so far, however, has proven that supplementation with lutein and/or zeaxanthin is capable of reducing the incidence or progression of AMD. Our study cannot elucidate this question, because neither the sample size nor the observation period was sufficient to obtain such data.

The effects of lutein on visual performance have been attributed to a reduction of chromatic aberration as well as to a preferential absorption of blue haze through the atmosphere. In the recent years evidence has accumulated that supplementation may also increase ERG responses in AMD patients. It has been shown that 180 days of supplementation with lutein, vitamin E, and nicotinamide in early AMD improves the focal ERG, indicating an effect on preganglionic macular elements. In the Carotenoids and Antioxidant in Age Related Maculopathy Italian Study (CARMIS), oral daily supplementation of vitamin C (180 mg), vitamin E (30 mg), zinc (22.5 mg), copper (1 mg), lutein (10 mg), zeaxanthin (1 mg), and astaxanthin (4 mg) improved multifocal ERG measures in the central, but not in the peripheral retina. These results may relate to the antioxidant properties of lutein, which are also supported by our results employing microperimetry.

The present study has several strengths. These include the relatively high number of patients; the randomized, double-masked, placebo-controlled design; and the objective method of measuring MPOD, which minimizes observer bias. Nevertheless, reflectometric measurement shows good correlation with other techniques, and the levels of MPOD obtained in the present study are in good agreement with those observed in previous experiments. A limitation of the present study is that plasma lutein was not measured. As such, we cannot rule out that those patients who had little increase in MPOD showed low adherence to the study medication. We deem this unlikely, however, because tablet count indicated good compliance and a significant association between baseline MPOD and the percentage change in MPOD after 6 months was seen.

In the present study, subjects who had lower MPODs at baseline showed a more pronounced increase in MPOD. This result is in keeping with data from the LUNA study, where MPOD was measured using autofluorescence. The reason for this remains unclear, but may simply be related to the usual dietary intake of these subjects. Since in the present study no food intake questionnaire was used, we cannot answer this question conclusively. In fact the data presented in Figure 3 indicate that patients who had baseline MPODs of 0.5 or higher showed almost no increase in MPOD during lutein supplementation, although the scattering of data was high. The data do indicate that lutein incorporation in the retina is saturable. This finding is in good agreement with the recent discovery of a member of the steroidogenic acute regulatory domain (STARD) family as a lutein-binding protein, which is saturable.

FIGURE 3. Correlation between MPOD at baseline and the change in MPOD after 6 months of lutein supplementation.

FIGURE 4. Correlation between the change in MPOD and the change in MDLT after 6 months of lutein supplementation.

FIGURE 5. Correlation between the change in MPOD and the change in VA after 6 months of lutein supplementation.
In conclusion, the present study demonstrates that lutein supplementation increases MPOD, as assessed with an objective method in patients with nonexudative AMD. Compared with placebo, no effect was seen on VA or visual function. Nevertheless, there was a significant correlation between the lutein-induced increase in MPOD and the change in VA and MDLT, indicating that patients who have pronounced increase in MPOD during lutein administration also benefit in terms of visual function.

References