

ders, even in the absence of visual loss.^{18–19} Furthermore, although the concentrations of lutein and zeaxanthin peak in the central fovea, zeaxanthin is the dominant carotenoid at this location. This specific distribution of the xanthophyll carotenoids suggests that zeaxanthin may play an essential role in the center of the retina; but until recently, the research specifically concerning the efficacy of zeaxanthin is still limited.^{20–21}

Therefore, we conducted a randomized, double-masked, placebo-controlled trial to investigate the effects of 48-week supplementation with lutein and zeaxanthin on retinal function by mfERG in a group of community-dwelling patients with early AMD.

METHODS

• **STUDY POPULATION:** Recruitment was directed to subjects with probable AMD, aged 50 to 79 years, from the local communities and from congregate living sites in Beijing. All study candidates underwent standard general and ophthalmic examination to screen for study eligibility. Clinical diagnosis of early AMD was established by slit-lamp examination and ophthalmoscopy using a Goldmann noncontact lens, as well as color fundus photograph (Exwave HAD 3CCD; Sony Electronics Inc, Park Ridge, New Jersey, USA) after pupillary dilation using 0.5% tropicamide and 0.5% phenylephrine (Santen Pharmaceutical Co. Ltd, Osaka, Japan), when either of the following lesions in the macular area of at least 1 eye was identified: soft distinct or indistinct drusen; or areas of retinal pigmentary abnormalities, without the presence of signs of late AMD. The AMD was independently classified by 2 masked ophthalmologists in accordance with the Age-Related Eye Disease Study (AREDS) classification and grading system.²²

Subjects were excluded if they had late AMD (choroidal neovascularization or geographic atrophy), unstable chronic illness, or eye disorders other than macular degeneration, including macular edema, macular holes, central serous chorioretinopathy, or macular epiretinal membrane. We did not enroll subjects who had taken drugs known to affect visual function within 1 month prior to enrollment (eg, chloroquine or oxazepam). Subjects who were vegetarian or had a history of retina-vitreous surgery or photodynamic therapy were also ineligible.

One hundred eight participants with early AMD (mean age, 69.1 ± 7.4 years) met the study criteria and were included in the study; 107 completed 48 weeks of treatment. Thirty-six age-matched controls without AMD (defined as absence of soft drusen or pigmentary abnormalities; mean age, 68.0 ± 7.9 years) were also enrolled according to the same exclusion criteria used for early AMD patients.

• **STUDY DESIGN:** After enrollment, eligible participants with early AMD were randomly allocated to 1 of the 4 groups in a 1:1:1:1 ratio according to a list of computer-generated random numbers in sex-stratified blocks of 8. Participants, study and clinical center personnel, and the data analysts were unaware of the treatment allocation through study completion. Only the pharmacist technician, who was not involved in the recruitment or assessment of participants, had access to the randomization list. The different capsules were identical in size, weight, and color.

Participants were randomly assigned to receive placebo ($n = 27$), 10 mg of lutein ($n = 27$), 20 mg of lutein ($n = 27$), or 10 mg lutein plus 10 mg zeaxanthin ($n = 27$) once a day for 48 weeks. Adherence to treatment was evaluated by monthly interviewing of the patient and by capsule counts. All participants were requested to maintain their usual diet and to abstain from taking supplements containing carotenoids. Dietary intake was assessed at baseline using a validated 120-item food frequency questionnaire.

MfERGs and macular pigment optical density assessments were performed at baseline (week 0) and at 24 and 48 weeks after the initiation of treatment. The controls without AMD were given only a baseline examination.

• **MULTIFOCAL ELECTRORETINOGRAMS:** MfERGs were recorded using a RETIscan system (Version 3.21, Roland Consult, Inc, Brandenburg, Germany), according to the recommended guidelines of the International Society for Clinical Electrophysiology of Vision (ISCEV) for basic mfERG.^{23,24} Pupils of the patients were maximally dilated to a diameter more than 7 mm with 0.5% tropicamide and 0.5% phenylephrine (Santen Pharmaceutical Co, Ltd, Osaka, Japan) and the cornea was anesthetized with 0.4% oxybuprocaine hydrochloride (Santen Pharmaceutical Co, Ltd). Retinal signals were acquired with a bipolar contact lens electrode (Hansen Ophthalmic, Coralville, Iowa, USA) filled with carboxymethylcellulose sodium (Refresh Celluvisc; Allergan Inc, Irvine, California, USA).

The stimulus consisted of 103 hexagonal elements presented on the CRT display with a frame rate of 75 Hz. Each hexagon was alternated pseudorandomly between white (200 cd/m^2) and black (less than 1.0 cd/m^2) according to a standard m-sequence. The recordings were performed under room light conditions, and a red central cross was presented for fixation. In each video frame, each stimulus element had an equal probability of being white or black, maintaining the overall mean luminance of the stimulus display at a fairly constant value. Retinal signals were band-pass filtered from 10 to 300 Hz, amplified 100 000 times, and sampled at 1200 Hz. Each recording consisted of 16 segments and was approximately 8 minutes long. During the test, the patient fixated on a small circle in the central hexagon. Recording quality was monitored

by observation of the real-time signal voltage. Recording segments contaminated by either electrical artifacts or loss of fixation were rejected and repeated.

The mfERG responses for the hexagons across the retina were separated into 6 concentric rings (rings 1 to 6) for data analysis. The response amplitudes in each ring were measured between the first negative trough (N1) and the first positive peak (P1), yielding the N1P1 response densities (amplitudes per unit retinal area in nV/deg²). The P1 peak latencies (ms) of the positive waveform were also measured.

• **MACULAR PIGMENT OPTICAL DENSITY:** The measurement of macular pigment optical density was performed with a confocal scanning laser ophthalmoscope (Heidelberg Retina Angiograph; Heidelberg Engineering, Heidelberg, Germany) using autofluorescence images centered on the fovea.^{25,26} Subjects were positioned in front of the tabletop and asked to look straight ahead and to remain steady. After using infrared (IR) light, the 488-nm wavelength of light is used to excite autofluorescence. A series of autofluorescence images were obtained for the excitation wavelengths quickly before recovery. An average image was generated from these images using the system software. The center of the fovea was defined as the center of a Gaussian distribution. We quantified macular pigment optical density by calculation of the average image and comparison of foveal and parafoveal autofluorescence. The reproducibility and variability of this measurement technique had been previously reported.²⁶ The coefficients of variation were less than 5%.

• **SAMPLE SIZE AND STATISTICAL ANALYSES:** It was estimated that a total sample size of 108 participants provides 90% power to detect a 30% to 40% increase in N1P1 response densities between groups, with a significance level of .05 and a dropout rate of 10%.²⁷

The data were analyzed according to the intention-to-treat principle. The Kolmogorov-Smirnov test was used to determine if continuous variables were normally distributed. The significance of differences between the early AMD cases and controls was determined by the independent *t* test, or Mann-Whitney rank sum test where appropriate, for continuous data and the χ^2 test for categorical data. Correlations between macular pigment optical density and the mfERG values for the AMD cases at baseline were analyzed using the Pearson test. Baseline characteristics among 4 treatment groups were compared using analysis of variance (ANOVA) for continuous variables or the χ^2 test for categorical variables. Absolute changes for each outcome variable at 24 and 48 weeks were normally distributed for macular pigment optical density and the mfERG values. Within-group changes from baseline were assessed using the paired *t* test, and between-group differences in terms of change from baseline at each time point were tested by analysis of covariance (ANCOVA), with

TABLE 1. Comparison of Demographic and Clinical Characteristics in Patients With Early Age-Related Macular Degeneration and in Controls

Variable	Study Group		P Value
	Controls (n = 36)	Early AMD Patients (n = 108)	
Mean age (SD), year	68.0 (7.9)	69.0 (7.4)	.46 ^a
Sex, n (% female)	21 (58.3)	63 (58.3)	>.99 ^b
Race (% Han people)	36 (100.0)	108 (100.0)	>.99 ^b
Current or past smoker, n (%)	3 (8.3)	13 (12.0)	.76 ^b
Dietary nutrient intake			
Vitamin A (SD), RE	0.75 (0.49)	0.72 (0.45)	.84 ^a
Vitamin C (SD), mg	81.9 (47.2)	83.0 (44.3)	.90 ^a
Vitamin E (SD), mg	7.4 (2.3)	7.5 (2.4)	.78 ^a
Zinc (SD), mg	7.6 (2.9)	8.0 (3.8)	.48 ^a
β -carotene (SD), mg	3.5 (2.4)	3.5 (2.1)	.85 ^a
Lutein and zeaxanthin (SD), mg	2.6 (1.4)	2.6 (1.5)	.89 ^a
Lycopene (SD), mg	0.86 (0.70)	0.73 (0.66)	.15 ^a
N1P1 response densities, nV/deg ²			
Ring 1 (SD)	85.7 (36.7)	67.4 (28.5)	.002 ^a
Ring 2 (SD)	48.7 (17.5)	40.5 (14.0)	.005 ^a
Ring 3 (SD)	33.3 (9.2)	28.7 (10.1)	.02 ^a
Ring 4 (SD)	22.7 (6.1)	20.9 (6.9)	.16 ^a
Ring 5 (SD)	16.4 (4.9)	15.0 (5.0)	.15 ^a
Ring 6 (SD)	12.6 (4.1)	11.4 (4.0)	.15 ^a
P1 peak latencies, ms			
Ring 1 (SD)	38.9 (6.4)	40.3 (5.8)	.26 ^a
Ring 2 (SD)	37.7 (3.0)	37.7 (3.4)	.97 ^a
Ring 3 (SD)	36.0 (3.2)	36.2 (2.7)	.57 ^a
Ring 4 (SD)	35.2 (1.9)	35.8 (3.0)	.23 ^a
Ring 5 (SD)	35.5 (2.1)	35.9 (3.3)	.49 ^a
Ring 6 (SD)	35.6 (1.7)	36.5 (3.4)	.12 ^a
MPOD (SD), DU	0.33 (0.16)	0.31 (0.13)	.53 ^a

AMD = age-related macular degeneration; DU = density unit; MPOD = macular pigment optical density; RE = retinol equivalent; SD = standard deviation.

^aBased on independent *t* test.

^bBased on χ^2 test.

age, sex, smoking, and baseline values included as covariates. The least significant difference procedure was used for multiple pairwise comparisons. Furthermore, overall significance of differences in changes over time was evaluated by repeated-measures ANOVA with time and treatment effects and their interactions, with age, sex, smoking, and baseline values included as covariates. The relationships between change in macular pigment optical density and change in mfERG responses were assessed using Pearson correlation analysis because these 2 variables follow a bivariate normal distribution. All analyses were performed using SPSS statistical software version 11.0 (SPSS Inc, Chicago, Illinois, USA).

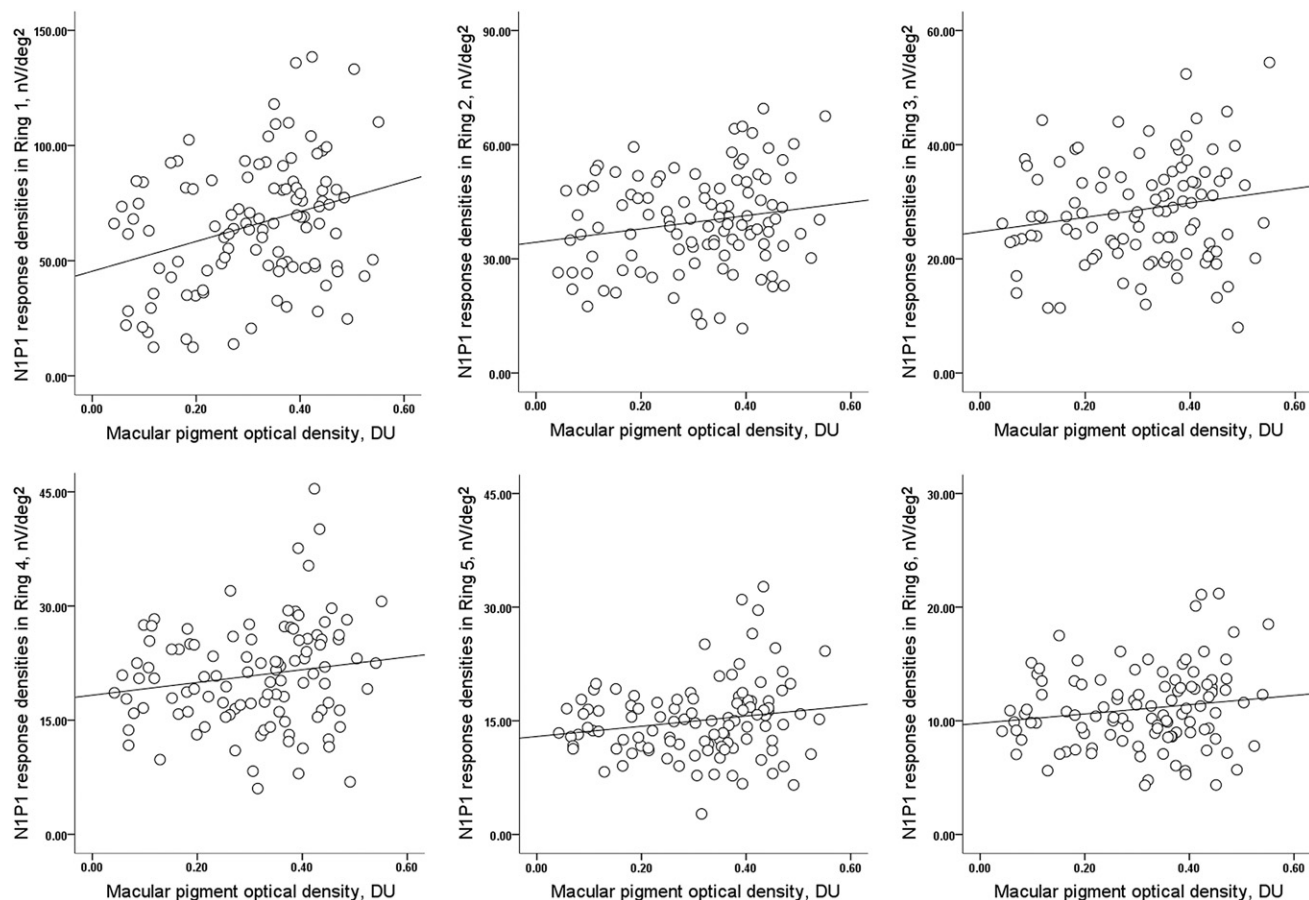


FIGURE 1. Scatterplots showing the correlation between macular pigment optical density and N1P1 response densities in 6 rings for all patients with early age-related macular degeneration before lutein and zeaxanthin supplementation. Statistical analyses were performed by Pearson correlation as these 2 variables follow a bivariate normal distribution. (Top left) Ring 1, $r = 0.31$, $P < .001$. (Top middle) Ring 2, $r = 0.18$, $P = .06$. (Top right) Ring 3, $r = 0.16$, $P = .09$. (Bottom left) Ring 4, $r = 0.16$, $P = .10$. (Bottom middle) Ring 5, $r = 0.18$, $P = .07$. (Bottom right) Ring 6, $r = 0.15$, $P = .12$.

TABLE 2. Baseline Demographic Characteristics of Patients With Early Age-Related Macular Degeneration in the 4 Treatment Groups

Variable	Placebo (n = 27)	10 mg Lutein (n = 26)	20 mg Lutein (n = 27)	Lutein and Zeaxanthin (n = 27)	P Value
Mean age (SD), y	68.9 (7.6)	69.9 (8.4)	69.0 (6.8)	68.6 (7.0)	.94 ^a
Sex, n (% female)	16 (59.3)	16 (61.5)	15 (55.6)	15 (55.6)	.96 ^b
Race (% Han people)	27 (100.0)	26 (100.0)	27 (100.0)	27 (100.0)	>.99 ^b
Current or past smoker, n (%)	3 (11.1)	3 (11.5)	3 (11.1)	4 (16.7)	.97 ^b

^aBased on analysis of variance.

^bBased on χ^2 test.

RESULTS

THE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS OF patients with the early AMD cases and of controls are shown in Table 1. The mean age of the participants was 68.8 years (SD 7.5 years; range 49–79 years). Of the 144 total participants, 84 (58.3%) were female. There was no significant difference in demographic characteristics be-

tween early AMD patients and controls. The patients with early AMD had lower N1P1 response densities in ring 1 than controls without AMD ($P < .01$). Significant differences in N1P1 response densities in ring 2 and ring 3 between groups were still present, but the magnitude of differences was diminished. The difference in N1P1 response densities in ring 4 to ring 6 was no longer significant between case and control groups. No statistically signifi-

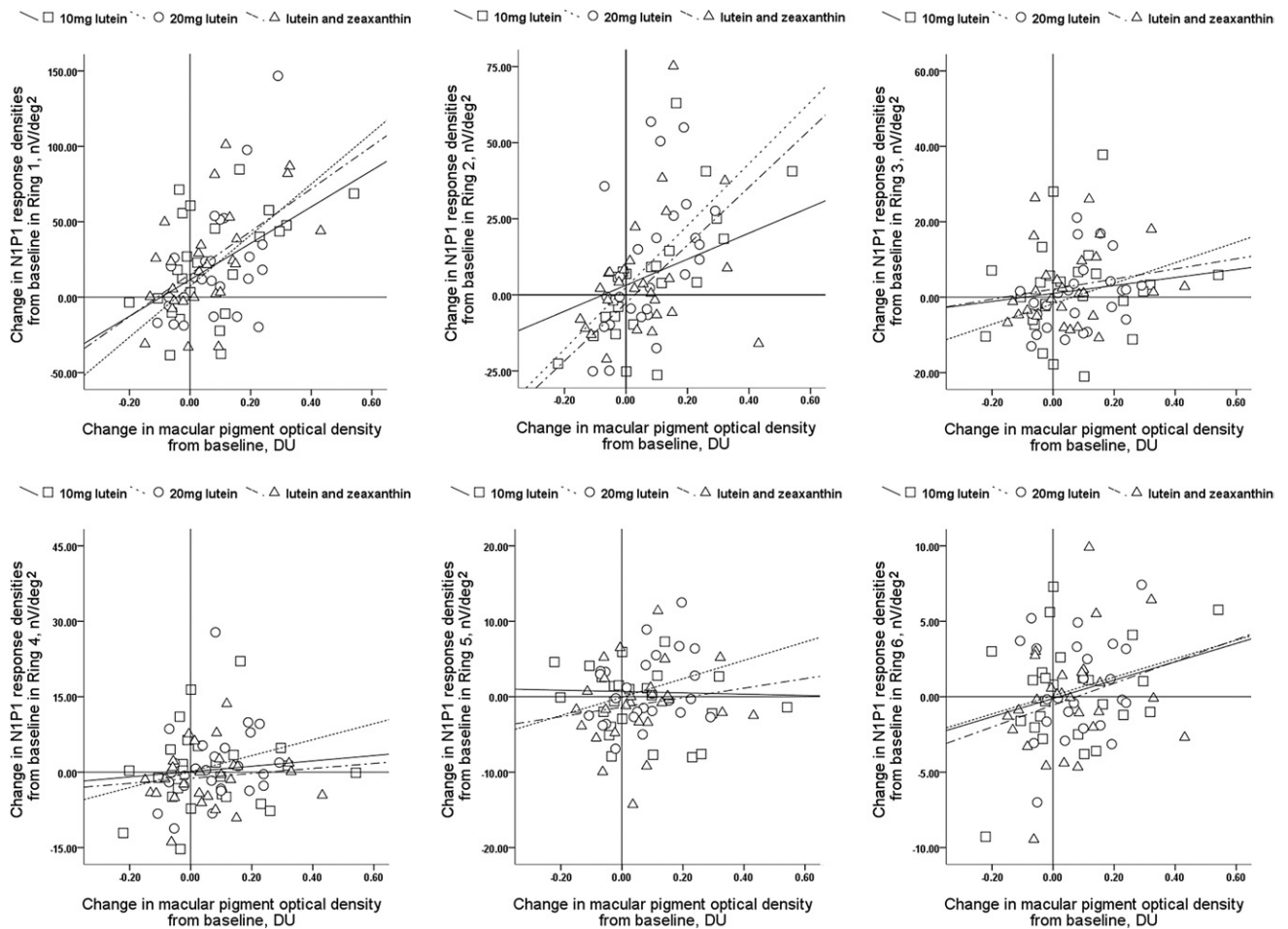


FIGURE 2. Bar graphs showing the change in N1P1 response densities in (Top left) ring 1, (Top right) ring 2, (Middle left) ring 3, (Middle right) ring 4, (Bottom left) ring 5, and (Bottom right) ring 6 for 4 treatment groups of patients with early age-related macular degeneration after lutein and zeaxanthin supplementation. *Statistically significant ($P < .05$, analysis of covariance with age, sex, smoking, and baseline values included as covariates, followed by least significant difference test to compare the differences between the groups). Error bars indicate standard error of the mean.

cant differences were found between these 2 groups in macular pigment optical density or P1 peak latencies. N1P1 response densities in ring 1 were highly associated with macular pigment optical density for early AMD at baseline (Pearson $r = 0.31$; $P < .001$), whereas N1P1 response densities in ring 2 to ring 6 were not related to macular pigment optical density (Figure 1). In addition, we found no significant relationships between the P1 peak latencies and macular pigment optical density for early AMD.

The baseline demographic characteristics of patients in the 4 treatment groups are summarized in Table 2. There were no significant between-group differences in any baseline demographic or clinical variables. The changes from baseline in N1P1 response densities over time are shown in Figure 2. During the first 24 weeks, all active treatment groups increased N1P1 response densities in ring 1, although this did not reach statistical significance in the 10 mg lutein group. An ANCOVA analysis showed partici-

pants assigned to the 20 mg lutein group had a much greater increase compared with the placebo group (0.3 vs 20.3; between-group difference, 19.9; 95% confidence interval [CI], 0.03–39.6; $P < .05$). After 48 weeks, N1P1 response densities in ring 1 showed a mean (standard error [SE]) increase of 18.0 (7.5) in the 10 mg lutein group, an increase of 22.4 (7.4) in the 20 mg lutein group, and an increase of 23.5 (6.9) in the lutein and zeaxanthin group (all $P < .05$), with maintenance in the placebo group. The changes in N1P1 response densities in ring 1 for the 20 mg lutein group (22.4 vs -0.3 ; between-group difference, 22.7; 95% CI, 3.1–42.3; $P = .02$) and the lutein and zeaxanthin group (23.5 vs -0.3 ; between-group difference, 23.8; 95% CI, 4.2–43.4; $P = .02$) were significantly greater than those for the placebo group. Results of repeated-measures ANOVA showed that lutein and zeaxanthin supplementation had both the significant treatment effect ($P = .02$) and the significant time effect ($P < .001$) on improving N1P1 response densities in ring 1. N1P1 re-

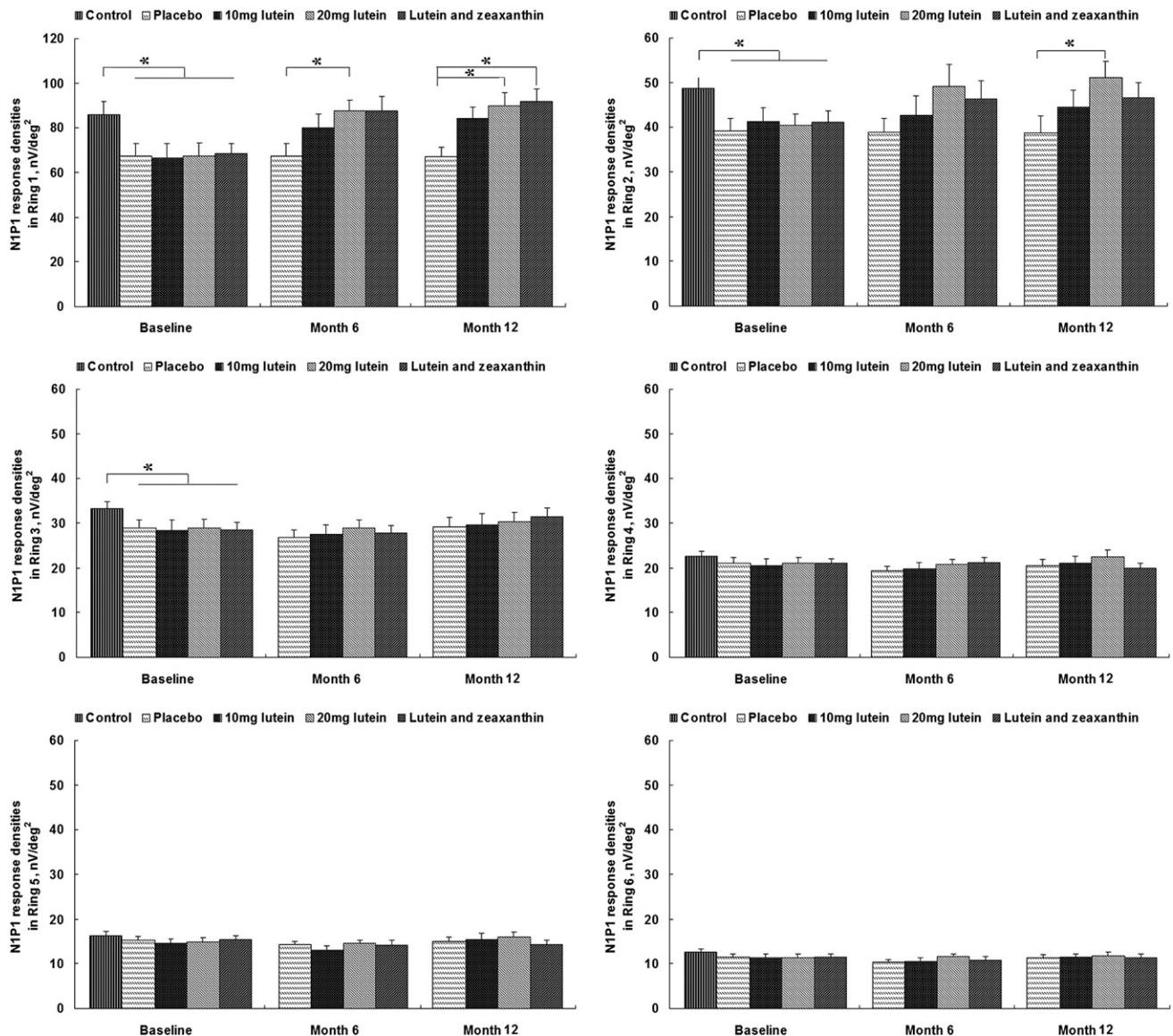


FIGURE 3. Scatterplots showing the correlation between change in macular pigment optical density and change in N1P1 response densities in 6 rings for 3 active treatment groups of patients with early age-related macular degeneration after 48-week lutein and zeaxanthin supplementation. Statistical analyses were performed by Pearson correlation as these 2 variables follow a bivariate normal distribution. (Top left) Ring 1, $r_{10 \text{ mg lutein}} = 0.54, P = .005$; $r_{20 \text{ mg lutein}} = 0.51, P = .008$; $r_{\text{lutein and zeaxanthin}} = 0.56, P = .003$. (Top right) Ring 2, $r_{10 \text{ mg lutein}} = 0.30, P = .13$; $r_{20 \text{ mg lutein}} = 0.51, P = .008$; $r_{\text{lutein and zeaxanthin}} = 0.53, P = .006$. (Middle left) Ring 3, $r_{10 \text{ mg lutein}} = 0.14, P = .50$; $r_{20 \text{ mg lutein}} = 0.34, P = .09$; $r_{\text{lutein and zeaxanthin}} = 0.18, P = .36$. (Middle right) Ring 4, $r_{10 \text{ mg lutein}} = 0.11, P = .60$; $r_{20 \text{ mg lutein}} = 0.24, P = .24$; $r_{\text{lutein and zeaxanthin}} = 0.12, P = .54$. (Bottom left) Ring 5, $r_{10 \text{ mg lutein}} = -0.02, P = .93$; $r_{20 \text{ mg lutein}} = 0.30, P = .13$; $r_{\text{lutein and zeaxanthin}} = 0.17, P = .40$. (Bottom right) Ring 6, $r_{10 \text{ mg lutein}} = 0.30, P = .15$; $r_{20 \text{ mg lutein}} = 0.21, P = .31$; $r_{\text{lutein and zeaxanthin}} = 0.27, P = .18$.

sponse densities in ring 2 also increased progressively over time in all active treatment groups; and significant within-group differences from baseline were only detected in the 20 mg lutein group (10.6; 95% CI, 1.7–19.5; $P < .05$) at week 48. The changes in N1P1 response densities in ring 2 for the 20 mg lutein group (10.6 vs -0.3 ; between-group difference, 10.9; 95% CI, 0.2–21.7; $P < .05$) had a significantly greater increase than those for the placebo group. A significant time effect ($P = .03$) with only a

tendency for a treatment effect ($P = .19$) was observed for N1P1 response densities in ring 2. Significant changes no longer existed in N1P1 response densities in ring 3 to ring 6 in the 4 groups. No significant differences were found between the groups with respect to changes in these N1P1 response densities.

Figure 3 shows the correlation between change in macular pigment optical density and change in N1P1 response densities in 6 rings for 3 active treatment groups

of patients with early AMD after 48-week supplementation. The change in macular pigment optical density was positively correlated with the changes in N1P1 response densities in ring 1 and in ring 2 for nearly all active treatment groups. No significant associations were found between the change in macular pigment optical density and the changes in N1P1 response densities in ring 3 to ring 6 ($P > .05$ for all).

In contrast with the significant changes in N1P1 response densities in central rings among the active treatment groups, we observed no significant changes in P1 peak latencies at various eccentricities in any group at any time point. The changes in macular pigment optical density were not related to the changes in P1 peak latencies in various rings over the study period.

DISCUSSION

IN THIS STUDY, WE FOUND THAT LUTEIN AND ZEAXANTHIN supplementation for patients with early AMD resulted in significant increases in N1P1 response densities in the central retina associated with early abnormalities of retinal function. Moreover, the improvement of N1P1 response densities was positively associated with the elevation of macular pigment optical density, suggesting a causative effect of macular pigment level on health of retinal function. These findings provided evidence that lutein and zeaxanthin might reverse the impairment in retinal function, and ultimately prevent the progression of AMD.

Early AMD is characterized by a deterioration of the retina that is associated with extracellular deposits forming yellow spots (drusen) on the retina under the macula and/or irregular focal hypopigmentations or hyperpigmentations.²⁸ Several lines of experimental and clinical evidence indicated that the retinal pigment epithelium cells became less efficient in the phagocytosis of photoreceptor outer segment tips with advancing age.^{29,30} The aging retina gradually accumulated fluorescent phototoxic chromophores, generally known as lipofuscin, which led to apoptosis of retinal pigment epithelial (RPE) cells and the formation of drusen. These changes in turn led to RPE cellular dysfunction and eventually resulted in the loss of central vision.^{31,32} In agreement with the results of previous studies, our study found that N1P1 response densities in central rings significantly decreased in early AMD patients compared with non-AMD controls, indicating the functional integrity of the macula had been compromised in early stages of AMD.^{33,34} On the contrary, there was only a trend toward decrease in macular pigment optical density in early AMD patients, suggesting that early AMD did not experience significant morphologic changes in macular pigment, when macular dysfunctions had occurred in the central retina. Therefore, it is conceivable that early detection and prompt treatment of AMD is more effective in promoting functional recovery of retina. In addition, the

decrease in macular pigment optical density may be responsible for the reduction of N1P1 response densities in the central retina, as a direct relationship was found between macular pigment optical density and N1P1 response densities in ring 1 in early AMD patients. These results are supported by experimental animal studies of carotenoid deprivation.³⁵ Monkeys raised on a xanthophyll-free diet showed a total loss of macular pigment that was accompanied by an increase in drusen-like bodies at the level of pigment epithelium.³⁵ In Japanese quails fed supplemental zeaxanthin, the number of apoptotic photoreceptors in light-damaged eyes was inversely correlated with retinal zeaxanthin concentration, and zeaxanthin supplementation for 6 months markedly decreased levels of light-induced photoreceptor apoptosis.^{36,37} This evidence confirms the hypothesis that macular pigment may prevent or retard some of the destructive processes that ultimately lead to photoreceptor death. Therefore, it is likely that the macular pigment optical density elevation produced by dietary intervention has a beneficial effect on retinal function.

Lutein and zeaxanthin are the major components of macular pigment, and reach their highest concentrations in the photoreceptor axon layer and the inner plexiform layer of the fovea.^{8,38} It comes as no surprise that lutein and zeaxanthin have beneficial effects on optimizing eye health, particularly for AMD patients. Past studies of lutein supplementation in AMD patients addressed its effect on preventing the loss of visual function and macular pigment optical density in general.^{15,17} Few supplementation trials that specifically focused on retinal function have been performed, especially in less well-nourished populations. Falsini and associates demonstrated that 180 days of supplementation with lutein, vitamin E, and nicotinamide in early AMD patients led to significant improvements in amplitude change of focal electroretinogram (F-ERG).³⁹ In the only previous study designed to examine the effect of carotenoid and antioxidant supplementation (including lutein) on mfERG responses, Parisi and associates administered placebo or carotenoids and antioxidants to 27 patients with nonadvanced AMD for 1 year, and indicated that significant increases in N1P1 response densities was observed in patients with AMD receiving active supplements.²⁷ As the supplementation regimen included many other carotenoids and antioxidants, the specific effects of any 1 component could not be assessed in these studies. In the current study, most vitamin, zinc, and carotenoid intakes of subjects were below the level of the Chinese Dietary Reference Intakes and the Third United States National Health and Nutrition Examination Survey (NHANES III); and none of the participants reported supplemental use of vitamins, zinc, or carotenoids. We found individuals assigned to receive lutein with or without zeaxanthin had significantly increased N1P1 response densities in central rings. The possible mechanism of action for this protective role may include powerful blue-

light filtering activities and antioxidant properties.^{8,40,41} Recently, evidence is accumulating to suggest that other mechanisms such as the stimulation of gap junction communications may be involved as well.^{42,43} Lutein and zeaxanthin have been shown to be an efficient inducer to enhance gap junction intercellular communication.⁴³ Increasing intake of these carotenoids could therefore improve signaling efficiency throughout the visual system. It had been observed that age-related declines in neuronal signal transduction could be reversed with dietary supplementation with lutein-rich foods in animal studies.⁴⁴ Furthermore, previous studies have suggested that supplementation with lutein and zeaxanthin may result in a measurable increase in macular pigment optical density.^{14,16} No study has yet measured macular pigment optical density and N1P1 response densities to confirm whether macular pigment actually improves retinal function. In the present study, significant associations were found between the change in macular pigment optical density and the changes in N1P1 response densities in the central retina for nearly all active treatment groups after 48-week supplementation, suggesting a causative role of structural integrity of the macula for maintenance of the normal retinal function. Our finding also supported the hypothesis that increased macular pigment level by supplementation with lutein and zeaxanthin might potentially produce beneficial changes in retinal function at early stages of AMD.

It should be noted that combination supplementation with zeaxanthin and lutein might improve N1P1 response densities in the foveal area more effectively, even compared to high-dose lutein supplementation. This was presumably because of the specific distribution characteristics of these carotenoids in the retina. The macular pigment mainly consists of the 3 carotenoids, lutein, zeaxanthin, and meso-zeaxanthin.^{45,46} Zeaxanthin is the dominant component and reaches its maximum at the center of the fovea, where the lutein-to-zeaxanthin ratio reaches a minimum, suggesting that zeaxanthin may play some essential roles in the fovea.^{20,45,47} With increasing eccen-

tricity, zeaxanthin declines more rapidly than lutein, and lutein becomes the dominant carotenoid in the perifoveal areas. This was also consistent with our findings that the gain in N1P1 response densities in ring 2 was greater in the patients receiving high-dose lutein. Since macula pigment dramatically decreases with increasing radial distance from the fovea, and becomes undetectable in the peripheral retina, it may not be surprising that lutein and zeaxanthin supplementation in our population did not affect mfERG responses in peripheral retinal areas.^{20,48}

Although some studies demonstrated that implicit times were significantly longer in AMD patients compared with those who do not have AMD, we did not observe increases in P1 peak latencies in the patients with early AMD.^{49,50} In addition, the supplementation with lutein and zeaxanthin also did not lead to significant changes in P1 peak latencies in all rings. The early AMD patients with relatively mild impairment of retinal function in our study might not experience P1 peak latency delays in this time frame and this might explain the lack of a lutein and zeaxanthin treatment effect.

There were limitations to this research. First, given the highly selective inclusion criteria for participants in randomized trials, we were unable to examine whether the intervention was efficacious for a broader population, and our sample may therefore not be fully representative. Second, we cannot fully exclude the possibility of residual confounding attributable to incomplete adjustment or on the basis of some other variables not considered. Third, the trial length of 48 weeks may not be long enough to assess potential long-term effects on the risk of AMD progression; and further research is needed to evaluate the effect of these carotenoids on progression of AMD.

In conclusion, our results demonstrate that the combined supplementation with lutein and zeaxanthin is effective treatment against macular dysfunction in the central retina for early AMD patients. Additional larger studies, however, will be needed to validate our findings and should evaluate the long-term effects of lutein and zeaxanthin on reducing the risk of AMD progression.

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