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Augmentation of Macular Pigment following Implantation of Blue Light–Filtering Intraocular Lenses at the Time of Cataract Surgery

John M. Nolan,[1] Philip O'Reilly,[1] James Loughman,[2] Jim Stack,[1] Edward Loane,[1] Eithne Connolly,[1] and Stephen Beatty[1]

PURPOSE. (Photo)-oxidative stress is believed to play a role in the pathogenesis of age-related macular degeneration (AMD), with the threshold for retinal damage being lowest for short-wavelength (blue) light. Macular pigment (MP), consisting of the carotenoids lutein (L), zeaxanthin (Z) and *meso*-Z, has a maximum absorption at 460 nm and protects the retina from (photo)-oxidative injury. This study was designed to investigate whether the blue light–filtering properties of the Alcon Acry-Sof Natural intraocular lens (ANIOL) implanted during cataract surgery affects MP optical density (MPOD).

METHODS. Forty-two patients scheduled for cataract surgery were recruited for the study. These patients all had a preoperative best corrected visual acuity rating (BCVAR) of at least 0.5 (logMAR) in the study eye. The patients were randomized to have either the standard Alcon AcrySof three-piece acrylic intraocular lens (AIOL) (controls) or the ANIOL implanted at the time of cataract surgery. The spatial profile of MPOD (i.e., at 0.25°, 0.5°, 1.0°, and 1.75° eccentricity) was measured with customized heterochromatic flicker photometry (cHFP) 1 week before and 1 week after surgery, and at 3, 6, and 12 months after surgery. Serum concentrations of L and Z were also measured at each study visit.

RESULTS. There was a highly significant and positive correlation between all MPODs (e.g., at 0.25°) recorded 1 week before and after surgery in eyes with an AIOL implant ($r = 0.915$, $P < 0.01$; paired samples t-test, $P = 0.631$) and in those ANIOL implants ($r = 0.868$, $P < 0.01$; paired samples t-test, $P = 0.719$). Average MPOD across the retina increased significantly with time (after 3 months) in the ANIOL group (repeated-measures, general linear model, $P < 0.05$), but remained stable in the AIOL group (repeated-measures, general linear model, $P > 0.05$). There were no significant time or lens effects observed for serum L over the study period ($P > 0.05$). There was a significant time effect for serum Z over the study period ($P < 0.05$), but not a significant time/lens interaction ($P > 0.05$).

CONCLUSIONS. Customized HFP can reliably measure the MPOD spatial profile in the presence of lens opacity, and cataract surgery does not artifactually alter MPOD readings. This study also provides evidence that implanting an IOL that filters blue light is associated with augmentation of MPOD in the absence of raised serum concentrations of L and Z. However, further and longitudinal study is needed to assess whether the observed increase in MPOD after implantation of blue-filtering IOLs is associated with reduced risk of AMD development and/or progression. (*Invest Ophthalmol Vis Sci.* 2009;50: 4777–4785) DOI:10.1167/iovs.08-3277

Age-related macular degeneration (AMD), which damages central vision, is the most common cause of age-related blindness in the western world.[1,2] Although the pathogenesis of AMD remains unclear, there is a growing body of evidence suggesting that oxidative stress is important in the pathogenesis of this condition and that cumulative short-wavelength (blue) light damage plays a role.[3–5]

Macular pigment (MP), which is entirely of dietary origin, and composed of the xanthophyll carotenoids: lutein (L), zeaxanthin (Z), and *meso*-Z, is thought to protect against AMD because it absorbs short-wavelength (blue) light at a preceptoral level and because of its antioxidant properties.[6,7] The absorption spectrum of MP peaks at 460 nm and may therefore limit photo-oxidative damage to retinal cells.[8] MP levels are maximum within the photoreceptor axons of the foveola and the plexiform layers of the macula.[6,9] Of importance, both the absorptive characteristics of MP and its location in the anterior portion of individual photoreceptors enables the pigment to attenuate the amount of blue light incident on the photoreceptor.

It has been hypothesized that cataracts provide protection against AMD by absorbing blue light, and thus reducing photo-oxidative damage to the retina.[10] However, this protective effect, if any, would be restricted to certain types of lens opacity, such as nuclear sclerosis. In contrast, however, some studies have shown increased risk of cataract in association with AMD, which may reflect the fact that these conditions share antecedents (such as age).[11–13] The positive association of AMD and cataract is considered to be an effect of similar causation and risk factors of both disorders. Although some studies have failed to find a link between cumulative sunlight exposure and the risk of development of AMD,[14–16] many other studies have found a positive association between lifetime exposure to sunlight and AMD.[17–20] Recently, the age-related maculopathy and macular degeneration in elderly European populations (EUREYE) study has provided evidence of a link between cumulative (lifetime) sunlight exposure (in the presence of low antioxidant levels) and the risk of AMD.[21] Those individuals with high cumulative lifetime exposure to sunlight but who were in the lowest quartile for combined antioxidant levels (especially vitamin C, zeaxanthin, vitamin E

and dietary zinc) were observed to have elevated odds ratios for AMD.[21]

Cataract surgery, where the natural crystalline lens is replaced with a clear artificial intraocular lens (IOL), has been shown to be an independent risk factor for the development or progression of AMD.[13,22] There is increased short-wavelength light transmission to the retina after cataract surgery[23,24] and an induced short-term intraocular inflammatory response (normally dampened by topical steroid administration), and either or both of these effects could enhance the risk of AMD progression and/or development. Indeed, ophthalmologists often observe the progression to advanced AMD shortly after cataract surgery.[25] These observations have prompted lens manufacturers to incorporate a blue-light filter into the intraocular lens, in an attempt to attenuate photo-oxidative retinal injury and thereby reduce the risk of AMD development and/or progression.

Alcon has been producing a yellow (blue-light filtering) IOL, the Alcon AcrySof Natural SN60AT (ANIOL) since 2000. The ANIOL is similar to the standard, and commonly used, AcrySof SA60AT single-piece acrylic IOL (AIOL); however, it has a blue-light filtering capacity. The ANIOL was one of the first foldable IOLs to imitate the transmittance of the natural crystalline lens by combining a UV blocker with a covalently bound chromophore that partly absorbs light in the 400- to 500-nm spectral range. This lens is designed to simulate the light transmission characteristics of the adult non-cataractous human crystalline lens.

This study was designed to test the effect of the standard AIOL implant compared with the ANIOL implant on MP optical density (MPOD) by measuring MP at baseline (soon before and after implantation), and 3, 6, and 12 months after implantation.

METHODS

Patients and Randomization

Forty-two patients scheduled for cataract surgery at Waterford Regional Hospital (WRH), Ireland, were recruited for the study, which was approved by the local Research Ethics Committee at WRH before study commencement. Informed written consent was obtained from each patient, and the experimental procedures adhered to the tenets of the Declaration of Helsinki.

Patients with a preoperative logMAR visual acuity of less than 0.5 (the minimum required for reliable measurement of MPOD) and those with any evidence of macular disease were not recruited. MPOD was measured 1 week before and 1 week after surgery, and at 3, 6, and 12 months after surgery. All study visits (five in total) were performed at the Macular Pigment Research Group's vision science laboratory at the Waterford Institute of Technology. The following details were recorded for each patient at baseline: lens prescription; general health status; tobacco use; body mass index (BMI) (defined as kilograms body weight/square meters height); ethnic background; skin color; iris color; and dietary assessment. Dietary assessment was also performed at the final visit. At all study visits (including baseline) the following study outcome measures were assessed: best corrected logMAR visual acuity; serum concentrations of L and Z (used to identify and control for any significant dietary and/or lifestyle changes); and MPOD, including its entire spatial profile across the retina.

Surgery was performed at WRH, and all patients had a clear corneal incision, continuous curvilinear capsulorrhexis, phacoemulsification, and in-the-bag IOL implantation. The patients were randomized to receive either the ANIOL or the AIOL implant at the time of surgery (in place of the cataractous crystalline lens). The trial was conducted in a double-blind, randomized, controlled fashion.

Dietary Assessment

Dietary assessment was performed at baseline and at the final study visit. A crude indicator of dietary intake and bioavailability of L and Z

was constructed according to the frequency of consumption of five food items (dark green leafy vegetables, colored fruits and vegetables, eggs, fish, and overall fat intake) with examples given. The frequency of consumption was scored as follows: 0, less than once a week; 1, once a week; 2, two to three times per week; 3, four to six times per week; 4, once a day; 5, more than once a day. Dietary fat intake (e.g., fried foods, snack foods, cheese, foods cooked in butter) was assessed due to its role in carotenoid absorption from the gut (fat intake was scored from 1 to 5, as just outlined)[26,27]; fish intake was assessed due to its high concentration of n-3 docosahexaenoic acid, which has been shown to influence MP concentration (fish intake was also scored from 1 to 5, as just outlined).[28] In this way, an aggregate score for all food items was assigned to each person that ranged from 0 to 25. The main purpose of assessing a person's dietary intake was to allow for adjustment of dietary confounding factors when performing statistical comparisons with other variables (e.g., lens type and MPOD).

Serum Carotenoid Assessment

Blood samples (6–8 mL) were collected from all patients on the same day as the dietary and MPOD assessment. Serum was separated from blood by centrifugation at 5000 rpm for 10 minutes and then aliquoted into two light-sensitive microcentrifuge tubes and stored at minus 70°C until the time of analysis. Duplicate extractions were performed for each serum sample. A 400-μL aliquot of serum was pipetted into a light-sensitive microcentrifuge tube (1.5 mL total capacity). Ethanol (300 μL) containing 0.25 g/L butylated hydroxytoluene (BHT) and 200 μL internal standard (α-tocopherol acetate) was added to each tube. Heptane (500 μL) was then added, and samples were vortexed vigorously for 1 minute followed by centrifugation at 2000 rpm for 5 minutes (MSC Micro Centaur; Davison & Hardy Ltd., Belfast, UK). The resulting heptane layer was retained and transferred to a second labeled light-sensitive microcentrifuge tube, and a second heptane extraction was performed. The combined heptane layers were immediately evaporated to dryness under nitrogen. These dried samples were reconstituted in 200 μL methanol (containing 0.25 g/L BHT), and 100 μL was injected for high-performance liquid chromatography (HPLC) analysis.

We used an HPLC (1200 series; Agilent Technologies Ltd., Dublin, Ireland) system with photodiode array detection. A 5-μm analytical/preparative 4.6×250-mm specialty reversed-phase column (201TP; Vydac, Hesperia, CA) was used with an in-line guard column. The mobile phase consisted of 97% methanol and 3% tetrahydrofuran. The flow rate was 1 mL/min, and the total run time was 13 minutes. All carotenoid peaks were integrated and quantified (ChemStation software; Agilent).

DSM Nutritional Products (Basel, Switzerland) provided the L and Z standards, which were used to generate standard curves for quantification of these carotenoids. This assay was validated against the National Institute of Standards and Technology (NIST) standards before analysis.

Macular Pigment Measurement

Apparatus. We used a macular densitometer, developed and originally described by Wooten et al.,[29] to measure MPOD, including its spatial profile across the retina. The densitometer uses heterochromatic flicker photometry (HFP) to obtain a valid measure of MPOD at a given retinal location.[30]

Procedure. The patient viewed a stimulus that alternated between a wavelength band absorbed by MP and one that was not. Test stimuli were presented in natural view and near the center of a 6°, 2.75-cd/mm^2, 470-nm circular background. The patient adjusted the radiance of the wavelength band absorbed by MP to minimize (or eliminate) their perception of flicker. The range of alternation rates where flicker is not perceived is called the null zone. For the 460-nm condition (maximum MP absorption), measurements at 0.25°, 0.5°, 1°, and 1.75° eccentricity were obtained along the horizontal meridian of the nasal retina (for the left eye) and temporal retina (for the right eye)

relative to a reference location at 7° eccentricity. For the measures at 0.25° and 0.5° eccentricities, test stimuli were solid disks with those radii, with a small black fixation dot in the center. With these stimuli, when the flicker frequency is optimized, the edge hypothesis holds true up to eccentricities of approximately 2°.[31-33] For the 1° and 1.75° eccentricities, centrally fixated, 20-minute wide annuli with mean radii corresponding to those eccentricities were used. For the 7° reference target, the test stimulus (2° diameter disc) was viewed eccentrically using a small red light-emitting diode as a fixation target. The order of stimulus presentation was as follows: 0.5°, 7°, 1°, 1.75°, and 0.25°.

For each stimulus condition/location, patients usually made five judgments of null flicker. However, there were patients for whom the initial, predicted HFP frequency value was either too high or too low. In these situations, the experimenter adjusted the frequency of the flickering stimulus in steps of 1 Hz, either increasing it (if the patient could not eliminate flicker), or decreasing it (if the patient exhibited a wide range of null flicker values). The range of null flicker was considered too wide if the patient provided values that spanned a range of more than ~15% radiance units (~0.07 MPOD).

Customized HFP. Efforts were made in this study to optimize and customize the method, to facilitate obtaining MP measurements and ensure their accuracy. Similar techniques have been used in recently published studies in which MP was measured with the macular densitometer.[34,35] Primarily, it is optimal to customize the HFP task for each patient (because of interindividual differences in flicker sensitivity) by selecting the alternation rate to achieve a narrow null zone and a precise setting. This method has been termed customized (c)HFP. Selecting the best flicker rate for each patient enables one to customize the variation in flicker sensitivity, which is influenced by variables such as age and disease.[36,37] If differences among patients in flicker sensitivity are not accounted for (i.e., a fixed flicker frequency is used for each patient), then a patient with low flicker sensitivity (i.e., low critical flicker fusion frequency [CFF]) will most likely experience a large null flicker zone. Although the patient may be able to complete the task by eliminating flicker from the test target, the settings are likely to be variable, and patients may exhibit systematic bias toward one end of the null range, resulting in either over- or under-estimation of MPOD. Alternatively, a patient with a high CFF may not be able to eliminate flicker from the test target, which would make the task difficult to complete. As described by Snodderly et al.[38] the flicker sensitivity issue can be addressed by introducing, as a preliminary test, a CFF task using a single-wavelength band outside the absorption band of MP. Based on an individual's CFF, the optimal HFP flicker frequency is estimated, which facilitates good patient performance and reduces measurement error. An algorithm developed by Nolan and Stringham[34] was used to estimate optimal HFP flicker frequencies for each retinal locus, including the reference locus. This algorithm (based on a patient's CFF) produced the following predicted flicker frequencies: 0.5° = CFF − 6; 7° = CFF − 12; 1° = CFF − 6; 1.75° = CFF − 7; and 0.25° = CFF − 7. Overall, the values produced by this algorithm yielded low variability in patient settings. The optimization of HFP flicker rate is particularly important in older patients (such as those recruited into this trial), who often demonstrate a significant reduction in their temporal visual sensitivity.[37,39]

An additional methodological consideration involves a test stimulus configuration in which the radiances of the two alternating components are inverse-yoked. In other words, when a patient adjusts the luminance of the blue component to a more intense level, the luminance of the green component is commensurately decreased, and vice versa. This procedure keeps the overall brightness of the test stimulus constant. This approach eliminates the potential distraction caused by changes in brightness experienced by some patients when performing the task in the unyoked setting. This aspect of cHFP is not customized by the experimenter, but is automatically customized for each patient because their settings reflect their own ocular absorption and retinal sensitivity.

MPOD values reported refer to average MPOD across the retina for all loci measured (0.25°, 0.5°, 1°, and 1.75° of retinal eccentricity), unless specifically stated.

Statistical Analysis

Statistical software (SPSS, ver. 15; SPSS Inc., Chicago, IL) was used for analysis and another program was used for graphic presentations (SigmaPlot, ver. 8.0; SPSS Inc.). All variables investigated exhibited a typical normal distribution. Results, expressed as the mean ± SD, are presented in the text. We conducted repeated-measures analysis of average MPOD across the retina, measured at each of five study visits with a general linear model approach, with lens type as a between-patients factor. Differences between two time points, within patients, were assessed using the paired-samples *t*-test. Pearson correlation coefficient analyses were conducted to investigate the relationship between bivariables. We used the 5% level of significance throughout our analysis.

RESULTS

Baseline Findings: V1

Patients. Forty-two patients were recruited. The patients were randomized to receive either the AIOL ($n = 21$) or the ANIOL ($n = 21$) implant as a lens replacement in their cataract surgery. Of the 42 patients recruited, 30 attended all study visits (1 week before surgery, 1 week after surgery, and 3, 6, and 12 months after surgery: V1, V2, V3, V4, and V5, respectively). One patient from the AIOL group withdrew after V1, two after V2, and two after V4 ($n = 5$ withdrawals in total). Three patients from the ANIOL group withdrew after V1, two after V2, and two after V4 ($n = 7$ withdrawals in total). The reasons for withdrawal were as follows: patient illness (non-ocular); patient deceased; logistics of transport; and not interested in participating further.

Age. The mean age of the patients recruited into the study was 73 ± 11 years. The mean age of the patients recruited into the AIOL arm was 71 ± 11 years, whereas the mean age of the patients recruited into the ANIOL arm was 74 ± 11 years ($P = 0.370$).

Sex. Twenty-five of the patients recruited into the study were men and 17 were women. In the AIOL group, 13 of the patients were men and 8 were women, whereas in the ANIOL group, 12 were men and 9 were women.

Body Mass Index. The mean BMI was 27 ± 5 in the entire study group, 29 ± 5 in the AIOL group, and 25 ± 4 in the ANIOL group ($P = 0.017$).

Diet. As described earlier, each patient was assigned a dietary score representing his/her overall dietary intake of foods containing the macular carotenoids. For the entire study group, the mean diet score was 9.7 ± 3.6 of a possible 25, for the AIOL arm it was 8.8 ± 3.3, and for the ANIOL arm it was 10.7 ± 3.8 ($P = 0.132$).

Serum L and Z. The mean serum concentration of L at V1 in the entire study group was 0.274 ± 0.095 μg/mL, in those in the AIOL arm it was 0.088 ± 0.013 μg/mL, and in those in the ANIOL arm it was 0.103 ± 0.016 μg/mL ($P = 0.505$). The mean serum concentration of Z at V1 was 0.013 ± 0.011 μg/mL in the entire study group, 0.013 ± 0.002 μg/mL in the AIOL arm, and 0.014 ± 0.002 μg/mL in the ANIOL arm ($P = 0.785$).

MPOD. The mean MPOD at V1 averaged across the retina (i.e., average of MPOD at 0.25°, 0.5°, 1°, and 1.75°) was 0.18 ± 0.12 in the entire study group, 0.18 ± 0.12 in the AIOL arm, and 0.17 ± 0.12 in the ANIOL arm ($P = 0.898$). The mean MPOD at V1 at 0.25° (i.e., peak value) was 0.29 ± 0.16 in the entire study group, 0.27 ± 0.14 in the AIOL arm, and 0.28 ± 0.17 in the ANIOL arm ($P = 0.870$). The mean MPOD at V1 at

TABLE 1. Foveal (0.25°) and Parafoveal (7°) Relative Radiance and Derived MPOD before and after Cataract Surgery in Subjects with the AIOL or the ANIOL Lens Implant

Subject	V1 Mean F Radiance	V1 Mean PF Radiance	V2 Mean F Radiance	V2 Mean PF Radiance	MPOD at 0.25 V1	MPOD at 0.25 V2	MPOD Change
AIOL							
2	1432	1145	1082	840	0.18	0.18	0
5	1778	853	1475	617	0.59	0.62	−0.03
7	1624	1174	1433	1095	0.28	0.22	0.06
11	1179	1095	909	730	0.06	0.14	−0.08
12	1629	1482	1114	1047	0.09	0.05	0.04
14	2180	1323	1641	830	0.55	0.54	0.01
16	1741	1261	1449	796	0.30	0.46	−0.16
18	1295	879	1191	839	0.28	0.25	0.03
21	2121	1571	1215	648	0.36	0.43	−0.07
24	1199	462	1158	474	0.62	0.60	0.02
27	1736	1350	1276	829	0.24	0.31	−0.07
29	1276	899	1277	993	0.26	0.21	0.05
31	1392	787	1411	712	0.42	0.47	−0.05
32	1364	1027	979	759	0.22	0.17	0.05
33	1162	915	1047	831	0.17	0.16	0.01
34	1408	974	939	709	0.28	0.18	0.1
42	1204	817	984	630	0.27	0.29	−0.02
Mean	1513	1060	1211	787	0.30	0.31	−0.01
SD	316	282	214	159	0.16	0.18	0.06
ANIOL							
3	2288	1576	2143	1383	0.48	0.49	−0.01
6	1858	1199	1727	1089	0.40	0.41	−0.01
8	1689	1415	1488	1185	0.17	0.19	−0.02
9	2216	2068	1500	1388	0.11	0.07	0.04
10	1455	1199	1355	1161	0.16	0.12	0.04
17	1181	773	1146	761	0.30	0.28	0.02
19	1819	740	1651	881	0.72	0.50	0.22
20	1183	1049	1197	1060	0.09	0.09	0
22	1526	1259	1274	1043	0.17	0.15	0.02
23	1492	1343	1331	1188	0.09	0.09	0
26	1960	1467	2122	1314	0.31	0.52	−0.21
37	1432	1015	1431	980	0.27	0.29	−0.02
40	1785	1272	1770	1329	0.32	0.27	0.05
41	1577	1004	1569	971	0.37	0.39	−0.02
43	1965	1560	1505	1129	0.26	0.24	0.02
Mean	1695	1263	1547	1124	0.28	0.27	0.01
SD	333	338	298	183	0.17	0.16	0.08

0.5° was 0.23 ± 0.15 for the entire study group, 0.24 ± 0.15 in the AIOL arm, and 0.21 ± 0.15 in the ANIOL arm. ($P = 0.643$).

MPOD 1 Week before (V1) and 1 Week after (V2) Cataract Surgery

The mean relative radiance units obtained for 0.25° (fovea, F) and 7° (parafovea, PF), along with MPOD for 0.25°, and the change in MPOD between V1 and V2 are presented in Table 1. The data show that MPOD recorded 1 week after cataract surgery was unchanged when compared with readings taken 1 week before surgery in eyes with an AIOL implant (mean MPOD at 0.25°, 0.30 ± 0.16 and 0.31 ± 0.18, for V1 and V2, respectively; mean difference, −0.01 ± 0.06; paired samples t-test, $P = 0.631$) and in eyes with an ANIOL implant (mean MPOD at 0.25°, 0.28 ± 0.17 and 0.27 ± 0.16, for V1 and V2, respectively; mean difference, 0.01 ± 0.08; paired samples t-test, $P = 0.719$). In contrast, the F and PF values used in the derivation of MPOD were significantly lower after cataract surgery in those with an AIOL implant (mean ± SD F and PF radiance units, 1513 ± 316 [FV1] and 1211 ± 214 [FV2], paired samples t-test, $P = 0.000$; and 1060 ± 282 [PFV1] and 787 ± 159 [PFV2], paired samples t-test, $P = 0.000$) and in those with an ANIOL implant (mean ± SD F and PF radiance units = 1695 ± 333 [FV1] and 1527 ± 298 [FV2], paired samples t-test, $P = 0.017$, and

1263 ± 338 [PFV1] and 1124 ± 183 [PFV2], paired samples t-test, $P = 0.02$) (Table 1).

MPOD Alterations for AIOL and ANIOL Groups over the Study Period: V1–V5

We conducted a repeated-measures analysis of average MPOD across the retina, measured at each of five study visits using a general linear model approach, with lens as a between-patients factor. This resulted in a statistically significant time/lens interaction effect, which remained significant ($P < 0.05$) using any of the standard corrections for violation of sphericity. It is clear from the means plots in Figure 1 and MPOD values presented in Table 2, how this significant time–lens interaction effect arises: MPOD increased with time (at least for some patients) in the ANIOL group, but remained virtually static in the AIOL group.

As the AIOL and ANIOL groups differ significantly with respect to BMI, we conducted further repeated measures analyses with BMI included as a covariate. When comparing average MPOD differences between visits 2 and 5 (i.e., comparing average MPOD immediately after surgery and 12 months later), we obtained $P = 0.008$ for the time–IOL type interaction, controlling for BMI. Including all five time points in the analysis, however, the time–IOL type interaction was no longer significant (e.g., $P = 0.108$, with Huynh-Feldt correction for
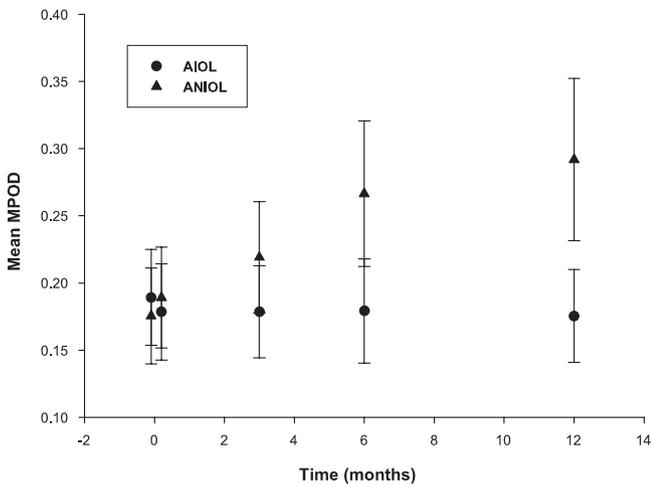
FIGURE 1. Mean MPOD across the retina, at all study visits, in patients in the AIOL and ANIOL groups. Mean MPOD measured at 0.25°, 0.5°, 1.0°, and 1.75° of retinal eccentricity. Standard error bars are included at each time point for both the AIOL and ANIOL groups.

TABLE 3. Difference in Average MPOD between Visits 2 and 5, at Each Degree of Retinal Eccentricity, in Subjects with the AIOL or the ANIOL Lens Implant

MPOD Eccentricity	AIOL		ANIOL	
	Mean Difference (V5 − V2)	*P*	Mean Difference (V5 − V2)	*P*
0.25	0.002	0.898	0.16	0.02
0.5	−0.017	0.393	0.123	0.02
1	−0.008	0.167	0.088	0.067
1.75	−0.0045	0.703	0.035	0.289

V5 − V2, change in macular pigment between visits 2 and 5; MPOD eccentricity, the eccentricity at which MPOD was measured; *P*, significance at $P \le 0.05$ (paired-sample *t*-test).

sphericity). Of note, the time–BMI interaction effect was also not significant, indicating that differences in BMI between the AIOL and ANIOL groups remained stable over time. The sensible conclusion to draw from our results therefore appears to be that there is no need to control for BMI differences between the two IOL groups.

Of interest, seven subjects (six in the ANIOL group and one in the AIOL group) showed an increase of 0.08 units or more in average MPOD between visits two and five. Comparing this group of seven with the remaining subjects, we found no significant differences in mean BMI (V1), serum L (V1) serum Z (V1), diet score (V1), or age (V1). Distribution of iris color or sex was also not significantly different ($P > 0.05$, for all tests). It appears therefore that the observed changes in average MPOD cannot be ascribed to any of these factors.

We also report some results (difference between V5 and V2 [final 12-month study visit minus time of lens implant]) for MPOD measured at each degree of retinal eccentricity (0.25°, 0.5°, 1.0°, and 1.75°) in both the AIOL and ANIOL groups (Table 3). It is clear from this table that the significant increases in MPOD over the study period in the ANIOL group arose primarily at the center (0.25° and 0.5°) of the fovea.

TABLE 2. Average MPOD at Each Study Visit in Subjects with the AIOL or the ANIOL Lens Implant and Differences in MPOD between Selected Study Visits

Subject	V1	V2	V3	V4	V5	V3 − V2	V4 − V2	V5 − V2
AIOL								
2	0.09	0.07	0.11	0.07	0.07	0.04	0	0
5	0.4	0.45	0.38	0.43	0.4	−0.07	−0.02	−0.05
7	0.3	0.17	0.14	0.11	0.12	−0.03	−0.06	−0.05
11	0.03	0.07	0.06	0.02	0.03	−0.01	−0.05	−0.04
12	0.05	0.01	0	0.01	0	−0.01	0	−0.01
14	0.43	0.38	0.38	0.42	0.37	0	0.04	−0.01
16	0.21	0.27	0.29	0.32	0.26	0.02	0.05	−0.01
18	0.18	0.13	0.19	0.19	0.25	0.06	0.06	0.12
21	0.33	0.28	0.3	0.27	0.27	0.02	−0.01	−0.01
27	0.14	0.13	0.09	0.09	0.11	−0.04	−0.04	−0.02
29	0.16	0.1	0.07	0.15	0.12	−0.03	0.05	0.02
32	0.12	0.13	0.12	0.12	0.16	−0.01	−0.01	0.03
34	0.15	0.13	0.15	0.13	0.12	0.02	0	−0.01
Mean	0.20	0.18	0.18	0.18	0.18	0.00	0.00	0.00
SD	0.13	0.13	0.12	0.14	0.12	0.04	0.04	0.04
ANIOL								
3	0.28	0.29	0.3	0.36	0.39	0.01	0.07	0.1
6	0.36	0.21	0.32	0.34	0.34	0.11	0.13	0.13
8	0.09	0.12	0.3	0.43	0.45	0.18	0.31	0.33
9	0.03	0.02	0.01	0.01	0	−0.01	−0.01	−0.02
10	0.12	0.1	0.07	0.07	0.06	−0.03	−0.03	−0.04
17	0.22	0.25	0.28	0.17	0.25	0.03	−0.08	0
19	0.37	0.43	0.28	0.38	0.52	−0.15	−0.05	0.09
20	0.04	0.06	0.07	0.15	0.08	0.01	0.09	0.02
22	0.12	0.17	0.26	0.36	0.47	0.09	0.19	0.3
26	0.13	0.32	0.44	0.58	0.54	0.12	0.26	0.22
40	0.17	0.11	0.08	0.08	0.11	−0.03	−0.03	0
Mean	0.18	0.19	0.22	0.27	0.29	0.03	0.08	0.10
SD	0.12	0.12	0.14	0.18	0.20	0.09	0.13	0.13

V3 − V2 = change in MPOD between visit 2 and visit 3 (AIOL: *P* = 0.964; ANIOL: *P* = 0.392)
V4 − V2 = change in MPOD between visit 2 and visit 4 (AIOL: *P* = 1.000; ANIOL: *P* = 0.050)
V5 − V2 = change in MPOD between visit 2 and visit 5 (AIOL: *P* = 0.474; ANIOL: *P* = 0.028)
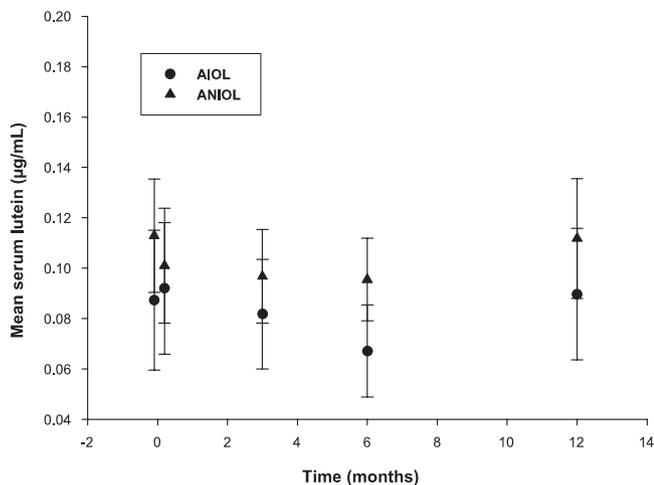
FIGURE 2. Mean serum concentrations of L, at all study visits, in patients in the AIOL and ANIOL groups. Mean serum L is the mean concentration of L at each study visit. Standard error bars are included at each time point for both the AIOL and ANIOL groups.

Serum L and Z Concentrations for AIOL and ANIOL Groups over the Study Period: V1–V5

No significant serum L effects were observed over the study period (Fig. 2). There was a significant time effect for serum Z over the study period (repeated-measures, general linear model, e.g., using Huynh-Feldt correction for sphericity, $P = 0.038$), but not a significant time–IOL interaction ($P > 0.05$ for all tests) (Fig. 3). Thus, serum Z was significantly different at different time points, but this was true in both the AIOL and ANIOL groups.

Visual Acuity

Visual acuity was assessed using a Bailey-Lovie distance chart and recorded with logMAR notation. For statistical analysis, logMAR acuity was converted to a visual acuity rating (VAR) notation. LogMAR 0 acuity (equivalent to 20/20 Snellen acuity) was assigned a score of 100. Acuity was calculated on the basis of every letter that was correctly identified above or below this line, with each letter worth one mark, and each line therefore, five marks. For example, a subject with corrected logMAR acuity of 0.3 (Snellen equivalent 20/40), was assigned a mark of 85 [$100 - 15$ (3 lines = 15 marks)]. If the subject could correctly identify two additional letters on the smaller logMAR 0.2 line, they were assigned a score of 87.

The mean BCVAR for the entire study group at V1 was 82.49 ± 7.68. There was a predictable and statistically significant improvement in acuity after cataract surgery and postoperative BCVAR at V2 for the entire study group was 89.69 ± 6.79 (paired samples t-test; $t = -4.703$, $P < 0.001$). The improvement in acuity was maintained throughout the study period, and BCVAR for the entire study group at V5 was 91.84 ± 5.20.

Visual acuity results were further analyzed to assess the impact of lens type on visual outcome. The mean BCVAR at V1 was 82.57 ± 8.37 for the AIOL group, and 82.39 ± 7.02 for the ANIOL group. Postoperative BCVAR at V2 was 89.72 ± 6.57 for the AIOL group and 89.64 ± 7.32 for the ANIOL group. Final BCVAR at V5 was 91.93 ± 6.16 for the AIOL group and 91.73 ± 4.18 for the ANIOL group. Statistical analysis confirms a significant time effect on BCVAR (repeated-measures, general linear model, e.g., using Huynh-Feldt correction for sphericity $P < 0.001$), but not a significant time–lens interaction ($P > 0.05$ for

all tests). Similar improvements in acuity were thus observed in the AIOL and ANIOL groups over the time course of the study.

DISCUSSION

This study was designed to measure and compare the effect of cataract surgery on MPOD over a 1-year period in eyes in which a standard UV-light filtering intraocular lens (AIOL) was implanted and in eyes in which a blue-light and UV-light filtering intraocular lens (ANIOL) was implanted. Forty-two patients scheduled for cataract surgery at WRH were randomized to have either an AIOL or an ANIOL implanted during surgery (in place of the cataractous lens). MPOD was measured at baseline (1 week before and 1 week after cataract surgery) and at 3, 6, and 12 months after surgery in all patients. Serum carotenoid concentrations were also measured at each study visit in all patients to control for any potentially confounding variables relating to their MPOD measurements. This study was prospective, randomized, controlled, double-blind in design, and, to our knowledge, it is the first of its kind.

Blue light has been implicated in the development and progression of AMD after cataract surgery.[4,5,22,40–44] Indeed, after cataract surgery, the retina is exposed to more blue light than at any stage in the patient's lifetime,[41] and Wang et al. reported a 5-year, two- to fivefold increased risk of development of late-stage AMD after cataract surgery in individuals without AMD at baseline.[22] Furthermore, in vitro, both RPE cell apoptosis and upregulation of vascular endothelial growth factor (VEGF), one of the most potent proangiogenic factors in the pathogenesis of neovascular AMD, have been demonstrated in A2E-laden RPE cells on exposure to light,[40,42] but these effects are relatively attenuated when the light is filtered through a blue-light filtering IOL.[43,44] Of interest, the human crystalline lens yellows with age, and transmits less blue light than a younger crystalline lens.[24] The transmission of blue light is further reduced with cataract formation, and this may confer some degree of protection against AMD at a stage in life when the concentration of RPE lipofuscin (the major chromophore in this line of cells) peaks at the macula.[45] If indeed cataract surgery is an independent risk factor for development or progression of AMD, replacement of the natural (blue light filtering) crystalline lens with a clear (non–blue light filtering) artificial IOL may contribute to any observed increase in risk for progression or development of AMD after cataract surgery.
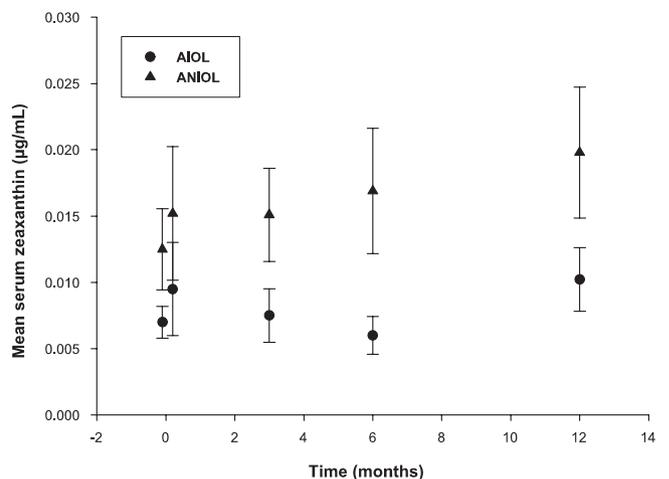

FIGURE 3. Mean serum concentrations of Z, at all study visits, in patients in the AIOL and ANIOL groups. Mean serum Z is the mean concentration of Z at each study visit. Standard error bars are included at each time point for both the AIOL and ANIOL groups.

Alcon has been producing a blue-light–filtering intraocular lens (ANIOL) since 2000, with a view to attenuating any increased risk of progression or development of AMD after cataract surgery. The ANIOL was the first blue-light–filtering IOL on the market in North America,[46] and was designed to mimic the transmittance characteristics of the adult human crystalline lens, with the absorption characteristics of a 20-D ANIOL being similar to that of a 53-year-old crystalline lens.[47] The ANIOL is entirely similar to the AIOL apart from a covalently bound chromophore that partially absorbs light in the 400- to 500-nm spectral range. Conventional UV-blocking IOLs (such as the AIOL) display a sharp increase in light transmission beyond 400 nm, whereas the ANIOL allows only a 10% transmittance at 406 nm increasing to a 50% transmittance at 459 nm, and an 80% transmittance at 500 nm,[23] thus blocking transmission of a large proportion of high-energy and potentially injurious short-wavelength light. Despite the greatly reduced transmission of short-wavelength (blue) light, visual acuity, color perception, and contrast sensitivity have repeatedly been found to be equivalent under photopic and mesopic conditions with the UV-only blocking AIOL and the ANIOL.[48–59] The acuity results reported herein are in general agreement with those in previous studies and provide further evidence that lens type, whether ANIOL or AIOL, has little impact on postoperative photopic, high-contrast visual acuity. Reduced scotopic sensitivity has been demonstrated in some studies with the ANIOL[47,60,61]; however, this has generally been accepted to be of little visual or functional significance[61–65] and does not affect patients' quality of life.[66]

In this study, we set out to evaluate the effect of implantation of a blue-light filtering IOL on MPOD and to compare the findings with control subjects in whom a non–blue-light–filtering IOL was implanted. Given the growing, but inconclusive, evidence base for a protective role of MP in AMD (recently reviewed by Loane et al.[67]), the results of this study indicate that implantation of an ANIOL at the time of cataract surgery may confer protection against progression or development of AMD. We postulated that reducing the amount of blue light incident on the retina (by implantation of an ANIOL as opposed to an AIOL) would lead to less generation of free radicals in response to irradiation with short-wavelength (blue) light.[68] As a consequence, in theory at least, depletion of MP over time (caused by neutralizing free radicals) would be attenuated in those eyes with an ANIOL implant compared with those with an AIOL implant.

MPOD measured 1 week after surgery was unchanged compared with readings taken 1 week before surgery in each study group (although foveal and parafoveal radiances were reduced after surgery as expected, but the relative radiance remained consistent). The ANIOL more closely approximates the transmittance characteristics of the natural crystalline lens and, as such, reduced radiances were more evident in the AIOL group. The stability of MPOD measured before and after surgery demonstrates that the measurement of MPOD using HFP is not influenced artifactually or otherwise by the event of cataract surgery (whether an AIOL or an ANIOL is implanted), and this stability therefore lends validity to MPOD measurements taken at 3, 6, and 12 months after surgery. These findings are consistent with those of Ciulla et al.,[69] who also found no significant change in MPOD measurements taken immediately before and after cataract surgery in a patient population with inclusion and exclusion criteria similar to those in our study (with no patients in their study having any evidence of macular disease and a median best corrected Snellen distance visual acuity before surgery of 20/50).

We found that MPOD remained stable over the course of the study in the group with an AIOL implant. However, and in contrast, in eyes in which an ANIOL was implanted, MPOD increased over the duration of the study period, with a statistically significant increase in MPOD at months 3, 6, and 12 after surgery. Of note, dietary levels and serum concentrations of L and Z remained largely unchanged over the course of the study. Nolan et al.[70] have demonstrated serial month-to-month consistency of MPOD measurements using HFP over a 24-month period in healthy subjects in whom serum concentrations of the macular carotenoids were stable, consistent with the findings of Wenzel et al.[71] (investigating MPOD in two male subjects over a 20-day period), who reported that the optical density of the macular carotenoids is unaffected by diurnal variations in exposure to ambient levels of light. Of note, Wenzel et al. and Nolan et al.[70] were uncontrolled observational studies. In other words, the stability of MPOD appears to be unaffected (in the context of a stable diet) over long periods, which renders our findings all the more interesting, given that we have (in the context of a randomized controlled trial) demonstrated that differential filtration of blue light after cataract surgery influences MPOD with the passage of time.[70,71]

Our findings prompt a discussion on the relationship, if any, between MPOD and age, as the yellowing of the crystalline lens with age results in an age-related increase in prereceptoral filtration of blue light. This phenomenon, given our finding that blue-filtering IOLs result in augmentation of MPOD, in theory at least, might be expected to give rise to an age-related increase in MPOD. However, most studies do not support such an association, perhaps reflecting the known age-related increase in oxidant load, which may offset any protective effect of prereceptorial filtration of blue light.[3]

Our initial hypothesis postulated a reduction in MPOD with implantation of an AIOL (due to the increased transmittance of short-wavelength blue light) and relative stabilization of MPOD with ANIOL implantation and, as such, our findings were somewhat unexpected. The MPOD in those eyes with the AIOL implant remained constant over the one-year study period, despite the fact that blue-light transmission with the AIOL implant is greater than that in a 71-year-old (mean age of patients in the AIOL group) cataractous lens. Indeed, a 74-year-old (mean age of patients in the ANIOL group) cataractous lens may also be expected to transmit less blue light than the ANIOL. However, in eyes with an ANIOL implant, MPOD increased over the 1-year follow-up period in our study. It is difficult to explain our findings, although it is possible that increased visible light irradiation of the retina after cataract surgery stimulates enhanced retinal capture of circulating L and Z in an attempt to offset a possible increase in photo-oxidative retinal injury, but that the heralded increase in photo-oxidative retinal injury does not occur in eyes with a blue-filtering IOL implant. Also, it is possible that there is some degree of autoregulation of MPOD in the context of a stable diet and that such autoregulation is disturbed by cataract surgery as a result of increased light incident on the macula and a consequential depletion of existing MP (because of increased photochemical oxidant load). However, the presence of a blue-filtering IOL attenuates the amount of blue light incident on the retina, with perhaps a parallel reduction in the extent of depletion of macular carotenoids (because of reduced photochemical injury), with a consequential rise in MPOD.

In conclusion, this study provides evidence that implanting an IOL that filters blue light (ANIOL) results in augmentation of MPOD. The importance of this finding rests on the fact that any benefits associated with augmentation of MPOD, in terms of AMD prevention or progression (yet to be proven), will be conferred on patients with an ANIOL implant at the time of cataract surgery, and may be of particular importance in the modern era when IOL implantation often occurs at an earlier stage in a patient's lifetime (such as in pediatric cataract surgery, refractive lens exchange and relatively early lens opacity

in patients with a long postoperative life expectancy). However, further study is required in the form of controlled long-term trials to investigate whether implantation of a blue-light filtering IOL is effective in preventing or delaying development or progression of AMD.

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