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Pre- and postoperative C-reactive protein levels in patients with cataract and age-related macular degeneration

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PURPOSE. *To assess whether patients with early or intermediate forms of age-related macular degeneration (AMD) benefit from cataract surgery in terms of visual acuity and contrast sensitivity, and to determine the levels of high sensitivity C-reactive protein (hsCRP) as a systemic marker of inflammation before and after cataract surgery in patients with AMD.*
METHODS. *Three groups of patients (n=132) were studied at baseline and 8–12 weeks later: 1) a study group of patients with AMD who underwent cataract surgery (n=47), 2) a control group of patients without ocular comorbidities who underwent cataract surgery (n=36), and 3) a second control group with AMD and no surgery (n=49). Visual acuity (VA) was obtained by letter charts and expressed as decimal notations ± SD. Contrast sensitivity was measured employing a Ginsburg Box, VSCR-CST-6500. The hsCRP was measured by means of particle enhanced immunonephelometry on a BN Systems.*
RESULTS. *Postoperatively in both groups of the operated patients an improvement of VA (0.23±0.17 vs 0.64±0.25 and 0.23±0.18 vs 0.83±0.17, respectively, $p<0.0001$) and contrast sensitivity (at different spatial frequencies, from 1.5 to 18 cycles/degree, $p<0.05$) was determined. At baseline, the hsCRP level in Group 1 patients was higher than the level in controls (2.67±2.36 vs 1.67±1.36, $p<0.01$, or 1.12±0.99 mg/L, $p<0.0001$, respectively). After 8–12 weeks, the hsCRB level only in Group 1 significantly increased (2.67±2.36 vs 3.74±3.54 mg/L, $p<0.05$), whereas in the controls it did not change.*
CONCLUSIONS. *Patients with AMD benefit from cataract surgery, both in terms of VA and contrast sensitivity. The level of hsCRP is significantly higher in patients with AMD and moderate cataract than in patients with one of these eye disorders. The hsCRP only increases after cataract surgery in patients with AMD. (Eur J Ophthalmol 2007; 17: 919-27)*

KEY WORDS. *Age-related macular degeneration, Cataract surgery, Contrast sensitivity, High sensitivity C-reactive protein*

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INTRODUCTION

Cataract and age-related macular degeneration (AMD) are not unusual findings in the aging eye. They are the two most important causes of decreased vision in the majority of developed countries, including Lithuania (1, 2). The number of cataract surgeries is steadily increasing in most countries (2, 3). There are several reasons for an increasing surgical volume, such as a higher frequency of second-eye cataract surgery (4), safe surgery with excellent results, and an aging society (5, 6). However, the benefits (and risks) of cataract surgery in patients with AMD are uncertain. Some investigators found that cataract surgery benefits patients with AMD, ensuing in improved visual

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function and quality of life in most patients (7-10), whereas others reported that in patients with AMD, improvement in visual outcome after cataract surgery can be limited (11-13). Furthermore, recent studies found progression from early to late stages of AMD in eyes after cataract surgery (14-18). Therefore, we must treat those patients who get the most benefit from cataract surgery or who may have the lowest risk level for late AMD.

There are several possible reasons that might explain, either individually or in concert, the association between cataract surgery and late AMD: 1) cataract and AMD share one or more common risk factors (18-21), 2) cataract surgery can increase photo-oxidative damage to the retina (19, 20, 22), 3) cataract surgery may increase intraocular inflammation (23-32).

Ocular inflammation, whether because of local factors or as part of systemic inflammatory conditions, also appears to increase the risk of age-related cataract (33, 34) and AMD (35, 36).

In light of the previous reports, an attempt was made to assess whether patients with early or intermediate forms of AMD benefit from cataract surgery in terms of visual acuity (VA) and contrast sensitivity, and to evaluate the potential relationships of the levels of high sensitivity C-reactive protein (hsCRP) as a systemic marker of inflammation before and after cataract surgery in patients with AMD.

METHODS

Study population

The study was carried out at the Departments of Ophthalmology and Cardiology of Kaunas University of Medicine Hospital. The study is part of a common project designed by ophthalmologists and cardiologists, the objective of which is to determine the association between AMD and morphologic changes in the cardiovascular system. Data were collected between March 2005 and April 2006. Ethical approval for the study was obtained at the Kaunas Regional Committee of Ethics.

Three groups of patients (n=132) were studied prospectively. Group 1 included patients scheduled for cataract surgery with early or intermediate AMD diagnosed clinically and by fluorescein angiography in the eye on which the operation was to be performed (n=47). Group 2 (control) comprised patients scheduled for cataract surgery with no other ocular comorbidity (n=36). Patients in Group 1 or 2 could have moderate cataract with an assigned severity score from two to four. Patients in the groups could have cataract but their fundus photographs had to be clear enough to allow grading of the AMD. Group 3 (a second control) included patients with early or intermediate AMD diagnosed clinically and by fluorescein angiography (n = 49). Patients in this group could have mild cataract with an assigned severity score less than two not contemplated for cataract surgery in the near future.

After the patients had consented to participate in the study, they were assessed twice: at baseline and 8–12 weeks later.

The assessment commenced with a brief medical and ocular history.

VA was obtained by letter charts and expressed as decimal notations.

Contrast sensitivity was measured employing a Ginsburg Box, VSCR-CST-6500 view-in tester (Vision Science Research Corp.) with a Functional Acuity Contrast Test chart (FACT chart). This instrument allows testing of contrast sensitivity under both mesopic (6 cd/m^2) and photopic (85 cd/m^2) lighting conditions. The chart observed by the patients displays sine-wave gratings at 5 standard spatial frequencies, from 1.5 to 18 cycles per degree. Patients were studied twice, following the examination protocol suggested by the manufacturer of the machine. The log (base 10) of the obtained values was then taken to obtain the contrast sensitivity values that were entered in the database for statistical analysis. A difference level of 0.15 log unit between tests at a given spatial frequency was selected to determine clinical significance (37).

Iris color was noted under standardized room illuminance. Color vision was tested using the Ishihara plates.

The patients' pupils were dilated using one drop of tropicamide 1% and one drop of phenylephrine 2.5% in each eye. Once the pupils were dilated, slit lamp biomicroscopy was performed.

Cataracts were graded for type of cortical, with severity score 0.1–5.9; nuclear opalescence, with severity score 0.1 –6.9; posterior subcapsular zone, with severity score 0.1–5.9; and nuclear, with severity score 0.1–5.9 according to the Lens Opacities Classification System III (38).

Color fundus photographs were taken with a semi-wide angle fundus camera (OPTON SBG, 30 degrees). The photographs were taken of the field centered to the fovea. The classification of AMD from the AREDS (39) was used. Early AMD consists of a combination of multiple small drusen, few intermediate drusen (63 to 124 μ in diameter), or retinal

pigment epithelium abnormalities. Intermediate AMD consists of extensive intermediate drusen, at least one large druse (≥125 μ in diameter), or geographic atrophy not involving the center of the fovea.

Two surgeons performed all the surgeries. Phacoemulsification was performed in all patients using classic divide and conquer phaco technique.

A thorough ophthalmic examination, including careful evaluation of the posterior capsule and the macular area, was performed 8–12 weeks later after the surgery to be sure of intraocular lens (IOL) stabilization and the absence of inflammation.

High-sensitivity CRP was measured by means of particle enhanced immunonephelometry on a BN Systems (BN and CardioPhase are trademarks of Dade Behring Marburg GmbH). The assay protocols are given in the BN Systems Instruction Manual and software of the instrument. All steps were performed automatically by the system.

The detection limit of this assay was 0.175 mg/L, working range 0.175 to 1100 mg/L, analytical sensitivity 0.175 mg/L, coefficient of variation for first level control was 3.7%, second level 2.8% (Dade Behring N/T Rheumatology controls SL). Intra-assay CV was 3.5%, inter-assay CV was 4.2%.

The statistical data analysis was performed by using the computer software programs SPSS/w 13.0 (Statistical Package for Social Sciences for Windows, Inc., Chicago, IL). The data are presented as real numbers (%), mean values and standard deviations (SD). The continuous variables were tested with analysis of variance (ANOVA) followed by Bonferroni test for all two-way comparisons and paired samples *t*-test used accordingly for the comparison of the means for two related samples. Since the test of normality of investigated variables was denied, for comparing the distribution of two independent and two related variables the Mann-Whitney *U* test and the paired Wilcoxon signed-ranks test were used accordingly. Pearson chi-square (χ^2) test was used to analyze the differences for categorical data. The differences were significant at $p<0.05$.

RESULTS AND DISCUSSION

The study population comprised 132 patients at the age of 71.4±6.9 years: 44 (33.3%) male and 88 (66.7%) female. Baseline demographic and clinical characteristics are shown in Table I.

At baseline, 49 (37.1%) of patients had mild and 83

TABLE I - BASELINE DEMOGRAPHIC AND CLINICAL CHARACTERISTICS

	Group 1, n=47	Group 2, n=36	Group 3, n=49	p value
Age ± SD	72.5±7.3	73.4±5.0	69.1±7.2	Group 1–Group 2, NS Group 1–Group 3, <0.05 Group 2–Group 3, <0.05
Male	26 (55.3%)	13 (36.1%)	5 (10.2%)	Group 1–Group 2, <0.05
Female	21 (44.7%)	23 (63.9%)	44 (89.8%)	Group 1–Group 3, <0.0001 Group 2–Group 3, NS
Hypertension	30 (63.8 %)	27 (75.0%)	39 (79.6%)	NS
Smoking	25 (53.2%)	10 (27.8%)	7 (14.3%)	Group 1–Group 2, <0.05 Group 1–Group 3, <0.0001 Group 2–Group 3, NS
Incision in the clear cornea (3.5–4 mm)	23 (48.9%)	26 (72.2%)	—	Group 1–Group 2, <0.05
Incision in the true limbal (6 mm)	24 (51.1%)	10 (27.8%)	—	Group 1–Group 2, <0.05
Foldable IOL	23 (48.9%)	26 (72.2%)	—	Group 1–Group 2, <0.05
Rigid IOL	24 (51.1%)	10 (27.8%)		Group 1–Group 2, <0.05
Duration of the operation (min)	17.80 ± 2.87	17.36 ± 2.59	—	Group 1–Group 2, NS
BMI ± SD	27.62±5.34	27.61±4.21	26.67±3.81	NS
LDL-C ± SD	3.61±0.86	3.71±1.09	3.89±0.89	NS
NHDL-C ± SD	4.29±1.00	4.37±1.20	4.54±1.05	NS

Group 1 = Cataract + age-related macular degeneration; Group 2 = Cataract; Group 3 = Age-related macular degeneration; BMI = Body mass index; LTL-C = Low-density lipoprotein cholesterol; NHDL-C = Non-high-density lipoprotein cholesterol; SD = Standard deviation; NS = Not significant

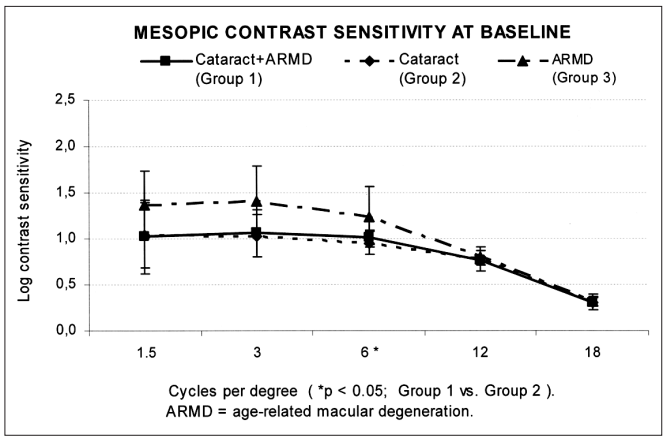

Fig. 1 - *Contrast sensitivity at mesopic (6 cd/m²) lighting conditions at baseline.*

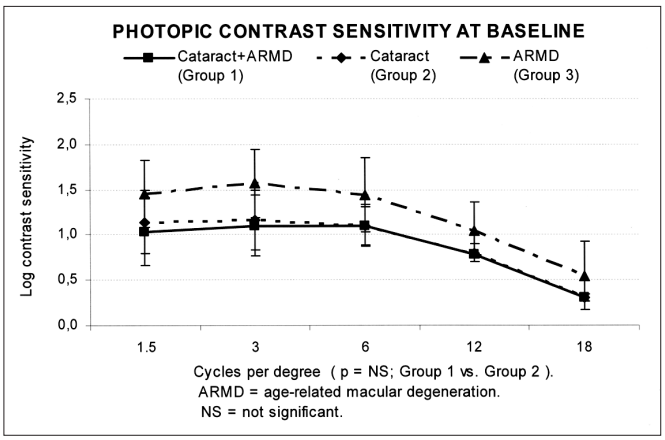

Fig. 2 - *Contrast sensitivity at photopic (85 cd/m²) lighting conditions at baseline.*

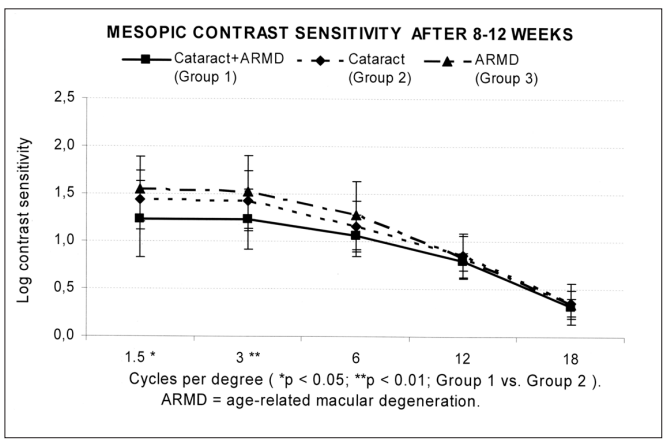

Fig. 3 - *Contrast sensitivity at mesopic (6 cd/m²) lighting conditions 8–12 weeks after baseline assessment.*

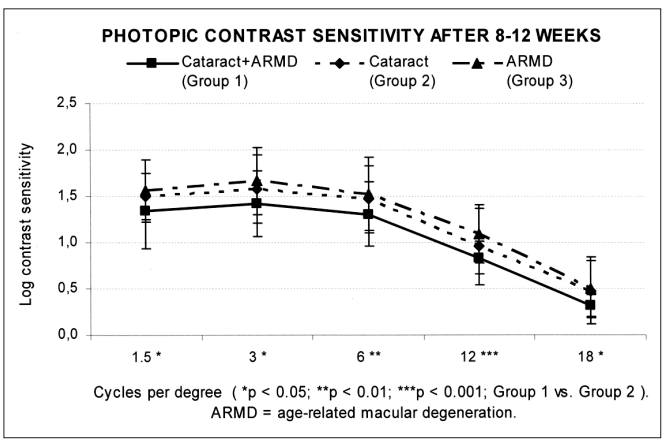

Fig. 4 - *Contrast sensitivity at photopic (85 cd/m²) lighting conditions 8–12 weeks after baseline assessment.*

(62.9%), moderate cataracts. With regard to macular grading, 36 (27.3%) patients had no AMD; 96 (72.7%) had early or intermediate AMD.

No intraoperative complications were recorded in this study. In particular, there were no capsular ruptures or IOL malpositions. The postoperative clinical course was normal in both groups of patients by checking systematically for complications such as CME. However, some different technical elements of cataract surgery and the type of IOL were observed. Incisions in the cornea but not true limbal, smaller incisions (3.5 vs 6 mm) and foldable vs nonfoldable IOL were performed in 23/47 (48.9%) Group 1 patients as compared with 26/36 (72.2%) Group 2 patients ($p<0.05$).

Preoperatively, there was no significant difference in VA between Group 1 and Group 2 (0.23±0.17 vs 0.22±0.17). The mean VA in the operated eyes postoperatively was 0.64±0.25 for Group 1 and 0.83±0.17 for Group 2 patients ($p<0.001$). Using paired samples test for VA in the operated eye postoperatively in both Groups 1 and 2 VA (0.23±0.17 vs 0.64±0.25 and 0.22±0.17 vs 0.83±0.17, respectively, $p<0.0001$) had improved. Meanwhile, VA in Group 3 (0.67±0.30 vs 0.68±0.27) did not change over time.

The results of contrast sensitivity testing are given in Figures 1 and 2. At baseline, there was no significant difference between Group 1 and Group 2 in testing contrast sensitivity at mesopic (6 cd/m^2) lighting conditions at 1.5, 3, 12, and 18 spatial frequencies and at photopic (85 cd/m^2) lighting conditions at all spatial frequencies. However, patients with AMD (Group 3) had significantly greater ($p < 0.001$) contrast sensitivity at photopic and mesopic lighting conditions as compared with both Groups 1 and 2.

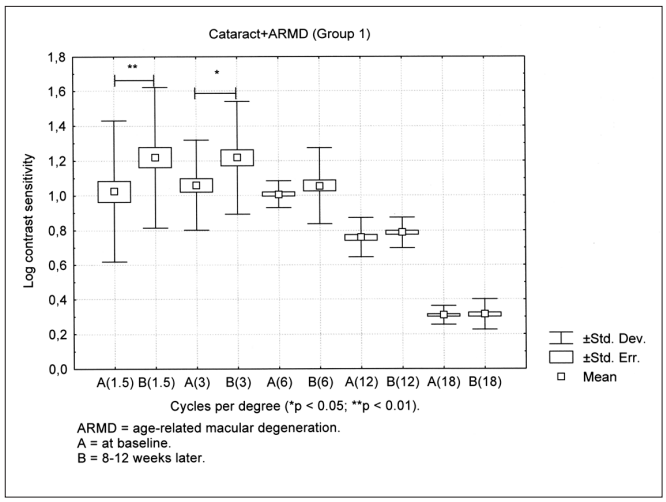

Fig. 5 - *Contrast sensitivity at mesopic (6 cd/m²) lighting conditions in patients with cataract and age-related macular degeneration at baseline and 8–12 weeks later.*

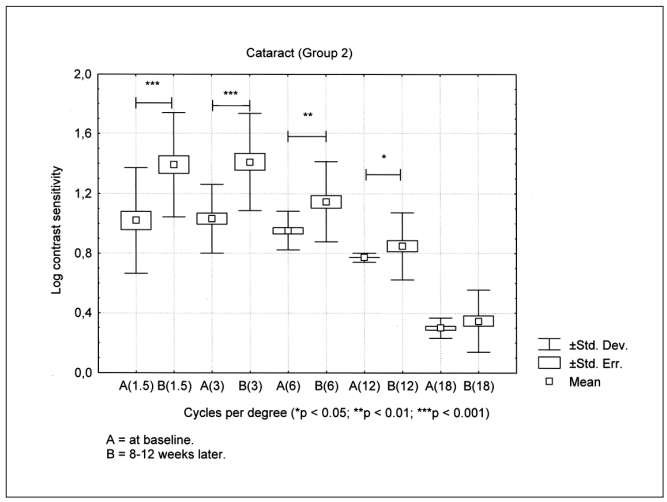

Fig. 6 - *Contrast sensitivity at mesopic (6 cd/m²) lighting conditions in patients with cataract at baseline and 8–12 weeks later.*

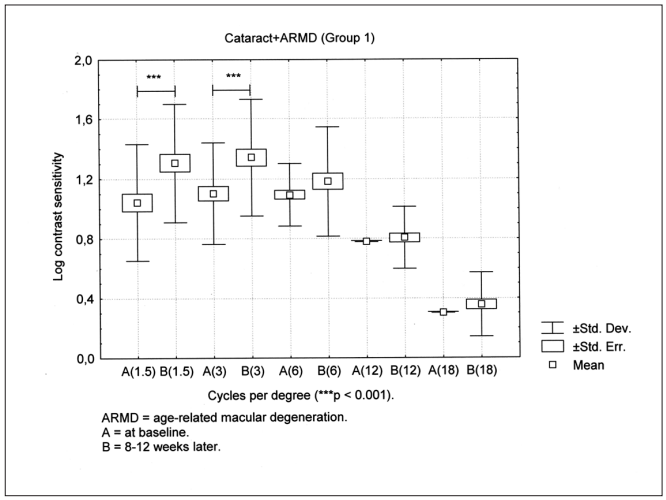

Fig. 7 - *Contrast sensitivity at photopic (85 cd/m²) lighting conditions in patients with cataract and age-related macular degeneration at baseline and 8–12 weeks later.*

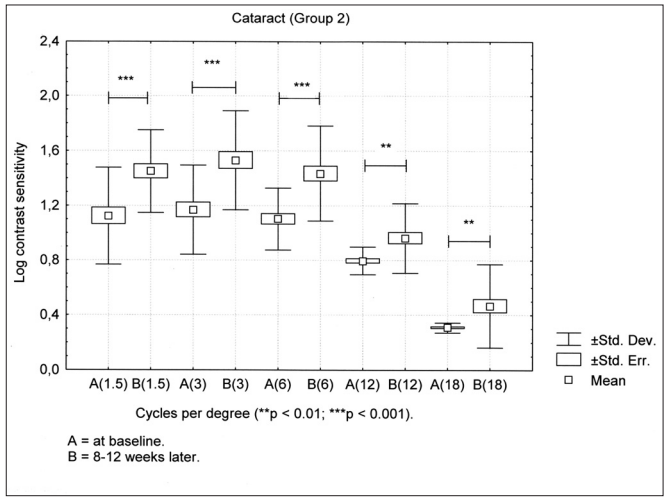

Fig. 8 - *Contrast sensitivity at photopic (85 cd/m²) lighting conditions in patients with cataract at baseline and 8–12 weeks later.*

After an 8- to 12-week follow-up the results of contrast sensitivity testing are given in Figures 3 and 4. The Group 1 eyes showed worse contrast sensitivity than eyes in Group 2 at mesopic lighting conditions at spatial frequencies of 1.5 and 3 cpd and photopic lighting conditions at all spatial frequencies. Moreover, the Group 1 eyes showed lower contrast sensitivity than eyes in Group 3 at mesopic lighting conditions at spatial frequencies of 1.5, 3, and 6 cpd ($p<0.05$, $p<0.001$, $p<0.0001$, respectively) and photopic lighting conditions at all spatial frequencies ($p<0.05$, $p<0.001$, $p<0.0001$, $p<0.0001$, $p<0.01$, respectively). However, in the operated eyes postoperatively in both Groups 1 and 2 contrast sensitivity at mesopic lighting conditions (Figs. 5 and 6) and photopic lighting conditions (Figs. 7 and 8) improved. Meanwhile, contrast sensitivity of Group 3 did not change over time.

It is not surprising that visual acuity and contrast sensitivity improve when cataracts are removed. The results of this study suggest that patients with early and intermediate forms of AMD benefit from cataract surgery, both in

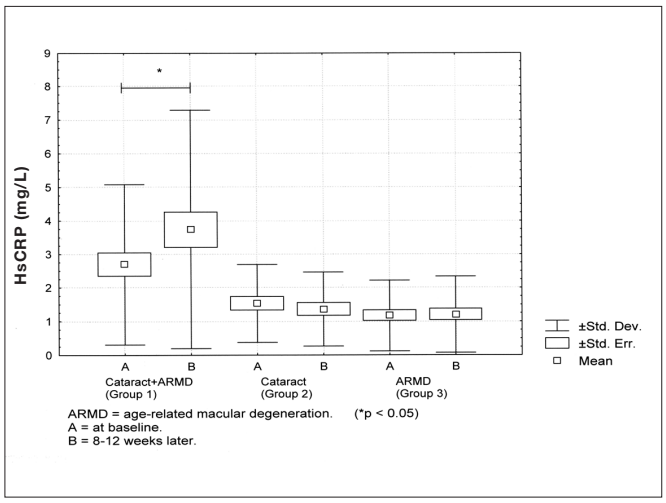

Fig. 9 - *The hsCRP levels at baseline and 8–12 weeks later.*

terms of visual acuity and contrast sensitivity measures. In patients with both AMD and cataract, both disorders contribute to the patient's visual disability. Other investigators found significant improvements in both visual function and quality of life among patients with AMD after cataract surgery in the short term (7-10). Improving visual function can make a significant difference to older people's quality of life and independent living (40). On the other hand, the early deficits of macular function will be losses of contrast sensitivity (41). Consequently, the improvement in contrast sensitivity achieved with cataract surgery in the presence of AMD could contribute significantly to daily living activities that involve the detection of objects at low physical contrasts. Furthermore, patients with AMD with better contrast sensitivity have better visual performance than those with poor contrast sensitivity (42).

At baseline, hsCRP levels in Group 1 patients was higher than levels in Group 2 or Group 3 (2.67±2.36 vs 1.67±1.36 mg/L, $p<0.01$, or 1.12±0.99 mg/L, respectively, $p<0.0001$). There was no significant difference in hsCRP levels between Group 2 and Group 3 patients.

After 8–12 weeks, the differences in hsCRP levels between Group 1 and Group 2 or Group 3 increased (3.74±3.54 mg/L vs 1.67±1.36 or 1.12±1.13 mg/L, respectively, $p<0.0001$). Moreover, using two-tailed paired samples test for hsCRB levels only in Group 1, the hsCRP levels significantly increased (Fig. 9).

Taking into an account that in the absence of acute illness, including myocardial injury, levels of hsCRP are stable (43, 44), we attempted to demonstrate the potential relationships between the levels of hsCRP as a systemic marker of inflammation before and after cataract extraction in patients with AMD. We put forward a hypothesis that cataract extraction might alter or have no effect on the levels of hsCRP in the study population over time. Our data indicate that the association between patients with early or intermediate AMD and moderate cataract and hsCRP was not only restricted to the increased levels hsCRP as compared with patients with one of these eye disorders. Moreover, the study data indicate that the amount of hsCRP does increase with time after the cataract surgery, suggesting that such an effect (if it exists) likely occurs soon after surgery.

Why should Groups 1 and 3 have different hsCRP levels at baseline? The age of Group 1 and Group 2 patients did not differ reliably, whereas the Group 3 patients were significantly ($p<0.05$) younger than the rest of the patients. The number of women in Group 1 was lower than in Group 2 and in Group 3 ($p<0.05$ and $p<0.0001$, respectively). In accordance with the lifestyle, body mass index, blood lipidogramme, previous drug treatment, and arterial hypertension in history, the studied patient groups did not differ, with an exception of cigarette smoking—more smokers were among Group 1 patients than among the study participants in Group 2 ($p<0.05$) or Group 3 ($p<0.0001$).

Several logistic regression models using SPSS 13.0 statistical software were applied. In a model that included age, gender, hsCRP level at baseline, smoking, body mass index, total cholesterol, LDL cholesterol, DTL cholesterol, triglyceride glucose levels, and systolic blood pressure, only gender ($p<0.03$) and hsCRP ($p<0.002$) showed significant association with cataract and AMD (Group 1). The adjusted odds ratio (OR) for gender was 0.27 (95% confidence interval [CI], 0.09–0.86), and the ajusted OR for hsCRP level was 1.65 (95% CI, 1.2–2.28).

Interestingly, we have demonstrated that there is considerable stability in the measurement of the amount of hsCRP in the study controls even in patients without AMD after cataract surgery over time. In tackling these results, why cataract surgery might possibly increase levels of hsCRP in one patient while it did not change in another might be explained by the differences in the location and size of the incision. Smaller incisions (3 to 4 mm) (45, 46) and incisions in the cornea result in lower early postoperative inflammation than true limbal incisions (47). In this study, the location and size of the incision depended on

the type of the implanted IOL. The true limbal incisions, greater incisions, and implantation of nonfoldable IOL were more frequently ($p<0.05$) performed in patients with AMD (51.1%) than in patients with cataract (27.8%). On the other hand, several logistic regression models that included the duration of the operation, location, size of the incision, and type of IOL have shown no significant association with hsCRP levels over time.

AMD is a complex multifactorial disorder with poorly understood pathogenesis. Friedman (48) proposed a hypothesis that AMD is a vascular disorder, which reflects both structural and hemodynamic factors in the pathogenesis of AMD. On the other hand, both the environment and multiple genes can alter a patient's susceptibility to AMD (49). Anatomic studies (50-53) provided initial evidence for the role of inflammation in choroidal neovascularization formation in AMD. Subsequently, molecular evidence for the role of inflammation in AMD pathogenesis has been developed and summarized by Hageman et al (54), Johnson et al (55), and Anderson et al (56).

Data from the Age-Related Eye Disease Study (35) showed that CRP was an independent risk factor for AMD, and levels of CRP and homocysteine were elevated significantly in individuals with AMD vs similar unaffected controls, and these factors remain associated with AMD upon adjustment for covariates of potential influence (57). In contrast, in the Cardiovascular Health Study (58) there was no association between CRP and AMD.

As there were a number of limitations in the present study, we could overlook the inherent possibility that constitutional and genetic variations within the CRP gene might influence both baseline and stimulate CRP levels (59). Some authors report that CRP levels fluctuate and vary in relation with gender and ethnicity (60). The study was limited by a rather short follow-up period and nonrandomized design due to ethical issues and problems related to randomization, masking, and objective assessment of benefits versus risk.

It is difficult to determine from this type of study design whether cataract surgery in some way may predispose an eye to develop AMD or increase progression from early to late AMD in eyes after surgery through inflammatory mechanisms. However, our data indicate that the hsCRP levels increase with time after cataract surgery only in patients with early or intermediate AMD. Thus, it would be helpful if additional studies could clarify the nature of this association.

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