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Endothelial function, intima-media thickness, and ankle-brachial index in patients with cataract and age-related macular degeneration

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PURPOSE. *To evaluate the association between cardiovascular risk factors, including endothelial dysfunction, increased intima-media thickness (IMT) of the carotid arteries, ankle-brachial index (ABI), and age-related macular degeneration (AMD), and cataract.*
METHODS. *Forty-seven patients with AMD and cataract, 35 with cataract only, and 49 with AMD were included. Carotid ultrasound, ischemia-induced brachial artery reactivity test, and ABI in conjunction with investigation of conventional cardiovascular risk factors were performed.*
RESULTS. *Increased levels (more than 1.23 mg/L) of high-sensitivity C-reactive protein (hsCRP) and IMT (more than 0.97 mm) increased prevalence odds for AMD and cataract 3.1 and 3.9 times, respectively.*
CONCLUSIONS. *Elevated hsCRP or increased IMT of the carotid arteries are associated with comorbid cataract and AMD, whereas there were no reliable differences between groups in respect to endothelial function and ABI. (Eur J Ophthalmol 2008; 18: 384-91)*

KEY WORDS. *Age-related macular degeneration, Ankle-brachial index, Cataract, Endothelial function, Intima-media thickness*

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INTRODUCTION

Both cataract and age-related macular degeneration (AMD) are common findings in the aging eye. They are two of the most important causes of decreased vision in the majority of developed countries, including Lithuania (1, 2). The relationship between these blinding diseases remains a topic of active investigation. Most investigators agree that pathogenesis of AMD is multifactorial and that it results from the interaction of genetic, environmental, and aging factors (3). Friedman (4) has raised a hypothesis that AMD is a vascular disorder conditioned by structural and hemodynamic factors. Some epidemiologic studies have identified an association between cardiovascular disease risk and AMD (5). Atherosclerosis has for a long time been hypothesized as a possible risk factor for AMD development, mainly via processes involving lipid deposition and its effects on the choroidal vasculature (4, 6). Furthermore, cataract is also an age-related disease. Certain types of cataract and AMD might occur together more frequently as cataract and AMD share one or more common risk factors (7-9).

There is enough strong base for use of carotid ultrasonography, brachial artery reactivity testing, and assessing the ankle-brachial index (ABI) in the noninvasive detection of the functional or anatomic manifestations of atherosclerosis (10). Thus obtained new noninvasive markers of atherosclerosis provide additional information on pathogenesis of the disorder beyond the traditional cardiovascular risk factors.

The aim of the study was to evaluate the association between cardiovascular risk factors, including endothelial dysfunction, increased intima-media thickness (IMT) of the carotid arteries, and ABI, in patients with AMD or cataract and with coexistent AMD and cataract.

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MATERIALS AND METHODS

Study sample

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 was to determine the association between AMD and morphologic changes in the cardiovascular system (11). 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 comprised patients scheduled for cataract surgery with no other ocular comorbidity (n=35). Patients in Group 1 or 2 could have moderate cataract with an assigned severity score from two to four. Group 3 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. Patients in the groups could have cataract but their fundus photographs had to be clear enough to allow grading of the AMD.

The assessment commenced with a brief medical and ocular history.

Information on smoking habits and current use of medication was derived from the baseline interview. Hypertension was assessed by the current use of antihypertensive medications, reported by the patient. Stroke, diabetes mellitus, family history of coronary artery disease, and family history of AMD were defined as reported by the patient. Cigarette smoking was defined as active and past smoking.

Physical examination variables included body mass, stature, waist circumference, and systolic and diastolic blood pressures. Stature and body mass were measured to the nearest 0.5 cm and 100 g, respectively. Body mass index was calculated as body mass/stature^2 (kg/m^2) and was used as an estimate of an overall adiposity. Waist circumference, a validated estimate of abdominal adiposity, was measured to the nearest 0.5 cm, using a steel tape. Blood pressure was measured three times in the right arm of seated subjects with standard mercury sphygmomanometer after a 5-minute still rest. The three readings were averaged for analysis.

The subjects were asked to abstain from food and drinks for 12 to 14 hours preceding the blood sampling. Total cholesterol, low density lipoprotein (LDL) cholesterol, high density lipoprotein (HDL) cholesterol, triglycerides, glucose, and high sensitivity C reactive protein (hsCRP) were measured. HsCRP 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* System Instruction Manual and software of the instrument. All steps were performed automatically by the system.

Visual acuity (VA) was obtained using 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 contrast sensitivity at mesopic (3 cd/m^2) and photopic (85 cd/m^2) luminance. The chart observed by the patients displays sine-wave gratings at five standard spatial frequencies, from 1.5 to 18 cycles per degree. Patients were studied following the examination protocol suggested by the manufacturer of the machine. The log of the obtained values was then taken to obtain the contrast sensitivity values that were entered in the database for statistical analysis (12).

Iris color was noted under standardized room illuminance. Color vision was tested using the Ishihara pseudo-isochromatic 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, a 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 (13).

Color fundus photographs were taken with a semi-wide angle fundus camera (OPTON SBG, 30 degrees). The photographs were taken of the field center to the fovea. The classification of AMD from the Age-Related Eye Disease Study (14) was used. Early AMD consists of a combination of multiple small drusen, few intermediate

drusen (63 to 124 μm in diameter), or retinal pigment epithelium abnormalities. Intermediate AMD is characterized by extensive intermediate drusen, at least one large (giant) druse (≥125 μm in diameter), or geographic atrophy not involving the center of the fovea.

The wall thickness of the carotid artery was assessed by means of an Acuson Sequoia C 256 scanner equipped with a 7.5 MHz linear array transducer, two windows for displaying the B-mode ultrasound images, and spectrum analysis of the Doppler signals. Three 10-mm segments were scanned bilaterally: the distal portion of the common carotid artery, the carotid bifurcation, and the proximal portion of the internal carotid artery. All the images were recorded on a videotape. In the supine position, the left and right carotid arteries, near and far walls were examined longitudinally at the angle that resulted in an optimal the IMT. IMT was defined as a distance between the leading edge of the lumen–intima interface and the leading edge of the media–adventitia interface. For each segment, three R wave-triggered images were stored. The three IMT measurements were averaged. The interobserver correlation coefficient for IMT measurements was 0.87. Intraobserver variability was detected with a correlation coefficient 0.92.

For each individual, an IMT was determined as an average of near and far wall measurements (excluding sites of plaque) of the left and right carotid arteries. Plaques were defined as focal widenings relative to adjacent segments with protrusion into the lumen composed of either only calcified deposits or a combination of calcified and noncalcified materials and demonstrating a thickness of ≥1.5 mm as measured from the media-adventitia interface to the intima-lumen interface.

Endothelial function was analyzed by the brachial artery ultrasound test. This test was performed for all participants by means of the same echocardiograph and transducer like for IMT measurement. Flow-mediated dilation (FMD) was assessed in the subject's right arm in the recumbent position according to the Guidelines for the Ultrasound Assessment of Endothelial-dependent Flow-mediated Vasodilation of the Brachial Artery (15). The artery was longitudinally imaged approximately 5 cm proximal to the antecubital crease, and brachial artery diameter was measured at end-diastole. After the baseline resting scan, a pneumatic cuff placed at the level of the mid-forearm (proximal to the target artery) was inflated to 220 mm Hg for 5 min. An increased flow was then induced by a sudden cuff deflation, and a continuous scan was performed for 1 min. For the reactive hyperemia scan, the longitudinal image of the brachial artery was recorded continuously during 2 min after the cuff deflation. FMD was expressed as a percent variation of the brachial artery diameter. The flow-mediated dilator response was used as a measure of endothelium-dependent vasodilation.

Then 0.5 mg of nitroglycerin was given sublingually, and the brachial artery was imaged for the ensuing 3–4 min to measure the peak diameter. The response to nitroglycerin (nitroglycerin-mediated dilation) is a measure of endothelium-independent vasodilation. The interobserver and intraobserver coefficients of variations for measurements of FMD were 4.2% and 3.3%, respectively.

For ABI measurement the patient was placed in a supine position, and the brachial and ankle systolic pressure measurements were obtained. The higher systolic pressure of the anterior tibial or posterior tibial measurements for each foot was divided by the highest brachial systolic pressure to obtain an ankle-brachial pressure ratio. We chose the higher of these two values as brachial artery pressure measurement and measured the left anterior tibial and posterior tibial arterial systolic pressures. The chosen ankle pressure measurement was divided by the previously chosen brachial artery systolic pressure measurement. ABI value less 0.9 was considered as abnormal (16).

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, USA). The data are presented as real numbers (percentages), 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* tests were used accordingly for the comparison of the means for two related samples. Since the test of normality of investigated variables was denied, for the comparison the distribution of two independent and two related variables were used according to the Mann-Whitney *U* test and the paired Wilcoxon signed ranks test. Pearson chi-square test was used to analyze the differences for categorical data. The binary logistic regression model was used for detection of associations between cardiovascular risk factors and AMD and cataract. Differences were considered significant at $p<0.05$.

RESULTS

Demographic and clinical characteristics are shown in Table I. A total of 132 subjects (44 male and 88 female, mean age 71.5±7 years) were investigated. Forty-nine (37.1%) patients had mild and 83 (62.9%) moderate cataracts. With regard to macular grading, 36 (27.3%) patients had no AMD; 96 (72.7%) had early or intermediate AMD.

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 style of life, body mass index, blood lipidogram, previous drug treatment, and arterial hypertension in history, the studied patient groups did not differ, with an exception of cigarette smoking, with more

TABLE I - GENERAL CHARACTERISTICS OF THE STUDY POPULATION

Variable	Group 1	Group 2	Group 3	p value
Age, yr	72±7	73±5	69±7	p1,3=0.01 p2,3=0.003
Male	26 (55.3)	13 (36.1)	5 (10.2)	p1,2=0.03 p1,3=0.001 p2,3=0.002
Systolic blood pressure, mmHg	150± 22	154±25	156±28	NS
Diastolic blood pressure, mmHg	82±13	84±10	84±13	NS
Mass, kg	77±15	76±12	71±13	p1,3=0.02
Stature, cm	167±9	166±6	162±8	p2,3=0.03 p1,3=0.004
BMI, kg/m^2	27.6±5.3	27.6±4.2	26.7±3.8	NS
Waist circumference, cm	30 (63.8)	27 (75.0)	39 (79.6)	NS
Arterial hypertension	30 (63.8)	27 (75)	39 (79.6)	p1,3=0.04
Family history of stroke	5 (10.6)	5 (13.9)	16 (32.7)	p2,3=0.032 p1,3=0.006
Family history of CAD	6 (12.8)	1 (2.8)	6 (12.8)	NS
Cigarette smokers	25 (53.2)	10 (27.8)	6 (12.2)	p1,2=0.016 p1,3=0.00
Diabetes mellitus	2 (4.3)	3 (8.3)	2 (4.1)	NS
Family history of AMD	0 (0)	0 (0)	4 (8.2)	p1,3=0.03 p2,3=0.04
Family history of cataract	8 (17.0)	7 (19.4)	6 (12.3)	NS
Total cholesterol, mmol/L	5.7±0.8	5.7±1.3	6.1±1.1	NS
LDL cholesterol, mmol/L	3.6±0.9	3.7±1.1	3.9±0.9	NS
HDL cholesterol, mmol/L	1.3±0.4	1.3±0.3	1.5±0.4	p1,2=NS p2,3=0.005 p1,3=0.002
Triglycerides, mmol/L	1.6±0.6	1.6±0.7	1.5±0.9	NS
Fasting glucose, mmol/L	5.3±0.8	5.4±1.0	5.4±0.6	NS
High-sensitivity CRP, mg/L	2.81±2.49	1.71±1.37	1.12±0.99	p1,2=0.008 p2,3=NS p1,3=0.0001
Hemoglobin, g/L	140±11	135±14	137±10	p1,2=0.037 p2,3=NS p1,3=NS
WBC ×10/9 L	6.4±1.2	5.9±1.4	6.2±2.2	NS
RBC ×10/12 L	4.6±0.3	4.3±0.6	4.4±0.5	p1,2=0.01 p2,3=NS p1,3=NS
PLT ×10/9 L	227±64	223±55	244±77	NS

Values are mean ± SD or n (%).

BMI = Body mass index; CAD = Coronary artery disease; AMD = Age-related macular degeneration; LDL = Low density lipoprotein; HDL = High density lipoprotein; CRP = C-reactive protein; WBC = White blood cells; RBC = Red blood cells; PLT = Platelets

smokers in Group 1 than in Group 2 ($p<0.05$) or Group 3 ($p<0.0001$). Also, more parents of Group 3 patients had had cerebral stroke than parents of Group 1 or Group 2 patients ($p<0.05$).

There was no difference in blood pressure, body mass index, white blood cell count, or blood lipids except HDL cholesterol concentration. Baseline hsCRP levels ranged from 0.15 to 9.58 mg/L, with a median of 1.23 mg/L. hsCRP levels in Group 1 patients were higher than levels in Group 2 or Group 3 (2.81±2.49 vs 1.71±1.37 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.

There was no significant difference in VA between Group 1 and Group 2 patients (0.23±0.17 vs 0.22±0.17). VA in Group 3 patients was significantly greater than in Group 1 and Group 2 patients (0.67±0.30 vs 0.23±0.17 or 0.22±0.17, respectively; $p<0.001$).

There was no significant difference between Group 1 and Group 2 in contrast sensitivity assessed at mesopic luminance of 3 cd/m^2 and linear sine-wave gratings of 1.5, 3, 12, and 18 cycles per degree (cpd) and at photopic luminance of 85 cd/m^2 in all spatial frequencies. However, patients with AMD (Group 3) had significantly greater ($p<0.001$) contrast sensitivity at photopic and mesopic luminance than Group 1 and Group 2 patients.

Median IMT value was 0.97 mm (range 0.73–1.48 mm). The intimal thickening of the common carotid artery, bifurcation, and internal carotid artery was significantly greater in Group 1 patients than in Group 2 and Group 3 subjects (Tab. II). The prevalence of carotid plaques did not differ significantly in the study groups.

The studied groups did not differ in mean endothelium-dependent vasodilation after ischemia induced by the pressure in a sphygmomanometer cuff and in endothelium-independent vasodilation after sublingual administra-

TABLE II - INTIMA-MEDIA THICKNESS (IMT) OF THE CAROTID ARTERY

Parameters	Group 1	Group 2	Group 3	p value
CCA far wall IMT (mm)	1.00±0.19	0.89±0.13	0.85±0.14	p1,2=0.008 p1,3=0.0001 p2,3=NS
Far wall bulbus IMT, mm	1.22±0.26	1.11±0.2	1.11±0.19	p1,2=0.028 p1,3=0.018 p2,3=NS
ICA far wall IMT, mm	0.98±0.22	0.84±0.14	0.88±0.19	p1,2=0.001 p1,3=0.011 p2,3=NS
Mean IMT, mm	1.07±0.17	0.96±0.13	0.96±0.13	p1,2=0.002 p1,3=0.0001 p2,3=NS

CCA = common carotid artery; ICA = internal carotid artery.

TABLE III - ENDOTHELIAL FUNCTION PARAMETERS AND ANKLE-BRACHIAL INDEX

Parameters	Group I	Group II	Group III	p value
FMD, %	4.59±5.23	3.92±4.84	5.37±4.75	NS
NMD, %	13.68±6.1	12.43±6.6	15.43±6.17	NS
Right ABI	1.08±0.15	1.09±0.16	1.03±0.14	NS
Left ABI	1.05±0.15	1.07±0.15	1.01±0.13	NS

FMD = Flow-mediated dilation; NMD = Nitroglycerin-mediated dilation; ABI = Ankle-brachial index

tion of nitroglycerin (Tab. III). The prevalence of endothelial dysfunction (FMD < 5%) was not significantly different among studied groups (Group 1 43% vs Group 2 40% vs Group 3 49%). There was no significant difference among these three groups in the recorded ABI.

In binary logistic regression model that included age, gender, smoking, body mass index, total cholesterol, LDL cholesterol, DTL cholesterol, triglyceride, glucose level, white blood cell count, systolic blood pressure, hsCRP, and IMT, only hsCRP level and IMT (Tab. IV) showed significant associations with coexistent AMD and cataract group (Group 1).

DISCUSSION

Patients with AMD and cataract more often were male, were cigarette smokers, and had more thickened intima-media in the carotid arteries than patients with only one disorder: cataract or AMD. In multivariate analysis, elevated hsCRP level and increased IMT of the carotid artery were more characteristic of Group 1. These findings confirm importance of atherosclerotic process, cigarette smoking, and inflammation in development of comorbid cataract and AMD.

Patients with only AMD were younger, were more often female (therefore, with lower stature), and more often had parents with stroke because of greater prevalence of arterial hypertension in them (the latter finding was determined only in comparison with comorbid patients). Multivariate analysis did not confirm association between these factors and AMD only.

Most studies analyzed risk factors for cataract or AMD separately. Atherosclerosis has for a long time been hypothesized as a key pathogenic factor for AMD (17, 18). Several investigators have suggested that increased arterial blood pressure and atherosclerosis, by virtue of their effects on the choroidal circulation and lipid deposition in Bruch membrane, may be related to AMD pathogenesis (4, 6). Our data also confirm significance of arterial hypertension in development of AMD.

Recent studies have shown that middle-aged persons with signs of early stage AMD have a higher risk of stroke, independent of traditional stroke risk factors (19). In the Rotterdam Study, plaques in the carotid bifurcation were shown to be associated with a 4.7 times increased prevalence odds of macular degeneration (95% CI, 1.8–12.2); those with plaques in the common carotid artery, with an increased prevalence odds of 2.5 (95% CI, 1.4–4.5) (17). The IMT of the common carotid arteries in patients with AMD did not significantly differ from the thickness in patients without the disorder (17). Moreover, measures of arterial stiffness (pulse pressure) and atherosclerosis (carotid IMT) appeared also not to be associated with early AMD (20). However, interactions of race/ethnicity and early AMD were found for the carotid IMT, increasing severity of maximum carotid artery stenosis, serum triglyceride level, subclinical cardiovascular disease

TABLE IV - LOGISTIC REGRESSION MODEL FOR PREDICTION OF GROUP 1 (patients with cataract and age-related macular degeneration)

Factor	Adjusted OR	OR (95% CI)	p value
Age	1.0	0.93, 1.07	0.98
Gender	0.33	0.09, 1.21	0.09
Cigarette smoking	3.12	0.93, 10.77	0.07
Systolic BP	0.98	0.96, 1.00	0.12
BMI	1.02	0.91, 1.13	0.76
Cholesterol	2.11	0.12, 36.27	0.61
HDL cholesterol	0.17	0.01, 4.52	0.29
LDL cholesterol	0.33	0.02, 6.37	0.33
Triglycerides	1.05	0.29, 3.83	0.94
White blood cells	1.02	0.69, 1.5	0.93
Glucose	0.68	0.35, 1.33	0.26
hsCRP (median)	3.17	1.16, 8.69	0.03
Mean IMT (median)	3.9	1.41, 10.83	0.01

BP = Blood pressure; BMI = Body mass index; LDL = Low density lipoprotein; HDL = High density lipoprotein; hsCRP = High sensitivity C-reactive protein; IMT = Intima-media thickness

severity, and Agatston calcium score (21). In our study, patients with coexistent AMD and cataract had a more thickened carotid intima-media than patients with only one of the disorders: AMD or cataract. The relation between the comorbidity of both the disorders and a thickened intima-media as a sign of atherosclerosis was confirmed by a logistic analysis.

Interestingly, there were no significant differences between the patient groups in respect of endothelial function and signs of peripheral artery disease–ABI. It is known that the endothelium plays a critical role in regulating vascular tone and structure. The single-cell layer lining all blood vessels releases a panoply of paracrine factors that effect vasomotion and vascular structure via interaction with circulating blood elements. In atherogenesis, endothelial dysfunction is the earliest measurable functional abnormality of the vessel wall and it is closely related to the risk factors for atherosclerosis (15, 16). Our findings may be related to a temporal dissociation between functional and structural vascular abnormalities in the studied population; indeed, many patients already had a vascular disease by the time they were clinically diagnosed with AMD and cataract or thickened intima-media, endothelial function, and therefore ABI, could provide distinct information identifying different stages in atherogenesis. Prospective data are needed to confirm the significance and temporality of these cross-sectional observations and to address the issue of causality.

CRP, a marker of the systemic inflammation, has been shown to be an independent indicator of risk for cardiovascular and peripheral arterial disease (22). In the Age-Related Eye Disease Study, CRP levels were shown to be significantly associated with the presence of intermediate and advanced stages of AMD. The odds ratio for the highest vs the lowest quartile of CRP was 1.65 (95% CI, 1.07–2.55; p for trend=0.02) (23). In our study, elevated hsCRP level above median increased probability of comorbidity of cataract and AMD three times in respect of only cataract or only AMD.

The main limitations of our study were a small number of patients and age and sex differences between the studied groups of subjects.

CONCLUSIONS

Cardiovascular risk factors like elevated high-sensitivity CRP or increased IMT of the carotid arteries were found to be associated with comorbid cataract and AMD, whereas there were no reliable differences between AMD and cataract or both disorders in respect to endothelial function and an indicator of peripheral artery disease–ABI.

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