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Early age-related maculopathy and risk factors of cardiovascular disease in middle-aged Lithuanian urban population

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PURPOSE. *To assess the prevalence of age-related maculopathy (ARM) in a middle-aged urban population and the relationship between ARM and the main risk factors of cardiovascular disease (CVD).*

METHODS. *The survey according to the WHO MONICA study protocol was carried out in Kaunas city, Lithuania, from 2001 to 2002. A total of 1403 persons aged 35 to 64 years were screened (626 men and 777 women: response rate 62.4%). Ophthalmologic investigation was performed for 1337 respondents (594 men and 743 women). Analysis of the relationship between ARM and risk factors of CVD was performed in case-control subdivision matching for sex, age, and education level.*

RESULTS. *Early ARM was diagnosed in 7.4% of men and 5.4% of women. Rate of current smoking in case and control groups did not differ in men but in case group of women it was greater than in control group. Mean systolic and diastolic blood pressure and body mass index (BMI) in male case group and mean fasting blood glucose concentration in female case group were higher than in corresponding control groups. Frequency of diastolic hypertension (diastolic blood pressure ≥90 mmHg) and obesity (BMI ≥30 kg/m^2) in male case group was higher than in control group. ARM was not associated with cholesterol and triglyceride levels in men and women.*

CONCLUSIONS. *Early ARM in middle-aged Lithuanian urban population was associated with current smoking in women but not in men; it was associated with diastolic blood pressure and BMI in men and with fasting glucose level in women. (Eur J Ophthalmol 2005; 15: 255-62)*

KEY WORDS. *Age-related maculopathy, Smoking, Arterial hypertension, Obesity, Hyperglycemia, Hypercholesterolemia, Hypertriglyceridemia*

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INTRODUCTION

Age-related maculopathy (ARM) is a degenerative disorder of the central area of the retina (the macula) often associated with visual impairment. The early stages of this pathology are characterized by the development of drusen and pigmentary abnormalities of retinal pigment epithelium (RPE) (hyper- and hypopigmentation). Later stages of ARM comprise two types: geographic atrophy and exudative age-relat-

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ed macular degeneration (ARMD). Degenerative conditions of the macula, which have been estimated to affect about 0.5% of Americans over the age of 40 years, steeply increase in prevalence with age (1). ARM is the most important cause of visual loss in developed countries (2, 3). In this part of the world ARM seems to exceed the other three major causes of blindness: cataract, diabetic retinopathy, and glaucoma. Therefore, there is considerable interest in preventing development of ARM, especially as there is no treatment that can restore vision in ARMD.

Although the natural history of ARM has been described, its pathogenesis remains poorly understood. Interest in the role of vascular factors has led to investigations of traditional cardiovascular disease (CVD) risk factors in the development of ARM (1, 4-7). We have already reported the relationship of ocular and social factors with ARM in a middle-aged Kaunas city population cohort (8).

The frequency of ARM in eyes with light iris color was higher than in eyes with dark iris color but the association was not significant. No significant associations were found between cataract (all types or nuclear cataract) and ARM. Exposure to noxious work was found to increase risk of ARM: the prevalence of ARM was significantly increased among men whose work conditions were associated with high temperature (8).

In this article we present the prevalence of ARM in the middle-aged urban population and the relationship between early ARM and the main risk factors of CVD: smoking, arterial hypertension, obesity, hyperglycemia, and hyperlipidemias.

MATERIALS AND METHODS

Subjects of the study

The survey according to the WHO MONICA study (MONItoring of trends and determinants in CArdiovascular disease) protocol (9) was carried out in Kaunas (Lithuania) from 2001 to 2002.

A random sample of subjects aged 35 to 64 was selected. The sample was stratified by age and sex so that at least 200 men and women would be screened in every 10-year age group (35–44, 45–54, 55–64). Health survey was performed by the scientific staff of the Institute of Cardiology of Kaunas University of Medicine. A total of 1403 persons were screened (626 men and 777 women: response rate 62.4%).

Ophthalmologic investigation was performed for 95.3% of respondents in the random sample of health survey. The responders were investigated for ARM, cataract, and glaucoma. Ophthalmologic investigation was performed by scientific staff the Institute for Biomedical Research of Kaunas University of Medicine (head, Prof. A. Paunksnis). The total number of responders of the

TABLE I - NUMBER OF ALL RESPONDERS OF HEALTH SURVEY AND NUMBER OF RESPONDERS INVESTIGATED OPTHALMOLOGICALLY DISTRIBUTED INTO 10-YEAR AGE GROUPS

	All responders of the health survey cohort			Number of persons from the health survey cohort examined ophthalmologically		
Age groups, yr	Both sexes, N	Men, N	Women, N	Both sexes, N (%)*	Men, N (%)*	Women, N (%)*
35–44	425	201	224	411 (96.7%)	195 (97.0%)	216 (96.4%)
45–54	482	204	278	460 (95.4%)	194 (95.1%)	266 (95.7%)
55–64	496	221	275	466 (92.8%)	205 (94.0%)	261 (94.9%)
Total number	1403	626	777	1337 (95.3%)	594 (94.9%)	743 (95.6%)

*Percent of responders of the study examined ophthalmologically

health survey and the number of responders from the study for ophthalmologic investigation distributed into 10-year age groups are shown in Table I.

Ophthalmologic investigations

Responders of the health survey underwent a comprehensive ophthalmic examination that included distant visual acuity test using the chart of C optotypes arranged after the Snellen principle, Schiotz tonometry (Riester, Germany), lens grading at the slit lamp using LOCS III (10), stereoscopic fundus examination using an indirect ophthalmoscope, and a slit lamp biomicroscope with a "superfield lens" (Volk, Mentor, OH) after pupil dilatation with 0.5% tropicamide. Scotoma and metamorphopsia were demonstrated with the Amsler's chart.

Color fundus photographs (Fuji 200 film) centered to the fovea were taken with a semi-wide angle fundus camera (OPTON SBG, 30 degrees). The presence of ARM was based on the fundus examinations by indirect ophthalmoscopy, slit lamp, and color fundus photographs. We used the International ARM Epidemiological Study Group grading protocol (11). This protocol divides ARM into early and late stages. Early ARM is defined as the presence of drusen or RPE pigmentary abnormalities within the grid in the absence of late ARM in either eye. The protocol distinguishes two types of late ARM: exudative ARM and geographic atrophy (sharply delineated roughly round or oval areas of apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas).

TABLE II - AGE- AND SEX-SPECIFIC PREVALENCE OF EARLY AGE-RELATED MACULOPATHY (ARM) AMONG KAUNAS CITY INHABITANTS AGED 40–64 YEARS

Age groups, yr	Men		Women	
	n/N	%	n/N	%
40-44	2/108	1.9	2/114	1.8
45-49	7/97	7.2	4/150	2.7
50-54	12/97	12.4	6/116	5.2
55-59	12/116	10.3	16/171	9.4
60-64	11/89	12.4	12/90	13.3
Total	44/507	8.7	40/641	6.2

N = number of persons investigated for ARM; n = number of cases with ARM

Cut-off points of risk factors of CVD

Information on smoking habits was obtained with the use of a standard questionnaire. Cigarette smoking status at the time of the examination was determined as follows. A subject was classified as current smoker if he or she smoked at least one cigarette per day and as being an ex-smoker (former smoker) if he or she had smoked at least one cigarette per day in his or her lifetime but had stopped smoking before the examination (12).

Arterial blood pressure was measured two times at each examination, and the average values were used for the analysis. Systolic hypertension was defined as systolic blood pressure ≥140 mmHg; diastolic hypertension was defined as diastolic blood pressure ≥90 mmHg. Body weight and height were measured in light clothing without shoes, and body mass index (BMI) was calculated as body weight (kg) divided by height squared (m^2).

Obesity was defined as BMI ≥30 kg/m^2. Concentration of glucose in capillary blood was determined by individual glucometer (13). Hyperglycemia was defined as a fasting glucose level ≥6.1 mmol/L. Serum total cholesterol and triglycerides concentrations were determined enzymatically: cholesterol by CHOD-PAP Monotest, Boehringer-Mannheim (14) and triglycerides by GPO-PAP method (15). High cholesterol level was defined as a total cholesterol level ≥6.2 mmol/L, hypertriglyceridemia as a serum triglycerides level ≥2.3 mmol/L.

Statistical methods

We defined a subject as having ARM if the subject had ARM in at least one eye. The association of the variables with ARM was assessed using Student t-test (unpaired) for the continuous variables and Pearson χ^2 test for the categorical variables. In this work data analysis was performed in case-control subdivision.

Case persons with ARM and control subjects were matched for age, sex, and education level. Logistic

regression analysis was performed to determine risk factors for ARM using odds ratio estimates with 95% confidence intervals (CI); p values of <0.05 were considered to be significant.

RESULTS

Prevalence of ARM

According to data of 1337 ophthalmologically investigated persons (594 men and 743 women) aged 35 to 64 years ARM was diagnosed in 84 persons: 44 men (7.4%) and 40 women (5.4%). The youngest persons with ARM were a woman aged 42 years and a man aged 44 years. All 84 subjects had an early stage of ARM.

Among persons with ARM soft drusen were observed in 94.0%, hypopigmentation in 9.5%, and hyperpigmentation in 14.3% of cases. ARM was diagnosed in one eye in 27 men (4.5%) and 20 women (2.7%) and in both eyes in 17 men (2.9%) and 20 women (2.7%).

Because in the investigated cohort the youngest person with ARM was 42 years old, further analysis of data was performed for 1148 persons aged 40 to 64 years (507 men and 641 women). After distribution of those persons into five 5-year age groups the percent rate of early ARM remarkably increased with age among both sexes and did not differ significantly among men and women (Tab. II).

Risk factors of CVD and ARM in case-control subdivision

Table III shows a significant difference in the prevalence of CVD risk factors among 507 men and 641 women aged 40 to 64 years who were ophthalmologically investigated. Among men, percent rate of current smokers was 4.4 times higher than among women; percent rate of increased systolic and diastolic blood pressure and hypertriglyceridemia was remarkably higher in men than in women; the percent rate of obesity and hypercholesterolemia was

TABLE III - PREVALENCE OF RISK FACTORS OF CARDIOVASCULAR DISEASE (CVD) AMONG OPTHALMOLOGICALLY INVESTIGATED MEN AND WOMEN AGED 40–64 YEARS FROM HEALTH SURVEY COHORT

Risk factors of CVD	**Men, N = 507**		**Women, N = 641**		**p**
	n/N	**%**	**n/N**	**%**	
Smoking habits					
Current	196/505	38.8	57/641	8.9	<0.001
Occasionally	14/505	2.8	21/641	3.3	>0.05
Former	127/505	25.1	53/641	8.3	<0.001
Never	168/505	33.3	510/641	79.6	<0.001
Hypertension					
Systolic (SBP ≥140 mmHg)	215/507	42.4	234/640	36.6	<0.05
Diastolic (DBP ≥90 mmHg)	223/507	44.0	184/640	28.8	<0.001
Obesity					
BMI ≥30 kg/m^2	134/506	26.5	277/641	43.2	<0.001
Hyperglycemia					
Glucose (fasting) ≥6.1 mmol/L	89/506	17.6	91/640	14.2	>0.05
Hyperlipidemias					
Total cholesterol ≥6.2 mmol/L	219/504	43.5	326/641	50.9	<0.01
Triglycerides ≥2.3 mmol/L	86/503	17.1	75/640	11.7	<0.01

N = Number of persons investigated for particular parameter; n = Number of cases with risk factors of CVD; p = Significance of difference of rate of risk factors between men and women; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI = Body mass index

remarkably lower in men than in women.

Analysis of the relationship between ARM and the main risk factors of CVD (smoking, arterial hypertension, obesity, hyperglycemia, and hyperlipidemias) was performed in case-control subdivision of the investigated cohort aged 40 to 64 years. A total of 84 cases with ARM and 84 controls (without ARM) were matched for sex, age, and education level. Data in case–control groups were compared separately in men and women because most of the risk factors analyzed were significantly different between men and women (Tab. III).

Smoking habits in case and control groups of men and women are demonstrated in Table IV. Percent rate of male current smokers did not differ significantly in ARM and control groups; there was a tendency that in male ARM group percent rate of never-smokers was lower and percent rate of former-smokers was higher than in controls. Significant difference in the prevalence of current smoking status was found between ARM and control women: in ARM group 17.5% of women were current smokers, and there was not a single current smoker in control group (χ^2=5.49; p=0.019).

Data comparing mean level of arterial blood pressure, BMI, glucose, and lipids in ARM and control groups of men and women are shown in Table V. In male ARM group mean levels of systolic and diastolic blood pressure and BMI were significantly higher than in control group. In female ARM group we found significantly higher level of glycemia than in control group.

Analysis of logistic regression of data in case-control subdivision demonstrated that increased diastolic blood pressure and obesity were associated with ARM in men (Tab. VI). Current smoking was associated with ARM in women (Tab. IV).

DISCUSSION

In the health survey carried out according to the WHO MONICA study protocol (9) the prevalence data on ARM from a random sample of Kaunas population that includes 1337 urban residential adults aged 35 to 64 years are presented. In this study popula-

TABLE IV - SMOKING HABITS IN AGE-RELATED MACULOPATHY (ARM) CASE AND CONTROL GROUPS FROM HEALTH SURVEY COHORT AGED 40–64 YEARS

Smoking habits	Men		Women	
	ARM, n=44, N (%)	Controls, n=44, N (%)	ARM, n=40, N (%)	Controls, n=40, N (%)
Current	16 (36.4)	16 (36.4)	7 (17.5)*	0 (0.0)
Occasionally	1 (2.3)	1 (2.3)	0	0
Former	13 (29.5)	9 (20.4)	1 (2.5)	2 (5.0)
Never	14 (31.8)	18 (40.9)	32 (80.0)*	38 (95.0)

*p<0.05 for the difference with control group. N = Number of persons in case and control groups; n = Number of cases with different smoking habits

TABLE V - COMPARISON OF THE MEAN LEVEL OF ARTERIAL BLOOD PRESSURE, BODY MASS INDEX, GLYCEMIA, AND SERUM LIPIDS CONCENTRATION IN AGE-RELATED MACULOPATHY (ARM) CASE AND CONTROL GROUPS FROM HEALTH SURVEY COHORT AGED 40–64 YEARS

Parameters	Men			Women		
	ARM, N=44	Controls, N=44	p	ARM, N=40	Controls, N=40	p
Systolic blood pressure, mmHg	150.2±26.4	136.1±20.8	0.007	145.5±27.4	144.3±21.4	0.828
Diastolic blood pressure, mmHg	94.3±13.8	86.5±13.1	0.008	88.0±14.0	84.5±11.3	0.222
Body mass index, kg/m^2	29.8±6.13	26.9±3.12	0.006	30.0±5.37	31.4±6.45	0.295
Glycemia, mmol/L	5.90±1.39	5.63±0.91	0.284	6.77±3.70	5.39±0.61	0.023
Total cholesterol,* mmol/L	6.26±1.14	6.25±1.05	0.966	6.45±1.31	6.84±1.38	0.199
Triglycerides,* mmol/L	1.67±0.92	1.41±0.72	0.202	1.66±0.97	1.56±0.76	0.609

Data are mean ±SD
*Cholesterol and triglycerides were not measured for one male with ARM, therefore serum concentration of lipids was compared for 43 persons of case and 43 persons of control group matched by age and education level

tion 6.3% of participants (7.4% of men and 5.4% of women) had signs of early ARM, most likely soft drusen, in one or both eyes. No late ARM was found. Similar frequency of early ARM was found in the VIP study of VanNewkirk and coworkers in persons aged 40 years and older (16) and the Hisayama study in persons aged 50 years or older (17). Prevalence of early ARM among middle-aged Kaunas city inhabitants was lower than in the Beaver Dam Eye Study cohort (13.1 %) (18), but higher than in the Blue Mountains Eye Study cohort (1.6%) (19).

In our study as well as in the Copenhagen (20), Rotterdam (21), Framingham (22), and Oulu (23) studies, no sex differences were found in the frequency of ARM. However, early ARM was more prevalent in women than in men in the Blue Mountains Eye Study (19), NHANES III (1), and the VIP study (16). By contrast, ARM was more prevalent in men than in women in the Hisayama study (17). The reasons for the sex differences in ARM in the pooled population-based data are not known.

CVD risk factors may increase the risk of ARM occurrence (24). In our middle-aged population the prevalence of main risk factors of CVD among men and women are different (25). In our study, current cigarette smoking was significantly associated with ARM

TABLE VI - ODDS RATIO (OR) WITH 95 PERCENT CONFIDENCE INTERVALS (CI) OF EARLY AGE-RELATED MACULOPATHY ACCORDING TO RISK FACTORS OF CARDIOVASCULAR DISEASE USING THE CASE-CONTROL STUDY DESIGN

Factors	Men			Women		
	ARM, N=44	Controls, N=44	OR (95%CI)	ARM, N=40	Controls, N=40	OR (95%CI)
Systolic hypertension						
No	17	25	1	19	18	1
Yes	27	19	2.09 (0.82-5.36) p=0.135	21	22	0.90 (0.34-2.39) p=1.000
Diastolic hypertension						
No	14	25	1	24	28	1
Yes	30	19	2.82 (1.08-7.43) p=0.032	16	12	1.56 (0.56-4.36) p=0.482
Obesity						
No	26	39	1	19	17	1
Yes	18	5	5.40 (1.61-19.2) p=0.004	21	23	0.82 (0.31-2.17 p=0.822
Hyperglycemia						
No	30	37	1	28	35	1
Yes	14	7	2.47 (0.80-7.83) p=0.133	12	5	3.00 (0.84-11.2) p=0.101
Hypercholesterolemia*						
No	22	24	1	21	16	1
Yes	21	19	1.21 (0.47-3.08) p=0.829 1	19	24	0.60 (0.23-1.60) p=0.815
Hypertriglyceridemia*						
No	33	38	1	32	35	1
Yes	10	5	2.30 (0.63-8.73) p=0.256	8	5	1.75 (0.45-6.98) p=0.544

*Hypercholesterolemia and hypertriglyceridemia were compared for 43 persons of case and 43 persons of control group.
Systolic hypertension: systolic blood pressure ≥140 mmHg; Diastolic hypertension: diastolic blood pressure ≥90 mmHg; Obesity: Body mass index ≥30 kg/m^2; hyperglycemia: Fasting glucose concentration ≥6.1 mmol/L; Hypercholesterolemia: Serum cholesterol ≥6.2 mmol/L; Hypertriglyceridemia: Serum triglycerides ≥2.3 mmol/L

in women, but not in men. Smoking is considered a risk factor for ARM in some studies (4, 26, 27). However, in the NHANES III Study there was no strong relation of cigarette smoking with ARM (1).

Our results show that increased diastolic blood pressure could be a risk factor of ARM. In the present study it was observed in our male urban population. There are inconsistent results on the association between arterial hypertension and ARM. Some studies have found a positive association with increased blood pressure (28-30), while others did not find such an association (4, 5, 23). In the Hisayama study arterial hypertension increased the risk of ARM only in men (17).

An association between BMI and ARM in men but not women was found in our study: obesity significantly increased odds of ARM. The same relationship was reported in the Oulu study (23).

We found that glycemia (fasting blood glucose level) was significantly higher in women with ARM than in controls. The effect of hyperglycemia on the development of ARM is unknown. Hyperglycemia may affect the normal structure and functioning of the choroidal circulation, the RPE, or Bruch's membrane (31, 32). Although some reports have suggested a positive association of elevated blood glucose values with ARM (33, 34), a number of case-control studies (35-37) and the population-based Framingham Eye Study (22) have failed to find an association between ARM and diabetes.

In our study association between ARM and serum lipids (total cholesterol and triglycerides) was not remarkable. Some studies have found an increased risk of ARM with increased serum cholesterol level (4, 29), while other studies have found no associations between ARM and serum cholesterol or triglyceride levels (37-39). There are several studies in which an inverse relationship between risk of ARM and cholesterol level was detected. In the Cardiovascular Health Study, a small but statistically significant inverse relationship was found between plasma total cholesterol and early ARM (6, 7). Similar inverse relationship of serum total cholesterol with ARM has been reported in other populations (1, 4, 5). The reason for this finding is not known. In conclusion, investigation of the association of ARM with risk factors of CVD among Lithuanian urban population aged 35–64 years suggests that early ARM (the prevalence of early ARM was 6.3%) is associated with current smoking in women but not in men, and it is associated with diastolic blood pressure and BMI in men and with fasting blood glucose level in women.

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REFERENCES

1. Klein R, Klein BEK, Jensen SC, Mares-Perlman JA, Cruickshanks KJ, Palta M. Age-related maculopathy in a multiracial United States population: the National Health and Nutrition Examination Survey III. Ophthalmology 1999; 106: 1056-65.
2. Leibowitz HM, Krueger DE, Mounder LR, et al. The Framingham Eye Study Monograph. Surv Ophthalmol 1980; 24 (Suppl): S 335-610.
3. Evans JR. Risk factors for age-related macular degeneration. Progr Retin Eye Res 2001; 20: 227-53.
4. Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy: the Beaver Dam Eye Study. Ophthalmology 1993; 100: 406-14.
5. Smith W, Mitchell P, Leeder SR, Wang JJ. Plasma fibrinogen levels, other cardiovascular risk factors, and age-related maculopathy: the Blue Mountains Eye Study. Arch Ophthalmol 1998; 116: 583-9.
6. Klein R, Klein BE, Marino EK, et al. Early age-related maculopathy in the Cardiovascular Health Study. Ophthalmology 2003; 110: 25-33.
7. Klein R, Klein BE, Tomany SC, Cruickshanks KJ. The associations of cardiovascular disease with the long-term incidence of age-related maculopathy. Ophthalmology 2003; 110: 1273-80.
8. Cimbalas A, Paunksnis A, Cerniauskiene LR, Domarkiene S. Prevalence and risk factors of age-related maculopathy among middle aged people. Medicina (Kaunas) 2003; 39: 1237-43.
9. World Health Organization MONICA Project. MONICA manual: monitoring of trends and determinants in cardiovascular disease. Geneva, Switzerland: Cardiovascular Disease Unit, WHO; 1990.
10. Chylack TL, Wolfe JK, Singer DM, et al. The Lens Opacities

Classification System. Arch Ophthalmol 1993; 111: 831-6.
11. Bird A, Bressler NM, Bressler SB, et al. An international classification and grading system for age-related macular degeneration. The International ARM Epidemiological Study Group. Surv Ophthalmol 1995; 39: 367-74.
12. Tamo%ьûnas A. Behavioral risk factors (Prevalence, trends, prognostic impact on morbidity of myocardial infarction and mortality from different causes). Academic dissertation: Kaunas; 1997: 5-23.
13. Pardini H, Pardini VC, Velho G. Impact of the new diagnostic criteria for diabetes on the number of affected subjects. Diabetologia 1998; 41(Suppl): S 122.
14. Siedel J, Hagele EO, Ziegenhorn J, Wahlefeld W. Monotest cholesterol. Clin Chem 1983; 29: 1075.
15. Stein EA, Myers GL. National Cholesterol Education Program recommendations for triglycerides measurement: executive summary. Clin Chem 1995; 41: 1421-6.
16. VanNewkirk MR, Nanjan MB, Wang JJ, Mitchell P, Taylor HR, McCarty CA. The prevalence of age-related maculopathy. The visual impairment project. Ophthalmology 2000; 107: 1593-600.
17. Miyazaki M, Nakamura H, Kubo M, et al. Risk factors for age-related maculopathy in a Japanese population: the Hisayama study. Br J Ophthalmol 2003; 87: 469-72.
18. Klein R, Klein BEK, Linton KLP. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1992; 99: 933-43.
19. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. Ophthalmology 1995; 102: 1450-60.
20. Vinding T. Age-related macular degeneration. Macular changes, prevalence and sex ratio. An epidemiological study of 1000 aged individuals. Acta Ophthalmol 1989; 67: 609-16.
21. Vingerling JR, Dielemans I, Hofman A, et al. Prevalence of age-related maculopathy in The Rotterdam Study. Ophthalmology 1995; 102: 205-10.
22. Kahn HA, Leibowitz HM, Ganley JP, et al. The Framingham Eye Study. 1. Outline and major prevalence findings. Am J Epidemiol 1977; 106: 17-32.
23. Hirvela H, Luukinen H, Laara E, Laatikainen L. Risk factors of age-related maculopathy in a population 70 years of age or older. Ophthalmology 1996; 103: 871-7.
24. Delcourt C, Michel F, Colvez A, Lacroux A, Delage M, Vernet MH. Associations of cardiovascular disease and its risk factors with age-related macular degeneration: the POLA study. Ophthalmic Epidemiol 2001; 8: 237-49.
25. Domarkiene S, Tamosiunas A, Reklaitiene R, et al. Trends in main cardiovascular risk factors among middle-aged Kaunas population between 1983 and 2002. Medicina (Kaunas) 2003; 39: 1193-9.
26. Age-Related Eye Disease Study Research Group. Risk factors associated with age-related macular degeneration. A case-control study in the age-related eye disease study: Age-Related Eye Disease Study Report Number 3. Ophthalmology 2000; 107: 2224-32.
27. Smith W, Mitchell P, Leeder SR. Smoking and age-related maculopathy. Arch Ophthalmol 1996; 114: 1518-23.
28. Klein BEK, Klein R. Cataracts and macular degeneration in older Americans. Arch Ophthalmol 1982; 100: 571-3.
29. Eye Disease Case-Control Study Group. Risk factors for neovascular age-related macular degeneration. Arch Ophthalmol 1992; 110: 1701-8.
30. Chaine G, Hullo A, Sahel J, et al. Case-control study of the risk factors for age-related macular degeneration. France-DMLA Study Group. Br J Ophthalmol 1998; 82: 996-1002.
31. Fryczkowski AW, Sato SE, Hodes BL. Changes in the diabetic choroidal vasculature: scanning electron microscopy findings. Ann Ophthalmol 1988; 20: 299-305.
32. Vinores SA, Campochiaro PA, May EE, Blaydes SH. Progressive ultrastructural damage and thickening of the basement membrane of the retinal pigment epithelium in spontaneously diabetic BB rats. Exp Eye Res 1988; 46: 545-58.
34. Vidaurri JS, Peer J, Halfon ST, Halperin G, Zauberman H. Association between drusen and some of the risk factors for coronary artery disease. Ophthalmologica 1984; 188: 243-7.
35. Algvere P, Efeldic S, Luft R, Waijngot A. Retinal microangiopathy and pigment epithelial lesions in subjects with normal, borderline, and decreased oral glucose tolerance. Br J Ophthalmol 1985; 69: 416-9.