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METABOLIC RISK FACTORS, COPING WITH STRESS, AND PSYCHOLOGICAL WELL-BEING IN PATIENTS WITH AGE-RELATED MACULAR DEGENERATION

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SUMMARY – The aim of this study was to determine the relationship between the risk factors (age, obesity, hypertension, hyperlipidemia, smoking, consumption of alchohol and drugs, positive family history, and exposure to sunlight), coping with stress, psychological well-being and age-related macular degeneration (ARMD). Forty patients with ARMD (case group) and 63 presbyopes (control group) participated in the study. Patient data were collected through general information questionnaire including patient habits, the COPE questionnaire that showed the way the patients handling stress, and the GHQ that analyzed the psychological aspects of their quality of life. These questionnaires were administered to the patients during ophthalmologic examination. The study involved 46 (44.66%) men and 57 (55.33%) women. Statistical analysis showed that the major risks for the development of ARMD were elevated cholesterol, triglycerides and LDL cholesterol in plasma. A significantly higher number of ARMD patients had a positive family history when compared with presbyopes. This study showed presbyopes to cope with emotional problems significantly better and to have a lower level of social dysfunction when compared with ARMD patients. However, it is necessary to conduct further studies in a large number of patients to determine more accurately the pathophysiological mechanisms of metabolic factors as well as the impact of the disease on the quality of life in patients with ARMD.

Key words: *Macular degeneration; Aging; Risk factors; Adaptation, psychological; Quality of life*

Introduction

Age-related macular degeneration (ARMD) is a progressive condition that leads to severe central vision loss by damaging the photoreceptor cell layer in the macula. ARMD occurs mainly in people older than 60 years and affects 30 to 50 million elderly individuals *per* year[1-3]. The clinical and histopathologic sign of ARMD is macular atrophy with drusen, discrete yellow lesions in the subretinal area[3]. Progression of dry ARMD characterized with drusen leads to geographic atrophy, while the wet form is recognized by retinal detachment from other layers, hemorrhage, and scarring of the retinal pigment epithelium (RPE)[4]. Other significant risk factors, besides age, include hypertension, hyperlipidemia, genetic factors, oxidative stress, smoking, consumption of alcohol, and the use of drugs[5-9]. Speaking of cardiovascular risk factors, studies found that smoking increased the risk of ARMD by elevating the level of oxidative stress and injuries in the blood vessels, and that hypertension was the most frequent cardiovascular risk factor for the development of ARMD[10,11]. Oxidative stress is defined

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as an imbalance between the formation and removal of reactive oxygen species (ROS)[12]. In addition, numerous studies have shown that ROS may play a role in the pathogenesis of ARMD by causing damage to the cell membrane of retinal rods and cones[13]. There are opposite attitudes about hypertension as a risk factor because some studies revealed that hypertension was not or was rarely associated with the genesis of ARMD[14,15]. However, there are studies that proved an existing correlation between hypertension and the progression of ARMD, especially in its wet form[1,14]. Dyslipidemia is a major cause of morbidity and it is the leading contributor to mortality worldwide[16]. Lipid level imbalance, i.e. high plasma concentrations of low-density lipoproteins (LDL), low concentrations of high-density lipoproteins (HDL), and elevated plasma triglyceride concentrations, has a huge impact on many organs of the body and it has been connected to a wide range of eye diseases such as ARMD[17,18]. There is clear evidence for heritability of ARMD, demonstrated in several genetic studies, and a strong association was found with the polymorphism complement factor H (CFH) gene[8]. Quality of life is defined in many different ways, and it can be understood and tested in different ways. Quality of life can be described as the individuals' perception of satisfaction with their lives and in most cases it is associated with health. However, its meaning is much wider including physical health, psychological state, level of independence, social relationships, and personal beliefs[19]. According to the literature, only a few researches show that depression and a restricted number of daily activities that can be accomplished without assistance from the others significantly reduce the quality of life of ARMD patients[20-22]. In elderly people affected with ARMD, the low quality of life is related to greater emotional stress, social isolation, poor general health and functional status, which impacts the patients' mobility and autonomy. Behavioral psychotherapy programs and psychosocial support have shown great results in reducing emotional distress, consequently improving the quality of life by enabling these patients to live more independently[23-27]. Based on previous research, the purpose of this study was to reveal the prevalence of risk factors in patients with ARMD as well as the relationship between chronic stress, psychological aspect of life quality and ARMD.

Patients and Methods

This case-control study was conducted in the period from September 1, 2012 until March 1, 2013, at the Clinical Department of Ophthalmology, Mostar University Hospital. Forty patients who underwent complete ophthalmologic examination were diagnosed to have ARMD and they were recruited as cases, while 63 individuals with presbyopia matched by age (±2 years) and sex were recruited as controls. Excluding criteria for participation in the study were eye diseases that can damage vision, such as keratitis, corneal dystrophy, cataract, glaucoma and diabetic retinopathy. The following parameters were considered to be associated with ARMD: age, obesity, hypertension, hyperlipidemia, smoking, consumption of alchohol, positive family history of ARMD, exposure to sunlight, use of nonsteroidal anti-inflammatory drugs (NSAIDs), chronic stress, and the psychological aspect of the quality of life. Data were collected using the following instruments: 1) questionnaire on general information such as age, body mass index (BMI), consumption of alcohol, cigarettes and NSAIDs, nutrition, professional orientation toward harmful effect of sun exposure (i.e. landscape and construction workers), and positive family history of ARMD affecting first-degree relatives; 2) Coping Orientation to Problems Experienced (COPE) questionnaire with 48 items describing people's reaction to different life difficulties, stress and upseting situations. It has five subscales: persistence, emotions, avoidance, fun and disarrangement. Answers were analyzed on Likert 5-point scale. Participants were asked to choose answers from 1 to 5, with 1 representing absolute disagreement and 5 indicating complete agreement. Items are summed for each subscale. Higher scores on a subscale indicate greater use of that coping mechanism[28]; and 3) General Health Questionnaire (GHQ) with 28 questions, where subjects were asked to compare their recent psychological state with their usual state. Patients would choose answers from 1 to 5 describing their psychological well-being. It is also a tool for measuring common mental health problems, i.e. depression, anxiety, somatic symptoms and social alienation. Answers were analyzed on Likert 4-point scale, with 1 representing not at all and 4 much more than usual. A higher score meant a poorer psychological well-being of patients[29].

An informed consent was obtained from study subjects, and all practices and procedures were in accordance with the Declaration of Helsinki and were approved by the Mostar University Hospital Ethics Committee. Questionnaires were completed by all participants during their visit to the ophthalmologist.

Statistical analysis was performed using the SPSS for Windows software (version 13.0, SPSS Inc., Chicago, Illinois, USA) and Microsoft Excel (version 11, Microsoft Corporation, Redmond, WA, USA). Normality of distribution for the equality of continuous variables was tested by Kolmogorov-Smirnov test and was presented with arithmetic mean and standard deviation (SD). For comparison of equality of the continuous variables, the t-test was used. Chi-square test was used for analysis of nominal variables, but when lower frequency was expected, Fisher exact test was introduced. Significant difference between the groups was set at $P<0.05$.

Results

This case control study was conducted in the period from September 1, 2012 until March 1, 2013. We examined 103 patients in total: 40 patients as cases (ARMD patients) and 63 as controls (presbyopes). There were 46 (44.66%) men and 57 (55.33%) women. The female to male ratio was 1.2:1.0 (χ^2 test=0.75; P=0.385). The mean age of all study subjects was 64±9.8 (age range 55-84) years.

Table 1 shows BMI values and hypertension prevalence in patients with ARMD (cases). Controls were patients with presbyopia. The number of patients with elevated BMI was 26 (65.0%) in ARMD group and 47 (74.6%) in control group. Statistical analysis showed no significant between-group difference (χ^2=1.09; P=0.296). Hypertension was present in 24 (60.0%) patients with ARMD and 29 (46.0%) patients with presbyopia. Statistical analysis yielded no significant between-group difference either (χ^2=1.91; P=0.167).

Table 1. Prevalence of hypertension and increase in body mass index in ARMD patients

Variable	Number (%) of patients		χ^2-test	P
	ARMD	Presbyopia		
Body mass index				
<25	14 (35.0)	16 (25.4)	1.09	0.296
≥25	26 (65.0)	47 (74.6)		
Hypertension				
Yes	24 (60.0)	29 (46.0)	1.91	0.167
No	16 (40.0)	34 (54.0)		

ARMD – age-related macular degeneration

Table 2. Plasma lipid levels in patients with presbyopia and ARMD

Variable	Number (%) of patients		χ^2 test	P
	ARMD	Presbyopia		
Triglycerides				
0.6-2.2 mmol/L	17 (42.5)	47 (74.6)	10.72	0.001
>2.2 mmol/L	23 (57.5)	16 (25.4)		
Cholesterol				
3.5-6.2 mmol/L	11 (27.5)	38 (60.3)	10.56	0.001
>6.2 mmol/L	29 (72.5)	25 (39.7)		
HDL cholesterol				
0.9-1.70 mmol/L	28 (70.0)	31 (49.2)	2.23	0.135
>1.70 mmol/L	12 (30.0)	32 (50.8)		
LDL cholesterol				
2.6-4.10 mmol/L	14 (35.0)	50 (79.4)	12.09	0.001
>4.10 mmol/L	26 (65.0)	13 (20.6)		

ARMD = age-related macular degeneration; HDL = high-density lipoprotein cholesterol; LDL = low-density lipoprotein cholesterol

Table 2 shows the levels of body lipids (triglycerides, cholesterol, LDL cholesterol and HDL cholesterol) in patients with ARMD and presbyopia. The number of patients with elevated levels of plasma triglycerides was significantly higher in ARMD group (n=23; 57.5%) than in control group (n=16; 25.4%) (χ^2=10.72; P=0.001). The number of patients with high plasma cholesterol concentration was also significantly higher in patients with ARMD (n=29; 72.5%) in comparison with control group (n=25; 39.7%) (χ^2=10.56; P=0.001). There was no significant difference between the study groups with respect to the number of patients with normal or elevated HDL level (χ^2=2.23; P=0.135). High plasma concentration of LDL was present in 26 (65.0%) ARMD patients and 13 (20.6%) presbyopia patients, yielding a significant between-group difference (χ^2=12.09; P=0.001).

Table 3. Association of ARMD with alcohol and cigarette consumption

Variable	Number (%) of patients		χ^2 test	*P*
	ARMD	Presbyopia		
Smoking				
No	28 (70.0)	47 (74.6)		
<1 pack of cigarettes	9 (22.5)	14 (22.2)	1.11*	0.620
>1 pack of cigarettes	3 (7.5)	2 (3.2)		
Alcohol consumption				
No/<2 glasses of wine	28 (70.0)	40 (63.5)		
>2 glasses of wine/one/more glasses of spirit	12 (30.0)	23 (36.5)	0.416	0.497

ARMD = age-related macular degeneration; *Fisher exact test

Table 3 shows consumption of cigarettes and alcohol in patients with ARMD and presbyopia. The number of patients who smoked more than one pack of cigarettes daily was higher in ARMD group (n=3; 7.5%) than in control group (n=2; 3.2%), however, the difference did not reach statistical significance (χ^2=1.11; *P*=0.620). Drinking more than two glasses of wine and/or one or more glasses of spirits *per* day was present in 12 (30.0%) ARMD patients and 23 (36.5%) presbyopia patients. There was no statistically significant between-group difference either (χ^2=0.416; *P*=0.497).

Table 4. Occupation and positive family history of ARMD patients

Variable	Number (%) of patients		χ^2 test	*P*
	ARMD	Presbyopia		
Occupation				
No sunlight exposure	13 (32.5)	31 (49.2)	2.79	0.095
Sunlight exposure	27 (67.5)	32 (50.8)		
Positive family history				
Yes	15 (37.5)	1 (1.59)	6.64	0.010
No	25 (62.5)	62 (98.41)		

ARMD = age-related macular degeneration

The prevalence of positive family history and exposure to sunlight in ARMD and presbyopia patients is shown in Table 4. Positive family history of ARMD was present in 15 (37.5%) ARMD patients and in one (1.59%) patient with presbyopia, the difference being statistically significant (χ^2=6.64; *P*=0.010). Sunlight exposure was present in a higher number of ARMD patients (n=27; 67.5%) as compared to controls (n=32; 50.8%), but without statistical significance (χ^2=2.79; *P*=0.095).

Table 5 shows relationship between NSAID consumption and etiology of ARMD. There were 8 (20.0%) ARMD patients and 17 (27.0%) presbyopes who were constant NSAID drug consumers, but statistical analysis showed no significant difference between the two groups (χ^2=0.65; *P*=0.420).

Difference between ARMD and presbyopia patients according to the results obtained by use of the COPE questionnaire subscales is presented in Table 6. The COPE questionnaire subscales are Persistence, Emotions, Avoidance, Fun and Disarrangement. Patients with ARMD showed lower indexes in all subscales of the COPE questionnaire in comparison to control group, with significant difference only in the Emotions subscale (Student's t-test=2.565; *P*=0.012).

Table 7 shows differences in general health characteristics between the study groups. These characteristics were measured by the GHQ questionnaire, which included 5 subscales: Somatic symptoms, Anxiety/insomnia, Social dysfunction, Depression and Total score. Patients with ARMD had higher indexes in all subscales of the GHQ questionnaire in comparison to control group (patients with presbyopia), with signifi-

Table 5. Use of NSAID in ARMD patients

Variable	Number (%) of patients		χ^2 test	*P*
	ARMD	Presbyopia		
Use of NSAID 8 (20.0)	17 (27.0)	0.65	0.420	

ARMD = age-related macular degeneration; NSAID = nonsteroidal anti-inflammatory drugs

Table 6. Results of COPE questionnaire in ARMD and presbyopia patients

COPE Questionnaire subscales	Mean ±SD		Student's t-test	*P*
	ARMD	Presbyopia		
Persistence	50.22±5.70	50.76±7.10	0.402	0.688
Emotions	50.50±8.70	55.00±8.66	2.565	0.012
Avoidance	52.57±6.74	54.73±7.71	1.449	0.150
Fun	17.17±2.63	18.00±2.98	1.431	0.156
Disarrangement	24.75±3.97	26.11±4.41	1.584	0.116

COPE = Coping Orientation to Problems Experienced; ARMD = age-related macular degeneration

Table 7. Results of GHQ in patients with ARMD and presbyopia

GHQ subscales	Mean ±SD		Student's t-test	*P*
	ARMD	Presbyopia		
Somatic symptoms	14.55±3.27	13.32±3.07	1.904	0.060
Anxiety/insomnia	14.00±4.73	13.45±4.56	0.583	0.561
Social dysfunction	17.25±3.62	15.32±2.83	2.857	0.005
Depression	9.30±3.79	9.22±3.44	0.301	0.764
Total score	55.11±11.58	51.62±11.23	1.505	0.135

GHQ = General Health Questionnaire; ARMD = age-related macular degeneration

cant difference only in the Social dysfunction subscale (Student's t-test=2.857; *P*=0.005).

Discussion

The exact etiology of ARMD is still unknown[5]. It is generally considered that the presence of some risk factors, i.e. age, hypertension, hyperlipidemia, etc., is associated with the genesis or progression of ARMD[24,30-33]. Results of this study showed that 95% of ARMD patients were older than 60, which confirmed the results found in the international literature[5,8]. The mean age of the patients in our study was 64±9.8 years; however, ARMD can develop in younger adults as well. Numerous studies have shown that people older than 60 have a significantly higher risk of ARMD, i.e. the incidence of ARMD rises up to 30% in people aged 75-85[34].

Smoking is a significant and an independent risk factor for the development of ARMD. Smoking is thought to reduce antioxidant level, decrease luteal pigments in the retina and reduce choroidal blood flow[35]. However, current smokers have the highest risk of developing ARMD, while former smokers also have an increased risk when compared to people who have never smoked[31,36]. Alcohol consumption causes different diseases that pose an important medical and social burden in the world today. Daily acceptable amount of alcohol varies from country to country; a glass of wine or beer and a half glass of liquor contain the same amount of alcohol[37]. It was shown that a high level of alcohol consumption (more than 7 drinks *per* week or 3 *per* occasion) increases the risk of ARMD[35]. Despite the fact that alcohol stands independently as a risk factor, we cannot completely exclude its correlation with smoking[6].

Our research showed that most of the ARMD patients were obese and had high blood pressure. Obesity is the leading problem worldwide and it is in persistent progress. The mechanism of how obesity (BMI ≥25 kg/m^2) increases the risk of ARMD development is described by physical changes caused by the increasing body weight. These changes include a higher level of oxidative stress, imbalance of blood lipids, and a higher risk of all inflammatory processes. These changes lead to lower production of macular pigment (lutein and zeaxanthin) which protects the photosensitive cell layer of the retina from harmful sunlight effect[32,38]. People with hypertension are more

likely to have ARMD. High blood pressure damages blood vessels of the retina causing vasoconstriction. Wieberdink *et al*. and Chen *et al*. have found that hypertension, obesity and high cholesterol levels are associated with the increased risk of ARMD[39,40]. Hypertension can exacerbate the wet form of ARMD, particularly the form with retinal neovascularization. Antihypertensive drugs do not have direct impact on the disease but can slow down its progression[41].

Our study recorded significantly higher levels of triglycerides, cholesterol and LDL cholesterol in the case group. Previous studies have shown that a higher serum level of cholesterol increases the risk of ARMD[42]. Over time, cholesterol accumulates in the posterior eye segment but its role is still unknown. As many details are still missing in the pathogenesis of ARMD, it is necessary to keep studying the links between hyperlipidemia and ARMD[43]. Cataract, dry eye syndrome and retinal hemorrhages can be induced by constant use of NSAID (acetylsalicylic acid and diclofenac). Paracetamol, even if it is not considered as a typical NSAID, can also be very harmful. There were only a few studies trying to prove relationship between the use of NSAID and ARMD, and their results are contradictory[44]. However, our study showed that long term usage of these drugs was not a significant risk factor for development of ARMD.

Our results revealed that a significant number of cases had positive family history of ARMD. In our study, there was no difference between the two groups according to sunlight exposure, although some studies confirmed long term exposure to intense direct sunlight as one of the most relevant risk factors for ARMD. Bone *et al*. found that the most damaged site on the retina in patients with ARMD was the one that had accumulated the most direct light over lifetime[45].

Emotional distress and depression are very common in elderly people suffering from vision loss on one or both eyes. ARMD highly reduces the psychosocial quality of life causing difficulties with reading, night driving, recognizing faces and entering rooms with dimmed lights. The negative effects of ARMD on the patient's life are also manifested in the unavoidable dependence on help from the others, which increases the level of depression[24]. There are only a few studies that assessed correlation between chronic stress and ARMD[25,26]. In our study, patients with ARMD had significantly worse results in the COPE Emotions subscale. The possible explanation for this might be the fact that people with ARMD have some level of depression, so their emotional functioning is decreased[24]. Further, in the COPE subscales that measure persistence, avoidance, fun and disarrangement, patients with ARMD also had worse results in comparison to presbyopes, but without significant difference.

With regard to the GHQ subscales, patients with ARMD had significantly poorer psychological wellbeing (higher score in the Social dysfunction subscale) when compared to control group. Considering the results in other GHQ subscales, no statistical difference was found between the two groups, although ARMD patients had higher scores in comparison to controls. A higher score of social dysfunction in patients with ARMD means that these patients are more socially dysfunctional because they are in greater need of the others' help and understanding. In general, the lack of free time, along with stressful and fast way of life contributes greatly to social dysfunction. ARMD is a disease that affects elderly people who are in most cases already retired and limited in activities that could improve their social functioning[46,47].

In conclusion, ARMD is a multiple risk factor disease with emphasis on metabolic factors as the main cause. Correlation between alcohol consumption and smoking and their cumulative effect on the development of ARMD is still unknown, and it is necessary to conduct further research to clarify this interaction. Also, the quality of life is considerably reduced in patients with ARMD, which is the main cause of blindness in the elderly, especially if they suffer from other ocular or general diseases. Decreased quality of life can contribute to the development of depression, which in addition reduces social functioning and pulls the individual into a vicious circle. Therefore, it is necessary to conduct additional studies in a large number of patients to determine more accurately the pathophysiological mechanisms of the metabolic factors involved, as well as the impact of the disease on the quality of life in patients with ARMD.

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Sažetak

METABOLIČKI ČIMBENICI RIZIKA, SUOČAVANJE SA STRESOM I PSIHOLOŠKO ZDRAVLJE U BOLESNIKA SA SENILNOM MAKULARNOM DEGENERACIJOM

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Cilj ovoga istraživanja bio je utvrditi povezanost između rizičnih čimbenika (dob, pretilost, hipertenzija, hiperlipidemija, pušenje, konzumacija alkohola i lijekova, pozitivna obiteljska anamneza, izloženost sunčevom zračenju), suočavanja sa stresom, psihološkog aspekta kvalitete života i senilne makularne degeneracije (SMD). U istraživanje su bili uključeni bolesnici oboljeli od SMD (n=40) koji su činili ispitivanu skupinu i prezbiopi (n=63) koji su činili kontrolnu skupinu. Podatci su se prikupili ispunjavanjem upitnika kojim su se dobili opći podatci i opisale navike bolesnika, upitnika COPE kojim su se ispitali načini reagiranja na stres te upitnika GHQ kojim se analizirao psihološki aspekt kvalitete života. Navedeni upitnici bili su osobno uručeni ispitanicima prilikom oftalmološkog pregleda. U istraživanje je bilo uključeno 46 (44,66%) muškaraca i 57 (55,33%) žena. Statistička obradba pokazala je da najveći rizik za obolijevanje od SMD predstavljaju povišene razine kolesterola, triglicerida i LDL kolesterola u krvi. Značajno veći broj bolesnika u ispitivanoj skupini imao je pozitivnu obiteljsku anamnezu u odnosu na kontrolnu skupinu. Ovo istraživanje pokazalo je da prezbiopi značajno bolje reagiraju u osjećajima usmjerenom suočavanju te da imaju niži stupanj socijalne disfunkcije u odnosu na bolesnike oboljele od SMD. Međutim, potrebno je provesti daljnja istraživanja na velikom broju bolesnika kako bi se točnije utvrdili patofiziološki mehanizmi metaboličkih čimbenika, kao i utjecaj bolesti na kvalitetu života u bolesnika sa SMD.

Ključne riječi: *Žuta pjega, degeneracija; Starenje; Čimbenici rizika; Adaptacija, psihološka; Kvaliteta života*