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The Effect of Metabolic Diseases on the Outcome of Bevacizumab Injection for Central Serous Retinopathy

M. Babaei (MD)[1], H. Shirafkan (PhD)[2], S. A. Rasoulinejad (MD)[*3]

1.Clinical Research Development Unite of Rouhani Hospital, Babol University of Medical Sciences, Babol, I.R.Iran.
2.Social Determinants of Health Research Center, Health Research Institute, Babol University of Medical Sciences, Babol, I.R.Iran.
3.Department of Ophthalmology, School of Medicine, Babol University of Medical Sciences, Babol, I.R.Iran.

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ABSTRACT

Background and Objective: Central serous retinopathy (CSR) is an idiopathic retinal disease that causes visual impairment and metamorphopsia. Due to the unknown etiology of CSR, the present study was conducted to investigate the role of metabolic disorders such as hyperlipidemia, diabetes, hypothyroidism, and hypertension (as a cardiovascular disease) in the treatment outcome of CSR patients.

Methods: This cross-sectional study was performed on 55 CSR patients whose problem was approved by ophthalmologic examinations in the Ophthalmology center of Ayatollah Rouhani Hospital, Babol, Iran. The patients were then treated with intravitreal injection of 1.25 mg/0.05 ml bevacizumab (Avastin®) 3 to 4 millimeters away from limbus under sterile conditions. Based on having and not having hypertension, diabetes, hypothyroidism and obesity, all patients underwent ophthalmological examination, including visual acuity (VA) and central macular thickness (CMT) by optical coherence tomography (OCT) before injection and one month after that.

Findings: The mean age of CSR patients (32 men and 23 women) was 42±11.50 years. After treatment, the CMT value in hypertensive patients (328.66±34.00 µm) was significantly higher than non-hypertensive patients (302.56±41.79) (p=0.025). The CMT value after treatment was considerably lower in non-diabetic patients (306.08±42.49 µm) compared to diabetic patients (336.77±17.42 µm) (p=0.039). Neither VA nor CMT was significantly different between hyperlipidemic patients and non-hyperlipidemic patients. In addition, there were no significant differences in VA and CMT between patients with hypothyroidism and without hypothyroidism.

Conclusion: The results of this study showed that hypertension and diabetes are important factors in CSR patients' response to bevacizumab injection.

Keywords: *Central Serous Chorioretinopathy, Bevacizumab, Visual Acuity, Optical Coherence Tomography.*

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[*]Corresponding Author: S. A. Rasoulinejad (MD)
Address: Department of Ophthalmology, School of Medicine, Babol University of Medical Sciences, Babol, I.R.Iran.
Tel: +98 (11) 32238301. **E-mail:** rasolisa2@gmail.com

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Introduction

Central serous retinopathy (CSR) is a retinal disease that causes blurred vision. The accumulation of fluid under the central macula leads to metamorphopsia or gray spots in visual fields. The decrease in visual acuity (VA) and increase in the central macular thickness (CMT) are the signs of CSR. The prevalence of CSR is estimated to be 6 per 100,000 individuals (1-3).

CSR is basically idiopathic retinopathy. Despite the efforts to investigate the etiology of CSR, the scientists have been unable to recognize the main reason for CSR development (4-6). Therefore, there are various studies to find the factors that affect CSR. It is expected that different metabolic diseases exacerbate the condition of CSR patients or affect the outcome of treatment, which is performed by intravitreal injection of bevacizumab (humanized monoclonal anti-VEGF-a antibody) to prevent abnormal neovascularization (7, 8). Furthermore, laser therapy, oral medications (e.g., spironolactone and ibuprofen), topical treatment, and lifestyle changes are other methods to reduce CSR symptoms (9-13). So far, the studies have shown that stress makes the condition worse in CSR patients. A higher level of cortisol is observed in CSR patients compared to normal individuals. Infection with *H. pylori* is also known as a risk factor of CSR. In addition, signs of membranoproliferative glomerulonephritis type II had been observed in CSR as a potential risk factor (12, 14-17).

Since the effect of some metabolic disorders such as hyperlipidemia, diabetes and hypothyroidism, and hypertension (as a cardiovascular disease) on CSR patients' response to treatment has not been addressed so far, this cross-sectional study was conducted to investigate the effect of hypertension, hyperlipidemia, diabetes, hypothyroidism, and other related factors on treatment outcome of patients with CSR.

Methods

After being approved by the Ethics Committee of Babol University of Medical Sciences with code IR.MUBABOL.HRI.REC.1398.145, this cross-sectional study (2018-2020) was performed on 55 CSR patients whose disease was approved by ophthalmologic examinations in the Ophthalmology Center of Ayatollah Rouhani Hospital, Babol, Iran. All CSR patients were diagnosed via clinical examination and optical coherence tomography (OCT) (13). After conforming CSR, the patients were treated with intravitreal injection of 1.25 mg/0.05 ml bevacizumab (Avastin®) 3 to 4 millimeters away from limbus under sterile conditions. To prevent unwanted infections, antibiotics were prescribed for a week, starting three days before the injection. Follow-up examinations were performed for three months. Before and one month after injection, all patients underwent ophthalmological examination, including VA and CMT, evaluated by OCT [Zeiss HD 5000, Germany]. Furthermore, all laboratory indices as well as history of medicine use were collected from medical records. Patients with total cholesterol more than 210 mg/dL as hyperlipidemic, fasting blood sugar more than 120 and HbA1c more than 48 mmol/mol as diabetic patients and blood pressure more than 140/90 mm Hg were considered hypertensive (18-20). Patients with diabetic retinopathy (ocular symptoms including bleeding, microaneurysm, exudate, etc.) and retinal vein occlusion were excluded from the study. Data were analyzed using SPSS software (IBM, USA) version 21 and Kolmogorov-Smirnov, Spearman, Independent samples t and Pearson correlation coefficient statistical tests, and $p<0.05$ was considered significant.

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Results

This study was performed on 55 CSR patients (32 men and 23 women) aged 42±11.50 years. The age of participants did not have a normal distribution (Kolmogorov-Smirnov, p<0.0001). Spearman test shows that age (year) was correlated with VA (before treatment) (Correlation Coefficient= -0.428, p<0.001), VA (after treatment) (Correlation Coefficient= -0.336, p=0.012), CMT (before treatment) (Correlation Coefficient= -0.333, p=0.013), and CMT (after treatment) (Correlation Coefficient= -0.327, p=0.015). The results of statistical analysis performed by the independent-sample T-test showed that the mean value of CMT after treatment in hypertensive patients (328.66±34.00 µm) was significantly higher than non-hypertensive patients (302.56±41.79) (p=0.025). Moreover, CMT before treatment in hypertensive patients (509.77±103.91 µm) was higher than non-hypertensive patients (448.13±132.21 µm), but this difference was not significant. In other hands, VA before treatment in hypertensive patients (0.137±0.123) was lower than non-hypertensive patients (0.173±0.132), and VA after treatment in non-hypertensive patients (0.686±2.309) was higher than hypertensive patients (0.580±0.249). However, the differences were not significant (Table 1).

The results showed that hypertensive patients have a poorer prognosis in terms of visual indicators of CSR. Our results showed that diabetes limits the treatment outcomes of CSR. VA of patients before treatment was lower in people with diabetes (0.127±0.042) than non-diabetic ones (0.167±0.139), which was not significant. After treatment, VA was also higher in non-diabetic patients (0.681±0.302) than patients with diabetes (0.502±0.179). CMT after treatment was significantly lower in non-diabetic patients (306.08±42.49 µm) than diabetic patients (336.77±17.42 µm) (p=0.039). In addition, the amount of CMT reduction in non-diabetic patients was 164.76±116.26 µm (31.88±13.43%) and in diabetic patients was 118.55±46.59 µm (25.35±7.31%). However, these differences were not statistically significant. Our results showed that VA and CMT in hyperlipidemic patients were not significantly different from non-hyperlipidemic patients as well as patients with hypothyroidism versus patients without hypothyroidism. However, the comparison of results showed that the non-hyperlipidemic state leads to higher increase in VA (%) compared to the hyperlipidemic state. The percentage of CMT reduction is higher in non-hyperlipidemic patients (31.27±13.26%) compared to hyperlipidemic patients (28.51±10.58%). Based on the results of Table 1, it could be said that non-hyperlipidemic state exacerbates the situation in VA and CMT of CSR patients but results in a better outcome of CSR treatment. There is no clear difference in the values of VA and CMT between patients with hypothyroidism and without hypothyroidism. The results showed that the mean value of different indices of CSR treatment are not significantly different between smokers and non-smokers (Table 2). Moreover, our results showed that corticosteroids do not have any role in the outcome of CSR treatment in terms of VA and CMT. Moreover, gender and the affected eye (left eye or right eye) are irrelevant to CSR treatment outcomes.

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Table 1. Effect of present diseases on the recovery rate of Central serous retinopathy in VA and CMT indicators

Disease and Indicators	Mean±SD		p-value
Hypertension	**Hypertensives (n=18)**	**Non-hypertensives (n=37)**	
VA (before treatment)	0.137±0.123	0.173±0.132	0.346
VA (after treatment)	0.580±0.249	0.686±2.309	0.208
Difference in VA	0.443±0.187	0.514±0.266	0.259
Increased VA (%)	460.10±284.87	400.27±240.73	0.419
CMT (before treatment) (µM)	509.77±103.91	448.13±132.21	0.089
CMT (after treatment) (µM)	328.66±34.00	302.56±41.79	0.025
CMT reduction (µM)	181.11±90.88	145.56±116.18	0.260
Decreased CMT (%)	33.92±10.16	29.30±13.79	0.213
Hyperlipidemia	**Hyperlipidemic (n=9)**	**Non-hyperlipidemic (n=46)**	
VA (before treatment)	0.229±0.214	0.147±0.103	0.082
VA (after treatment)	0.657±0.284	0.650±0.296	0.952
Difference in VA	0.427±0.198	0.503±0.252	0.403
Increased VA (%)	386.38±381.48	426.40±227.69	0.671
CMT (before treatment) (µM)	468.88±90.05	468.19±132.83	0.988
CMT (after treatment) (µM)	328.55±38.47	307.69±41.00	0.165
CMT reduction (µM)	140.33±80.06	160.50±114.24	0.616
Decreased CMT (%)	28.51±10.58	31.27±13.26	0.560
Diabetes	**Diabetics (n=9)**	**Non-diabetics (n=46)**	
VA (before treatment)	0.127±0.042	0.167±0.139	0.400
VA (after treatment)	0.502±0.179	0.681±0.302	0.089
Difference of VA	0.372±0.177	0.513±0.250	0.060
Increased VA (%)	316.25±154.89	440.12±266.74	0.072
CMT (before treatment) (µM)	455.33±52.26	470.84±136.24	0.739
CMT (after treatment) (µM)	336.77±17.42	306.08±42.49	0.039
CMT reduction (µM)	118.55±46.59	164.76±116.26	0.055
Decreased CMT (%)	25.35±7.31	31.88±13.43	0.051
Hypothyroidism	**Hypothyroid (n=16)**	**Non-hypothyroid (n=39)**	
VA (before treatment)	0.163±0.159	0.160±0.116	0.942
VA (after treatment)	0.613±0.292	0.667±0.294	0.539
Difference in VA	0.450±0.256	0.507±0.240	0.449
Increased VA (%)	420.29±281.51	419.67±247.12	0.994
CMT (before treatment) (µM)	491.81±103.25	458.66±134.41	0.331
CMT (after treatment) (µM)	319.62±42.26	307.61±40.50	0.341
CMT reduction (µM)	172.18±87.94	151.05±117.04	0.469
Decreased CMT (%)	33.47±10.76	29.72±13.54	0.286

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Table 2. Effect of different factors on the recovery rate of Central serous retinopathy in VA and MT indicators

Factors and Indicators	Mean±SD		p-value
Smoking	**Smokers (n=21)**	**Non-smokers (n=34)**	
VA (before treatment)	0.135±0.088	0.176±0.147	0.231
VA (after treatment)	0.651±0.301	0.652±0.291	0.998
Difference in VA	0.516±0.275	0.475±0.225	0.570
Increased VA (%)	467.16±288.80	390.63±231.27	0.311
CMT (before treatment) (µM)	474.38±144.60	464.55±115.39	0.794
CMT (after treatment) (µM)	314.61±44.15	308.94±39.45	0.632
CMT reduction (µM)	159.76±129.13	155.61±96.60	0.900
Decreased CMT (%)	30.54±12.97	30.99±12.91	0.901
Corticosteroids	**Use (n=6)**	**Not use (n=49)**	
VA (before treatment)	0.120±0.073	0.166±0.133	0.231
VA (after treatment)	0.561±0.238	0.663±0.298	0.369
Difference in VA	0.440±0.175	0.497±0.252	0.499
Increased VA (%)	442.13±211.10	417.12±261.53	0.798
CMT (before treatment) (µM)	496.50±148.92	464.85±124.38	0.636
CMT (after treatment) (µM)	324.00±16.49	309.53±42.89	0.420
CMT reduction (µM)	172.50±140.86	155.32±106.15	0.783
Decreased CMT (%)	30.20±18.50	30.81±12.20	0.933
Gender	**Male (n=32)**	**Female (n=23)**	
VA (before treatment)	0.171±0.130	0.146±0.128	0.473
VA (after treatment)	0.670±0.305	0.626±0.277	0.588
Difference in VA	0.498±0.254	0.480±0.235	0.793
Increased VA (%)	410.84±277.58	432.40±225.06	0.752
CMT (before treatment) (µM)	473.68±138.89	460.82±108.43	0.702
CMT (after treatment) (µM)	308.15±45.78	315.21±33.80	0.513
CMT reduction (µM)	165.53±120.85	145.60±91.36	0.489
Decreased CMT (%)	32.00±12.92	29.16±12.75	0.421
Affected eye	**Right (n=27)**	**Left (n=28)**	
VA (before treatment)	0.164±0.139	0.158±0.120	0.855
VA (after treatment)	0.659±0.275	0.644±0.312	0.853
Difference in VA	0.495±0.219	0.486±0.270	0.901
Increased VA (%)	407.04±202.38	432.21±300.3	0.718
CMT (before treatment) (µM)	481.85±143.40	455.25±107.92	0.442
CMT (after treatment) (µM)	311.85±32.67	310.3±48.30	0.896
CMT reduction (µM)	170.00±129.61	144.85±85.25	0.402
Decreased CMT (%)	31.66±14.42	30.00±11.25	0.638

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Discussion

The results of the present study confirmed the role of hypertension in the progression of CSR. Due to the unknown etiology of CSR, there are no certain target-specific CSR medications (21). Therefore, the identification of CSR-related risk factors is critical in the management of this disease. In addition to the role of risk factors on CSR development, various risk factors impact the outcome of CSR treatment with different medications (22, 23). In this study, CMT after treatment in patients with hypertension was significantly higher than patients without hypertension, indicating a poor prognosis. Nevertheless, our results did not confirm the critical role of hypertension in the reduction of CMT or increase in VA after one month of bevacizumab therapy. Moreover, Lee et al. demonstrated that hypertension is associated with the development of choroidal neovascularization secondary to central serous chorioretinopathy, as an independent risk factor (24). In their study, all CSR patients received intravitreal bevacizumab. Therefore, their findings are consistent with our results. In a study by Bousquet et al., the results showed the reductive role of mineralocorticoid receptor antagonism in CSR treatment (25). In this study, subretinal fluid (measured by OCT) decreased, and VA improved after three months of treatment with oral eplerenone in CSR patients. In a similar study by Chin et al., the oral mineralocorticoid antagonist, spironolactone, was shown to improve CSR in hypertensive patients (26). In their study, VA and CMT improved significantly compared to controls.

Diabetes is significantly associated with poor prognosis of CSR. As described above, VA before treatment was lower in people with diabetes compared to non-diabetic patients, but this difference was not significant. After treatment, VA was also higher in non-diabetics compared to diabetics. This result showed that the condition of diabetes exacerbates VA in CSR. Moreover, CMT confirmed the poor prognostic role of diabetes in the development of CSR. In addition, the mean reduction of CMT in non-diabetic patients was higher than diabetic patients, but this difference was not significant. Therefore, it could be said that the condition of diabetes is significantly correlated with adverse outcomes in one-month bevacizumab therapy. There is no previous study about the correlation between diabetes and CSR progression to compare results. Our results show no association between the two diseases, hypothyroidism and hyperlipidemia, and CSR therapy outcomes. In 2019, Ulaş et al. reported the relationship between hypothyroidism and higher prevalence of acute CSR (27). Takkar et al. reported the relationship between autoimmune thyroiditis and CSR progression (28).

Our results demonstrated that a higher age is significantly correlated with lower VA scores before and one month after treatment. These results showed that age is a critical factor in the prediction of VA in CSR patients. Moreover, higher age is significantly correlated with lower CMT, before and one month after treatment. Therefore, age is a poor prognostic factor in terms of VA, and it is a good prognostic factor in terms of CMT in CSR patients. However, poor prognosis of VA may be associated with age-related eye diseases.

Since this is a cross-sectional study, we did not have access to disease-specific indicators such as fasting blood sugar level (FBS), thyroid-stimulating hormone level (TSH), lipid profile, etc. Finally, we suggest further studies on the role of diabetes and hypertension in CSR progression and the response to therapy by applying different indicators such as FBS, HbA1c, systolic and diastolic blood pressure, and any other related condition.

Conflict of interest: The authors declare that there is no conflict of interest.

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