The comparison of the relationships about the presence of branch retinal vein occlusion and endothelial functions between diabetic and non-diabetic patients

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Objectives The aim of this study was to investigate the endothelial functions in both patients with diabetics and non-diabetics with branch retinal vein occlusion by using pulse wave analysis and flow-mediated dilatation methods.

Patients and methods This cross-sectional study included a total of 136 participants (47 diabetic patients with branch retinal vein occlusion, 43 non-diabetic patients with branch retinal vein occlusion, and 46 otherwise healthy subjects). Evaluation of endothelial functions was performed by flow-mediated dilatation and pulse wave analysis methods. Stiffness index, reflection index (RI), and pulse propagation time were calculated.

Results The mean stiffness index and RI were significantly higher in the diabetic branch retinal vein occlusion group compared with the non-diabetic branch retinal vein occlusion and the healthy controls (for stiffness index: 11.5 ± 2.8 vs. 10.1 ± 2.5 and 8.3 ± 2.0, $P <$ 0.001; and for RI: 75.1 ± 11.7 vs. 65.4 ± 8.4 and 60.2 ± 18.8, $P <$ 0.001, respectively), whereas the pulse propagation time was significantly lower in the diabetic group (156.4 ± 32.3 vs. 174.4 ± 46.5 and 205.0 ± 58.5, $P <$ 0.001, respectively). There was a significant negative correlation between visual acuity and stiffness index (r = –0.512, $P <$ 0.001). Besides, there was also a significant positive correlation between visual acuity and pulse propagation time (r = 0.398, $P <$ 0.001).

Conclusion This study demonstrated that the stiffness index and RI values were higher in patients with branch retinal vein occlusion compared to the healthy subjects. *Cardiovasc Endocrinol Metab* 8: 109–114 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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Keywords: branch retinal vein occlusion, endothelial functions, flow-mediated dilatation, pulse wave analysis

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Introduction

The pathogenesis of branch retinal vein occlusion (BRVO) is influenced by a number of factors, including vein entrapment at an arteriovenous junction, degenerative changes of vessel walls, and abnormal hematologic and hemoreological factors associated with endothelial dysfunction [1–4]. Not only does it cause visual morbidity, but it is also a risk for many concomitant systemic diseases. Previous studies have shown that the incidence rate for cerebrovascular accidents in patients with BRVO is almost twice that observed in controls. In addition, BRVO has been shown to be associated with abnormal blood viscosity and risk of developing hypertension, congestive heart failure and cerebrovascular disease due to hemostasis, atherosclerosis and endothelial dysfunction [2–9].

In clinical practice, there is not any direct method to measure endothelial functions. On the other hand, some of the indirect and practical methods can aid to evaluate the endothelial functions via measurement of responses to shear stress. Flow-mediated dilatation (FMD) and pulse wave analysis (PWA) are the most practical and effective methods [10,11]. FMD method is depending on measuring the dilatation ratio of brachial artery. Dilatation of brachial artery is occurred by the help of enhanced nitric oxide (NO) levels in response to augmented vessel wall shear stress [12,13]. PWA shows the tonometric pattern of blood pressure waves by using generally a finger tonometricprobe. Pulse waves and their comparative ratios could give some indirect data about the resistance of arterial bed, which is also related to NO production capacity of endothelial layer [13]. In literature, some authors have pointed out that there was also a close association between diabetes mellitus (DM) and BRVO [14,15]. Presence of DM was found to be a risk factor for visual acuity in patients with BRVO. Since both pathological conditions are associated with endothelial dysfunction, loss of visual acuity is closely associated with endothelial dysfunction. On the other hand, there is insufficient data on the comparison of endothelial functions in diabetic and non-diabetic BRVO patients.

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In this study, we aimed to evaluate endothelial functions in patients with BRVO using PWA and FMD methods, and also to compare the relationship between BRVO and endothelial functions between diabetic and non-diabetic patients.

Methods and materials

Ethics statement

This study was approved by the local Ethics committee (2017-KAEK-189_2018.06.06_03), and methods were carried out in accordance with institutional guidelines on human subject experiments. This study was conducted in accordance with the Declaration of Helsinki. Written and informed consent was obtained from all patients and control subjects. BROV patients gave written and verbal consent.

Patient selection

This is a cross-sectional study. One hundred fifty-eight patients admitting to the Department of Ophthalmology at the tertiary center with decreased visual acuity and related symptoms were screened among May 2017 and September 2018. In all patients, basic clinical data including age, sex, disease duration, and BMI were investigated. Exclusion criteria were acute coronary syndromes, systolic heart failure (EF < 50%), coronary and peripheral artery disease, secondary hypertension, congenital heart diseases, moderate and severe valvular heart disease, thoracic/abdominal aortic aneurysm, acute or a history of treatment for or diagnosis of carotid artery stenosis, chronic renal dysfunction (serum creatinine level >1.5 mg/dl), malignancies, morbid obesity (BMI ≥ 40 kg/m^2), asthma or chronic obstructive lung disease, infections, connective tissue disorders, neurological problems, psychiatric diseases (psychotic and major depressive patients and the patients with anxiety disorders), endocrine diseases, alcohol and drug abuse, and taking hormone supplements. After ophthalmologic evaluation, patients with central and hemicentral vein occlusion and any type of glaucoma were also excluded from the study.

Twenty-two patients were excluded from the study due to the development of any exclusion criteria. The data for the control group were obtained from retrospective data of individuals who were examined previously and did not diagnose ophthalmologic or other pathologies. A total of 136 people were included in the study. The patients were divided into three groups. Forty-seven diabetic patients with BRVO and 43 non-diabetic patients with BRVO; and age and sex-matched 46 patients without cardiovascular disease.

Laboratory

Fasting blood samples were taken between 09.00 and 10.00. Detailed biochemical analysis including complete blood count, fasting blood glucose, urea, creatinine, aspartate aminotransferase, alanine aminotransferase, and serum lipid profile (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride) were performed.

Ophthalmologic evaluation

Complete ophthalmic examination including corrected best visual acuity, biomicroscopy, and fundoscopy was conducted. Intraocular pressure was measured with Goldmann applanation tonometer at 9.00 a.m. Dilated fundus examination and fundus fluorescein angiography were performed in all patients.

Cardiologic evaluation

After a detailed medical history, physical examination including blood pressure measurement on two arms using sphygmomanometer was performed; and also the 12-channel electrocardiography and the transthoracic echocardiography (Ge-Vivid 7 Pro; General Electric, Florida, USA)

Non-invasive evaluation of endothelial functions

Non-invasive evaluation of endothelial functions was measured by FMD and PWA methods [16].

Flow-mediated dilatation

FMD measurements were performed by using Ge-Vivid 7 Pro, 12L Doppler probe (General Electric, Clearwater, Florida, USA) according to method of Celermajer *et al.* [16].

We used

(1) FMD basal (cm): Basal brachial artery diameter
(2) FMD hyperemia (cm): Brachial artery diameter at Hyperemia phase
(3) FMD basal/FMD Hyperemia ratio (%)

Parameters to evaluate FMD measurements.

Pulse wave analysis

PWA measurements were performed by using a photoplethysmography device (Pulse Trace PCA 2; Micro Medical, Rochester, UK). Stiffness index (SI), reflection index (RI) and pulse propagation time (PPT) were calculated (Fig. 1) [17,18].

The formula of SI which is related with large arteries stiffness:

$$SI = \text{Height of patient} / \text{PPT formula}$$

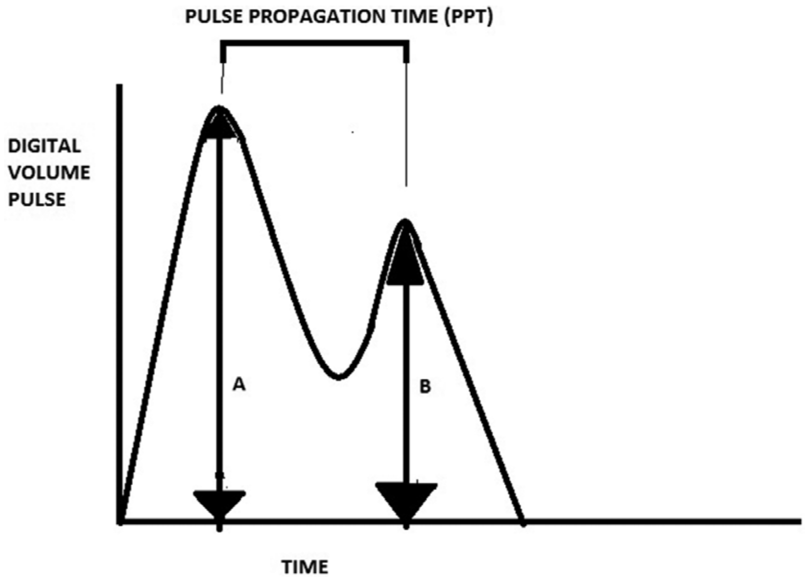
Reflection index (RI) formula which is related to peripheral arterial resistance and vascular tonus:

$$RI = B / A \text{ formula}$$

Statistical analyses

All statistical analysis was performed using SPSS version 20.0 (SPSS; Chicago, Illinois, USA). The normally

Fig. 1



A pattern of digital volume pulse recordings.

Table 1 **The statistically comparison about anthropometric and blood pressure characteristics of branch retinal vein occlusion patients**

Patient characteristics	Control (n = 46)	BRVO DM (–) (n = 43)	BRVO DM (+) (n = 47)	*P* value
Age (years)	61.0 ± 6.3	62.4 ± 13.8	66.2 ± 9.3	0.326
Height (cm)	163.2 ± 8.5	167.4 ± 9.3	161.7 ± 8.5	0.345
Weight (kg)	79.0 ± 9.8	84.0 ± 6.7	77.8 ± 9.7	0.567
BMI (kg/m^2)	29.8 ± 4.2	30.3 ± 4.6	30.0 ± 5.0	0.180
SBP (mmHg)	122.3 ± 10.9	122.5 ± 3.4	125.6 ± 6.3	0.663
DBP (mmHg)	77.4 ± 7.9	78.0 ± 3.8	77.7 ± 3.9	0.323

One-way ANOVA test, mean ± SD, $P < 0.05$.
BRVO, branch retinal vein occlusion; DBP, diastolic blood pressure; SBP, systolic blood pressure.

distributed data are presented as mean ± SD and non-normally distributed data are expressed as median (25%–75%). For continuous data Student's *t* and one-way analysis of variance tests were used for comparing normally distributed data. Mann–Whitney *U* and Kruskal–Wallis tests were used for comparing non-normally distributed data. A *P*-value of <0.05 was accepted as statistically significant.

Results

In the present study, a total of 136 participants (90 BRVO patients and 46 control participants, minimum age: 35, maximum age: 88, mean age 62.7 ± 9.4 years) were admitted to the study. The mean age was 64.76 ± 12.18 years (range: 35–88 years) in the BRVO group and 61.15 ± 6.32 years (range: 48–78 years) in the control group ($P > 0.05$).

Table 1 shows the comparison of anthropometric and blood pressure characteristics of BRVO patients. There was no statistically significant difference between the groups. As expected, no statistically significant difference was found between the groups except the glucose levels in the biochemical analyzes of the groups (Tables 2 and 3). When we compare pulse wave and FMD measurements, we found statistically significant differences in SI, RI, and PPT values. After Bonferroni adjustment, we found that SI was higher in patients with DM than in the control group ($P < 0.001$). We also found that there was no statistically significant difference in FMD measurements between diabetic or non-diabetic patients with BRVO. We found that RI was higher in diabetic patients with BRVO than those of the control participants ($P < 0.001$). There were no statistically significant difference in RI and SI measurements between the diabetic or non-diabetic patients with BRVO. On the other hand, we determined that PPT was shorter in diabetic patients with BRVO than those of the control participants ($P < 0.001$). Furthermore, there was no statistically significant difference in PPT measurements between the diabetic or non-diabetic patients with BRVO (Table 4). There was a significant negative correlation between visual acuity and SI ($r = -0.512$, $P < 0.001$). Besides, there was also a significant positive correlation between visual acuity and

PPT (r = 0.398, $P < 0.001$). These correlations were still statistically significant after controlling the effects of age, systolic and diastolic blood pressure and the presence of DM ($P < 0.001$ and $P < 0.005$, SI and RI values, respectively). Ophthalmologic evaluation was shown that there was statistically significant difference in visual acuity ($P < 0.001$) and intraocular pressure ($P < 0.05$) among the groups (Table 5).

Table 2 The statistically comparison about biochemical blood analysis of branch retinal vein occlusion patients with and without diabetes mellitus

Patient characteristics	BRVO DM (–) (n = 43)	BRVO DM (+) (n = 47)	*P* value
Glucose (mg/dl)	90.9 ± 6.5	169.2 ± 39.1	<0.001
Urea (mg/dl)	35.6 ± 10.1	35.7 ± 9.9	0.982
Creatinine (mg/dl)	0.78 ± 0.16	0.87 ± 0.17	0.678
AST (U/L)	18.3 ± 4.1	22.4 ± 4.5	0.567
ALT (U/L)	22.1 ± 9.3	19.8 ± 6.8	0.867
Total cholesterol (mg/dl)	216.7 ± 38.5	207.4 ± 45.2	0.667
HDL (mg/dl)	52.9 ± 11.4	49.8 ± 10.6	0.234
LDL (mg/dl)	126.9 ± 31.5	128.9 ± 31.5	0.165
Triglyceride (mg/dl)	180.9 ± 77.5	177.1 ± 73.2	0.256

One-way ANOVA test, mean ± SD, $P < 0.05$.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BRVO, branch retinal vein occlusion; DM, diabetes mellitus; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Table 3 The statistically comparison about blood count of branch retinal vein occlusion patients with and without diabetes mellitus

Patient characteristics	BRVO DM (–) (n = 43)	BRVO DM (+) (n = 47)	*P* value
Hemoglobin (mg/dl)	13.7 ± 1.2	13.6 ± 1.3	0.456
Leukocyte (10^3/μl)	6.51 ± 0.94	8.34 ± 2.72	0.180
Neutrophil (%)	62.99 ± 6.56	58.50 ± 12.07	0.175
Lymphocyte (%)	28.21 ± 6.42	29.55 ± 9.07	0.228
Monocyte (%)	6.51 ± 1.15	6.88 ± 2.86	0.234
Eosinophil (%)	1.39 ± 0.84	207.4 ± 45.2	0.450
Basophil (%)	52.9 ± 11.4	3.29 ± 1.86	0.899
Platelet (%)	252.89 ± 27.66	238.30 ± 61.14	0.567
Mean platelet volume (fl)	8.68 ± 1.04	8.72 ± 1.01	0.789

One-way ANOVA test, mean ± SD, $P < 0.05$.
BRVO, branch retinal vein occlusion; DM, diabetes mellitus.

Discussion

In this study, we found that there was no statistically significant difference between diabetic and non-diabetic patients with BRVO in terms of PWA and FMD measurements. In addition, we found a significant negative correlation between visual acuity and SI, and a significant positive correlation between visual acuity and PPT.

In clinical practice, FMD and PWA measurements are utilized for the evaluation of endothelial functions. FMD measures give us an indirect information about NO-releasing capacity and endothelial function; however, PWA measures show that there are chronical changes about arterial bed. Pulse-wave velocity provides important information about the regional arterial resistance and stiffness [19–21].

Some authors who used PWA measurements have shown that increased systemic arterial stiffness is associated with the presence of age-related macular degeneration [21], and there is statistically significant association between carotid arterial stiffness and retinal arterial narrowing, a marker of arteriolosclerosis [22]. Cheung *et al.* [23] have been reported that retinal vein occlusion is associated with hypertension and dyslipidemia. Endothelial dysfunction and related pathological processes pay the way for the evaluation of atherosclerosis, which is an end-stage pathologic pathway not only for hypertension, but also for other risk factors like hyperlipidemia, DM, cigarette smoking, and obesity. There are many common pathophysiological pathways between endothelial dysfunction related pathologies and BRVO [23–26]. Some authors pointed out that there are some severe atherosclerotic changes in

Table 4 The statistically comparison about pulse wave analysis and flow-mediated dilatation measurements of branch retinal vein occlusion patients with and without diabetes mellitus

Patient characteristics	Control (n = 46)	BRVO DM (–) (n = 43)	BRVO DM (+) (n = 47)	*P* value
Reflection index (RI)	60.19 ± 18.84	65.45 ± 8.40	75.13 ± 11.75	0.001
Stiffness index (SI)	8.37 ± 2.07	10.14 ± 2.50	11.53 ± 2.85	<0.001
Pulse propagation time (PPT)	205.07 ± 58.55	174.45 ± 46.50	156.42 ± 32.32	0.001
FMD basal (mm)	4.03 ± 0.57	4.16 ± 0.51	4.12 ± 0.73	0.607
FMD hyperemia (mm)	4.37 ± 0.56	4.53 ± 0.48	4.59 ± 0.77	0.123
FMD-B/FMD-ratio (%)[a]	92.13 ± 3.20	91.79 ± 4.61	89.77 ± 6.46	0.345

BRVO, branch retinal vein occlusion; DM, diabetes mellitus; FMD, flow-mediated dilatation.
[a]FMD basal/FMD hyperemia ratio, Student *t*-test, mean ± SD, $P < 0.05$.

Table 5 The statistically comparison about ophthalmic characteristics of branch retinal vein occlusion patients with and without diabetes mellitus

Patient characteristics	Control (n = 46)	BRVO DM (–) (n = 43)	BRVO DM (+) (n = 47)	*P* value
Visual acuity (×100)[a]	1.00 (0.00–1.00)	0.100 (0.03–0.048)	0.100 (0.04–0.85)	<0.001
Intraocular pressure (mmHg)	15.00 (14.00–17.25)	16.00 (15.00–17.75)	18.00 (16.00–23.25)	0.012

BRVO, branch retinal vein occlusion; DM, diabetes mellitus.
[a]Kruskal–Wallis Test, $P < 0.05$.

retinal arterioles in the patients with BRVO [23,27,28]. Furthermore, it was also shown that BRVO patients had higher intima-media thickness than control subjects [19,22]. DM is one of the most important disease which causes endothelial dysfunction, increased arterial resistance, and stiffness [19]. There are few studies in the literature showing the relationship between DM and the presence of BRVO. Although this relationship leads to endothelial dysfunction by similar pathophysiological pathways; There is insufficient data on whether there is a difference in PWA and FMD measurements [29]. In our study, we found that there was no statistically significant difference in endothelial functions between diabetic and non-diabetic patients with BRVO. In patients with BRVO, endothelial dysfunction is thought to be as severe as in diabetic patients. There is insufficient data on how endothelial dysfunction affects visual acuity in patients with BRVO. In the literature, the presence of DM is an extra risk factor for the loss of visual acuity in patients with BRVO. According to our data, intraocular pressure was higher in DM and BRVO patients than in other groups. Although it is said to be multifactorial. There is no complete data on which factors affect visual acuity.

Limitations

This is a small-scale study. One of the most important limitations is the PWA method. Pulse wave was measured by PWA of the brachial artery. Because of the non-invasive and indirect characteristics of PWA, the PWA method was unable to provide data that were consistent with the pressure waves in the aorta. Further studies are needed to determine the role of endothelial dysfunction, arterial resistance, and stiffness in the pathogenesis of BRVO.

Conclusion

The results of this study show that the SI and RI values are higher in patients with BRVO compared to the healthy controls. Increased arterial resistance and stiffness may play a role in pathological process of BRVO. There is not significant difference about endothelial dysfunction in non-diabetic vs. diabetic patients with BRVO. The presence of BRVO is a clinical marker of the presence of endothelial dysfunction.

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H.K. and MT.D. analyzed and interpreted the data and wrote the manuscript; H.K., V.D., and MT.D. performed experiments and collected data. V.D., Z.O., H.K., C.A., and MT.D. have paid considerable attention to the critical input of the manuscript. All authors contributed to the writing and gave final approval.

Conflicts of interest

There are no conflicts of interest.

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