



Early Ophthalmic Artery Blood Flow Parameter Changes in Patients with Type I Diabetes Mellitus

Serdar Ozates,¹ Betul Emine Derinkuyu,² Ufuk Elgin,³ Meliksah Keskin,⁴
 Nursel Muratoglu Sahin,⁴ Zehra Aycan⁴

¹Department of Ophthalmology, Kars Harakani State Hospital, Kars, Turkey

²Department of Radiology, Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

³Department of Ophthalmology, Ulucanlar Eye Training and Research Hospital, Ankara, Turkey

⁴Department of Endocrinology, Dr. Sami Ulus Maternity, Children's Health and Diseases Training and Research Hospital, Ankara, Turkey

Abstract

Objectives: The aim of this study was to assess initial changes in blood flow parameters of the ophthalmic artery (OA) in pediatric patients with type I diabetes mellitus (DM).

Methods: Sixty-three subjects were included in this prospective, cross-sectional, observational study. Thirty-one (49.2%) patients with type I DM without diabetic retinopathy formed the DM group. The control group comprised 32 (50.8%) healthy subjects. The OA of all of the patients was examined with Doppler ultrasonography. The main outcomes were peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI), and resistivity index (RI) measurements.

Results: The mean age at onset of type I DM was 10.7 ± 2.0 years and the mean duration was 11.4 ± 11.0 months. The mean PSV and EDV outcomes in both eyes were significantly higher in the control group than in the DM group, whereas, the mean PI and RI outcomes in both eyes were significantly higher in the DM group ($p < 0.05$). A mean RI of ≥ 0.75 indicated vascular hemodynamic changes associated with type I DM with a sensitivity of 72% and a specificity of 65% (area under the curve: 0.702; $p = 0.007$). A mean PI of ≥ 1.69 predicted vascular hemodynamic changes associated with type I DM with a sensitivity of 79% and a specificity of 71% (area under the curve: 0.742; $p = 0.001$).

Conclusion: The results of this study revealed that disturbances in ocular hemodynamics might be present as early as the first year after a type I DM diagnosis. Changes in ocular hemodynamic parameters could be used to predict or screen for the development of vascular changes.

Keywords: Arterial resistance, blood flow, Doppler sonography, ophthalmic artery, type I diabetes mellitus

Introduction

Diabetes mellitus (DM) is a common systemic metabolic disorder; a significant proportion of the population across the globe suffers from long-term damage associated with DM, such as diabetic retinopathy (DR) (1, 2). It has been reported that 83% of patients with type I DM develop some stage of DR within 10 years of DM onset (3). The period before

DR develops in patients varies; however, it has been found that retinal and vascular changes can occur even if no clinically significant DR is present (4, 5). Vascular changes have an impact on ocular hemodynamics, and previous studies have documented how DM influences ocular hemodynamics (6–8). In the current body of literature, several studies have reported similar results for ocular hemodynamic changes, such as lower blood velocity and higher peripheral vascular

Address for correspondence: Serdar Ozates, MD. Kars Harakani Devlet Hastanesi, Goz Hastaliklari Anabilim Dalı, Yenisehir Mahallesi, Ismail Aytemiz Biv. No: 55, 36200 Merkez, Kars, Turkey
Phone: +90 537 717 91 10 **E-mail:** serdarozates@gmail.com

Submitted Date: November 04, 2019 **Accepted Date:** January 22, 2020 **Available Online Date:** February 14, 2020

©Copyright 2020 by Beyoglu Eye Training and Research Hospital - Available online at www.beyoglu.eyec.com

OPEN ACCESS This work is licensed under a Creative Commons Attribution-NonCommercial 4.0 International License.



resistance, in patients with DR (9, 10), however, conflicting results have been described with regard to ocular hemodynamic changes before the development of clinically significant DR (8, 11).

DR is a consequence of microvascular disorder and altered insulin metabolism; it causes significant histopathological changes in the ocular vascular structure, such as endothelial changes, loss of pericytes, a narrowed vessel lumen, and a thickened basement membrane (12, 13). Therefore, it is not clear when the vascular structure and related ocular hemodynamic parameters begin to change. The objective of the present study was to investigate initial changes in ocular hemodynamics in pediatric patients with recently diagnosed type I DM without DR.

Methods

This prospective, cross-sectional, observational study was conducted at a tertiary referral hospital in accordance with the ethical standards of the Declaration of Helsinki. The study protocol was approved by the Ankara Kecioren Training and Research Hospital Clinical Research Ethics Committee in Ankara, Turkey (2012-KAEK-15/1664). All of the participants and their parents provided written, informed consent prior to undergoing any examination.

Patients aged between 5 and 21 years were included in the study, which was conducted between January 2018 and May 2018. Patients with retinal diseases, a history of retinopathy of prematurity, myopia or hyperopia greater than 3 diopters, uveitis, glaucoma, congenital cataract, or a history of ocular trauma were excluded. Patients using a vasodilator, vasoconstrictor, or inotropic drugs, and those with cardiovascular diseases, chromosomal anomalies, a history of vaso-occlusive diseases, or a history of metabolic diseases other than type I DM were also excluded. Patients with type I DM without DR were consecutively recruited and assigned to the DM group. Age-matched healthy participants without any ocular or systemic disease were consecutively recruited and assigned to the control group.

The type I DM diagnosis was confirmed by the endocrinology department of the hospital. Ophthalmological examinations were performed, including a best-corrected visual acuity test with a Snellen chart, non-contact tonometry, and a slit-lamp examination. One clinician (S.O.) performed the fundus examination of all of the patients. Fundus fluorescein angiography and optical coherence tomography were performed, if needed.

Doppler ultrasonography of the ophthalmic artery (OA) was performed using the Aplio 500 system (Canon Medical Systems Co, Ltd, Otawara, Japan) with a 10 MHz linear transducer by a single radiologist (B.E.D.) to standardize the measurements. Doppler examination of the orbit was per-

formed through the closed eyelid with the patient in the supine position. Care was taken to apply as little pressure as possible to the globe to avoid incorrect vascular recordings. The main arterial supply to the orbit is through the OA, which could be seen easily with color Doppler ultrasound by scanning medial to the optic nerve just 1.5 cm posterior to the globe. The main outcomes were peak systolic velocity (PSV), end diastolic velocity (EDV), pulsatility index (PI), and resistivity index (RI) measurements. RI is an indicator of peripheral arterial resistance; it is calculated using the formula $(PSV-EDV)/PSV$. PI refers to the vascular impedance distal to the measurement site; it is calculated as $(PSV-EDV)/\text{mean velocity}$. The flow parameters of the OA were measured bilaterally 3 times and the mean was used as the outcome value.

Statistical analyses were performed with IBM SPSS Statistics for Windows, Version 22.0 (IBM Corp., Armonk, NY, USA). The assumption of normal distribution of data was assessed with the Kolmogorov-Smirnov test. Differences in descriptive data between groups were tested using a chi-square test. Differences in the outcomes between groups were tested with an independent samples t-test. The relationship between the outcomes was evaluated using Pearson's correlation. Receiver operating characteristic (ROC) curve analysis was performed, and the point that maximized Youden's index on the ROC curve was selected as the cut-off value. A level of $p < 0.05$ was considered statistically significant for all tests.

Results

Thirty-two (50.8%) healthy subjects [13 (40.6%) males, 19 (59.4%) females] were included in the control group and 31 (49.2%) patients [18 (58.1%) males, 13 (41.9%) females] with type I DM were included in the DM group. Of the 31 patients in the DM group, 24 (77.4%) were metabolically well-controlled and 7 (22.6%) were not metabolically well-controlled. The mean age was 11.7 ± 2.5 years in the DM group and 12.8 ± 2.8 years in the control group. Gender and mean age did not differ significantly between groups ($p = 0.166$, $p = 0.097$, respectively). In the DM group, the mean age at onset of type I DM was 10.7 ± 2.0 years, and the mean duration of type I DM was 11.4 ± 11.0 months.

Table 1 shows the mean Doppler sonography outcomes and a comparison of outcomes between the 2 groups. The mean PSV and EDV results in the right eye were significantly higher in the control group (43.9 ± 11.9 cm/seconds, 11.1 ± 3.6 cm/seconds, respectively) than in the DM group (37.6 ± 9.2 cm/seconds, 8.6 ± 2.5 cm/seconds, respectively), while the mean PI and RI outcomes in the right eye were significantly higher in the DM group (1.82 ± 0.40 , 0.77 ± 0.08 , respectively) than in the control group (1.62 ± 0.22 , 0.74 ± 0.03 , respectively). The mean PSV and EDV outcomes in the left eye were sig-

Table 1. Mean outcomes of ocular hemodynamics, comparison of outcomes within and between groups and the p values

	Diabetes mellitus group (n=31)		Control group (n=32)		Comparison between groups					
	Right eye	Left eye	Right eye	Left eye	P	Mean difference	95% CI	P	Mean difference	95% CI
						Right eye	Left eye		Right eye	Left eye
PSV (cm/s)	37.6±9.2	37.0±8.7	43.9±11.9	43.3±14.2	0.768	-6.2	-6.26	0.039*	-11.6 - -0.7	-12.2 - -0.3
EDV (cm/s)	8.6±2.5	8.5±2.7	11.1±3.6	10.7±4.2	0.477	-2.4	-2.1	0.003*	-4.0 - -0.8	-3.9 - -0.3
PI	1.82±0.40	1.80±0.38	1.62±0.22	1.62±0.24	0.895	0.20	0.18	0.016*	0 - 0.3	0 - 0.3
RI	0.77±0.08	0.77±0.04	0.74±0.03	0.74±0.04	0.246	0.04	0.02	0.010*	0.01 - 0.07	0 - 0.4

EDV: End diastolic velocity; PI: Pulsatility index; PSV: Peak systolic velocity; RI: Resistivity index; *Statistically significant.

nificantly higher in the control group (43.3±14.2 cm/seconds, 10.7±4.2 cm/seconds, respectively) than in the DM group (37.0±8.7 cm/seconds, 8.5±2.7 cm/seconds, respectively), while the mean PI and RI outcomes in the left eye were significantly higher in the DM group (1.80±0.38, 0.77±0.04, respectively) than in the control group (1.62±0.24, 0.74±0.04, respectively). The mean outcomes of ocular hemodynamics did not differ significantly between the right eye and the left eye in either group. According to the ROC analysis, a mean RI of ≥0.75 indicated vascular hemodynamic changes associated with type I DM with a sensitivity of 72% and a specificity of 65% (area under the curve=0.702; p=0.007). A mean PI of ≥1.69 predicted vascular hemodynamic changes associated with type I DM with a sensitivity of 79% and specificity of 71% (area under the curve=0.742; p=0.001).

In the DM group, the mean glycated hemoglobin (HbA1c) level was 6.8±2.3% at the time of DM diagnosis and 5.9±1.1% at the time of examination with Doppler sonography. No correlation was found between the HbA1c level and ocular hemodynamic outcomes (p>0.05 for each). The mean ocular hemodynamic outcomes were similar between patients with metabolically well-controlled DM and patients with metabolically uncontrolled DM. No correlation was found between the ocular hemodynamic outcomes and the duration and age of onset for type I DM (p>0.05 for each).

Discussion

Our study revealed decreased blood velocity and increased PI in the OA of patients who had recently been diagnosed with type I DM. The combination of decreased blood velocity and increased PI indicates increased vascular resistance. Similarly, Kawagishi et al. (9) reported that the PSV and EDV values were significantly lower and the RI was significantly higher in the central retinal artery of type I DM patients without retinopathy in comparison with healthy control subjects. Arai et al. (10) found that the RI of central retinal artery was significantly higher in DM patients without DR. Gil et al. (14) observed that there was an increase in OA resistance as the duration of DM increased. However, Ovali et al. (8) and Lockhart et al. (11) reported no change in the RI of the OA in patients with type I DM without DR. Many factors, such as age, race, duration of DM, glycemic control, site of measurement, and measurement technique, may affect ocular hemodynamics and lead to conflicting results (14–16). Although there is no consensus on changes in ocular hemodynamics before the development of DR, clear evidence has demonstrated that both micro- and macrovascular changes occur even if there is no clinical sign of DR (17).

Our study showed that the RI was elevated in patients with type I DM. Increased vascular resistance is a consequence of changes in vascular structure. Thickening of the

basement membrane, protein composition changes, and hyaline deposition are initial changes seen in the capillaries at the early stages of DM (12). Consistent with our findings, Romney et al. (4) noted that vascular compliance was reduced in both large and small arteries in type I DM before clinically apparent microvascular complications. Järvisalo et al. (17) and Pena et al. (18) found that the intima-to-media ratio thickness of the carotid artery was significantly higher in type I DM patients in comparison with healthy individuals. It is not clear whether microvascular changes trigger macrovascular changes, or if they progress simultaneously; however, it has been clearly established that the presence of DR predicts and increases the risk of macrovascular complications (19–21). Our study demonstrated altered hemodynamic changes in the OA in the absence of clinically significant microvascular changes, including DR and nephropathy. Changes in the hemodynamic parameters of the OA could potentially be used to detect initial macrovascular changes in patients with type I DM. Supporting our suggestion, Inoue et al. (22) showed that increased PI could be used to predict macrovascular changes. Our study revealed that a mean RI of ≥ 0.75 and a mean PI of ≥ 1.69 predicted vascular hemodynamic changes associated with type I DM with a sensitivity of 72% and 79% and a specificity of 65% and 71%, respectively. Arai et al. (10) suggested that an RI of ≥ 0.80 in the central retinal artery could distinguish patients with any stage of DR from healthy subjects with a sensitivity of 66% and a specificity of 88%. Unlike some previous research, the present study highlighted the potential of Doppler sonography to predict vascular changes in the peripheral ocular vascular bed.

Previous epidemiological evidence has shown that proper glycemic control and lower HbA1C levels have a significant association with DR progression (23, 24). It has been suggested that intensive glycemic control be initiated as soon as possible after the onset of type I DM and that doing so is the best way to prevent DM complications (23, 25). Kawaguchi et al. (26) observed that higher plasma levels of glucose were associated with a higher RI in patients with type I DM and they suggested that intensive glycemic control decreased the RI. Although our patients received intensive treatment with the onset of type I DM and HbA1C levels decreased, changes in the ocular hemodynamic parameters occurred as early as at a mean of 11 months of DM duration. Vascular changes in DM have been attributed to several factors, including vascular endothelial growth factor (VEGF), insulin-like growth factor I (IGF-I), glycated proteins, free-radicals, and oxidized low density lipoprotein (LDL) (4, 5, 18). The serum level of IGF-I has been found to begin to increase in the prepubertal period (27). IGF-I stimulates vascular smooth muscle proliferation; moreover, physiological elevations of the IGF-I level in puberty may trigger development

of DR (28). The VEGF level was also found to be elevated in patients with DM with no microvascular changes in comparison with healthy subjects (5). High levels of IGF-I and VEGF may cause initial changes in the vascular structure prior to clinically significant complications. Furthermore, it has been speculated that insulin increases smooth muscle cell proliferation and the mass of extracellular matrix proteins, causing reduced vessel compliance (4, 28). Rodriguez-Fontal et al. (29) and Chantelau E. (30) reported that intensive glycemic control or acute reduction of hyperglycemia increased the risk of paradoxical worsening and the progression of DR in type I DM. Although there was no clinical sign of DR in the DM group, changes in the ocular hemodynamic parameters might be caused by tight glycemic control. However, histological and pathophysiological investigations are needed to provide evidence to support this suggestion.

There are several limitations to our study. HbA1C levels of all of the patients decreased after receiving intensive treatment; however, 7 patients had not yet reached the intended HbA1C level due to a short DM duration. Data obtained from those patients with metabolically uncontrolled DM may have caused bias and distorted our study results. DR was excluded based on a fundus examination without routinely using more objective methods, such as optical coherence tomography angiography, which could show microvascular changes before clinical presentation. In future studies, the exclusion of microvascular changes with optical coherence tomography angiography will improve the strength of the results.

Our results revealed that disturbances in ocular hemodynamics might be present as early as the first year after diagnosis of type I DM. Changes in ocular hemodynamic parameters could potentially be used to predict or screen for development of vascular changes; however, further longitudinal studies with more patients are needed to prove if this approach would be effective.

Disclosures

Ethics Committee Approval: The Ethics Committee of Ankara Kecioren Training and Research Hospital provided the ethics committee approval for this study (2012-KAEK-15/1664, 25.1.2018).

Peer-review: Externally peer-reviewed.

Conflict of Interest: None declared.

Authorship Contributions: Involved in design and conduct of the study (SO, BED, UE); preparation and review of the study (SO, BED, UE, ZA); data collection (BED, MK, NMS, ZA); and statistical analysis (SO, BED, UE).

References

1. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus-present and future perspectives. *Nat*

- Rev Endocrinol 2011;8:228–36. [CrossRef]
2. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes care* 2014;37:81–90. [CrossRef]
 3. Klein R, Knudtson MD, Lee KE, Gangnon R, Klein BE. The Wisconsin Epidemiologic Study of Diabetic Retinopathy XXII: the twenty-five-year progression of retinopathy in persons with type 1 diabetes. *Ophthalmology* 2008;115:1859–68. [CrossRef]
 4. Romney JS, Lewanczuk RZ. Vascular compliance is reduced in the early stages of type 1 diabetes. *Diabetes Care* 2001;24:2102–6.
 5. Chiarelli F, Spagnoli A, Basciani F, Tumini S, Mezzetti A, Cipollone F, et al. Vascular endothelial growth factor (VEGF) in children, adolescents and young adults with type 1 diabetes mellitus: relation to glycaemic control and microvascular complications. *Diabet Med* 2000;17:650–6. [CrossRef]
 6. Nguyen NX, Kuchle M, Naumann GO. Quantification of blood-aqueous barrier breakdown after phacoemulsification in Fuchs' heterochromic uveitis. *Ophthalmologica* 2005;219:21–5.
 7. Dimitrova G, Kato S, Tamaki Y, Yamashita H, Nagahara M, Sakurai M, et al. Choroidal circulation in diabetic patients. *Eye (Lond)* 2001;15:602–7. [CrossRef]
 8. Lockhart CJ, McCann A, Agnew CA, Hamilton PK, Quinn CE, McClenaghan V, et al. Impaired microvascular properties in uncomplicated type 1 diabetes identified by Doppler ultrasound of the ocular circulation. *Diab Vasc Dis Res* 2011;8:211–20. [CrossRef]
 9. Kawagishi T, Nishizawa Y, Emoto M, Konishi T, Maekawa K, Hagiwara S, et al. Impaired retinal artery blood flow in IDDM patients before clinical manifestations of diabetic retinopathy. *Diabetes Care* 1995;18:1544–9. [CrossRef]
 10. Arai T, Numata K, Tanaka K, Kiba T, Kawasaki S, Saito T, et al. Ocular arterial flow hemodynamics in patients with diabetes mellitus. *J Ultrasound Med* 1998;17:675–81. [CrossRef]
 11. Yilmaz Ovali G, Ersoy B, Tuncyurek O, Urk V, Ozkol M, Ozhan B, et al. Doppler ultrasonography imaging of hemodynamic alteration of retrobulbar circulation in type 1 diabetic children and adolescents without retinopathy. *Diabetes Res Clin Pract* 2008;79:243–8. [CrossRef]
 12. Halfter W, Moes S, Asgeirsson DO, Halfter K, Oertle P, Melo Herraiz E, et al. Diabetes-related changes in the protein composition and the biomechanical properties of human retinal vascular basement membranes. *PLoS One* 2017;12:e0189857. [CrossRef]
 13. Beltramo E, Porta M. Pericyte loss in diabetic retinopathy: mechanisms and consequences. *Curr Med Chem* 2013;20:3218–25.
 14. Gil Hernández MA, Abreu Reyes P, Quintero M, Ayala E. Doppler ultrasound in type 1 diabetes: preliminary results. [Article in Spanish] *Arch Soc Esp Oftalmol* 2001;76:175–80.
 15. Groh MJ, Michelson G, Langhans MJ, Harazny J. Influence of age on retinal and optic nerve head blood circulation. *Ophthalmology* 1996;103:529–34. [CrossRef]
 16. Williamson TH, Lowe GD, Baxter GM. Influence of age, systemic blood pressure, smoking, and blood viscosity on orbital blood velocities. *Br J Ophthalmol* 1995;79:17–22. [CrossRef]
 17. Peña AS, Liew G, Anderson J, Giles LC, Gent R, Wong TY, et al. Early atherosclerosis is associated with retinal microvascular changes in adolescents with type 1 diabetes. *Pediatr Diabetes* 2018;19:1467–70. [CrossRef]
 18. Jarvisalo MJ, Putto-Laurila A, Jartti L, Lehtimäki T, Solakivi T, Rönnemaa T, et al. Carotid artery intima-media thickness in children with type 1 diabetes. *Diabetes* 2002;51:493–8. [CrossRef]
 19. Chawla A, Chawla R, Jaggi S. Microvascular and macrovascular complications in diabetes mellitus: Distinct or continuum. *Indian J Endocrinol Metab* 2016;20:546–51. [CrossRef]
 20. Rosenson RS, Fioretto P, Dodson PM. Does microvascular disease predict macrovascular events in type 2 diabetes?. *Atherosclerosis* 2011;218:13–8. [CrossRef]
 21. Juutilainen A, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Retinopathy predicts cardiovascular mortality in type 2 diabetic men and women. *Diabetes Care* 2007;30:292–9. [CrossRef]
 22. Inoue M, Azumi A, Yamamoto M. Ophthalmic artery blood flow velocity changes in diabetic patients as a manifestation of macroangiopathy. *Acta Ophthalmol Scand* 2000;78:173–6. [CrossRef]
 23. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002;287:2563–9. [CrossRef]
 24. Group DCaCTR. The relationship of glycemic exposure (HbA1c) to the risk of development and progression of retinopathy in the diabetes control and complications trial. *Diabetes* 1995;44:968–83. [CrossRef]
 25. Nathan DM; DCCT/EDIC Research Group. The diabetes control and complications trial/epidemiology of diabetes interventions and complications study at 30 years: overview. *Diabetes Care* 2014;37:9–16. [CrossRef]
 26. Kawaguchi T, Mochizuki M, Miyata K, Miyata N. Phacoemulsification cataract extraction and intraocular lens implantation in patients with uveitis. *J Cataract Refract Surg* 2007;33:305–9. [CrossRef]
 27. Juul A, Bang P, Hertel NT, Main K, Dalgaard P, Jørgensen K, et al. Serum insulin-like growth factor-I in 1030 healthy children, adolescents, and adults: relation to age, sex, stage of puberty, testicular size, and body mass index. *J Clin Endocrinol Metab* 1994;78:744–52. [CrossRef]
 28. Berk BC. Vascular smooth muscle growth: autocrine growth mechanisms. *Physiol Rev* 2001;81:999–1030. [CrossRef]
 29. Rodriguez-Fontal M, Kerrison JB, Alfaro DV, Jablon EP. Metabolic control and diabetic retinopathy. *Curr Diabetes Rev* 2009;5:3–7. [CrossRef]
 30. Chantelau E. Evidence that upregulation of serum IGF-I concentration can trigger acceleration of diabetic retinopathy. *Br J Ophthalmol* 1998;82:725–30. [CrossRef]