Central Retinal Artery hemodynamic flow amongst diabetic patients attending the Mulago Hospital diabetic clinic

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Research article

Keywords: Retinal blood flow, Retinal Hemodynamic flow, Color Doppler Imaging, Diabetes Mellitus, Diabetic Retinopathy, Peak Systolic velocity, End diastolic velocity, Resistivity index, Pulsatile index, Hemoglobin A1c

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ABSTRACT

Background

The prevalence of diabetes mellitus (DM) is rapidly increasing worldwide, with low-and-middle income countries bearing the heaviest burden. In these countries, majority of newly diagnosed DM in is incidental, with many new patients unaware of their prior glycaemic status; which increases the likelihood that they may present with DM-related complications, like diabetic retinopathy (DR). The mechanisms underlying the development of diabetic retinopathy are still not fully understood, although elevated glucose levels are thought to be responsible for alterations in retinal vessel architecture, leading to perfusion abnormalities. The current study sought to determine the relationship between hemodynamic flow in the central retinal artery and long-term glycaemic control as measured by serum haemoglobin A1c.

Methods

This was a cross-sectional study involving 140 diabetic patients attending an outpatients DM clinic at Mulago national referral hospital. Color Doppler imaging (CDI) of the orbit was used to determine hemodynamic flow parameters (end-diastolic velocity (EDV), peak-systolic velocity (PSV), resistivity index (RI), and pulsatile index (PI)) in the central retinal artery. The hemodynamic flow parameters in these patients where compared to the levels of haemoglobin A1c, which was used as measure of long-term glycaemic control.

Results

Generally, the mean central retinal artery hemodynamic flow parameters-- peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index-- did not differ significantly among diabetic patients with either normal (<7%), well-regulated (7-8%), or poorly regulated (>8%) glucose levels upon HbA1c measurement. However, the mean pulsatile index of the right retinal artery differed significantly among diabetics with varying degrees of glycaemic control ($P < 0.05$). Additionally, the duration which an individual has

been diabetic was negatively correlated to the EDV in both the right (r = -0.201, n = 140, p = 0.017), and the left orbit (r = -0.181, n = 140, p = 0.033).

Conclusion

Our findings of no significant correlation between hemodynamic flow in the central retinal artery and HbA1c may indicate that the effects of glucose on ocular hemodynamic flow in DM are possibly short-lived and not long-term.

Keywords: Retinal blood flow, Retinal Hemodynamic flow, Color Doppler Imaging, Diabetes Mellitus, Diabetic Retinopathy, Peak Systolic velocity, End diastolic velocity, Resistivity index, Pulsatile index, Hemoglobin A1c

INTRODUCTION

The prevalence of diabetes is rapidly increasing worldwide. A systematic review that pooled prevalence data from 130 countries estimated 382 million people were diabetic in 2013, with the prevalence projected to rise to 592 million by 2035 (1). Low-and-middle income countries, especially those found in the sub-Saharan region of Africa accounted for the lion's share of this enormous burden. Uganda however, has a low prevalence of diabetes. A nationwide cross sectional survey conducted in 2014 reported the prevalence of diabetes to be 1.4%, and that of impaired fasting glycaemia to be 2.1% (2). The majority of participants in this study who were found to be hyperglycaemic were unaware of their hyperglycaemic status prior, which increased their likelihood of presenting late with complications. Diabetic retinopathy (DR) is one such complication.

Diabetic retinopathy is a major microvascular complication of diabetes that accounts for 5% of the total global burden of blindness, and is also the leading cause of blindness in working-age adults in developed countries (3). The prevalence of DR amongst diabetics ranges from 19% to 56%, depending on the geographical location, type and duration of DM, insulin use, blood pressure and glycaemic control (4-8). In Uganda, a recent study by Kahigi found that 32.3% of diabetic patients who attended the diabetic clinic at the National referral hospital had DR (9). If prompt action is not taken, the number of people with DR and vision-threatening diabetic retinopathy is projected to increase almost 2-fold by 2030 (10).

The pathogenesis of DR involves vascular changes and subsequent ocular hemodynamic changes in the ophthalmic blood vessels (11). Color Doppler imaging is one of the most widely used and well-established techniques for assessing ocular blood flow velocities in ocular vessels. This technique is non-invasive and highly reproducible, with its robust

potential for imaging the ophthalmic artery, central retinal artery, posterior ciliary artery, and central retinal vein vital to detecting early retinopathy in diabetic patients (11, 12). Moreover, unlike other diagnostic techniques for DR, it does not involve addition of pharmacological agents, nor require abnormal intraocular pressure for a diagnosis of DR (12).

The microvascular features of DR are believed to arise from hyperglycemia-induced biomechanical processes involving formation of advanced glycated end products, oxidative stress, polyol accumulation, and activation of protein kinase C (13). Ultimately, these form the foundation of the microvascular damage that characterizes DR. Therefore, an intensive therapy regimen aimed at maintaining near-normal blood glucose levels is believed to markedly reduce the risks of development or progression of DR (14). Hemoglobin A1c (HbA1c) is an important indicator of long-term glycaemic control, making it important for long-term follow-up care of patients with DR. However, there have been contradicting reports on the relationship between the glycaemic control and the characteristics of the retrobulbar circulation. Specifically, some studies have shown a positive correlation between HbA1c levels and the resistivity indices of the central retinal artery and central retinal vein (11, 15), whereas others have not (16, 17). Coupled to this, none of these studies had been conducted in sub-Saharan Africa, where majority of diabetics remain undiagnosed until they develop DM-related complications warranting a clinic visit. As a result, this study sought to determine the relationship between long-term glycemic control and orbital blood vessel flow patterns at Doppler ultrasound among adult patients attending the diabetic clinic at Mulago hospital.

METHODS

Study design and setting

This was a cross sectional study conducted on 140 adult diabetic patients attending the diabetic clinic at Mulago teaching and National referral hospital. The study was conducted between October 2017 and February 2018 in the departments of Ophthalmology, Radiology and Internal medicine. The hospital is a 1,500-bed unit providing tertiary diagnostic, curative, rehabilitative, preventive services. It is located on Mulago Hill in the northern part of Kampala city, at coordinates of 0°20'16.0"N, 32°34'32.0"E (Latitude:0.337786; Longitude:32.575550). The hospital receives patients from the suburbs around Kampala and referrals from all over the country as well as the great lakes region and South Sudan. In the current study, the study

participants were recruited from the medical outpatient Diabetic clinic. This clinic operates once a week from 9:00 AM to 2:00PM, and attends to about 100 patients daily.

Participants

For the study to achieve >80% power, we used the correlation formula for cross sectional studies (18) to infer a sample size of 127 subjects. We anticipated a 10% loss to follow up; thus we approached 140 participants. We got a response rate of 100% as all the 140 patients approached consented to take part in the study. The median age of study participants was 49yrs. Majority of these subjects were female (70.7%), were from the bantu ethnic group (96%), lived in urban or peri-urban areas (76%), were employed (58%), and had at least attained a primary school level education (48.6%). (Refer to table 1 for a complete demography of the study sample)

Table 1: Socio-demographic characteristics of study subjects

Socio-demographic characteristic	Category.	Freq. (N = 140)	Percent. (%)
Gender.	Male	41	29.29
	Female	99	70.71
Ethnic group	Bantu	133	95.68
	Nilotes	4	2.88
	Hamites	2	1.44
Residence	Urban	106	75.71
	Rural	34	24.29
Employment.	Employed	76	58.02
	Unemployed	55	41.98
Level of Education	No Formal education.	4	2.86
	Primary	68	48.57
	Secondary	54	38.57
	Tertiary	14	10
Family History DM.	Positive.	63	50.4

Patients who were critically ill, reported a history of laser photocoagulation or ocular trauma, had an existing ocular infection, glaucoma or other non-diabetic vascular disease, were taking medications known to affect the retinal, renal or systemic circulation, or were pregnant or nursing mothers were excluded. Consecutive sampling was used during participant recruitment. Independent variables included patient socio-demographic characteristics, life style characteristics such as alcohol consumption and smoking, and clinical characteristics such as, type and duration of diabetes, body mass index (BMI), blood pressure, visual acuity, and serum glycosylated haemoglobin ($HBA1_C$) levels. The study dependent variables were Doppler spectral analysis and velocity calculations of the CRA, and resistivity, and pulsatile indices of the CRA.

Procedure and data collection

Clinical assessment involved taking a relevant clinical history, a focused general examination (BMI from body weight and height and blood pressure), and an eye examination (visual acuity assessment and intra-ocular pressure measurement) by specialized eye clinic nurses and an Ophthalmologist.

Approximately 4 mls of peripheral venous blood samples were drawn from the ante-cubital vein of each participant into heparinized vacutainers and promptly analysed for glycosylated haemoglobin (HBA1c) using an automated glycated haemoglobin analyzer (COBAS 400).

Orbital ultrasonography scanning was performed using a 7.5 MHz linear probe of a SIUI sonography unit (SIUI Medical Systems, CHINA) with the patient lying supine, eyes closed and directing gaze toward the ceiling. The threshold levels were set on the ultrasound machine, to optimize sensitivity without producing excessive system noise. Color Doppler displays were also set so that blood flow toward the transducer appeared red, whereas blood flow away from the transducer appeared blue. Using a 7.5 MHz linear array transducer, contact jelly was applied on the closed upper lid. With the examiner's hand rested upon the lower orbital margin to minimize the pressure on the globe, an adequate B-mode image of the globe was obtained on screen. The posterior chamber structures, including the vitreous humor, inner wall lining, choroid and the optic nerve were assessed. The blood flow through the central retinal artery (CRA) was detected by the production of a colour box in the area of the optic nerve. Pulsed Doppler ultrasonography aimed at the CRA colour display followed. A spectral waveform of the resultant Doppler frequency shift was then obtained after correction for the angle of insonation, and a velocity analysis was done. The angle was always less than 60 degrees, and every measurement was made at a constant angle to the vessel. A reading was then taken from at least three consecutive pulse waveforms to avoid any effects of the respiratory cycle upon the velocities. The peak systolic (PSV) and end diastolic velocities (EDV) in the CRA was then determined automatically from the machine. For the current study, PSV represented the maximum flow velocity recorded during each cardiac cycle while EDV was recorded immediately before the next systolic upstroke. The resistive index (RI) for the central retinal artery (CRA) was then automatically calculated by the machine using the formula [(PSV – EDV)/PSV]. Two experienced Radiologists double checked the findings of the Retinal Doppler ultrasound examination. Systolic and diastolic blood pressures were measured before and after the study. Clinical history and examination and orbital ultrasonography findings were captured on a pre-coded and pre-tested, interviewer administered questionnaire. The questionnaire was checked by the P.I for completeness and accuracy before the patient left the clinic.

Analysis

Data was entered in to the computer using Epi-Data 3 software, and then be exported to STATA software (version 13) for statistical analysis. Participant demographic and clinical characteristics were expressed as means, medians and proportions and presented in form of tables and graphs. Glycosylated hemoglobin ($HbA1_C$) was categorized into three distinct groups: normal (less than 6%), well regulated (6.1–8%), and poorly regulated (8.1% and above). The proportions for each category were also calculated. A multi-variate analysis was performed to adjust for other associated factors (sex, age, history of smoking, BMI, hypertension and history of alcohol consumption), using linear regression. The relationship between the HBA1c and the hemodynamic flow parameters (peak systolic velocity (PSV), end diastolic velocity (EDV), resistivity index (RI), and pulsatile index (PI)) was obtained using logistic regression. With the help of scatter diagrams, the correlation between the different HBA1c levels and the hemodynamic flow parameters of the CRA was determined using Spearman's correlation coefficient. A significance level of ≤ 0.05 was considered.

Ethical considerations

Approval to carry out the research was sought from the Institutional Review Boards of the School of Medicine (SOM-REC), at Makerere University College of health sciences, and the Mulago Hospital ethics review board. Informed consent was obtained from study patients and all patients' records were handled with confidentiality.

RESULTS

Clinical Characteristics of study participants

The clinical characteristics of study participants are shown in table 2. Majority of the study participants had Type 2 diabetes mellitus (96.4%). Considering both type 1 and type 2 DM participants in the current study, majority were on oral hypoglycemic agents (57.9%), while the rest were on insulin (38.6%). Five percent (5%) of the study participants were not on any medication. The median duration of DM amongst participants in the current study was 6yrs, whereas the median age of onset of DM was 43yrs. Most of the study participants had well regulated glucose levels as measured on HBA1c (42%), whereas 39% had normal HBA1c levels. About 1/5 (19%) of the study participants had poorly controlled blood glucose levels (HBA1c ≥8.1%). Hypertension was prevalent in 56.4% of study participants, whereas impaired visual acuity (~ 93% in either the right or left eye) was widespread amongst study participants.

Table 2: Clinical characteristics of the study participants			
Clinical characteristics	**Category.**	**Freq. (N = 140)**	**Percent. (%)**
Type of DM	Type 1	34	24.46
	Type 2	105	75.54
DM Medication	Yes	135	96.43
	No	5	3.57
Type of DM medication	No	5	3.57
	OHDs	81	57.86
	Insulin	54	38.57
Median duration of DM (yrs)	6	N/A	N/A
Median age of DM onset (yrs)	43	N/A	N/A
HBA1c	Normal (<6%)	55	39%
	Well regulated (6-8%)	59	42%
	Poorly regulated(>8.1%)	26	19%
BMI	Normal	39	28.06
	Over weight	59	42.45
	Obese	41	29.5
Hypertension	Normal	61	43.57
	Hypertensive (SBP>140mmHg, DBP>90 mmHg).	79	56.43
History of cigarette smoking	Yes	18	12.95
	No	121	87.05
History of alcohol consumption	No	77	55.8
	Yes	61	44.2
Eye symptoms	Itchiness.	3	2.97
	Blurry vision	74	73.27
	Blindness.	16	15.84
	Others	8	7.92
Visual Acuity	**RIGHT EYE.**		
	Normal vision	10	7.14
	Low vision	126	90
	Blind	4	2.86
	LEFT EYE.		
	Normal vision	10	7.14
	Low vision	123	87.86
	Blind	7	5

Legend: N/A-Not applicable, OHD's- Oral hypoglycaemic drugs.

Blood flow parameters

Table 3. Means (SE) of Hemodynamic parameters obtained from colour Doppler imaging in the Central Retinal artery of the Right Orbit							
	Glycosylated Haemoglobin-Right Orbit						
Hemodynamic Parameters	**Normal (<6%) N=**		**Well Regulated (6.1-8.0%) N=**		**Poorly regulated (>8%) N=**		
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**P value**
PSV (cm/sec)	13.1	0.42	12.5	0.47	11.9	0.51	0.06
EDV (cm/sec)	4.40	0.18	4.20	0.18	4.20	0.01	0.16
Resistivity Index	0.64	0.01	0.65	0.01	0.64	0.01	0.99
Pulsatile Index	7.31	0.19	6.96	0.26	6.75	0.30	**0.04***

Legend: Data are mean ± SE. The mean hemodynamic parameters are compared within normal glycaemic (<6%), well regulated glycaemic (6.1-8.0%), and poorly regulated (>8%) glycaemic diabetic study participants. The indices are calculated as follows: resistivity index = (PSV-EDV)/PSV, pulsatile index = (PSV-EDV)/V_{mean}, with V_{mean} = 1/3 (PSV-EDV) +EDV. Abbreviations: HbA1c- Hemoglobin A1c, EDV - end-diastolic velocity, PSV - peak systolic velocity, V_{mean} - mean time velocity. *$p < 0.05$, for comparisons across all three groups.

Table 4. Means (SE) of Hemodynamic parameters obtained from colour Doppler imaging in the Central Retinal artery of the Left Orbit							
	Glycosylated Haemoglobin-Left Orbit						
Hemodynamic Parameters	**Normal HbA1c (<6%) N=**		**Well Regulated HbA1c (6.1-8.0%) N=**		**Poorly regulated HbA1c (>8%) N=**		
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**	**P value**
PSV (cm/sec)	12.5	0.37	13.0	0.53	12.6	0.72	0.97
EDV (cm/sec)	4.50	0.19	4.30	0.16	4.20	0.32	0.54
Resistivity Index	0.63	0.01	0.65	0.01	0.66	0.01	0.18
Pulsatile Index	7.15	0.21	7.22	0.26	7.00	0.44	0.77

Legend: Data are mean ± SE. The mean hemodynamic parameters are compared within normal glycaemic (<6%), well regulated glycaemic (6.1-8.0%), and poorly regulated (>8%) glycaemic diabetic study participants. The indices are calculated as follows: resistivity index = (PSV-EDV)/PSV, pulsatile index = (PSV-EDV)/V_{mean}, with V_{mean} = 1/3 (PSV-EDV) +EDV. Abbreviations: HbA1c- Hemoglobin A1c, EDV - end-diastolic velocity, PSV - peak systolic velocity, V_{mean} - mean time velocity. *$p < 0.05$, for comparisons across all three groups.

Table 3 and table 4 show the mean (SE) values for hemodynamic parameters obtained from colour Doppler imaging measurements in the central retinal artery in the right (table 3) and left (table 4) orbits of the study participants in relation to the glycaemic control in the following groups.

1. Patients with normal HbA1c (<6%)
2. Patients with well-regulated HbA1c (6.1-8.0%)
3. Patients with poorly regulated HbA1c (>8%)

The Pulsatility index in the central retinal artery of the right orbit for participants in the current study was lower for diabetics with poorly regulated HbA1c (>8%) compared to diabetics with normal HbA1c (<6%) (p= 0.04). However, this difference was not observed in the left orbit. The other central retinal artery blood flow parameters (PSV, EDV and resistivity index) did not significantly differ between subjects with either normal, well controlled or poorly regulated HbA1c levels.

Blood flow in relation to HbA1c and duration of diabetes

We evaluated the relationship between HbA1c, duration of diabetes, and hemodynamic parameters in the right and left orbit of study participants (Table 5). The analysis showed significant negative correlation between HbA1c levels and the pulsatile index of the right central retinal artery, as well as a significant negative correlation between duration of diabetes and the EDV of both the right and left central retinal arteries.

Table 5: Pearson correlation coefficients between HbA1c, duration of diabetes, and hemodynamic parameters

Orbit	Variable	HbA1c	Duration of Diabetes
Right Orbit	PSV (cm/sec)	-0.1592	-0.0610
	EDV (cm/sec)	-0.1192	-0.2011*
	Resistivity Index	-0.0004	0.1532
	Pulsatile Index	-0.1724*	-0.1344
Left Orbit	PSV (cm/sec)	0.0035	-0.0766
	EDV (cm/sec)	-0.0526	-0.1806*
	Resistivity Index	0.1141	0.1565
	Pulsatile Index	-0.0253	-0.1413

Legend; *p < 0.05

DISCUSSION

The current study used Color Doppler ultrasonography (CDI) of the orbit to determine the hemodynamic flow parameters in the central retinal artery of diabetic patients attending an outpatient DM clinic at the Mulago national referral hospital. The hemodynamic flow parameters in these patients where compared to the levels of haemoglobin A1c; a parameter used to indicate the degree of glycaemic control in DM patients in the current study. Generally, the mean central retinal artery hemodynamic flow parameters-- peak systolic velocity (PSV), end-diastolic velocity (EDV), and resistivity index-- did not differ significantly among diabetic patients with either normal (<7%), well-regulated (7-8%), or poorly regulated (>8%) glucose levels upon HbA1c measurement. However, the mean pulsatility index of the right retinal artery differed significantly among diabetics with varying degrees of glycaemic control.

Color Doppler imaging (CDI) is an ultrasound-based technique that combines B-scan images with velocity information obtained from the doppler shift of the moving erythrocytes (19). CDI enables ophthalmologists to examine ocular blood flow, even in the presence of dense ocular opacities preventing a direct view of the posterior eye segment (20). This technique has numerous potential applications in the diagnosis and monitoring of ocular disease processes (12). The advantages CDI has over other investigative and diagnostic tests of the orbit lie in its safety and repeatability profile. Compared to fluorescein angiography, CDI neither requires addition of pharmacologic agents nor application of abnormal globe pressure during hemodynamic flow measurements (12). As a result, doppler spectra can be obtained from the central retinal artery, posterior ciliary artery, and the ophthalmic artery. The current study utilized measurements from the central retinal artery because prior measures of hemodynamic flow in this blood vessel were found to be superior to those of the ophthalmic artery in diabetes, especially in detecting diabetic retinopathy (21). Moreover, the central retinal artery reflects more sensitively the vascular changes associated with diabetes due to the fact that it is located in the periphery of the ocular vasculature, compared to the ophthalmic artery (21). During CDI, the operator can identify the peak-systolic velocity (PSV), and the end-diastolic velocity (EDV), which represent the fastest velocities in systole and diastole respectively. Using these measurements, the resistive index (RI) can be calculated as a measure of downstream vascular resistance (19).

The retina is one of the major sites of the body affected by diabetic microvascular pathology (22). Abnormalities of the retinal circulation, including but not limited to microaneurysms,

capillary closure, haemorrhages, venous beading, intraretinal microvascular abnormalities, and neovascularization, are known to occur in the eyes of diabetic patients with retinopathy (23). The mechanisms underlying the development of diabetic retinopathy are still not fully understood, although elevated glucose levels are thought to be responsible for alterations in retinal vessel architecture, leading to perfusion abnormalities. Early diabetic retinopathy is depicted by retinal ischemic changes, characterized by capillary basement membrane thickening, pericyte loss, retinal capillary non-perfusion, and capillary loss (23). The resultant retinal ischaemia fuels the production of angiogenic and vasoproliferative factors, which stimulate neovascularization in proliferative diabetic retinopathy (23, 24). All these features are thought to contribute to retinal blood vessel hyperperfusion, alongside slowing of retinal blood flow in diabetic retinopathy.

Indeed, Arai et. al (21), found the resistivity index of ocular arterial flow in patients with diabetes mellitus to be significantly greater than that of normal subjects, and to be further increased in the presence of diabetic retinopathy. These results are congruent with those from several other studies that have shown a reduction in retinal blood flow in diabetic patients who possess, or lack features of diabetic retinopathy (25-29). Unlike what was reported from previous studies that linked the abnormal retinal blood flow to glycaemic control (25, 30, 31), our study did not find a significant relationship between hemodynamic flow parameters in the central retinal artery, and long term glycaemic control. i.e., peak systolic velocity, end-diastolic velocity and resistivity index did not differ significantly between diabetics who had either normal, well controlled or poorly controlled HbA1c. This discrepancy could have resulted from differences in study designs, investigative modality used for hemodynamic flow measurements, or inherent study limitations. Lee-Ann et al.'s study (31) that had reported a reduction in total retinal blood flow in DM patients with a high HbA1c was limited in power due to the small sample size as the study only examined eyes of 5 diabetics, in contrast to the current study that examined eyes from 140 diabetics. Similarly, Lorenzi M. et.al (30), and Bursell S. et.al (25), found a significant relationship between hyperglycemia and retinal circulation abnormalities in type I DM patients, unlike the current study that reported no retinal circulation abnormalities in type 1 and 2 DM patients with poor long-term glycaemic control. Moreover, different techniques were used to measure hemodynamic flow in these earlier studies compared to the current studz. i.e., whereas the current study which used Color Doppler imaging to measure hemodynamic flow in the central retinal artery, Lorenzi et. al (30) and Bursell et.al (25) used Laser Doppler flowmetry and video fluorescein

angiography respectively. Therefore, differences in instrumentation and technique may also have contributed to variances in results, just as it was reported elsewhere (11).

Cross-sectional studies (11), and shorter longitudinal studies (32) have reported a positive correlation between changes in ocular blood flow, and the duration of diabetes. In contrast, except for slightly significant correlations with end-diastolic velocity (EDV), duration of diabetes was not correlated with other hemodynamic flow parameters [resistivity index (RI), peak-systolic velocity (PSV), and pulsatile index (PI)] in the current study. However, the present study's finding are supported by findings from a longitudinal study that reported a reduction in resistance to flow among DM patients with diabetic retinopathy during a 10-year period of follow-up (19), contradicting a commonly accepted theory of progressive increases in resistance to ocular blood flow as part of the deterioration characteristic of progressive retinopathy.

There are some critical issues to consider in the current study. Firstly, it's possible that we could have missed important findings from examining hemodynamic flow in other orbital blood vessels, such as the Ophthalmic artery, the posterior ciliary artery and the central retinal vein; as hemodynamic flow was only determined from the central retinal artery in the current study. However, our choice was informed by the fact that vascular changes that characterize DM are better reflected in the central retinal artery because of more superior hemodynamic flow as opposed to flow in other orbital blood vessels (21). Secondly, the current study did not factor in the presence or absence of diabetic retinopathy in the analysis of hemodynamic flow parameters at different gradations of long-term glycaemic control, which could have confounded the final analysis. This could be a subject for future research.

Generally, our findings show no significant correlation between hemodynamic flow parameters (peak-systolic velocity, end-diastolic velocity, and resistive index) in the central retinal artery and HbA1c, which may indicate that the effects of glucose on ocular hemodynamic flow in diabetic patients are possibly short-term and not long-term. Further studies, with larger groups of patients, stratified for diabetic retinopathy are needed to better understand the role of long-term glycaemic control on ocular hemodynamics in DM.

LIST OF ABBREVIATIONS

BMI	Body mass index
CDI	Color Doppler Imaging
CRA	Central retinal artery

DM	Diabetes Mellitus
DR	Diabetic Retinopathy
EDV	End diastolic velocity
HbA1c	Hemoglobin A1c
PI	Pulsatile index
PSV	Peak systolic velocity
RI	Resistivity index
V_{mean}	mean-time velocity

DECLARATIONS

Ethics approval and consent to participate

This research was carried out in compliance with the Helsinki Declaration, and approval to conduct the study was obtained from the Institutional Review Board of the School of Medicine Research and Ethics Committee (SOM-REC) (Protocol number: REF 2017 -125). Written informed consent was obtained from all study participants.

Consent for publication

Not applicable

Availability of data and material

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author's contributions

SK contributed to study conceptualization, data collection, data analysis, and manuscript writing. HM contributed to the study conceptualization, data analysis, and manuscript writing. AF & SM contributed to the study conceptualization, review of images and editing of manuscript. EM & JG contributed to study conceptualization. All authors read and approved the final manuscript.

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