Original Article

Retinal Hemodynamics in Early Diabetic Macular Edema

Kit Guan,[1] Chris Hudson,[1,2] Tien Wong,[1] Mila Kisilevsky,[1] Ravi K. Nrusimhadevara,[1] Wai Ching Lam,[1] Mark Mandelcorn,[1] Robert G. Devenyi,[1] and John G. Flanagan[1,2]

The objective of this study was to establish the baseline retinal hemodynamic characteristics of stratified groups of diabetic patients at increasing risk for the development of diabetic macular edema (DME). Group 1 had 50 control subjects, group 2 had 56 diabetic patients without clinically visible retinopathy, group 3 had 54 diabetic patients with microaneurysms and/or hard exudates within two disc diameters of the fovea in the absence of clinically manifest DME, and group 4 had 40 patients with clinically manifest DME. Retinal hemodynamics (diameter, velocity, maximum-to-minimum velocity ratio, and flow) were assessed. Intraocular pressure, blood pressure, and relevant systemic markers of diabetes control and complications were also undertaken. The maximum-to-minimum velocity ratio was elevated with increasing risk of clinically significant DME ($P < 0.0001$). No significant differences were found between the groups with respect to diameter, velocity, or flow. The maximum-to-minimum velocity ratio was correlated to age, duration of diabetes, blood pressure, pulse rate, intraocular pressure, and serum potassium levels. In conclusion, the maximum-to-minimum velocity ratio was significantly increased with increasing risk of development of DME. Retinal arteriolar hemodynamics were positively correlated to age, duration of diabetes, and blood pressure. These findings suggest a reduction in the compliance (i.e., an increase of vascular rigidity) of the arteriolar circulation with increasing risk of DME. *Diabetes* 55:813–818, 2006

Diabetic retinopathy is a leading cause of visual impairment in the world, including North America (1). Due to the increasing prevalence of diabetes, the financial, societal, and personal burden of diabetic retinopathy is increasing dramatically despite improvements in patient education and glycemic control (2–4). Diabetic retinopathy results from microvascular decompensation beginning with basement membrane thickening (5) and eventually leading to vascular occlusion and neovascularization (6). Diabetic macular edema (DME) can occur at virtually any stage during diabetic retinopathy development, and it represents the leading cause of visual impairment in people with diabetes (7). Laser photocoagulation is the established treatment for clinically significant DME (8). Although laser photocoagulation is effective in arresting visual acuity loss due to DME, it is also destructive (9,10). The prevention of the retinal complications of diabetes is becoming increasingly important from a public health standpoint. There is a clear need for improved diagnostic and therapeutic techniques in the management of diabetic retinopathy (11,12).

Disturbance of retinal hemodynamics is an accepted surrogate marker of early diabetic retinopathy (13–18). Retinal vasodilation has been proposed to occur before the onset of clinically evident diabetic retinopathy. An increase in retinal blood flow has been suggested to eventually lead to the development of diabetic retinopathy, possibly due to increased frictional forces (i.e., shear stress) on the endothelial cells lining the walls of retinal vessels (16). However, the precise nature of the blood flow disturbance is controversial, due, in part, to the diversity of techniques used to quantify retinal hemodynamics, the various stages of retinopathy studied, and the heterogeneity of the diabetic groups (17).

Bidirectional laser Doppler velocimetry is a technique used to quantify centerline blood velocity. The Canon Laser Blood Flowmeter (CLBF) is the only hemodynamic assessment technique that can simultaneously measure vessel diameter and centerline blood velocity and, therefore, for the first time, quantify volumetric blood flow in absolute units (19). The CLBF determines centerline blood velocity (in millimeters per second) using bidirectional photodetectors and vessel diameter (in micromoles) using densitometry of the retinal arterioles and venules. In addition, an eye tracker system is incorporated into the optical system of the CLBF to minimize the impact of eye movement. It subsequently quantifies blood flow (in microliters per minute) based on the Poiseuille principle. The minimum vessel diameter that the CLBF can measure is ~80 μm, and, therefore, the instrument cannot be used to assess capillary hemodynamics. The assessment of retinal blood flow with the CLBF will provide new insights into retinal vascular disease (20). Evaluation of the instrument in normal subjects to determine its variability and repeatability has been established (21,22). There is a need to reveal the precise nature of the disturbance of retinal hemodynamics in a defined population of patients with diabetes. The purpose of this study was to report baseline retinal arteriolar hemodynamics in a cohort of patients with varying levels of risk for the development of sight-threatening DME and to correlate these parameters to systemic measures of diabetes control and complications.

RESEARCH DESIGN AND METHODS

Research ethics approval was obtained from the research ethics board at the University Health Network, University of Toronto and the Office of Research

From the [1]Department of Ophthalmology and Vision Science, University of Toronto, Toronto, Ontario, Canada; and the [2]School of Optometry, Faculty of Science, University of Waterloo, Waterloo, Ontario, Canada.

Address correspondence and reprint requests to Chris Hudson, PhD, Department of Ophthalmology and Vision Science, University of Toronto, Toronto, Ontario M5T 2S8, Canada. E-mail: chudson@uwaterloo.ca.

Received for publication 22 July 2005 and accepted in revised form 15 December 2005.

CLBF, Canon Laser Blood Flowmeter; DME, diabetic macular edema; IOP, intraocular pressure.

Ethics, University of Waterloo. All procedures followed the principles expressed in the Declaration of Helsinki. Subjects were recruited from patients, family members, or staff of the Toronto Western Hospital after the nature of the study was explained and informed consent was obtained. Subjects were between 39 and 72 years of age. The sample was composed of four groups: group 1: 51 nondiabetic control subjects ([means ± SD] aged 52.7 ± 8.5 years); group 2: 59 patients with diabetes but no clinically visible diabetic retinopathy (aged 54.2 ± 8.2 years, mean duration of diabetes 8.4 years); group 3: 57 patients with diabetes with hard exudates and/or microaneurysms within two disc diameters of the fovea but no clinically detectable retinal edema (aged 56.7 ± 7.5 years, mean duration of diabetes 15.8 years); and group 4: 45 patients with diabetes with clinically evident retinal edema (aged 58.6 ± 7.1 years, mean duration of diabetes 16.6 years). Our group definitions are based on features of diabetic retinopathy that reflect greater propensity for the development of DME, such as the presence of hard exudates, which are frequently associated with edema. Our groups are therefore defined in such a manner to increase the propensity (i.e., progression from groups 1 to 4) for blood-retinal barrier breakdown and the presence of DME. The definition of group 3 patients was based on risk factors identified in the Early Treatment of Diabetic Retinopathy Study for the development of macular edema (23,24). Group 4 patients have a pretreatable form of macular edema, i.e., based upon the Early Treatment of Diabetic Retinopathy Study classification of clinically significant DME (8). Patients with diabetes with any eye disease other than mild nonproliferative diabetic retinopathy, such as moderate-to-severe nonproliferative, proliferative, or ischemic retinopathy or laser treatment for retinopathy, were excluded. Seven of 161 patients with diabetes had type 1 diabetes (the remainder had type 2 diabetes), and 65 patients were treated with insulin (16 in group 2, 30 in group 3, and 18 in group 4). All patients had a logMAR visual acuity of 0.3 (Snellen equivalent 20/40) or better. Patients with a refractive error >±6.00D sphere or ±2.50D cylinder, significant lenticular opacity (Lens Opacity Classification System III grading for nuclear color >3.5, nuclear opalescence >3.5, cortical cataract >3, or posterior subcapsular cataract >2), family history of glaucoma in a first-degree relative, or use of medications with known central nervous system effects (i.e., antiepileptics, anticonvulsants, antidepressants, or muscle relaxants) were excluded. Nondiabetic control subjects with any eye disease or family history of diabetes in a first-degree relative were excluded. Nondiabetic subjects were also screened for diabetes using a semiquantitative urine dipstick test (Diastix Reagent Strips; Bayer, Etobicoke, Canada).

Clinical procedures. Intraocular pressure (IOP) was assessed using Goldmann applanation tonometry. Resting blood pressure and pulse rate were measured using an average of three automated monitor readings after the patients were seated for 10 min. The anterior segment was examined for any abnormalities before pupillary dilation with 1% tropicamide and/or 1% cyclopentolate. A retinal exam by a retinal specialist using stereo fundus biomicroscopy documented the level of retinopathy and/or area of edema for patients with diabetes and confirmed normality for control subjects. The eye with the worse level of retinopathy and still meeting the inclusion criteria was chosen for the study. If both eyes had an equal level of retinopathy, one eye was randomly assigned to the study. Simultaneous stereophotos were taken using the Nidek 3-Dx stereo fundus camera (Nidek, Freemont, CA) onto 35-mm Kodak Elite Chrome 100 film. Each stereo image was composed of a rectangular area 24.8 (vertical) × 20.2 (horizontal) degrees. The fields were centered on the optic nerve head, fovea, and superior, inferior, and temporal retina. The overlapping images yielded a maximum stereo field of 75 (vertical) × 60 (horizontal) degrees. Images were mounted into slides and later assessed by two ophthalmologists (R.K.N. and M.K.) to document the extent of retinopathy and/or area of edema. The presence, or absence, of DME was determined clinically by a single retinal specialist and then subsequently confirmed by another two independent graders using simultaneous stereo photographs. Axial length was measured by I^3 System ABD A-scan ultrasound (I^3 Innovative Imaging, Sacremento, CA) to correct hemodynamic measurements for magnification effects. Patients with diabetes underwent blood and urine tests within an hour of retinal blood flow measurements. Blood tests included measurement of HbA_{1c} (A1C), random glucose, potassium, creatinine, and albumin. Urine tests included urinary creatinine, albumin, and the calculation of the albumin-to-creatinine ratio. Normal control subjects did not undergo routine blood tests.

Measurement of retinal arteriolar hemodynamics. Retinal hemodynamics were noninvasively assessed using the CLBF model 100. The principle underlying the CLBF is that of bidirectional laser Doppler velocimetry. By utilizing two photo multipliers separated by a known angle, the CLBF provides an absolute, pointwise measurement of centerline blood velocity (25,26). A measurement window of 2 s permits continuous velocity readings, and a plot of velocity versus time is acquired. The CLBF simultaneously measures the diameter of the vessel of interest using a densitometry technique (27,28) and also uses a vessel tracking system that is used to stabilize the image. In combination with the average velocity over a pulse cycle and the diameter, flow through the vessel can be calculated based on the Poiseuille principle. Measurement of retinal arteriolar diameter (in micromoles), velocity (in millimeters per second), maximum-to-minimum velocity ratio, and flow (in micromoles per minute) were undertaken in a superior temporal arteriole located within two disc diameters of the optic nerve head. All measurements were taken as close to the optic nerve head as possible to optimize signal-to-noise ratio and were typically undertaken after the first bifurcation in a straight segment of the arteriole. Smaller arterioles, proximity to bifurcations, and curved segments were avoided due to poor signal-to-noise ratio or turbulent flow characteristics. The data across groups were quite similar, with group mean diameters ranging from 103.1 to 106.3 μm and 95% confidence limits for each of the four groups of 3 μm. The maximum-to-minimum velocity ratio reflects the pulsatility, frequently termed compliance, of the retinal vasculature. An increase in maximum-to-minimum velocity ratio would result from a loss of compliance, that is, an increase in vascular rigidity. Three to five measurements were taken at each retinal location and the results averaged for each patient. A detailed, standardized postacquisition analysis of the velocity profiles was used to remove any measurements adversely affected by eye movement, tear film break-up, or inaccurate tracking of the measurement laser (21). The variability of this instrument in measuring retinal hemodynamics has been previously defined (21).

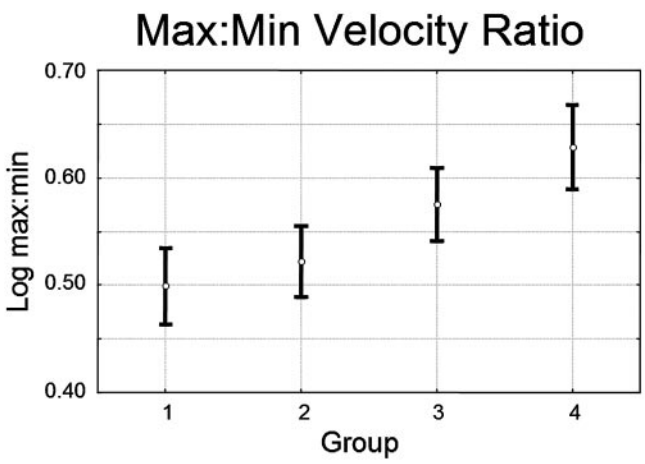

FIG. 1. Maximum-to-minimum (max:min) velocity ratio plotted as a function of group. The error bars represent 95% CIs.

Analysis. Outliers were identified on box plots for diameter, velocity, and flow. One patient was removed from group 1, 3 from group 2, 3 from group 3, and 5 from group 4 of the possible 212 participants, leaving 200 patients in the analysis. The maximum-to-minimum velocity ratio and the albumin-to-creatinine ratio were log transformed to satisfy normality. One-way ANOVA was used to determine any significant differences between groups for all measured parameters. Post hoc Student's t tests were conducted between control and diabetic groups. Pearson correlation matrices were used to examine relationships between retinal hemodynamic parameters and measured systemic parameters (i.e., blood pressure, pulse rate, blood, and urine tests). Significantly correlated parameters were entered into multivariate models to examine the independence of each relationship to retinal hemodynamics. The level of significance was set at 0.05. Calculations were done using SAS 8.02 (SAS Institute, Cary, NC) and Statistica 6.1 (Statsoft, Tulsa, OK).

RESULTS

The maximum-to-minimum velocity ratio showed a significant increase across the four groups (ANOVA $P < 0.0001$), with groups 3 and 4 demonstrating significantly higher maximum-to-minimum velocity ratios than group 1 (Student's t, $P < 0.0249$, Fig. 1). The maximum-to-minimum velocity ratio was positively correlated to age, duration of diabetes, systolic blood pressure, IOP, and serum potassium and negatively correlated to diastolic blood pressure and pulse rate (Table 1).

There were no significant differences across groups for the retinal hemodynamic parameter of diameter, velocity, and flow (Fig. 2). Among the patients with diabetes, diameter was not significantly correlated with any of the

TABLE 1
Pearson correlation coefficients (with associated *P* values) among diameter, velocity, flow, and maximum-to-minimum velocity ratio to measured systemic parameters

	Pearson correlation coefficient (*P* value)			
	Diameter	Velocity	Flow	Log max/min
Age (years)	0.1385 (0.0505)	0.2028 (0.0040)	0.2217 (0.0016)	0.3869 (<0.0001)
Diabetes duration (years)	0.0567 (0.4940)	0.0699 (0.3982)	0.0650 (0.4324)	0.3070 (0.0001)
Systolic blood pressure (mmHg)	0.0308 (0.6649)	0.2000 (0.0045)	0.1666 (0.0183)	0.1838 (0.0092)
Diastolic blood pressure (mmHg)	0.0284 (0.6897)	0.1788 (0.0113)	0.1414 (0.0458)	−0.2086 (0.0030)
Mean arterial pressure (mmHg)	0.0318 (0.6546)	0.2034 (0.0039)	0.1651 (0.0195)	−0.0280 (0.6940)
Pulse rate (beats/min)	−0.0605 (0.3949)	0.0109 (0.8783)	−0.0269 (0.7052)	−0.1491 (0.0351)
IOP (mmHg)	0.0284 (0.6904)	−0.0821 (0.2491)	−0.0502 (0.4813)	0.1562 (0.0275)
Potassium (mmol/l)	0.0930 (0.2674)	−0.0005 (0.9951)	0.0458 (0.5860)	0.2143 (0.0099)
Creatinine (μmol/l)	−0.0230 (0.7863)	0.0723 (0.3927)	0.0377 (0.6564)	0.0050 (0.9534)
Albumin (g/l)	−0.0074 (0.9300)	−0.0405 (0.6323)	−0.0323 (0.7029)	−0.0748 (0.3765)
A1C (%)	−0.1640 (0.0528)	−0.0840 (0.3239)	−0.1423 (0.0934)	−0.0695 (0.4143)
Glucose (mmol/l)	−0.1413 (0.0879)	−0.1575 (0.0567)	−0.1812 (0.0281)	−0.0509 (0.5404)
Log (albumin to creatinine)	0.1529 (0.1434)	0.1390 (0.1838)	0.1730 (0.0973)	0.1302 (0.2136)

Data are Pearson correlation coefficients (associated *P* values). A significant correlation was taken at $r > 0.140$ and $P < 0.05$. The maximum-to-minimum velocity ratio and albumin-to-creatinine ratio were transformed using a log function to satisfy normality.

systemic parameters, although borderline associations were noted for age, A1C, and random glucose. Velocity was positively correlated with age and systolic, diastolic, and mean arterial blood pressure. Retinal blood flow was positively correlated with age and systolic, diastolic, and mean arterial blood pressure and negatively correlated to random glucose. Removal of the seven type 1 diabetic patients did not significantly alter the primary outcome measures of diameter, velocity, flow, and maximum-to-minimum velocity ratio. Subsequent analyses included all patients.

With increasing risk of DME, age ($P = 0.0025$), duration of diabetes ($P < 0.0001$), systolic blood pressure ($P < 0.0001$), mean arterial blood pressure ($P = 0.0014$), pulse rate ($P = 0.0007$), A1C ($P = 0.0319$), and the urinary albumin-to-creatinine ratio ($P = 0.0157$) were all significantly elevated (Table 2).

Multivariate models were implemented for variables that were significantly correlated to hemodynamic parameters. The maximum-to-minimum velocity ratio remained significantly related to age ($P < 0.0001$) and duration of diabetes ($P = 0.0030$) after adjusting for IOP, serum potassium, pulse rate, and blood pressure. Diameter was significantly related to age ($P = 0.0072$) after adjusting for A1C and glucose. Velocity was significantly related to systolic blood pressure ($P = 0.0261$) and mean arterial pressure ($P = 0.0311$) after adjusting for age and glucose. Age was significantly related to velocity ($P = 0.0410$) only when diastolic blood pressure was used in the model. Flow was significantly related to age ($P < 0.0204$) after adjusting for A1C, glucose, and blood pressure. Models including the albumin-to-creatinine ratio showed no significant relation of this parameter to flow, and the variable was abandoned from other models due to an incomplete dataset ($n = 94$). Further adjustment of the models, if needed, for duration of diabetes, blood pressure, and A1C did not significantly alter the results.

DISCUSSION

To the best of our knowledge, this is the first study to investigate retinal arteriolar hemodynamics and relate the findings to systemic measures of control in a defined cohort of patients at increasing risk for the development of DME. The defined groups represent a relatively early form of diabetic retinopathy and are classified based on identified risk factors for the development of DME. Bidirectional laser Doppler velocimetry combined with a simultaneous measurement of vessel diameter is the only method to truly quantify volumetric blood flow in absolute units. This new technique has provided valuable insight into the early hemodynamic disturbances in diabetic retinopathy (20,29–31). This study characterizes early retinal hemodynamic disturbances and systemic correlates in diabetic patients with increasing risk for the development of DME.

In our cohort, we found a clear increase in the maximum-to-minimum velocity ratio with increasing risk for the development of DME. Groups 3 and 4, those with visible retinopathy and macular edema, respectively, had significantly higher maximum-to-minimum velocity ratios compared with normal control subjects. The univariate correlations of systolic and diastolic blood pressure, IOP, serum potassium, and pulse rate on the maximum-to-minimum velocity ratio were not apparent in a multivariate analysis. However, age and duration of diabetes remained significantly related to the maximum-to-minimum velocity ratio using multivariate analysis. Although age and duration of disease are often correlated to each other, they were not in our cohort of patients, which supports their independent relation to the maximum-to-minimum velocity ratio. The positive correlations of maximum-to-minimum velocity ratio to age and duration of diabetes suggest a loss of compliance of the arterial circulation. The site of the decreased compliance could be up- or downstream from the point of retinal hemodynamic assessment. Work is currently being undertaken in our lab to determine whether the increase of vessel rigidity is at the point of measurement of retinal hemodynamics. With decreased compliance of the arterial circulation, an increase in the pulsatility of blood is expected due to a lack of dampening of the pulse wave. An effect of increased arterial rigidity with diabetes, hypertension, and age is well documented in the macrovasculature (32–35), with possible resulting detrimental effects on the retinal microvasculature (36–39).

One previous study (20) using laser Doppler velocimetry in a small number of subjects showed an increase in the

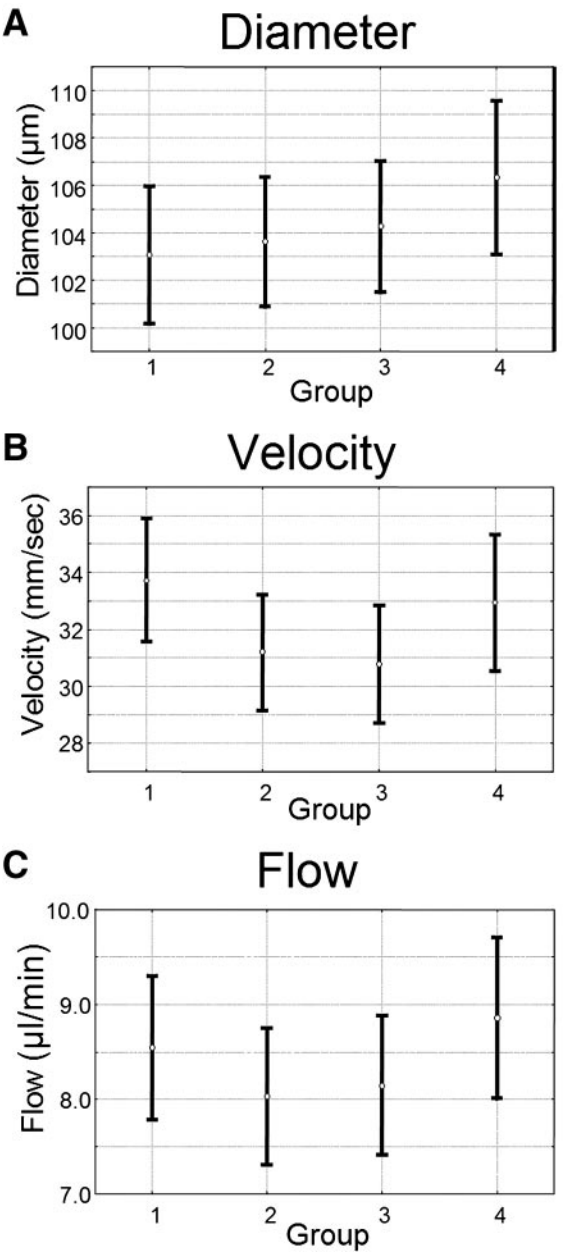

FIG. 2. Hemodynamic results plotted as a function of group for diameter (μm) (*A*), velocity (mm/s) (*B*), and flow (μl/min) (*C*). The error bars represent 95% CIs.

maximum-to-minimum velocity ratio with increasing severity of retinopathy, although there was a decrease in the maximum-to-minimum velocity ratio compared with control subjects. A more recent study (40) in patients with age-related macular degeneration showed a clear increase in the maximum-to-minimum velocity ratio with increasing disease severity. It was also shown that the maximum-to-minimum velocity ratio was decreased after panretinal photocoagulation, suggesting that an increased maximum-to-minimum velocity ratio was detrimental in the progression to proliferative retinopathy (41). Using Doppler sonography, Kawagishi et al. (42) found an increase in resistance index in the central retinal artery of patients with type 1 diabetes before the development of retinopathy. It was hypothesized that the increased resistance index resulted from a combination of increased vessel rigidity and peripheral vascular resistance. However, Dimitrova et al. (43) did not find an increased resistive index in the central retinal artery in patients with progressive retinopathy using color Doppler imaging. In their relatively small sample, Dimitrova et al. found an increased resistive index in the central retinal vein only. It has been shown by Polska et al. (44) that resistive index, as assessed by color Doppler imaging of the retrobulbar circulation, and retinal vascular resistance, as assessed by laser Doppler velocimetry, do not always correlate. In agreement with our study, Ino-ue et al. (45) found increased pulsatility indexes in the ophthalmic artery using color Doppler imaging in patients with background and proliferative retinopathy. In animal models of diabetes, the basement membrane of both arteries and veins are thickened (46). This basement membrane thickening is aggravated by the presence of hypertension (47). An accelerated arteriosclerosis within the retinal arterioles may represent one of the earliest changes associated with the development of diabetic retinopathy.

A prevailing theory in the pathogenesis of diabetic retinopathy is that of hyperperfusion (16). Kohner et al. (16) suggested that increased blood flow led to increased shear stress on the vessel wall. Support for this was found in a number of studies that showed decreased blood flow with insulin treatment to lower blood glucose (48) and increased blood flow with advancement of retinopathy (20,49). However, the nature of the blood flow alteration is far from conclusive, even when only considering data published by the same authors. Grunwald et al. (30) found no significant changes in retinal blood flow in any of his untreated diabetic groups. Others, using fluorescein angiographic techniques, have found a decrease in retinal blood flow in patients with diabetes and no retinopathy at the level of the arterioles (14) and capillaries (50). Konno et al. (51) found an initial decrease in blood flow and then an increase as duration of diabetes increased in a prospective series of patients. Our cross-sectional study showed similar nonsignificant trends (Fig. 2*C*). A review of the retinal hemodynamic alterations in diabetes shows much controversy, but there is some indication that retinal arterioles are dilated before visible retinopathy and that a hyperperfusion of the retina occurs (17). In our sample, diameter, velocity, and flow values were independently related to age. Velocity was also independently related to systolic blood pressure and mean arterial blood pressure. However, we did not find any significant alterations in retinal arteriolar diameter, velocity, or flow across the groups with respect to the development of DME. Our sample represents a relatively early stage of the pathogenesis of diabetic retinopathy due to the fact that we excluded patients with moderate-to-severe nonproliferative and proliferative retinopathy.

Our study showed that systolic blood pressure and mean arterial blood pressure were elevated in those with retinopathy and DME compared with control subjects. Duration of diabetes was longer and A1C was higher in those with retinopathy and DME compared with those without retinopathy. The effects of hypertension and elevated A1C are well-documented risk factors for the development of DME (52–55). Duration of diabetes is an established risk factor for retinopathy (56,57) and more specifically for macular edema (52). Our study grouped patients with DME together regardless of severity, and this group clearly had decreased vascular compliance as assessed by the maximum-to-minimum velocity ratio. It is not surprising that a significant correlation exists between

TABLE 2
Group mean baseline characteristics of the subject groups

	Univariate ANOVA				
	Group 1	Group 2	Group 3	Group 4	*P* value
n	50	57	55	41	
Age (years)	52.68	54.41	56.76	58.51	0.0025
Diabetes duration (years)		8.64	15.76	16.56	<0.0001
Diameter (μm)	103.07	103.81	104.12	106.32	0.4906
Velocity (mm/s)	33.73	31.02	30.77	32.96	0.1406
Flow (μl/min)	8.54	8.01	8.12	8.86	0.3858
Log (max/min) velocity	0.499	0.521	0.578	0.625	<0.0001
Systolic blood pressure (mmHg)	118.49	123.87	133.56	129.05	<0.0001
Diastolic blood pressure (mmHg)	73.75	75.51	78.64	76.94	0.0713
Mean arterial pressure (mmHg)	88.66	91.63	96.94	94.31	0.0014
Pulse rate (bpm)	68.99	77.06	76.17	78.18	0.0007
IOP (mmHg)	14.90	15.68	15.49	16.12	0.2832
Potassium (mmol/l)	—	4.10	4.19	4.25	0.1523
Creatinine (μmol/l)	—	73.70	79.27	75.83	0.4796
Albumin (g/l)	—	42.96	42.20	42.15	0.1433
A1C (%)	—	0.077	0.084	0.085	0.0280
Glucose (mmol/l)	—	10.85	11.76	11.49	0.6035
Log (albumin to creatinine)	—	0.40	0.64	0.73	0.0157

the maximum-to-minimum velocity ratio and duration of disease, given that macular edema occurs more frequently as the duration of disease increases. Pulse rate was elevated in all diabetic groups compared with control subjects. In the Cardiovascular Health Study (34), elevated pulse rate was a strong predictor of aortic stiffness in men and women. Elevated pulse rates also predict incident DME, but this effect was not independent of hypertension (58). The urinary albumin-to-creatinine ratio was higher in those with retinopathy and DME compared with those without retinopathy. Increased urinary albumin-to-creatinine ratio with increasing risk of DME reflects a decline in renal function and a shift in the osmotic balance of blood that might favor the development of DME (59,60).

These results establish the baseline characteristics of a cohort of patients with diabetes at increasing risk for DME. These patients are being followed prospectively to confirm the factors that alter retinal hemodynamics and to determine the impact of changes in retinal hemodynamics in the development of DME. Cross-sectionally, we found an increase in the maximum-to-minimum velocity ratio with increasing risk of DME. This finding suggests an increase of vascular rigidity in the arterial circulation and may indicate accelerated arteriosclerosis early in the development of diabetic retinopathy.

ACKNOWLEDGMENTS

This work was funded by the Canadian Institutes of Health Research (Operating Grant to C.H. and J.G.F. and New Investigator Award to C.H.), a Premier's Research Excellence Award (to C.H.), a Canada Foundation for Innovation New Opportunities Infrastructure Grant (to C.H.), and a Vision Science Research Program Fellowship, University of Toronto (to K.G.).

Aspects of this work were presented at the 2004 Annual Meeting of the Association for Research in Vision and Ophthalmology.

We acknowledge the staff of the Toronto Western Hospital Eye Clinic and the Retina Research Group for their support in the recruitment and follow-up of patients. The authors thank Erin Harvey in Department of Statistics and Actuarial Science, University of Waterloo, for her assistance with the statistical analysis.

REFERENCES

1. Zimmet P, Alberti KG, Shaw J: Global and societal implications of the diabetes epidemic. *Nature* 414:782–787, 2001
2. Brown JB, Pedula KL, Summers KH: Diabetic retinopathy: contemporary prevalence in a well-controlled population. *Diabetes Care* 26:2637–2642, 2003
3. Centers for Disease Control and Prevention (CDC): Prevalence of diabetes and impaired fasting glucose in adults: United States, 1999–2000. *MMWR Morb Mortal Wkly Rep* 52:833–837, 2003
4. Hogan P, Dall T, Nikolov P: Economic costs of diabetes in the U.S. in 2002. *Diabetes Care* 26:917–932, 2003
5. Ruggiero D, Lecomte M, Michoud E, Lagarde M, Wiernsperger N: Involvement of cell-cell interactions in the pathogenesis of diabetic retinopathy. *Diabetes Metab* 23:30–42, 1997
6. Porta M, Bandello F: Diabetic retinopathy: a clinical update. *Diabetologia* 45:1617–1634, 2002
7. Ferris FL 3rd, Patz A: Macular edema: a complication of diabetic retinopathy. *Surv Ophthalmol* 28 (Suppl.):452–461, 1984
8. Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for diabetic macular edema: Early Treatment Diabetic Retinopathy Study report number 1. *Arch Ophthalmol* 103:1796–1806, 1985
9. Lee CM, Olk RJ: Modified grid laser photocoagulation for diffuse diabetic macular edema: long-term visual results. *Ophthalmology* 98:1594–1602, 1991
10. Maeshima K, Utsugi-Sutoh N, Otani T, Kishi S: Progressive enlargement of scattered photocoagulation scars in diabetic retinopathy. *Retina* 24:507–511, 2004
11. Tranos PG, Wickremasinghe SS, Stangos NT, Topouzis F, Tsinopoulos I, Pavesio CE: Macular edema. *Surv Ophthalmol* 49:470–490, 2004
12. Ciulla TA, Amador AG, Zinman B: Diabetic retinopathy and diabetic macular edema: pathophysiology, screening, and novel therapies. *Diabetes Care* 26:2653–2664, 2003
13. Archer DB: Bowman Lecture 1998: Diabetic retinopathy: some cellular, molecular and therapeutic considerations. *Eye* 13:497–523, 1999
14. Bursell SE, Clermont AC, Kinsley BT, Simonson DC, Aiello LM, Wolpert HA: Retinal blood flow changes in patients with insulin-dependent diabetes mellitus and no diabetic retinopathy. *Invest Ophthalmol Vis Sci* 37:886–897, 1996
15. Feke GT, Buzney SM, Ogasawara H, Fujio N, Goger DG, Spack NP, Gabbay KH: Retinal circulatory abnormalities in type 1 diabetes. *Invest Ophthalmol Vis Sci* 35:2968–2975, 1994
16. Kohner EM, Patel V, Rassam SM: Role of blood flow and impaired autoregulation in the pathogenesis of diabetic retinopathy. *Diabetes* 44: 603–607, 1995

17. Schmetterer L, Wolzt M: Ocular blood flow and associated functional deviations in diabetic retinopathy. *Diabetologia* 42:387–405, 1999
18. Yoshida A, Feke GT, Morales-Stoppello J, Collas GD, Goger DG, McMeel JW: Retinal blood flow alterations during progression of diabetic retinopathy. *Arch Ophthalmol* 101:225–227, 1983
19. Harris A, Jonescu-Cuypers C, Kagemann L, Ciulla TA, Krieglstein GK: *Atlas of Ocular Blood Flow: Vascular Anatomy, Pathophysiology, and Metabolism*. Philadelphia, Butterworth-Heinemann (Elsevier), 2003
20. Feke GT, Tagawa H, Yoshida A, Goger DG, Weiter JJ, Buzney SM, McMeel JW: Retinal circulatory changes related to retinopathy progression in insulin-dependent diabetes mellitus. *Ophthalmology* 92:1517–1522, 1985
21. Guan K, Hudson C, Flanagan JG: Variability and repeatability of retinal blood flow measurements using the Canon Laser Blood Flowmeter. *Microvasc Res* 65:145–151, 2003
22. Wong T, Rose P, Gilmore E, Guan K, Venkatamaran S, Hudson C: Inter- and intra-operator variability in Canon Laser Blood Flowmeter measurements of retinal arteriolar diameter, blood velocity and flow (Abstract). *Invest Ophthalmol Vis Sci* 45:E3033, 2004
23. Kinyoun J, Barton F, Fisher M, Hubbard L, Aiello L, Ferris F III: Detection of diabetic macular edema: ophthalmoscopy versus photography: Early Treatment Diabetic Retinopathy Study report number 5: the ETDRS Research Group. *Ophthalmology* 96:746–750, 1989
24. Early Treatment Diabetic Retinopathy Study Research Group: Grading diabetic retinopathy from stereoscopic color fundus photographs: an extension of the modified Airlie House classification: ETDRS report number 10. *Ophthalmology* 98:786–806, 1991
25. Riva CE, Feke GT, Eberli B, Benary V: Bidirectional Ldv system for absolute measurement of blood speed in retinal vessels. *Applied Optics* 18:2301–2306, 1979
26. Feke GT, Goger DG, Tagawa H, Delori FC: Laser Doppler technique for absolute measurement of blood speed in retinal vessels. *IEEE Trans Biomed Eng* 34:673–680, 1987
27. Milbocker MT, Feke GT, Goger DG: Laser Doppler velocimetry stabilized in one dimension. *IEEE Trans Biomed Eng* 38:928–930, 1991
28. Delori FC, Fitch KA, Feke GT, Deupree DM, Weiter JJ: Evaluation of micrometric and microdensitometric methods for measuring the width of retinal vessel images on fundus photographs. *Graefes Arch Clin Exp Ophthalmol* 226:393–399, 1988
29. Grunwald JE, Brucker AJ, Grunwald SE, Riva CE: Retinal hemodynamics in proliferative diabetic retinopathy: a laser Doppler velocimetry study. *Invest Ophthalmol Vis Sci* 34:66–71, 1993
30. Grunwald JE, Riva CE, Sinclair SH, Brucker AJ, Petrig BL: Laser Doppler velocimetry study of retinal circulation in diabetes mellitus. *Arch Ophthalmol* 104:991–996, 1986
31. Sullivan PM, Davies GE, Caldwell G, Morris AC, Kohner EM: Retinal blood flow during hyperglycemia: a laser Doppler velocimetry study. *Invest Ophthalmol Vis Sci* 31:2041–2045, 1990
32. Sigurdardottir V, Fagerberg B, Hulthe J: Preclinical atherosclerosis and inflammation in 61-year-old men with newly diagnosed diabetes and established diabetes. *Diabetes Care* 27:880–884, 2004
33. Henry RM, Kostense PJ, Spijkerman AM, Dekker JM, Nijpels G, Heine RJ, Kamp O, Westerhof N, Bouter LM, Stehouwer CD: Arterial stiffness increases with deteriorating glucose tolerance status: the Hoorn Study. *Circulation* 107:2089–2095, 2003
34. Mackey RH, Sutton-Tyrrell K, Vaitkevicius PV, Sakkinen PA, Lyles MF, Spurgeon HA, Lakatta EG, Kuller LH: Correlates of aortic stiffness in elderly individuals: a subgroup of the Cardiovascular Health Study. *Am J Hypertens* 15:16–23, 2002
35. Salomaa V, Riley W, Kark JD, Nardo C, Folsom AR: Noninsulin-dependent diabetes mellitus and fasting glucose and insulin concentrations are associated with arterial stiffness indexes: the ARIC study: Atherosclerosis Risk in Communities study. *Circulation* 91:1432–1443, 1995
36. Wong TY, Duncan BB, Golden SH, Klein R, Couper DJ, Klein BE, Hubbard LD, Sharrett AR, Schmidt MI: Associations between the metabolic syndrome and retinal microvascular signs: the Atherosclerosis Risk In Communities study. *Invest Ophthalmol Vis Sci* 45:2949–2954, 2004
37. Liao D, Wong TY, Klein R, Jones D, Hubbard L, Sharrett AR: Relationship between carotid artery stiffness and retinal arteriolar narrowing in healthy middle-aged persons. *Stroke* 35:837–842, 2004
38. Rema M, Mohan V, Deepa R, Ravikumar R: Association of carotid intima-media thickness and arterial stiffness with diabetic retinopathy: the Chennai Urban Rural Epidemiology Study (CURES-2). *Diabetes Care* 27:1962–1967, 2004
39. Ogawa O, Hayashi C, Nakaniwa T, Tanaka Y, Kawamori R: Arterial stiffness is associated with diabetic retinopathy in type 2 diabetes. *Diabetes Res Clin Pract* 68:162–166, 2005
40. Sato E, Feke GT, Menke MN, Wallace McMeel J: Retinal haemodynamics in patients with age-related macular degeneration. *Eye* [Epub ahead of print]
41. Feke GT, Green GJ, Goger DG, McMeel JW: Laser Doppler measurements of the effect of panretinal photocoagulation on retinal blood flow. *Ophthalmology* 89:757–762, 1982
42. Kawagishi T, Nishizawa Y, Emoto M, Konishi T, Maekawa K, Hagiwara S, Okuno Y, Inada H, Isshiki G, Morii H: Impaired retinal artery blood flow in IDDM patients before clinical manifestations of diabetic retinopathy. *Diabetes Care* 18:1544–1549, 1995
43. Dimitrova G, Kato S, Yamashita H, Tamaki Y, Nagahara M, Fukushima H, Kitano S: Relation between retrobulbar circulation and progression of diabetic retinopathy. *Br J Ophthalmol* 87:622–625, 2003
44. Polska E, Kircher K, Ehrlich P, Vecsei PV, Schmetterer L: RI in central retinal artery as assessed by CDI does not correspond to retinal vascular resistance. *Am J Physiol Heart Circ Physiol* 280:H1442–H1447, 2001
45. Ino-ue M, Azumi A, Yamamoto M: Ophthalmic artery blood flow velocity changes in diabetic patients as a manifestation of macroangiopathy. *Acta Ophthalmol Scand* 78:173–176, 2000
46. Anderson HR, Stitt AW, Gardiner TA, Archer DB: Diabetic retinopathy: morphometric analysis of basement membrane thickening of capillaries in different retinal layers within arterial and venous environments. *Br J Ophthalmol* 79:1120–1123, 1995
47. Dosso AA, Rungger-Brandle E, Leuenberger PM: Ultrastructural alterations in capillaries of the diabetic hypertensive rat retina: protective effects of ACE inhibition. *Diabetologia* 47:1196–1201, 2004
48. Grunwald JE, Riva CE, Martin DB, Quint AR, Epstein PA: Effect of an insulin-induced decrease in blood glucose on the human diabetic retinal circulation. *Ophthalmology* 94:1614–1620, 1987
49. Patel V, Rassam S, Newsom R, Wiek J, Kohner E: Retinal blood flow in diabetic retinopathy. *BMJ* 305:678–683, 1992
50. Arend O, Wolf S, Remky A, Sponsel WE, Harris A, Bertram B, Reim M: Perifoveal microcirculation with non-insulin-dependent diabetes mellitus. *Graefes Arch Clin Exp Ophthalmol* 232:225–231, 1994
51. Konno S, Feke GT, Yoshida A, Fujio N, Goger DG, Buzney SM: Retinal blood flow changes in type I diabetes: a long-term follow-up study. *Invest Ophthalmol Vis Sci* 37:1140–1148, 1996
52. Klein R, Moss SE, Klein BE, Davis MD, DeMets DL: The Wisconsin Epidemiologic Study of Diabetic Retinopathy. XI. The incidence of macular edema. *Ophthalmology* 96:1501–1510, 1989
53. Stratton IM, Kohner EM, Aldington SJ, Turner RC, Holman RR, Manley SE, Matthews diabetic retinopathy: UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. *Diabetologia* 44:156–163, 2001
54. Service FJ, O'Brien PC: The relation of glycaemia to the risk of development and progression of retinopathy in the Diabetic Control and Complications Trial. *Diabetologia* 44:1215–1220, 2001
55. Leese G: Longitudinal study examining the risk factors for proliferative retinopathy and maculopathy in type-I diabetes: the Royal College of Physicians of Edinburgh Diabetes Register Group. *Eye* 18:814–820, 2004
56. Leske MC, Wu SY, Hennis A, Hyman L, Nemesure B, Yang L, Schachat AP: Hyperglycemia, blood pressure, and the 9-year incidence of diabetic retinopathy: the Barbados Eye Studies. *Ophthalmology* 112:799–805, 2005
57. United Kingdom Prospective Diabetes Study (UKPDS) Group: Risks of progression of retinopathy and vision loss related to tight blood pressure control in type 2 diabetes mellitus: UKPDS 69. *Arch Ophthalmol* 122:1631–1640, 2004
58. Wong TY, Moss SE, Klein R, Klein BE: Is the pulse rate useful in assessing risk of diabetic retinopathy and macular oedema? The Wisconsin Epidemiological Study of Diabetic Retinopathy. *Br J Ophthalmol* 85:925–927, 2001
59. Stephenson JM, Fuller JH, Viberti GC, Sjolie AK, Navalesi R: Blood pressure, retinopathy and urinary albumin excretion in IDDM: the EURODIAB IDDM Complications Study. *Diabetologia* 38:599–603, 1995
60. Knudsen ST, Bek T, Poulsen PL, Hove MN, Rehling M, Mogensen CE: Macular edema reflects generalized vascular hyperpermeability in type 2 diabetic patients with retinopathy. *Diabetes Care* 25:2328–2334, 2002