Progressive Retinal Vasodilation in Patients With Type 1 Diabetes: A Longitudinal Study of Retinal Vascular Geometry

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Purpose. Retinal vessels can be used to noninvasively monitor changes in microvasculature. These changes in retinal vascular geometry (RVG) may predict chronic diabetes complications. We evaluated longitudinal RVG changes in adolescents with type 1 diabetes.

Methods. We followed 102 adolescents (baseline: 47.1% male, mean [SD] age 14.4 [1.6] years, diabetes duration 7.2 [3.1] years, HbA1c 8.1% [1.3%] [65 (9.3) mmol/mol]) over three visits, with a mean follow-up of 2.6 years. Retinal vascular geometry was measured using a standardized computer-assisted protocol from retinal photographs at each visit. Multivariable linear mixed-models and logistic regression were used to examine predictors of RVG and diabetic retinopathy.

Results. During follow-up, mean arteriolar caliber, venular caliber, and venular tortuosity increased, from 156.0 (SD, 14.5) to 164.9 (14.0) μm, 215.9 (22.5) to 230.3 (20.6) μm, and 1.096 (0.014) to 1.099 (0.016), respectively (all $P < 0.005$). Other RVG measurements (fractal dimension, branching angle, length to diameter ratio) remained stable. Higher than baseline HbA1c and longer diabetes duration were associated with greater venular vasodilation. Retinopathy developed at any time-point in 24% of subjects, and the highest tertile arteriolar fractal dimension was associated with cumulative incidence of retinopathy (multivariable odds ratio 3.2, 95% confidence interval 1.0–9.6; $P = 0.04$).

Conclusions. Higher HbA1c and longer diabetes duration in early adolescence predicts greater venular vasodilation over time. Arteriolar fractal dimension predicts subsequent retinopathy development, suggesting value as a potential biomarker for diabetic complications.

Keywords: diabetic retinopathy, retinal microvasculature, metabolic memory

The retina allows noninvasive, direct, and repeated visualization of the microvascular bed, and hence the opportunity to study microvasculature changes in vivo.[1] Retinopathy is a classic microvascular complication of diabetes. Other more subtle retinal vascular changes, including alterations in arteriolar and venular calibers, may precede over retinopathy.[2] We and other researchers have shown that such retinal vascular features predict onset and progression of retinopathy and risk of other diabetic complications, such as nephropathy, acute myocardial infarction, stroke, and amputation.[1–9] New methods to document and measure other vascular architectural changes in the retina from digital photographs using computer software have provided information on fractal dimension, tortuosity, and branching angles.[1,9] These retinal vascular geometry (RVG) parameters are of interest as they may be subclinical measures of microvascular damage, and may be potential biomarkers for future retinopathy, nephropathy, and other chronic diabetes complications, independent of the effects of glycemic control and blood pressure (BP).[10–12] They may also be biomarkers of early responses to therapeutics and may demonstrate vascular memory, which exists for glycemia (as demonstrated by the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications [DCCT/EDIC] cohort),[13] and possibly for BP and lipid control as well.[14] In the DCCT/EDIC cohort, which included adolescents and adults, 6.9 years of intensive versus conventional diabetes control was associated with 2-fold less need for diabetes-related ocular surgery (mainly cataract extraction, vitrectomy, and retinal detachment repair) 25 years later.[13]

Despite this interest as a potential biomarker for diabetic complications, there are scarce data regarding longitudinal changes in RVG over time and the factors influencing these changes. Most studies to date have been cross-sectional, with very few prospective longitudinal data. We therefore conducted

a longitudinal study of RVG changes in a well-characterized cohort of adolescents with type 1 diabetes.

Methods

Participant Population

Participants were recruited through the Diabetes Complications Assessment Service (DCAS) at the Children's Hospital at Westmead, Sydney, Australia; this is a prospective longitudinal cohort of children and adolescents with type 1 diabetes established in 1990.[10,15] For this analysis, adolescents aged between 12 and 20 years with type 1 diabetes of at least 2-years duration were followed-up at 1- to 2-year intervals. Participants with a minimum of three visits contributed data to this longitudinal analysis. The Children's Hospital Human Research Ethics Committee approved the study, and written informed consent was obtained from all participants and/or their legal guardian. The study adhered to the tenets of the Declaration of Helsinki.

Assessment of Systemic Vascular Risk Factors

Participants were prospectively followed up with standardized interviews, clinical examinations, and laboratory investigations at baseline and at subsequent visits, as previously described.[10] Body mass index (BMI) was determined from height and weight measured at the visit, and BP was measured with a sphygmomanometer using an appropriately sized cuff in seated patients after resting for 5 minutes. Venous blood samples were obtained for measurement of HbA1c, total cholesterol, and high-density lipoprotein (HDL) cholesterol levels.

Assessment of Retinopathy and RVG

Experienced retinal photographers took seven field mydriatic stereoscopic digital fundal photographs of both eyes using a TRC 50-VT Topcon Fundus Camera (Tokyo Optical, Tokyo, Japan). These digitized images were used to assess RVG at each visit. Retinopathy was assessed and graded from these images by a single ophthalmologist (SH) masked to participants' clinical characteristics, according to the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification.[10,15] Cumulative incident retinopathy was defined as at least one microaneurysm in either eye (ETDRS level 21, minimal nonproliferative diabetic retinopathy or greater) at any visit, including the baseline visit.

Retinal vascular geometry was analyzed from digitized retinal images of the right eye of each patient by a single grader (LH) masked to participants' characteristics, using a semiautomated computer-assisted image program (Singapore I Vessel Assessment [SIVA], National University of Singapore, Singapore) as previously described.[9,10] The correlation between eyes for RVG is high (>0.70) and we used right eye measures for analyses.[16,17] The software detects the optic disc and divides the image into three concentric zones: zone A, within 0.5-disc diameter from the optic disc margin; zone B, 0.5- to 1.0-optic disc diameter away; and zone C, 1.0- to 2.0-disc diameter away. Once the optic disc and zones were identified vessels were traced automatically by the software and corrected as required by the grader. Retinal vessel caliber measurements were based on the largest six arterioles and six venules within zone B.[9,10] Fractal dimension was calculated from vessel tracings of all arterioles and venules, as well as for arterioles and venules separately.[9,10] This measure quantifies the complexity of the retinal microvasculature, with lower values signifying a less complex (or more rarefied) microvasculature network.[18] Tortuosity was calculated as the ratio between the actual path length of the arteriole or venule segment (measured by tracking) and the straight-line length of the same segment, with higher values signifying more tortuous vessels.[9,10] Length to diameter ratio (LDR) was calculated as the length from the midpoint of the first branch to the midpoint of the second branch divided by the diameter of the parent vessel at the first branch.[9,10] Higher LDR suggests less branching of the microvascular network, and therefore a more rarefied network. Branching coefficient was measured as the change in the total cross-sectional area across a bifurcation and calculated using the following formula: branching coefficient = $(d_1^2 + d_2^2) / d_0^2$ where d_0 is the trunk caliber and d_1 and d_2 are the branch calibers.[9,10] Higher branching coefficient suggests wider daughter branch vessels. Branching angle of arterioles was defined as the angle subtended between the two daughter arterioles at the first degree (i.e., earliest) bifurcation.[9,10] The average branching angles of the six largest arterioles is calculated and the mean reported.

The inter- and intragrader correlation coefficients (ICCs) for each parameter were as follows: arteriolar caliber 0.99, 0.97; venular caliber 0.99, 0.97; branching angle arterioles 0.78, 0.78; simple tortuosity arteriole 0.99, 0.98; simple tortuosity venules 0.99, 0.97. The intragrader correlation coefficients for length to diameter ratio venules was 0.80, arterioles 0.84.[19]

Statistical Analysis

Mean and SD of clinical variables, biochemical measurements, and RVG parameters over time are presented. Any retinopathy was defined as the presence of retinopathy at any of the three time-points. We constructed plots of change in RVG over time by baseline tertiles of HbA1c and systolic blood pressure (SBP). Multivariable linear mixed-models for the associations between baseline RVG parameters were constructed in a stepwise manner, which adjusted for variables such as age, sex, SBP, total cholesterol, BMI (kg/m^2), and HbA1c (% and mmol/mol) depending on whether they were associated with the outcome in univariable analyses. Similar multivariable logistic regression models were constructed for the presence of retinopathy at any time-point. Statistical procedures were performed using SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

RVG Changes Over Time

Complete data were available on 102 adolescents with type 1 diabetes and three visits at which retinal vascular geometry measurements were obtained ($N = 306$ visits). Over this time period, 24 adolescents had retinopathy present at least one of these visits.

Table 1 shows the temporal trends of clinical/biochemical characteristics and RVG measurements over three visits. Mean arteriolar caliber and mean venular caliber both increased over this period significantly, from 156.0 to 164.9 μm, and 215.9 to 230.3 μm, respectively ($P < 0.001$ for both). Venular tortuosity likewise increased from 1.096 to 1.099, $P = 0.005$. Other RVG measurements did not change significantly over this time period.

Figures 1 and 2 show the longitudinal relationship of mean arteriolar and venular calibers according to tertiles of HbA1c at baseline. Participants in the upper HbA1c tertile had the narrowest arterioles and venules. Over time, arteriolar and venular calibers increased in all tertile groups. At the end of the study, venular calibers in the highest HbA1c tertile group had

Table 1. Temporal Trends in Clinical Characteristics and Retinal Vascular Geometry Measurements ($n = 102$)

Patient Data	Visit 1 Mean (SD)	Visit 2 Mean (SD)	Visit 3 Mean (SD)	*P* Value*
Clinical characteristics				
Age, y	14.4 (1.6)	15.7 (1.6)	17.0 (1.6)	<0.001
HbA1c, %	8.1 (1.3)	8.5 (1.4)	8.5 (1.5)	0.001
Diabetes duration, y	7.2 (3.1)	8.5 (3.1)	9.8 (3.1)	<0.0001
Mean arterial pressure, mm Hg	76.9 (7.4)	79.5 (8.2)	80.4 (8.4)	0.0003
Pulse pressure, mm Hg	42.1 (10.2)	C43.7 (9.8)	48.4 (12.7)	0.0001
SBP, mm Hg	104.8 (10.8)	108.5 (11.0)	112.3 (12.4)	<0.0001
Diastolic BP, mm Hg	62. 7 (7.4)	64.7 (8.4)	64.1 (9.1)	0.17
Height	163.3 (10.5)	166. (9.9)	168.3 (9.5)	<0.0001
Weight	61.3 (13.0)	65.9 (12.0)	68.5 (10.6)	<0.0001
Total cholesterol, mM	4.6 (0.8)	4.5 (0.9)	4.4 (0.8)	0.01
HDL cholesterol, mM	1.5 (0.3)	1.44 (0.28)	1.43 (0.32)	0.3
BMI, kg/m^2	22.9 (4.1)	23.7 (3.7)	24.2 (3.4)	<0.0001
Retinal vessel caliber				
Mean arteriolar caliber, μm	156.0 (14.5)	156.0 (12.9)	164.9 (14.0)	<0.001
Mean venular caliber, μm	215.9 (22.5)	220.3 (20.4)	230.3 (20.6)	<0.001
Retinal vascular geometry				
Fractal dimension	1.497 (0.030)	1.491 (0.031)	1.497 (0.028)	0.70
Fractal dimension (arteriolar)	1.299 (0.040)	1.294 (0.043)	1.301 (0.038)	0.43
Fractal dimension (venular)	1.250 (0.037)	1.243 (0.038)	1.250 (0.036)	0.83
Simple tortuosity	1.108 (0.0188)	1.108 (0.018)	1.109 (0.020)	0.22
Simple tortuosity (arteriolar)	1.119 (0.029)	1.116 (0.027)	1.118 (0.031)	0.43
Simple tortuosity (venular)	1.096 (0.014)	1.099 (0.017)	1.099 (0.016)	0.005
Branching coefficient	1.383 (0.135)	1.386 (0.143)	1.393 (0.137)	0.62
Branching angle	82.68 (7.19)	83.54 (5.47)	83.18 (6.20)	0.57
Junctional exponent	−0.322 (0.212)	−0.320 (0.210)	−0.346 (0.208)	0.37
LDR	14.12 (3.59)	14.13 (3.66)	13.34 (10.20)	0.46

* Comparing difference from the mean at baseline and visit 3, using mixed linear-models for repeated measures, which use all available data.

increased the most (213.0–235.0 μm, $P = 0.02$). Arteriolar caliber also increased the most in the upper HbA1c tertile group, but the difference was not statistically significant. Arteriolar and venular calibers in the lower and middle baseline HbA1c tertiles demonstrated a smaller increase over time.

Longitudinal changes in arteriolar and venular calibers by baseline SBP tertiles are depicted in Supplementary Figures S1 and S2. Both mean arteriolar (Supplementary Fig. S1) and venular (Supplementary Fig. S2) calibers increased over time, and in a similar manner in all tertiles. Baseline SBP, DBP, mean arterial BP, and pulse pressure had no significant effect on subsequent arteriolar and venular caliber changes.

Figure 3 shows longitudinal changes in venular caliber by tertiles of baseline diabetes duration. Participants with the longest duration of diabetes (highest tertile of diabetes duration) had the greatest increase in venular caliber ($P = 0.03$). No association between baseline duration of diabetes and increase in arteriolar caliber was detected.

RVG and Diabetic Retinopathy

Participants who developed retinopathy had wider arterioles and venules at all times points than those who did not (Supplementary Figs. S3, S4). Similarly, participants who developed retinopathy had greater fractal dimension at

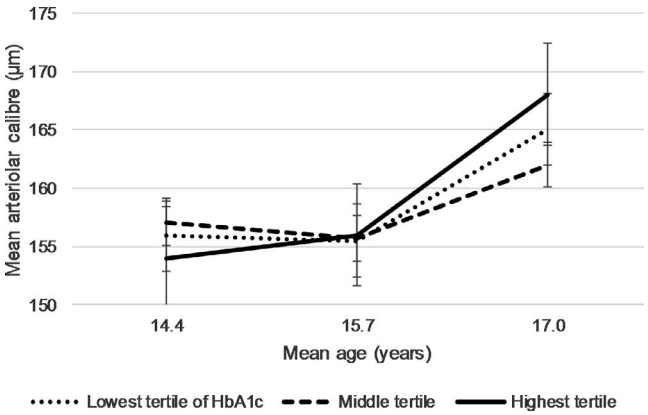

Figure 1. Longitudinal changes in mean arteriolar caliber (μm), by baseline HbA1c (%) tertiles. Included are 95% CIs.

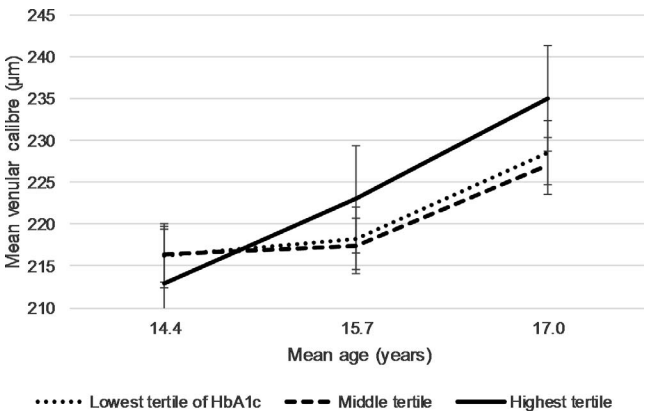

Figure 2. Longitudinal changes in mean venular caliber (μm), by baseline HbA1c (%) tertiles. Included are 95% CIs.

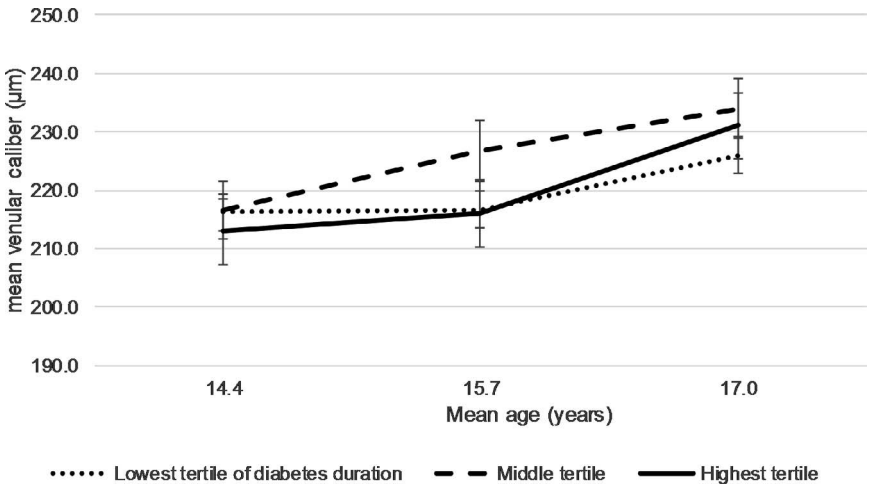

FIGURE 3. Longitudinal changes in mean venular caliber (μm), by tertiles of diabetes duration. Included are 95% CIs.

baseline and study-end, while visit 2 showed possible regression to the mean (Fig. 4).

Participants who developed retinopathy had higher SBP, total cholesterol, and HbA1c levels at baseline (Table 2) than those who did not develop retinopathy. Fractal dimension was higher among participants who developed retinopathy (1.51 vs. 1.49, $P = 0.03$) relative to those who did not. Other measures of RVG were similar at baseline.

RVG Tertile Analyses

The widest tertile of baseline arteriolar caliber was weakly associated with retinopathy (multivariable odd ratio [OR] 4.3, 95% confidence interval [CI] 0.9, 20.4, $P = 0.07$) while the widest tertile of venular caliber was not (multivariable OR 1.2, 95% CI 0.3, 4.9, $P = 0.85$).

The upper tertile of fractal dimension was significantly associated with increased risk of retinopathy (unadjusted OR 3.4, 95% CI 1.2, 9.8, $P = 0.03$). This association persisted after adjustment for age, BMI, and HbA1c (multivariable adjusted OR 2.6, 95% CI 1.0, 7.6, $P = 0.05$). The association was strongest for arteriolar fractal dimension (multivariable OR 3.2, 95% CI 1.0–9.6, $P = 0.04$). Other RVG measures were not significantly associated with retinopathy. Sex was not associated with retinal vascular changes.

DISCUSSION

We report on the longitudinal changes in retinal vascular caliber and other RVG measures in a cohort of adolescents with type 1 diabetes. We demonstrated that retinal vessels dilated and became more tortuous over the follow-up period of 2.6 years. Other measures of RVG did not alter appreciably over this period of time. Poorer glycemic control and longer diabetes duration at baseline were associated with greater subsequent venular vasodilation, while BP was not associated with longitudinal changes in vessel calibers.

There are few studies with which to compare our data. Only one smaller study of 45 adolescents with type 1 diabetes (mean age 15 years), conducted over 20 years ago using less precise retinal vessel assessment methods, also found a similar increase in arteriolar and venular caliber over 2.4 years.[20] This earlier study did not examine other retinal geometry measures and did not assess associations with clinical characteristics. A similar result was reported in patients with type 1 diabetes aged 15 to 58 years (mean 31 years) from the Renin-

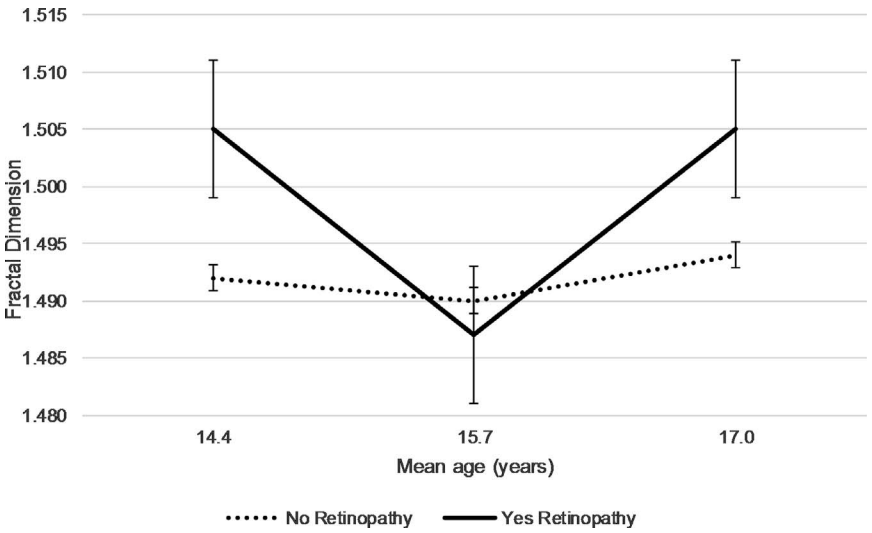

FIGURE 4. Longitudinal changes in fractal dimension by presence and absence of any diabetic retinopathy at any visit. Included are 95% CIs.

Table 2. Baseline Characteristics of Participants With and Without Retinopathy (Ever at Any of the Three Visits)

Patient Data	Participants With No Retinopathy, $n = 78$, Mean (SD) at Baseline	Participants Who Ever Developed Retinopathy, $n = 24$, Mean (SD) at Baseline	*P* Value*
Baseline characteristics			
Age, y	14.3 (1.6)	15.0 (1.3)	0.06
Sex (male)	51.3%	33.3%	0.12
Height, cm	163.3 (10.3)	163.3 (11.7)	0.99
Weight, kg	59.2 (11.1)	68.4 (16.3)	0.01
SBP, mm Hg	103.7 (11.4)	108.3 (7.8)	0.03
Diastolic BP, mm Hg	62.4 (6.9)	63.7 (8.8)	0.43
Diabetes duration, y	7.0 (3.0)	7.9 (3.1)	0.19
Mean arterial pressure, mm Hg	76.3 (7.3)	78.7 (7.4)	0.17
Pulse pressure, mm Hg	41.4 (10.5)	44.6 (9.2)	0.18
Total cholesterol, mmol	4.5 (0.7)	5.0 (1.0)	0.03
HDL cholesterol, mmol	1.4 (0.3)	1.5 (0.4)	0.64
HbA1c, %	7.9 (1.2)	8.7 (1.2)	0.005
Retinal vessel caliber			
Mean arteriolar caliber	155.6 (15.1)	157.6 (15.5)	0.55
Mean venular caliber	215.0 (23.5)	218.6 (19.2)	0.50
Fractal dimension	1.49 (0.03)	1.51 (0.03)	0.03
Retinal vessel geometry			
Fractal dimension (arteriolar)	1.30 (0.04)	1.31 (0.04)	0.25
Fractal dimension (venular)	1.25 (0.03)	1.26 (0.05)	0.07
Simple tortuosity	1.11 (0.02)	1.11 (0.01)	0.48
Simple tortuosity (arteriolar)	1.12 (0.03)	1.12 (0.02)	0.70
Simple tortuosity (venular)	1.10 (0.01)	1.10 (0.01)	0.53
Branching coefficient	1.38 (0.14)	1.39 (0.12)	0.75
Branching angle	82.5 (7.0)	83.3 (7.8)	0.61
Junctional exponent	−0.31 (0.21)	−0.37 (0.21)	0.21
LDR	14.0 (3.5)	14.4 (3.9)	0.69

* Calculated as *t*-test.

Angiotensin System Study (RASS) during which mean arteriolar and venular calibers both increased over 5 years.[21] In contrast, among adults with type 1 and type 2 diabetes aged 40+ years from the Wisconsin Epidemiologic Study of Diabetic Retinopathy, mean arteriolar calibers narrowed slightly, while mean venular calibers widened with increasing age.[22] In older adults without diabetes (aged 45–64), however, both arteriolar and venular calibers narrow with age and are associated with hypertension and cardiovascular risk, likely related to increased vessel stiffness.[23]

The effect of aging on other RVG measures has not been described previously, partly because the ability to measure these changes reproducibly has only recently become available. Cross-sectional studies in older adults (aged 49–90 years) suggest fractal dimension reduces with age, consistent with rarefaction of the microvasculature in aging.[24]

In our study, we report that mean arteriolar and venular calibers increased by approximately 6% to 7% from the ages of 14 to 17 years, while venular tortuosity increased by a smaller amount. The increase in mean vessel calibers is in line with continued slow growth of the globe from the age of 13 to adulthood.[25,26] Progressive venular vasodilation was greatest in adolescents with higher baseline HbA1c and longer duration of diabetes. This likely represents the adverse effects of hyperglycemia on endothelial function, by impairing the ability of retinal vessels to autoregulate.[27,28] In line with some other studies, our results suggest past hyperglycemia has a greater effect on vascular structure than past elevated BP.[17,29] We have previously shown reduced ability of retinal arterioles and venules to dilate in response to flicker light stimuli in patients with diabetes, but not in healthy controls, supporting the role of endothelial dysfunction in underlying wider retinal vessels in diabetes.[30]

The significance of the increase in venular tortuosity over this period is unclear but may be related to dilatation, and thus vessel engorgement, the effect of longer duration of hyperglycemia[10,31] and the small increase in BP that occurs with aging in adolescence.[32] These factors have been shown to be associated with increased vascular tortuosity.[10,31,32]

Retinal vascular geometry measures are associated with increased rates of chronic complications in persons with type 1 diabetes, and may therefore be useful as risk biomarkers. This was not the main aim of the study and as such our results should be viewed as preliminary and hypothesis generating, as our study was not powered to detect retinopathy. Nevertheless, the potential roles of fractal dimension and wider arteriolar caliber as predictive biomarkers for retinopathy should be investigated further. Our group has previously shown in cross-sectional analyses of patients with type 1 diabetes that greater arteriolar tortuosity is associated with retinopathy and early nephropathy,[33] while greater fractal dimension is associated with retinopathy.[34] We have also previously shown that wider retinal arteriolar caliber,[35] greater arteriolar tortuosity, and lower arteriolar LDR predict 4-year incident retinopathy,[36] while some other studies have shown wider venular caliber rather than arteriolar caliber predicts retinopathy.[7] In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, both wider retinal arterioles and venules predicted higher 4-year risk of developing retinopathy.[37] In contrast to the current results, the Fyn County study in Denmark found smaller fractal dimension was associated with severe proliferative diabetic retinopathy.[38] The different findings might have been related to the laser panretinal photocoagulation Fyn

County patients received, and the more severe level of retinopathy studied, as well as the older age of patients (40+ years) of adult patients aged 40+ with type 1 diabetes.[38] These older subjects may also have been more likely to have renal disease, to be smokers or ex-smokers, and to be taking other vasoactive drugs such as those modulating BP, the renal angiotensin aldosterone system (which exists in the eye), and lipid drugs such as statins and fenofibrate.[38]

Strengths of this study include the well-characterized longitudinally evaluated cohort with data on clinical characteristics, biochemical measures including HbA1c and BP control, stereoscopic retinal photography with seven standard fields, and use of consistent photographic and grading methods, with the same operators at all three time-points. There were low rates of diabetes complications and other health conditions. Limitations of the study are first, the small sample size, although this is larger than many other published studies. This reduced our ability to include more predictors of incident retinopathy in multivariable models. There were also a relatively large number of statistical tests performed, which requires a more stringent level for statistical significance than the traditional P less than 0.05. We suggest that our results should be viewed as hypothesis generating and exploratory. Second, participants had to return for follow-up at three time-points. Less-motivated participants who may have poorer systemic metabolic control may not have been included in the study so our results may not be generalizable to this group. The intereye correlation of 0.70 may also have reduced power to detect associations. Finally, it is possible that use of medications such as vasodilators and angiotension converting enzyme inhbitors may have affected the changes observed, although very few of our young participants were taking these antihypertensive medicines.

In summary, we report progressive arteriolar and venular vasodilation as well as increased venular tortuosity in adolescents with type 1 diabetes. Venular vasodilation was greatest in participants with the highest HbA1c and longest duration of diabetes at baseline. Participants who developed retinopathy had greater fractal dimension at baseline, which may be an early biomarker of retinopathy risk. Our results support ongoing studies focusing on using retinal vessel changes as potential biomarkers of diabetes complications, in particular retinopathy, and its response to therapeutic interventions.

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