Retinal Arteriolar Dilation Predicts Retinopathy in Adolescents With Type 1 Diabetes

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OBJECTIVE — Alterations in retinal vascular caliber may reflect early subclinical microvascular dysfunction. In this study, we examined the association of retinal vascular caliber to incident retinopathy in young patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a prospective cohort study of 645 initially retinopathy-free type 1 diabetic patients, aged 12–20 years. Participants had seven-field stereoscopic retinal photographs taken of both eyes at baseline and follow-up. Retinal vascular caliber was measured from baseline photographs using a computer-based program following a standardized protocol. Incident retinopathy was graded according to the modified Airlie House classification from follow-up photographs.

RESULTS — Over a median follow-up of 2.5 years, 274 participants developed retinopathy (14.8 per 100 person-years). After adjustments for age, sex, diabetes duration, glycemia, mean arterial blood pressure, BMI, and cholesterol levels, larger retinal arteriolar caliber (fourth versus first quartile) was associated with a more than threefold higher risk of retinopathy (hazard rate ratio 3.44 [95% CI 2.08–5.66]). Each SD increase in retinal arteriolar caliber was associated with a 46% increase in retinopathy risk (1.46 [1.22–1.74]). This association was stronger in female than in male participants. After similar adjustments, retinal venular caliber was not consistently associated with incident retinopathy.

CONCLUSIONS — Retinal arteriolar dilatation predicts retinopathy development in young patients with type 1 diabetes. Our data suggest that arteriolar dysfunction may play a critical role in the pathogenesis of early diabetic retinopathy and that computer-based retinal vascular caliber measurements may provide additional prognostic information regarding risk of diabetes microvascular complications.

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Children and adolescents with type 1 diabetes have a significant lifetime risk of blindness from retinopathy (1). Identifying high-risk patients early is the key to allow timely implementation of effective interventions to prevent this diabetes microvascular complication. However, clinically useful predictors of retinopathy risk in young patients with type 1 diabetes remain limited.

There is emerging evidence that quantitative measurement of retinal vascular caliber may provide prognostic information regarding the risk of diabetes microvascular complications, including retinopathy (2–7). Studies in older adult populations have shown that wider retinal arterioles are associated with the incidence and progression of diabetic retinopathy (3,4,7). These findings are consistent with experimental work that indicates a role of retinal arteriolar dysfunction, reflected as vasodilatation, in the pathogenesis of early diabetic retinopathy (3,7–9). According to the laws of Starling and Laplace, retinal arteriolar dilatation may increase capillary pressure and lead to capillary wall dilatation (microaneurysm), leakage (edema), and rupture (hemorrhage), which are all classical signs of diabetic retinopathy (3,9).

However, most previous studies were conducted in older patients with type 2 diabetes, in whom residual confounding from coexisting metabolic diseases and retinopathy risk factors (e.g., hypertension, insulin resistance, and dyslipidemia) is difficult to fully account for. The value of measuring retinal vascular caliber changes in younger patients with type 1 diabetes for retinopathy risk prediction is less clear, with only a small retrospective case-control study to date (10). In the current study, we examined prospectively the association of retinal vascular caliber with incident retinopathy risk in a cohort of children and adolescents with type 1 diabetes.

RESEARCH DESIGN AND METHODS

— This is a prospective cohort study of children and adolescents with type 1 diabetes, aged 12–20 years old, managed at The Children's Hospital at Westmead in Sydney, Australia. Detailed characteristics of this cohort have been reported in previous publications (11–15). Children and adolescents with type 1 diabetes, referred by their physicians, were assessed for complications in our clinics. Complications were assessed during a 2-h visit that consisted of clinical assessment by an endocrinologist; anthropometry, blood pressure measurement, and pubertal staging; screening for retinopathy, nephropathy, and neuropathy; and A1C and biochemical analyses, as described previously (11–15). For this report, 650 eligible patients who had retinal photographs, who had no evidence of diabetic retinopathy at baseline between 1990 and 2002, and who returned for follow-up examination were included. Of these, we excluded those with photo-

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Table 1—*Baseline characteristics of participants, by incident retinopathy status*

Characteristics	All	No retinopathy	Retinopathy	*P* value
n	645	371	274	
Age (years)	13.5 (12.8–14.9)	13.7 (12.9–15.1)	13.3 (12.6–14.6)	<0.001
Sex (% male)	45.6	45.8	45.3	0.886
Diabetes duration (years)	4.7 (3.2–7.4)	3.9 (2.8–6.5)	5.6 (3.9–8.9)	<0.001
BMI (kg/m^2)	21.0 (19.2–23.5)	21.4 (19.6–23.9)	20.6 (18.8–23.0)	0.001
Mean arterial blood pressure (mmHg)	83.3 (80.0–88.3)	83.3 (80–88.3)	83.3 (80–88.3)	0.411
A1C (%)	8.4 (7.7–9.3)	8.2 (7.5–9.1)	8.6 (7.8–9.5)	0.005
Albumin excretion rate (μg/min)	4.4 (3.3–6.9)	4.5 (3.2–8.0)	4.2 (3.4–6.2)	0.348
Microalbuminuria present	2.5	3.2	1.4	0.269
Total cholesterol (mmol/l)	4.3 (3.7–4.8)	4.2 (3.8–4.8)	4.3 (3.7–4.8)	0.866
Tanner pubertal stage				0.038
1	5.7	4.2	7.5	
2	13.3	11.0	16.2	
3	14.2	12.9	15.8	
4	25.3	25.6	24.9	
5	41.5	46.3	35.6	
Retinal arteriolar caliber (μm)	170.51 (157.35–182.86)	165.98 (153.07–178.67)	176.11 (163.50–187.43)	<0.001
Retinal venular caliber (μm)	246.60 (232.22–263.53)	245.41 (231.19–260.70)	249.86 (233.76–267.12)	0.019

Data are medians (interquartile range) or proportions. *P* values relate to Wilcoxon rank-sum or χ^2 test for difference between those who did and did not develop retinopathy during follow-up.

graphs of insufficient quality for retinal vascular caliber measurements ($n = 5$), leaving 645 participants for the current analysis. The excluded patients did not differ significantly from the included patients in any of the characteristics shown in Table 1.

Retinal photography and assessment

Retinal photography was performed according to a standardized protocol, as detailed elsewhere (11–15). In brief, seven-field stereoscopic retinal photographs were taken of both eyes after pupil dilation. Diabetic retinopathy was graded from these photographs by an ophthalmologist, masked to participants' characteristics, according to the Early Treatment Diabetic Retinopathy (ETDRS) adaptation of the modified Airlie House classification. Incident retinopathy was defined as ETDRS level 21 (minimal nonproliferative diabetic retinopathy) or greater after at least 1 year of follow-up visits and at least two clinic visits. The overall agreement based on 30% of photographs graded independently by another ophthalmologist, also masked to subject characteristics, was high (weighted $k = 0.80$) (10).

Retinal vascular caliber was measured using a computer-based program following a previously validated protocol (16,17). For each photograph, all arterioles and venules coursing through an area one-half to one disc diameter from the optic disc margin were measured and summarized as the central retinal arteriolar and venular equivalents, using formulas described elsewhere (16,17). These equivalents represented the average of projected calibers for the central retinal vessels. For this study, retinal vascular caliber in the right eye was measured. Left eye measurements were performed when photographs of the right eye were ungradable. Retinal vascular caliber measurements have been shown to be highly correlated between the right and left eye (16). Reproducibility data have been reported previously, with intra- and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99 (16–18).

Risk factors and definitions

Participants underwent standardized interviews, clinical examinations, and laboratory investigations at baseline and follow-up visits (11–15). Pubertal stage was assessed by an endocrinologist according to the Tanner stage classification (14). BMI was calculated as weight in kilograms divided by the square of height in meters. Blood pressure was measured in the seated position with a sphygmomanometer using the appropriate cuff size after 5 min of rest. Mean arterial blood pressure was calculated as one-third of the systolic plus two-thirds of the diastolic blood pressure. Venous blood was obtained for measurement of A1C and total cholesterol levels. Albumin excretion rate was also measured at baseline and determined from three consecutive timed overnight urine collections. Microalbuminuria was defined as albumin excretion rate >20 μg/min (15).

Statistical analysis

Crude incidence rates were calculated per 100 person-years. Many participant characteristics of interest were found to be not normally distributed, and thus nonparametric statistics were applied as appropriate. Differences between those who did and did not develop retinopathy were assessed using Wilcoxon rank-sum and χ^2 tests. We used Cox proportional hazards regression to determine the hazard ratio (HR) for retinopathy in relation to retinal arteriolar and venular calibers, initially adjusting for age and sex and additionally for diabetes duration, A1C, Tanner pubertal stage, mean arterial blood pressure, BMI, and total cholesterol levels. All covariates were measured at the baseline visit. Both arteriolar and venular calibers were modeled simultaneously. Supplementary analysis adjusted further for log(albumin excretion rate), although the data for this measure were limited to 60% of participants. We also performed the above analyses stratified by sex. All analyses were performed with Intercooled Stata 9.2 for Windows (StataCorp, College Station, TX).

RESULTS — Table 1 shows baseline characteristics of our study population by

Table 2—*Association of retinal vascular caliber and incident diabetic retinopathy*

	n	Incidence (per 100 person-years)	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value
Retinal arteriolar caliber						
Per SD increase, 18.90 μm	645	274 cases	1.43 (1.23–1.66)	<0.001	1.46 (1.22–1.74)	<0.001
Quartile 1, ≤157.2 μm	161	8.5	Reference		Reference	
Quartile 2, 157.3–170.5 μm	161	13.5	1.72 (1.15–2.58)	0.009	1.75 (1.11–2.75)	0.017
Quartile 3, 170.51–182.85 μm	160	15.3	1.94 (1.29–2.92)	0.001	1.82 (1.15–2.89)	0.010
Quartile 4, ≥182.86 μm	163	22.5	3.13 (2.01–4.86)	<0.001	3.44 (2.08–5.66)	<0.001
P_{trend}			<0.001		<0.001	
Retinal venular caliber						
Per SD increase, 22.63 μm	643	272 cases	0.89 (0.77–1.04)	0.134	0.82 (0.69–0.98)	0.028
Quartile 1, <232.2 μm	160	12.8	Reference		Reference	
Quartile 2, 232.2–246.59 μm	161	11.7	0.81 (0.56–1.17)	0.255	0.75 (0.50–1.13)	0.165
Quartile 3, 246.6–263.5 μm	161	16.3	0.98 (0.68–1.42)	0.922	0.91 (0.60–1.37)	0.640
Quartile 4, ≥263.5 μm	161	18.3	0.94 (0.63–1.40)	0.757	0.78 (0.50–1.23)	0.281
P_{trend}			0.975		0.457	

Model 1 HR adjusted for age and sex. Model 2 HR adjusted for model 1 covariates plus diabetes duration, A1C, mean arterial blood pressure, Tanner pubertal stage, BMI, and total cholesterol. Models for arteriolar caliber were adjusted for venular caliber and vice versa.

incident retinopathy status. Participants who developed retinopathy had longer duration of diabetes, lower BMI, higher A1C, lower pubertal stage, and larger retinal arteriolar and venular caliber than those who did not develop retinopathy.

Over a median follow-up of 2.5 years (interquartile range of 1.4–3.9 years), 274 participants developed retinopathy, an incidence of 14.8 per 100 person-years. Table 2 shows that after adjustments for age, sex, diabetes duration, A1C, mean arterial blood pressure, pubertal stage, BMI, and cholesterol levels, larger retinal arteriolar caliber was associated with higher risk of incident retinopathy. Compared with participants with arteriolar caliber in the lowest quartile, those with arteriolar caliber in the highest quartile had a nearly 3½-fold higher risk of retinopathy (HR 3.44 [95% CI 2.08–5.66]). For each SD increase in retinal arteriolar caliber, there was a 46% increase in retinopathy risk (1.46 [1.22–1.74]). In supplementary analysis, we further adjusted for renal function in participants with albumin excretion rate measured at baseline (60%). The association of larger retinal arteriolar caliber and diabetic retinopathy remained and appeared to be even stronger (2.23 [1.74–2.85] for each SD increase in retinal arteriolar caliber; 8.18 [3.97–16.87] for highest compared with lowest quartile of retinal arteriolar caliber). Retinal venular caliber was not associated with incident retinopathy.

In analyses stratified by sex, the association between larger retinal arteriolar caliber and incident retinopathy risk was stronger in female than in male participants (HR 4.39 [95% CI 2.34–8.23] for female and 2.44 [1.09–5.45] for male participants in the highest compared with the lowest quartile of arteriolar caliber) (Table 3). However, there was no statistically significant interaction ($P < 0.10$) for sex. Participants' characteristics by sex are summarized in supplemental Table 1 (available in an online appendix at http://dx.doi.org/10.2337/dc08-0189). In general, female participants differed signi-

Table 3—*Association of retinal arteriolar caliber and incident diabetic retinopathy in young females and male patients*

Retinal arteriolar caliber	*n*	Incidence (per 100 person-years)	Model 1 HR (95% CI)	*P* value	Model 2 HR (95% CI)	*P* value
Female	351	14.6				
Per SD increase, 18.7 μm			1.61 (1.32–1.96)	<0.001	1.82 (1.45–2.28)	<0.001
Quartile 1, <160.0 μm	87	8.33	Reference		Reference	
Quartile 2, 160.0–172.1 μm	88	11.22	1.45 (0.83–2.54)	0.187	1.39 (0.77–2.54)	0.276
Quartile 3, 172.2–183.5 μm	88	16.58	2.40 (1.39–4.17)	0.002	2.39 (1.30–4.39)	0.005
Quartile 4, >183.5 μm	88	23.51	3.80 (2.12–6.81)	<0.001	4.39 (2.34–8.23)	<0.001
P_{trend}			<0.001		<0.001	
Male	294	14.9				
Per SD increase, 19.0 μm			1.25 (1.00–1.56)	0.050	1.12 (0.85–1.48)	0.424
Quartile 1, <154.8 μm	73	8.36	Reference		Reference	
Quartile 2, 154.8–168.8 μm	74	16.32	2.01 (1.11–3.65)	0.021	2.12 (1.04–4.31)	0.039
Quartile 3, 168.9–181.7 μm	72	14.84	1.76 (0.95–3.24)	0.072	1.71 (0.83–3.53)	0.148
Quartile 4, >181.7 μm	75	20.76	2.42 (1.25–4.67)	0.008	2.44 (1.09–5.45)	0.030
P_{trend}			0.026		0.088	

Model 1 HR adjusted for age. Model 2 HR adjusted for age, diabetes duration, A1C, mean arterial blood pressure, Tanner pubertal stage, BMI, and total cholesterol. Models for arteriolar caliber were adjusted for venular caliber and vice versa.

ficantly from male participants in that they were further through puberty and had higher cholesterol levels, higher BMI, and larger retinal arteriolar and venular calibers.

CONCLUSIONS — Our study shows that larger retinal arteriolar caliber predicts a higher risk of incident retinopathy in young individuals with type 1 diabetes, independent of diabetes duration, blood pressure, glycemic control, and other risk factors. This finding is consistent with previous population-based studies in older adults with diabetes. In the Wisconsin Epidemiological Study of Diabetic Retinopathy, the investigators reported an association of larger retinal arteriolar caliber with 4-year progression of diabetic retinopathy (relative risk 2.04 [95% CI 1.20–3.47]) in type 1 diabetes and with 10-year incident retinopathy risk in type 2 diabetes (odds ratio 1.78 [95% CI 1.06–3.00]) (3,4). These findings are further reinforced by data from the Australian Diabetes Obesity and Lifestyle Study of predominantly type 2 diabetic adults (7). Our study now extends these observations to young children and adolescents with type 1 diabetes and findings from our previous retrospective case-control study (10).

Our study supports the hypothesis that retinal arteriolar dilatation is a physiological indicator of diabetes-related retinal microvascular dysfunction (3,9). Arteriolar dilatation is a sign of impaired arteriolar autoregulation, which has been suggested to play a pivotal role in the initiation and progression of diabetic retinopathy (8). Experimental studies show that an increase in retinal blood flow and associated arteriolar dilatation are frequently found in the retinas of diabetic patients, reflecting underlying arteriolar autoregulatory dysfunction (8). This could be due to hyperglycemia-mediated endothelin-1 resistance and calcium influx channel inhibition in smooth muscle cells. Such processes could impair retinal arteriolar constriction and also augment retinal arteriolar dilatory response by reducing oxygen tension from retinal capillary nonperfusion (8). In contrast, retinal venular dilatation may represent a later sign of established diabetic retinopathy, explaining the lack of associations with incident retinopathy risk in our study and others (3,5,7,10), although there is evidence of associations with the prevalence and progression of retinopathy in older adults with type 2 diabetes (4,19,20).

Our data also suggest a possible sex difference in the association of retinal arteriolar caliber with retinopathy risk. To the best of our knowledge, this aspect has not been examined in previous studies. The reasons for this observation are not apparent. Although epidemiological studies offer inconsistent evidence that the risk of diabetic retinopathy differs by sex, it has long been hypothesized that women are more susceptible to microvascular disease development than men (21). Moreover, hormonal changes associated with puberty have been suggested to contribute to the development of diabetic retinopathy (14,22–24). Because these changes are different for boys and girls, they may provide another source of explanation for our finding of an apparent sex difference (e.g., vasodilatory effects of estrogen and progesterone). However, it is important to note that we did not find a statistically significant interaction with sex. Thus, additional studies are needed to confirm and further elucidate the importance of this observation.

Strengths of our study include its prospective design, quantitative evaluation of retinal vascular caliber, and standardized assessment of diabetic retinopathy using stereoscopic seven-field retinal photographs. Potential limitations may merit consideration. First, the generally short period of follow-up (3 years) may result in some misclassifications, as some participants could potentially still develop retinopathy after the end of follow-up. Second, there may be limited generalizability of our findings to the general community, as our study population was derived from a tertiary hospital-based setting. Our results might have been biased toward exceptionally good endocrinological and ophthalmological monitoring, and mild retinopathy or no retinopathy could be over-represented relative to the general diabetic population. For example, we had no cases of proliferative retinopathy in our population. However, in Australia, most individuals with type 1 diabetes are seen at a tertiary referral center (11,12). Finally, findings from our stratified analyses should be interpreted with caution, as there might be power concerns after stratification.

In summary, our study shows that retinal arteriolar dilatation, measured quantitatively from retinal photographs, is a clinical predictor of future retinopathy risk in children and adolescents with type 1 diabetes, independent of standard risk factors. Further research and developments in computer-based techniques to analyze retinal vascular changes may uncover insights into early microvascular disease and open new avenues to improve risk stratification of retinopathy in young people with diabetes.

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