Retinal Vascular Fractal Dimension and Risk of Early Diabetic Retinopathy

A prospective study of children and adolescents with type 1 diabetes

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OBJECTIVE — To examine the prospective association of retinal vascular fractal dimension with diabetic retinopathy risk in young people with type 1 diabetes.

RESEARCH DESIGN AND METHODS — This was a hospital-based prospective study of 590 patients aged 12–20 years with type 1 diabetes free of retinopathy at baseline. All patients had seven-field retinal photographs taken of both eyes. Incident retinopathy was ascertained from retinal photographs taken at follow-up visits. Fractal dimension was measured from baseline photographs using a computer-based program following a standardized protocol.

RESULTS — Over a mean ± SD follow-up period of 2.9 ± 2.0 years, 262 participants developed mild nonproliferative diabetic retinopathy (15.0 per 100 person-years). After adjusting for age, sex, diabetes duration, A1C, and other risk factors, we found no association between retinal vascular fractal dimension and incident retinopathy.

CONCLUSIONS — Retinal vascular fractal dimension was not associated with incident early diabetic retinopathy in this sample of children and adolescents with type 1 diabetes.

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Fractal objects are self-similar structures that retain a similar level of complexity across all scales. For example, blood vessels repeatedly subdivide downstream into smaller blood vessels with similar network patterns. Fractal dimension (D_f) quantifies the degree of complexity into a single value and is particularly useful for quantifying non-Euclidean geometric shapes such as vascular networks. The retinal circulation is a fractal object (1–3), and fractal analysis has been used to study the embryological development of the retinal vasculature (2) and vascular changes associated with diabetic retinopathy (3–7). Variations in retinal vascular D_f may reflect geometric alterations in the vascular network in response to hypoxia (2,7).

Earlier case-control studies showed that retinal vascular D_f was associated with proliferative diabetic retinopathy (5,6), suggesting that neovascularization increases the complexity of the retinal vascular branching pattern. More recently, using a computer-based program to reliably measure D_f of the retinal vasculature (8), we reported that retinal vascular D_f was cross-sectionally associated with the prevalence of early retinopathy in patients with type 1 diabetes (9). However, prospective data are needed to elucidate the significance of this interesting finding. We therefore aimed to determine whether retinal vascular D_f measured from baseline photographs of eyes without retinopathy is associated with subsequent risk of retinopathy development in a cohort of type 1 diabetic subjects.

RESEARCH DESIGN AND METHODS

— The study participants were children and adolescents (aged 12–20 years) with type 1 diabetes managed at the Children's Hospital at Westmead, Sydney, Australia. The methodology of this study has been described previously (10–12). Type 1 diabetes was defined following the Australasian Pediatric Endocrine Group diabetes register and national guidelines. All participants had retinal photography and assessment at baseline (1990–2002) and had at least one follow-up assessment before reaching 20 years of age.

Stereoscopic retinal photographs of seven fields were taken of both eyes following a standardized protocol (10–12). Diabetic retinopathy was graded by an ophthalmologist masked to participants' characteristics following the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification of diabetic retinopathy. Incident diabetic retinopathy was defined as ETDRS level 21 (minimal nonproliferative diabetic retinopathy) or greater at the follow-up visits in those free of diabetic retinopathy at baseline. We performed fractal analysis using ETDRS field one (centered on the optic disc) photographs and a computer-based program with a standardized protocol (8). Reproducibility of the measurements was high, with an intragrader intraclass correlation coefficient of 0.98. Retinal arteriolar and venular calibers were measured as described previously (13–15). Participants also underwent standardized interviews, clinical examinations, and laboratory investigations (10–12). All risk factors were collected at baseline.

Statistical analysis

Cox proportional hazards regression model was used to determine the hazard ratio (HR) for incident diabetic retinopa-

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Table 1—*Relationship between retinal vascular D_f and incident diabetic retinopathy*

Retinal vascular D_f	*n*	Incidence per 100 person-years	Model 1*		Model 2†		Model 3‡	
			HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Right eye only								
Quartile 1 (≤1.4497)	132	10.7	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Quartile 2 (1.4498–1.4628)	132	9.1	0.84 (0.56–1.26)	0.39	0.80 (0.52–1.21)	0.29	0.82 (0.53–1.26)	0.36
Quartile 3 (1.4629–1.4738)	132	10.4	0.97 (0.65–1.46)	0.89	0.95 (0.62–1.45)	0.80	0.97 (0.63–1.49)	0.88
Quartile 4 (≥1.4739)	133	10.3	0.95 (0.63–1.45)	0.82	0.90 (0.58–1.40)	0.64	0.93 (0.60–1.45)	0.75
P_{trend}				0.84		0.75		0.82
Right and left eyes combined§								
Quartile 1 (≤1.4471)	279	10.8	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Quartile 2 (1.4472–1.4598)	278	9.3	0.89 (0.67–1.18)	0.41	0.88 (0.65–1.19)	0.41	0.90 (0.66–1.21)	0.47
Quartile 3 (1.4599–1.4730)	266	10.3	0.98 (0.74–1.30)	0.89	0.98 (0.73–1.32)	0.88	0.99 (0.73–1.33)	0.93
Quartile 4 (≥1.4731)	257	9.5	0.91 (0.67–1.22)	0.52	0.92 (0.68–1.26)	0.92	0.95 (0.69–1.30)	0.74
P_{trend}				0.82		0.84		0.89

*Model 1 adjusted for age and sex. †Model 2 adjusted for age, sex, diabetes duration, A1C, mean arterial blood pressure, BMI, and total cholesterol. ‡Model 3 adjusted for variables in model 2 as well as central retinal arteriolar equivalent and central retinal venular equivalent. §Analysis performed using the generalized estimation equation model.

thy in relation to D_f. Three multivariable-adjusted models were constructed: model 1 adjusted for age and sex; model 2 adjusted additionally for other diabetic retinopathy risk factors; model 3 adjusted for all variables in model 2 plus retinal arteriolar or venular calibers, given their previously documented associations with diabetic retinopathy (13–15). Retinal vascular D_f was categorized into quartiles. Eye-specific analyses, using data from the right eyes, were performed initially and then repeated using data from both eyes and generalized estimation equation models (SPSS version 16.1). With a sample of 590 subjects, our study has 80% power to detect a minimum HR of 1.5 for diabetic retinopathy by D_f quartiles.

RESULTS — Of the 810 baseline participants, 807 were followed. We excluded patients with diabetic retinopathy at baseline (n = 136), with photographs of insufficient quality for analysis (n = 80), or with diabetic retinopathy assessment (n = 1), leaving 590 (72.8%) participants included. Baseline characteristics were similar between excluded and included participants (9).

The median D_f was 1.462 (interquartile range [IQR] 1.450–1.472). Over a mean ± SD follow-up period of 2.9 ± 2.0 years, 262 (44%) developed diabetic retinopathy in one or both eyes, with an incidence of 15.0 per 100 person-years. All incident cases had mild nonproliferative diabetic retinopathy (ETDRS level ≤31). The median D_f in participants with incident diabetic retinopathy (1.4597 [IQR 1.4485–1.4696]) was not significantly different from that of those without incident diabetic retinopathy (1.4613 [1.4479–1.4706]; P = 0.886). There was no significant association between retinal vascular D_f and incident retinopathy after adjusting for covariables (Table 1).

CONCLUSIONS — There has been increasing evidence showing structural retinal vascular changes associated with diabetic retinopathy (13–15). However, previous studies largely focused on the associations with retinal vascular caliber (13–15), which represents only one of the many geometric properties of the retinal vascular network. Retinal vascular D_f is a global measure of complexity of the vascular branching pattern. Recently, we reported a strong cross-sectional association between retinal vascular D_f and the prevalence of diabetic retinopathy (9). In the present study, we could not find similar a association using the longitudinal data from the same study sample of young patients with type 1 diabetes over a median follow-up of 2.9 years. This suggests that variations in retinal vascular D_f are likely consequential, rather than antecedent to, the development of diabetic retinopathy.

Our study has several limitations. First, the follow-up period was relatively short, and all of the incident cases had mild nonproliferative diabetic retinopathy only. Therefore, it remains unclear whether retinal vascular D_f could predict the risk of more severe diabetic retinopathy (e.g., proliferative diabetic retinopathy). Second, the possibility of selection bias may exist because this cohort was not a population-based sample and some patients (10.0%) were further excluded due to ungradable photographs. Third, there are potential sources of measurement error in fractal analysis (8), but these random errors could only bias our findings toward the null. Finally, although our study has adequate power to detect clinically important associations with a HR of 1.5 or greater (i.e., 50% difference in diabetic retinopathy risk by fractal quartiles), we have limited power to detect weaker associations.

In summary, our data demonstrate no longitudinal association between retinal vascular D_f and risk of developing early diabetic retinopathy in young patients with type 1 diabetes. Further studies with larger sample size and longer follow-up are required to determine whether retinal fractal analysis is useful in predicting more severe levels of diabetic retinopathy and whether similar associations are present in older patients with type 2 diabetes.

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