Retinal Vascular Fractal Dimension and Risk of Early Diabetic Retinopathy: A Prospective Study of Children and Adolescents with Type 1 Diabetes

Running title: Fractal Dimension and Retinopathy

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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: A hospital-based prospective study of 590 patients aged 12-20 years with type 1 diabetes free of retinopathy at baseline. All patients had 7-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 median follow-up period of 2.9 (±2.0) years, 262 participants developed mild non-proliferative diabetic retinopathy (15.0/100-person-years). After adjusting for age, gender, diabetes duration, HbA1c 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.
Fractal Dimension and Retinopathy

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 (Df) 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 Df may reflect geometric alterations in the vascular network in response to hypoxia (2, 7).

Earlier case-control studies showed that retinal vascular Df 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 Df of the retinal vasculature (8), we reported that retinal vascular Df 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 Df measured from baseline photographs of eyes without retinopathy is associated with subsequent risk of retinopathy development in a cohort of type 1 diabetes.

RESEARCH DESIGN AND METHODS

The study participants were children and adolescents (12 to 20 years old) 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 old.

Stereoscopic retinal photographs of 7-fields were taken of both eyes following a standardized protocol (10-12). Diabetic retinopathy (DR) 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 DR. Incident DR was defined as ETDRS level 21 (minimal non-proliferative DR) or greater at the follow-up visits in those free of DR at baseline. We performed fractal analysis using ETDRS Field 1 (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’s proportional-hazards regression was used to determine the hazard rate ratio (HR) for incident DR in relation to Df. Three multivariable-adjusted models were constructed: Model 1 adjusted for age and gender; Model 2 adjusted additionally for other DR risk factors; Model 3 adjusted for all variables in Model 2 plus retinal arteriolar or venular calibers, given their previously documented associations with DR (13-15). Retinal vascular Df was categorized into quartiles. Eye-specific analyses, using data from the right eyes, were performed initially,
then repeated using data from both eyes and Generalized Estimation Equation (GEE) Models. SPSS (version 16.1) was used. With a sample of 590 subjects, our study has 80% power to detect a minimum HR of 1.5 for DR by $D_f$ quartiles.

RESULTS

Of the 810 baseline participants, 807 were followed. We excluded patients with DR at baseline (n=136), with photographs of insufficient quality for analysis (n=80) or DR 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 median follow-up period of 2.9 ($\pm$2.0) years, 262 (44%) developed DR in one or both eyes, with an incidence of 15.0 per 100 person-years. All incident cases had mild non-proliferative DR (levels $\leq 31$). The median $D_f$ in participants with incident DR (1.4597; IQR: 1.4485-1.4696) was not significantly different from that of those without incident DR (1.4613; IQR: 1.4479-1.4706) ($p=0.886$). There was no significant association between retinal vascular $D_f$ and incident retinopathy after adjusting for co-variables (Table 1).

CONCLUSIONS

There has been increasing evidence showing structural retinal vascular changes associated with DR.\(^{(13-15)}\). 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 DR\(^{(9)}\). In the present study, we could not find similar 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 DR.

Our study has several limitations. Firstly, the follow-up period was relatively short, and all of the incident cases had mild non-proliferative DR only. Therefore, it remains unclear whether retinal vascular $D_f$ could predict the risk of more severe DR (e.g. proliferative diabetic retinopathy). Second, the possibility of selection bias may exist as 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 errors in fractal analysis \(^{(8)}\), but these random errors could only bias our findings towards the null. Finally, while our study has adequate power to detect clinically important associations with a HR of 1.5 or greater (i.e., 50% difference in DR 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 DR and if similar associations are present in older patients with type 2 diabetes.

ACKNOWLEDGEMENTS:

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Disclosure: None
REFERENCES
Table 1. Relationship between Retinal Vascular Fractal Dimension, $D_f$ and Incident Diabetic Retinopathy (Eye-specific)

<table>
<thead>
<tr>
<th>Retinal Vascular $D_f$</th>
<th>N</th>
<th>Incidence per 100p-yr</th>
<th>Model 1* HR (95% CI)</th>
<th>$p$</th>
<th>Model 2† HR (95% CI)</th>
<th>$p$</th>
<th>Model 3‡ HR (95% CI)</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Right eyes only</strong></td>
<td></td>
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<tr>
<td>Quartile 1 ($\leq 1.4497$)</td>
<td>132</td>
<td>10.7</td>
<td>1.00 (Ref)</td>
<td>0.39</td>
<td>0.80 (0.52, 1.21)</td>
<td>0.29</td>
<td>0.82 (0.53, 1.26)</td>
<td>0.36</td>
</tr>
<tr>
<td>Quartile 2 (1.4498 – 1.4628)</td>
<td>132</td>
<td>9.1</td>
<td>0.84 (0.56, 1.26)</td>
<td>0.39</td>
<td>0.80 (0.52, 1.21)</td>
<td>0.29</td>
<td>0.82 (0.53, 1.26)</td>
<td>0.36</td>
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<tr>
<td>Quartile 3 (1.4629 – 1.4738)</td>
<td>132</td>
<td>10.4</td>
<td>0.97 (0.65, 1.46)</td>
<td>0.89</td>
<td>0.95 (0.62, 1.45)</td>
<td>0.80</td>
<td>0.97 (0.63, 1.49)</td>
<td>0.88</td>
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<tr>
<td>Quartile 4 ($\geq 1.4739$)</td>
<td>133</td>
<td>10.3</td>
<td>0.95 (0.63, 1.45)</td>
<td>0.82</td>
<td>0.90 (0.58, 1.40)</td>
<td>0.64</td>
<td>0.93 (0.60, 1.45)</td>
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<tr>
<td>P for trend</td>
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<td></td>
<td>0.84</td>
<td></td>
<td>0.75</td>
<td></td>
<td>0.82</td>
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<tr>
<td><strong>Right and left eyes combined</strong></td>
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<tr>
<td>Using Generalized Estimation Equation (GEE model)</td>
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<tr>
<td>Quartile 1 ($\leq 1.4471$)</td>
<td>279</td>
<td>10.8</td>
<td>1.00 (Ref)</td>
<td>0.41</td>
<td>0.88 (0.65, 1.19)</td>
<td>0.41</td>
<td>0.90 (0.66, 1.21)</td>
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<td>Quartile 2 (1.4472 – 1.4598)</td>
<td>278</td>
<td>9.3</td>
<td>0.89 (0.67, 1.18)</td>
<td>0.41</td>
<td>0.88 (0.65, 1.19)</td>
<td>0.41</td>
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<td>Quartile 3 (1.4599 – 1.4730)</td>
<td>266</td>
<td>10.3</td>
<td>0.98 (0.74, 1.30)</td>
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<td>0.98 (0.73, 1.32)</td>
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<td>0.99 (0.73, 1.33)</td>
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<td>Quartile 4 ($\geq 1.4731$)</td>
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<td>9.5</td>
<td>0.91 (0.67, 1.22)</td>
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<td>0.92 (0.68, 1.26)</td>
<td>0.92</td>
<td>0.95 (0.69, 1.30)</td>
<td>0.74</td>
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<tr>
<td>P for trend</td>
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<td></td>
<td>0.82</td>
<td></td>
<td>0.84</td>
<td></td>
<td>0.89</td>
<td></td>
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</tbody>
</table>

* Model 1 hazard ratios adjusted for age and gender.
† Model 2 hazard ratios adjusted for age, gender, diabetes duration, glycosylated haemoglobin (HbA1c), mean arterial blood pressure, body mass index and total cholesterol
‡ Model 3 hazard ratios adjusted for variables in Model 2 plus central retinal arteriolar equivalent (CRAE) and central retinal venular equivalent (CRVE)