

**Retinal Arteriolar Caliber Predicts Incident Retinopathy:  
The Australian Diabetes, Obesity and Lifestyle (AusDiab) Study**

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## **ABSTRACT**

Changes in retinal vascular caliber may reflect subclinical microvascular disease and provide prognostic information regarding risk of retinopathy. In this study, we examined the prospective association of retinal vascular caliber with retinopathy risk in an Australian population-based cohort. 906 participants without retinopathy at baseline had retinal vascular caliber measured from photographs and were followed up for 5 years for incident retinopathy. After adjusting for age, gender, systolic blood pressure, HbA1c and other risk factors, persons with wider retinal arteriolar caliber (widest 25% versus remaining three-quarters of the population) were more likely to develop incident retinopathy (odds ratio 4.79; 95% CI: 1.57-14.58). This association was not significant in people without diabetes. Venular caliber did not predict incident retinopathy. Our findings suggest that retinal arteriolar dilatation is a specific sign of diabetic microvascular dysfunction and may be a preclinical marker of diabetic retinopathy.

**E**merging evidence suggests that quantitative assessment of retinal vascular caliber may provide prognostic information regarding the risk of diabetic microvascular complications such as retinopathy (1-4). Wider retinal arterioles were shown to predict the incidence (1) and progression (2) of diabetic retinopathy, in keeping with experimental work that indicates a role for retinal arteriolar dilatation in the pathogenesis of diabetic retinopathy (5). According to the laws of Starling and Laplace, retinal arteriolar dilatation causes a rise in capillary pressure, which in turn can lead to capillary wall dilatation (microaneurysm), leakage (edema), and rupture (hemorrhage), which are classical signs of diabetic retinopathy (6-8).

However, not all studies have reported an association of retinal arteriolar dilatation with risk of retinopathy (4). Reasons for these inconsistencies are not apparent but could be related to imprecise diagnosis of diabetes (i.e., not based on oral glucose tolerance test). Additional studies are clearly indicated. Here, we examined the relationship of retinal vascular caliber and 5-year incident retinopathy in the Australian Diabetes, Obesity and Lifestyle (AusDiab) study.

## RESEARCH DESIGN AND METHODS

Detailed methodology for the AusDiab study has been described (9-14). Diabetes was defined based on oral glucose tolerance test using WHO recommendations. Of the original cohort (n=2476), 906 participants were included in the current analyses (see **Online Appendix** available at <http://care.diabetesjournals.org>). At baseline and the 5-year follow-up visits, retinal photographs were taken of both eyes using a non-mydratic digital fundus camera, one centered on the optic disc and the other on the macula (9-11), which were viewed on color monitors. A single trained grader, masked to participants' characteristics,

graded all photographs according to the simplified version of the Wisconsin grading system (15). Incident retinopathy was defined as presence of retinal microaneurysm(s) and/or hemorrhage(s) at the 5-year examination. All retinopathy cases were adjudicated by a retinal specialist. Retinal vascular caliber was measured from baseline photographs of the left eye by trained graders according to a standardized protocol (16-19) (see **Online Appendix**).

Logistic regression was used to determine the odds of retinopathy in persons with wider retinal arteriolar or venular caliber, defined as widest quartile versus remaining three-quarters, with adjustment for age, gender, BMI, systolic blood pressure, HbA1c and cholesterol. Both arteriolar and venular calibers were modeled simultaneously (20). Stratified analysis by diabetes status was also performed. All analyses were performed using Intercooled Stata 9.0 (StataCorp, College Station, TX).

## RESULTS

Of the 906 participants, 250 (27.7%) had diabetes (7 were type 1) and 455 (50.4%) had IFG or IGT. After 5 years of follow-up, 27 (3.0%) participants had developed retinopathy: 20 (8.0%) in the diabetes group, 3 (0.7%) in the IFG/IGT group and 4 (2.0%) of those with normal glucose levels.

The **Table** shows that after adjusting for age, gender, venular caliber, BMI, systolic blood pressure, HbA1c and cholesterol, wider retinal arteriolar caliber was associated with 5-year incident retinopathy (OR=4.79). This association was significant in people with diabetes only (OR=2.68 in non-diabetic participants; 95% CI: 0.38, 18.96). In supplementary analysis after excluding participants with type 1 diabetes (n=7), the direction of association was similar but not statistically significant (multivariable-adjusted OR=3.41; 95% CI: 0.69, 16.80). Wider retinal venular caliber was not associated with incident retinopathy.

## **CONCLUSION**

Our study shows that wider retinal arteriolar caliber predicts an excess risk of retinopathy independent of blood pressure, glycemic control and other retinopathy risk factors. This association was significant among subjects with diabetes, but attenuated in analysis conducted in subjects with type 2 diabetes only. The attenuation in this association could suggest either a reduced study power or a stronger association in subjects with type 1 than type 2 diabetes. We did not observe associations between venular caliber and incident retinopathy in this sample.

Our findings are supported by other studies. A case-control study in children and adolescents with type 1 diabetes reported an association of wider retinal arterioles with incident retinopathy (1). Wider retinal arterioles were also associated with 4-year progression of retinopathy in younger-onset diabetes in the Wisconsin Epidemiological Study of Diabetic Retinopathy (WESDR), although the positive association with incident retinopathy was not statistically significant (2). More recent WESDR data from older adults with type 2 diabetes also demonstrated an association of wider retinal arterioles with incident retinopathy (4,7). The lack of association seen in people without diabetes in our study may suggest that retinal arteriolar dilation is a specific indicator of diabetic microvascular damage and is not a preclinical marker of non-diabetic retinopathy.

Our study provides further support for the hypothesis that retinal arteriolar dilatation plays an important role in the pathogenesis of developing retinopathy in persons with diabetes. Experimental studies indicate that an increase in retinal blood

flow and associated arteriolar dilatation are frequent in the retina of people with diabetes, that may reflect underlying arteriolar autoregulation dysfunction (5). This could be due to hyperglycemia-mediated endothelin-1 resistance and calcium influx channel inhibition in smooth muscle cells. These processes could impair retinal arteriolar constriction and could also augment retinal arteriolar dilatatory response by reducing oxygen tension from retinal capillary non-perfusion (5). Conversely, retinal venular dilation may represent a later sign of diabetic retinopathy explaining why no consistent relationships with the development of early retinopathy have been found (1,4), whilst there is some evidence of associations with progression of retinopathy (2).

Strengths of our study include its prospective design, population-based sample, and use of validated methods in measuring retinal vascular caliber. Potential limitations include selection bias due to the large proportion of excluded cases. Because retinopathy was not ascertained from 7-field retinal photographs, there may also be an underestimation of both retinopathy prevalence and incidence. Finally, the number with incident diabetic retinopathy was relatively small in this sample limiting the power and precision of our risk estimates.

In summary, we show that retinal arteriolar dilatation, measured from retinal photographs, may be a preclinical marker of early diabetic retinopathy. Further research and developments in retinal image analysis may offer the potential for this technique to improve risk stratification of this blinding condition in people with diabetes.

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**TABLE.** Association between Retinal Vascular Caliber and 5-year Incident Retinopathy in the AusDiab Study.

		N	Incidence (%)	Age-gender-adjusted OR (95%CI)*	<i>p</i>	Multivariable-adjusted OR (95%CI)†	<i>p</i>
Retinal Arteriolar	All participants						
Caliber	Narrower 75% (<191.0 μm)	679	2.7	1.0	--	1.0	--
	Widest 25% (≥191.0 μm)	227	4.0	3.62 (1.42, 9.25)	0.007	4.79 (1.57, 14.58)	0.006
	Participants with diabetes						
	Narrower 75% (<189.0 μm)	187	7.0	1.0		1.0	
	Widest 25% (≥189.0 μm)	63	11.1	3.52 (1.12, 10.99)	0.031	5.21 (1.24, 21.88)	0.024
Retinal Venular	All participants						
Caliber	Narrower 75% (<220.9 μm)	679	3.4	1.0	--	1.0	--
	Widest 25% (≥220.9 μm)	227	1.8	0.68 (0.22, 2.12)	0.501	0.77 (0.23, 2.60)	0.670
	Participants with diabetes						
	Narrower 75% (<219.0 μm)	187	9.1	1.0		1.0	
	Widest 25% (≥219.0 μm)	63	4.8	0.59 (0.15, 2.28)	0.442	0.47 (0.09, 2.40)	0.364

\*Adjusted for age and gender. Models for arteriolar caliber were adjusted for venular caliber, and vice versa.

†Adjusted for age, gender, systolic blood pressure, HbA1c, total cholesterol and BMI. Models for arteriolar caliber were adjusted for venular caliber, and vice versa.