SCIENTIFIC REPORT

Do retinopathy signs in non-diabetic individuals predict the subsequent risk of diabetes?

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Background/aims: Isolated retinopathy signs are common in non-diabetic individuals and have been shown to be associated with impaired glucose metabolism. In a cohort of people without diabetes, the association of these retinopathy signs and subsequent development of diabetes were examined.

Methods: A population based cohort study of 7992 people aged 49–73 years without diabetes was conducted. Retinal photographs of these participants were evaluated for the presence of retinopathy signs according to a standardised protocol. Incident cases of diabetes were identified prospectively.

Results: After a follow up of 3 years, 291 (3.6%) people developed incident diabetes. In the total cohort, retinopathy was not significantly associated with incident diabetes (4.7% *v* 3.6%, multivariable adjusted odds ratio (OR) 1.1, 95% confidence intervals (CI), 0.7 to 1.9). However, among participants with a positive family history of diabetes, retinopathy was associated with incident diabetes (10.4% *v* 4.8%, multivariable adjusted OR 2.3, 95% CI, 1.0 to 5.3). Among participants without a family history of diabetes, retinopathy was not associated with incident diabetes

Conclusions: In individuals with a family history of diabetes, retinopathy signs predict subsequent risk of clinical diabetes.

Isolated retinal microaneurysms and haemorrhages are some of the earliest visible lesions of retinopathy in people with diabetes.[1 2] In those without diabetes, the clinical significance of these retinopathy signs is less clear.[3] Population based studies indicate that retinopathy signs are common,[4 5] associated with hypertension,[6] and predict cardiovascular events.[7 8]

Few studies, however, have investigated if retinopathy is preclinical marker of diabetes. Previous cross sectional studies in non-diabetic individuals have shown that retinopathy signs are associated with impaired glucose metabolism,[9–12] but there are no prospective data linking retinopathy to subsequent risk of clinical diabetes. In the current study, we examined the predictive value of retinopathy signs to the incidence of diabetes.

MATERIALS AND METHODS

The Atherosclerosis Risk In Communities study is a population based cohort study that included 15 792 people 45–64 years of age selected from four US communities at baseline (1987–9).[13] Participants underwent follow up at 3 yearly intervals, and retinal photographs were taken at the third examination (1993–5). Of the 12 887 participants who returned for the third examination, we excluded 80 non-white, non-black participants, 2399 with prevalent diabetes, 1392 with no retinal photographs or ungradeable photographs, and 1024 who did not return for the fourth examination (1996–8), leaving 7992 for this study.[14] Institutional review boards at each study site and at the Fundus Photograph Reading Center at the University of Wisconsin, Madison, approved the study. Informed consent was obtained from all participants and the study was conducted in accordance with the Declaration of Helsinki.

The retinal photography procedure has been described.[14 15] Briefly, a non-mydriatic retinal photograph of one randomly selected eye was taken and graded for retinopathy according to standardised protocol. Retinopathy was defined as presence of microaneurysms, haemorrhages, cotton wool spots, and/or hard exudates.[15]

Incident diabetes mellitus was defined as participants with a fasting serum glucose of ⩾7.0 mmol/l, non-fasting glucose ⩾11.1 mmol/l, diabetic medications use or physician diagnosis of diabetes at the fourth visit.[14] An alternative definition of incident diabetes included the additional criterion of a 2 hour post-load serum glucose of ⩾11.1 mmol/l based on a 75 g oral glucose tolerance test at the fourth examination (this was not performed at the third examination).[14]

Participants underwent interview, physical examination, and laboratory investigations.[13] A positive family history of diabetes was defined by self report of diabetes in either biological parent. The mean arterial blood pressure (⅔ diastolic + ⅓ systolic), averaged over the first three examinations (that is, 6 year mean arterial blood pressure), was included as a covariate in the analysis.[7]

We used logistic regression to estimate odds ratio of incident diabetes according to retinopathy status, adjusting initially for other factors. We evaluated associations initially in the total cohort and then performed stratified analysis with a number of potential effect modifiers: family history of diabetes (absence, presence), hypertension (absence, presence), fasting glucose (<6.1, 6.1–6.9 mmol/l), and body mass index (<28, ⩾28 kg/m^2). We also formally tested for interactions by adding cross product terms in these models (for example, retinopathy × family history).

RESULTS

Participants with retinopathy (n = 381, 4.8%) were more likely to be men and be African-Americans, and to have higher systolic and diastolic blood pressure and higher fasting insulin levels than participants without retinopathy (all comparisons $p<0.05$, data not shown). Participants with and without retinopathy did not differ with respect to age, family history of diabetes, fasting glucose, body mass index, and cigarette smoking status ($p>0.05$, data not shown)

Over a median follow up of 3.5 years, 291 people developed incident diabetes. In the total cohort, retinopathy was not significantly associated with incident diabetes (table 1). However, when stratified by family history of diabetes, among participants with a positive family history, retinopathy was significantly associated with incident diabetes. This association was not present among participants without

Table 1 Incidence and odds ratio of diabetes mellitus, by retinopathy signs, in all people and stratified by family history of diabetes

Non-specific retinopathy	Numbers at risk	Incident diabetes*			Incident diabetes (alternative)*		
			Age, sex, race	Multivariate		Age, sex, race	Multivariate
		%	OR (95% CI)†	OR (95% CI)‡	%	OR (95% CI)†	OR (95% CI)‡
All people							
Absent	7,611	3.6	1.0	1.0	8.9	1.0	1.0
Present	381	4.7	1.2 (0.7 to 2.0)	1.1 (0.7 to 1.9)	10.9	1.2 (0.9 to 1.7)	1.1 (0.8 to 1.6)
No family history of diabetes							
Absent	5,961	3.2	1.0	1.0	8.3	1.0	1.0
Present	304	3.3	0.9 (0.4 to 1.7)	0.8 (0.4 to 1.6)	8.7	1.0 (0.6 to 1.5)	0.9 (0.5 to 1.3)
Family history of diabetes							
Absent	1,650	4.8	1.0	1.0	11.0	1.0	1.0
Present	77	10.4	2.5 (1.1 to 5.3)	2.3 (1.0 to 5.3)	19.5	2.1 (1.2 to 3.8)	2.0 (1.1 to 3.8)

*Incident diabetes defined as fasting serum glucose of ⩾7.0 mmol/l, casual glucose ⩾11.1 mmol/l, diabetic medications use, or physician diagnosis of diabetes. Alternative definition of incident diabetes includes these criteria or a 2 hour post-load serum glucose of ⩾11.1 mmol/l.
†Odds ratio (95% confidence interval) of incident diabetes, adjusted for age, sex, and race
‡Odds ratio (95% confidence interval) of incident diabetes, adjusted for age, sex, race, fasting glucose, fasting insulin, 6 year mean arterial blood pressure, and body mass index.

a family history of diabetes. The interaction between retinopathy and family history of diabetes was statistically significant ($p = 0.04$).

There were 713 cases of incident diabetes using the alternative definition. The pattern of associations was largely similar (table 1).

Other diabetes risk factors (hypertension, fasting glucose, body mass index) did not significantly modify the relation of retinopathy and incident diabetes (data not shown).

DISCUSSION

Overall, retinopathy was not associated with the 3 year incidence of diabetes. However, among those with a positive family history of diabetes, retinopathy predicted subsequent onset of clinical diabetes, independent of blood pressure, fasting glucose, fasting insulin, and body mass index.

Individuals with a family history of diabetes have been reported to have early abnormalities of glucose metabolism,[16] microvascular dysfunction,[17 18] and an increased risk of overt diabetes.[19 20] Previous studies have shown that retinopathy signs are common in people with impaired glucose metabolism.[9–12] Thus, among individuals with a family history of diabetes, retinopathy may be a marker of underlying abnormalities in glucose metabolism or microvascular disease.

The lack of association between retinopathy and incident diabetes among people without a family history of diabetes may be because retinopathy signs in these people reflect other pathogenic conditions (for example, hypertension).[3 6] It is also possible that the modification of the association of retinopathy and incident diabetes by family history is a chance finding.

Strengths of this study include a well characterised sample, masked evaluation of retinopathy, and standardised identification of incident diabetes. Limitations include the following. Firstly, retinopathy may be missed because of availability of only one eye for assessment. Secondly, the single glucose determination and relatively short follow up may have led to misclassification of diabetes. However, the fact that our results were similar with an alternative diabetes definition probably minimises misclassification.

In conclusion, in people with a family history of diabetes, retinopathy is predictive of subsequent risk of clinical diabetes independent of other risk factors.

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