Retinal Arteriolar Narrowing, Hypertension, and Subsequent Risk of Diabetes Mellitus

Tien Yin Wong, MD, PhD; Anoop Shankar, MD, MPH; Ronald Klein, MD, MPH; Barbara E. K. Klein, MD, MPH; Larry D. Hubbard, MAT

Background: Microvascular disease and hypertension have been linked with risk of diabetes mellitus. We examined the association of retinal arteriolar narrowing, a marker of chronic hypertension, with incident diabetes.

Methods: Prospective cohort study of 3251 nondiabetic persons aged 43 to 86 years living in Wisconsin. The diameters of retinal vessels were measured from baseline retinal photographs of participants. Retinal measurements were summarized as the retinal arteriole-to-venule ratio, with smaller ratios indicating narrower arteriolar diameters. Incident diabetes cases were ascertained at the 5-year and 10-year follow-up examinations.

Results: There were 249 incident diabetes cases. Participants with narrower retinal arteriolar diameters had a higher incidence of diabetes (cumulative incidences of 5.1%, 7.0%, 9.2%, and 11.7%, comparing decreasing quartiles of arteriole-to-venule ratio). After controlling for baseline casual blood glucose level, glycosylated hemoglobin level, body mass index, and other risk factors, retinal arteriolar narrowing was significantly associated with risk of incident diabetes (multivariable-adjusted relative risk, 1.53; 95% confidence interval, 1.03-2.27; comparing smallest to largest arteriole-to-venule ratio quartiles). Participants with both hypertension and retinal arteriolar narrowing had a 3-fold higher risk of incident diabetes (multivariable-adjusted relative risk, 3.41; 95% confidence interval, 1.66-6.98) than normotensive participants without arteriolar narrowing.

Conclusions: Retinal arteriolar narrowing is related to risk of incident diabetes. These data suggest a possible link between systemic arteriolar narrowing associated with hypertension and diabetes development.

Arch Intern Med. 2005;165:1060-1065

TYPE 2 DIABETES MELLITUS IS a significant public health problem in middle-aged and older people, affecting approximately 18 million people in the United States alone.[1] A clear understanding of the pathogenesis of diabetes is important, as it may provide new strategies for prevention and treatment.

Microvascular disease has been hypothesized as a possible pathogenic factor in diabetes development.[2,3] This hypothesis is largely based on observations of microvascular abnormalities, such as arteriolar narrowing and impaired microvascular blood flow, in the skin and skeletal muscles of persons with or at high risk of diabetes (eg, those with impaired glucose tolerance and a family history of diabetes).[4-6] However, most previous studies were cross-sectional and conducted in selected patient samples not readily applicable to the general community. Therefore, it is not known if small-vessel disease is prospectively related to subsequent risk of diabetes.

Hypertension, a common comorbid condition of diabetes, has been implicated as a risk factor for diabetes development.[7-9] However, the specific biological mechanisms responsible for this association remain uncertain.

The retinal blood vessels can easily be viewed and photographed. Narrowing of the retinal arterioles has been suggested to reflect microvascular changes related to chronically elevated blood pressure[10] and other processes.[11] The objective of this study was to examine the relationship of retinal arteriolar narrowing, hypertension, and subsequent risk of diabetes in a population-based cohort.

METHODS

STUDY POPULATION

The Beaver Dam Eye Study is a population-based cohort study in Wisconsin. The study population and research methods have been previously described.[12-14] In brief, a private cen-

Author Affiliations: Centre for Eye Research Australia, University of Melbourne, Melbourne, Victoria, and Singapore Eye Research Institute, National University of Singapore, Singapore (Dr Wong); and Department of Ophthalmology and Visual Sciences, University of Wisconsin, Madison (Drs Shankar, R. Klein, and B. E. K. Klein and Mr Hubbard).
Financial Disclosure: None.

sus of the population of Beaver Dam, Wis, was performed in 1987 and 1988. Of 5924 eligible individuals, 4926 participated in the baseline examination (1988-1990),[12] 3684 (81.1% of survivors) participated in the 5-year examination (1993-1995),[13] and 2764 (82.9% of survivors) participated in the 10-year examination (1998-2000).[14] Comparisons between participants and nonparticipants at each examination have been presented.[12-14] All data were collected with institutional review board approval, and informed consent was obtained from all participants.

For this study, 3251 nondiabetic individuals contributed data to the present analysis. Subjects in the following categories, which are not mutually exclusive, were excluded: those with prevalent diabetes at the baseline examination (n=218), those with missing casual glucose level (n=11), those with missing important covariate information (cigarette smoking [n=17], systolic or diastolic blood pressure [n=14], physical activity [n=16], and total or high-density lipoprotein cholesterol level [n=34]), and those with ungradable retinal photographs (n=295).

BASELINE RETINAL VESSEL DIAMETER

All participants had color retinal photographs taken of both eyes at baseline.[15] Methods for measuring retinal vessel diameters from these photographs have been published.[15] In brief, photographs of right eyes were digitized by a high-resolution scanner using standard settings. The diameters of all arterioles and venules coursing through a specified area 0.5 to 1 disc diameter surrounding the optic disc were measured using a computer imaging program. The program was based on microdensitometric techniques and measured the width of the blood column (generally equivalent to the width of the vessel lumen). Graders who were masked to participant characteristics performed this measurement. These measurements were combined into summary indexes, the central retinal arteriolar and venular equivalents, which represented the mean arteriolar and venular diameters of that eye, respectively.[16] These were also expressed as the retinal arteriole-to-venule ratio (AVR). The AVR compensated for possible magnification differences between eyes, and an AVR of 1.00 indicated that arteriolar diameters were, on average, the same as venular diameters in that eye, while a smaller AVR suggested narrower arterioles. Reproducibility of these retinal measurements has been previously reported, with intragrader and intergrader intraclass correlation coefficients ranging from 0.78 to 0.99.[15]

BASELINE HYPERTENSION STATUS

Blood pressure was measured at baseline with a random-zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol, and the mean of 2 measurements was used for analysis.[17] Hypertension was defined as systolic blood pressure of 140 mm Hg or higher, diastolic blood pressure of 90 mm Hg or higher, or the combination of a self-reported hypertension diagnosis and the use of antihypertensive medications.

INCIDENT DIABETES

At each examination, casual blood specimens were obtained. Serum glucose level was determined using the hexokinase method, and glycosylated hemoglobin level was determined using affinity chromatography.[18] Persons were defined as having diabetes based on a casual blood glucose level higher than 200 mg/dL (>11.1 mmol/L) or if they had a history of diabetes and were treated with insulin, oral hypoglycemic agents, or diet therapy.[18] Whenever the diagnosis was in doubt, primary care physicians of participants were consulted for confirmation of a history of diabetes and treatment. Persons with prevalent diabetes at baseline were excluded from the study, and incident diabetes was defined as cases identified at the 5-year or 10-year follow-up examination.

OTHER BASELINE VARIABLES

A standardized interview and examination were performed at each examination. Height and weight were measured to quantify the body mass index. Serum total cholesterol and high-density lipoprotein cholesterol levels were determined using enzymatic methods.[19] Questions were asked relating to physical activity, cigarette smoking, and alcohol consumption. Physical activity was defined as the frequency per week of physical exercise intense enough to work up a sweat. Cigarette smoking was defined as the number of pack-years of smoking and alcohol consumption as the number of ounces of alcohol per week.

STATISTICAL ANALYSIS

Retinal vessel data (the AVR and its components, arteriolar and venular diameters) were categorized into quartiles, with the first quartile indicating smaller diameters, and further analyzed as continuous variables (per standard deviation change in the AVR and arteriolar and venular diameters). Hypertension was defined as a binary variable (normotensive vs hypertensive). Systolic and diastolic blood pressure was categorized into quartiles and analyzed as a continuous variable (per 10–mm Hg change).

We used analysis of variance models and χ^2 tests to compare the relationship of various baseline characteristics in association with the AVR quartiles. Cox proportional hazards regression models (using the logistic approach to handle ties) were used to determine the relative risk of incident diabetes in relation to retinal arteriolar narrowing, baseline hypertension status, or baseline systolic and diastolic blood pressure levels. Initial models were adjusted for age and sex. In multivariable models, we included the following covariates: baseline casual blood glucose level, glycosylated hemoglobin level, body mass index, physical activity status, total and high-density lipoprotein cholesterol level, and cigarette smoking and alcohol consumption status. For analysis of retinal vessel diameter and incident diabetes, we also adjusted for systolic and diastolic blood pressure. We performed a subsidiary analysis of baseline AVR (independent variables) and the 10-year change in casual glucose levels and change in glycosylated hemoglobin levels (dependent variables) in multiple linear regression models, adjusting for similar covariates.

To examine the joint effects of hypertension and retinal vessel diameter on the risk of incident diabetes, we categorized participants into 8 groups (based on the combination of hypertension status and quartiles of the AVR). We examined the relative risk of diabetes in a particular group in comparison with the reference group (normotensive participants with an AVR in the fourth quartile).

RESULTS

Baseline characteristics of participants according to the AVR quartiles are shown in **Table 1**. Smaller AVR quartiles were significantly associated with older age; with higher levels of glucose, glycosylated hemoglobin, systolic blood pressure, diastolic blood pressure, and total cholesterol; with higher body mass index; with cigarette smoking; and with alcohol consumption.

Table 1. Baseline Characteristics of the Study Population

Characteristic	Retinal Arteriole-to-Venule Ratio				
	First Quartile (n = 801)	Second Quartile (n = 822)	Third Quartile (n = 818)	Fourth Quartile (n = 810)	*P* Value*
Age, mean, y	61.7	60.4	60.1	59.2	<.01
Male, %	49.6	49.2	48.9	46.2	.51
Annual family income, × $10 000	5.0	5.0	5.0	5.0	.82
Education, mean, y	12.2	12.1	12.4	12.2	.17
Casual blood glucose, mean, mg/dL	158.6	218.0	223.4	127.9	<.01
Glycosylated hemoglobin, mean, %	6.9	6.1	5.8	5.6	<.01
Systolic blood pressure, mean, mm Hg	128.8	127.4	127.2	125.7	<.05
Diastolic blood pressure, mean, mm Hg	78.6	78.2	76.7	76.8	<.01
Total cholesterol, mean, mg/dL	6.7	6.6	6.4	6.1	<.01
High-density lipoprotein cholesterol, mean, mg/dL	1.4	1.4	1.4	1.4	.03
Body mass index,† mean	28.7	28.4	27.8	27.1	<.01
Cigarette smoking, mean, pack-years	16.7	16.2	15.6	15.0	.02
Alcohol intake, mean, g/d	7.6	7.1	7.0	6.4	.04
Physical activity frequency >2 times/wk, %	17.2	18.1	19.2	19.4	.62

SI conversion factors: To convert glucose to millimoles per liter, multiply by 0.0555; to convert cholesterol to millimoles per liter, multiply by 0.0259.
*P value represents difference in characteristic by arteriole-to-venule ratio quartiles, using analysis of variance or χ^2 test as appropriate.
†Body mass index calculated as weight in kilograms divided by the square of height in meters.

There were 249 participants who developed incident diabetes during a 10-year period. Of these, 165 (66.3%) were identified from casual glucose measurements, 49 (19.7%) from a self-reported physician diagnosis of diabetes, 6 (2.4%) from antidiabetic medications, and 29 (11.6%) from a combination of 2 or more of these criteria.

After adjusting for age and sex, participants who subsequently developed incident diabetes had a significantly smaller baseline AVR (0.69 vs 0.73, $P<.001$) and smaller mean retinal arteriolar diameters (168.1 vs 173.6 µm, $P<.001$), compared with participants who did not develop diabetes. In contrast, the baseline mean retinal venular diameter was similar among participants who did and did not develop diabetes (242.8 vs 242.0 µm, $P=.12$).

The relative risk of diabetes in relation to retinal AVR, as well as arteriolar and venular diameters, is shown in **Table 2**. The cumulative incidence of diabetes increased with decreasing AVR (cumulative incidences of 5.1%, 7.0%, 9.2%, and 11.7%, comparing decreasing quartiles of the AVR). After controlling for age and sex, smaller AVR was associated with a higher risk of diabetes. Further adjustment for diabetes risk factors had minimal effect on this association. When analyzed as a continuous variable, each standard deviation decrease in the retinal AVR (a decrease of 0.07) was associated with a 16% increase in risk of diabetes. The association for retinal arteriolar diameter was essentially similar to that for the AVR, but baseline retinal venular diameter was unrelated to incident diabetes.

Multiple linear regression models of the retinal AVR and the 10-year change in casual glucose and glycosylated hemoglobin levels are shown in **Table 3**. After controlling for risk factors, lower baseline AVR was associated with a greater increase in casual glucose and glycosylated hemoglobin levels. The multivariable model R^2 value ranged from 0.53 (casual glucose model) to 0.42 (glycosylated hemoglobin model). The R^2 value increment associated with dropping the variable AVR from these models ranged from 0.07 (casual glucose model) to 0.05 (glycosylated hemoglobin model) ($P<.01$ for both, F test).

The incidence of diabetes in relation to baseline hypertension status, systolic blood pressure, and diastolic blood pressure is shown in **Table 4**. Baseline hypertension, higher systolic blood pressure, and higher diastolic blood pressure were independently associated with increased risk of diabetes, after controlling for diabetes risk factors.

The **Figure** shows results of the analysis of the joint effects of hypertension status and retinal AVR on the risk of diabetes. After controlling for risk factors, persons with hypertension and an AVR in the first quartile were 3 times (multivariable-adjusted relative risk, 3.41; 95% confidence interval, 166-6.98) as likely to develop incident diabetes as normotensive people with an AVR in the fourth quartile.

COMMENT

In this population-based prospective cohort study, retinal arteriolar narrowing and hypertension were independently associated with an increased risk of incident diabetes. After controlling for possible diabetes risk factors, participants with narrower retinal arteriolar diameters were more likely to develop diabetes than participants with larger retinal arteriolar diameters, and participants who were hypertensive at baseline were more likely to develop diabetes than those who were normotensive. There was a joint effect of hypertension and retinal arteriolar narrowing on the risk of diabetes, and hypertensive participants with retinal arteriolar narrowing were 3 times more likely to develop incident diabetes than normotensive participants without arteriolar narrowing.

Histopathologically, the retinal arterioles undergo a series of pathophysiological changes in response to elevated blood pressure.[20] Initially, arteriolar narrowing re-

Table 2. Relative Risk of Diabetes Mellitus in Relation to Retinal Vessel Diameters

Variable	AVR Range	No. at Risk	Incident Diabetes Mellitus		
			No. of Cases	Relative Risk (95% Confidence Interval)*	Multivariable Relative Risk (95% Confidence Interval)†
Retinal AVR					
First quartile	0.50-0.67	801	87	1.71 (1.17-2.51)	1.53 (1.03-2.27)
Second quartile	0.68-0.71	822	69	1.52 (1.03-2.24)	1.36 (0.91-2.04)
Third quartile	0.72-0.75	818	54	1.35 (0.90-2.01)	1.24 (0.83-1.87)
Fourth quartile	0.76-1.04	810	39	1.00 (Referent)	1.00 (Referent)
1-SD decrease	NA	**3251**	**249**	1.24 (1.12-1.37)	1.16 (1.02-1.32)
Retinal arteriolar diameter, μm					
First quartile	103.2-163.0	808	87	1.67 (1.14-2.46)	1.47 (0.99-2.18)
Second quartile	163.1-171.8	819	68	1.47 (0.99-2.18)	1.24 (0.83-1.87)
Third quartile	171.9-182.9	814	55	1.33 (0.89-1.99)	1.17 (0.77-1.78)
Fourth quartile	183.0-229.4	810	39	1.00 (Referent)	1.00 (Referent)
1-SD decrease	NA	**3251**	**249**	1.21 (1.07-1.37)	1.11 (1.00-1.23)
Retinal venular diameter, μm					
First quartile	166.4-227.4	802	59	1.10 (0.71-1.43)	1.03 (0.73-1.46)
Second quartile	227.5-242.3	814	61	0.95 (0.67-1.35)	0.92 (0.64-1.31)
Third quartile	242.4-257.6	821	60	1.01 (0.71-1.43)	0.94 (0.66-1.34)
Fourth quartile	257.7-357.8	814	69	1.00 (Referent)	1.00 (Referent)
1-SD decrease	NA	**3251**	**249**	1.03 (0.92-1.15)	0.99 (0.89-1.10)

Abbreviation: AVR, arteriole-to-venule ratio NA, not applicable.
*Adjusted for age and sex.
†Adjusted for age, sex, casual blood glucose level, glycosylated hemoglobin level, systolic and diastolic blood pressure, body mass index, physical activity status, total and high-density lipoprotein cholesterol levels, and cigarette smoking and alcohol consumption status.

Table 3. Ten-Year Change in Casual Blood Glucose and Glycosylated Hemoglobin Levels in Relation to Baseline Retinal Arteriole-to-Venule Ratio (AVR) Among the 3251 Study Participants

Independent Variable of Retinal AVR	Casual Blood Glucose, mg/dL		Glycosylated Hemoglobin, %	
	β (SE)*	*P* Value	β (SE)*	*P* Value
Adjusted for age and sex	−1.65 (0.14)	<.01	−1.56 (0.12)	<.01
Multivariable adjusted†	−1.37 (0.16)	<.01	−1.29 (0.18)	<.01

SI conversion factor: To convert glucose to millimoles per liter, multiply by 0.0555.
*Log transformed, with standard error (SE) of the slope estimate (β) of the regression equation.
†Adjusted for age, sex, baseline casual blood glucose level, glycosylated hemoglobin level, systolic and diastolic blood pressure, body mass index, physical activity status, total and high-density lipoprotein cholesterol levels, and cigarette smoking and alcohol consumption status.

flects an active vasoconstriction phase secondary to local autoregulatory mechanisms. Persistently elevated blood pressure leads to intimal thickening, media wall hyperplasia, and hyaline degeneration in the arteriolar walls. It has previously been demonstrated that retinal arteriolar narrowing, assessed from photographs, is related not only to concurrently measured blood pressure[10,15,21] but also to blood pressure measured 6 to 8 years previously,[10,21] suggesting an association with chronic hypertension. In addition, independent of blood pressure, retinal arteriolar narrowing has been associated with systemic markers of inflammation and endothelial dysfunction.[11]

There are few relevant studies for comparison. In the Atherosclerosis Risk in Communities Study, retinal arteriolar narrowing was associated with a 70% increased odds of diabetes ascertained after 3 years.[22] However, that study was limited by a short follow-up (3 years), a study population with a narrow age range (age range, 49-73 years), and the possibility of selection biases, because retinal photography was only performed 6 years into the study. The present study of persons aged 43 to 86 years, with photography at baseline and incident diabetes cases identified after more than 10 years of follow-up, provides stronger prospective evidence of narrowed retinal arteriolar diameter preceding diabetes development.

Specific mechanisms that could explain an association of retinal arteriolar narrowing with incident diabetes are not known, but it is possible that this reflects the role of microvascular disease in type 2 diabetes pathogenesis. Previous studies have suggested functional microcirculatory changes, estimated typically from microvascular reactivity and blood flow in the skin and skeletal muscles in persons at high risk of developing diabetes (eg, persons with impaired glucose tolerance and first-degree relatives of persons with diabetes)[4-6] and in persons with type 2 diabetes.[23,24] These changes have been further hypothesized to be related to abnormalities in the capillary and arteriolar endothelium, which is in con-

Table 4. Relative Risk of Diabetes Mellitus in Relation to Baseline Hypertension Status and Systolic and Diastolic Blood Pressure

Variable	Blood Pressure Range	No. at Risk	Incident Diabetes Mellitus		
			No. of Cases	Relative Risk (95% Confidence Interval)*	Multivariable Relative Risk (95% Confidence Interval)†
Hypertension status					
Normotensive	NA	2189	129	1.00 (Referent)	1.00 (Referent)
Hypertensive	NA	1062	120	2.01 (1.58-2.56)	1.71 (1.33-2.20)
Baseline systolic blood pressure, mm Hg					
First quartile	78-122	805	32	1.00 (Referent)	1.00 (Referent)
Second quartile	135-159	822	55	1.19 (0.76-1.86)	1.13 (0.71-1.78)
Third quartile	160-181	823	70	1.54 (1.01-2.36)	1.42 (0.92-2.19)
Fourth quartile	182-252	801	92	1.86 (1.23-2.81)	1.64 (1.08-2.51)
10–mm Hg increase	NA	**3251**	**249**	1.40 (1.26-1.56)	1.27 (1.12-1.44)
Baseline diastolic blood pressure, mm Hg					
First quartile	42-70	802	37	1.00 (Referent)	1.00 (Referent)
Second quartile	71-82	818	58	1.22 (0.80-1.86)	1.13 (0.72-1.71)
Third quartile	83-89	820	72	1.48 (0.99-2.22)	1.22 (0.80-1.85)
Fourth quartile	88-132	811	82	1.71 (1.15-2.53)	1.36 (0.90-2.06)
10–mm Hg increase	NA	**3251**	**249**	1.35 (1.21-1.51)	1.19 (1.07-1.32)

Abbreviation: NA, not applicable.
*Adjusted for age and sex.
†Adjusted for age, sex, retinal arteriole-to-venule ratio, casual blood glucose level, glycosylated hemoglobin level, body mass index, physical activity status, total and high-density lipoprotein cholesterol levels, and cigarette smoking and alcohol consumption status.

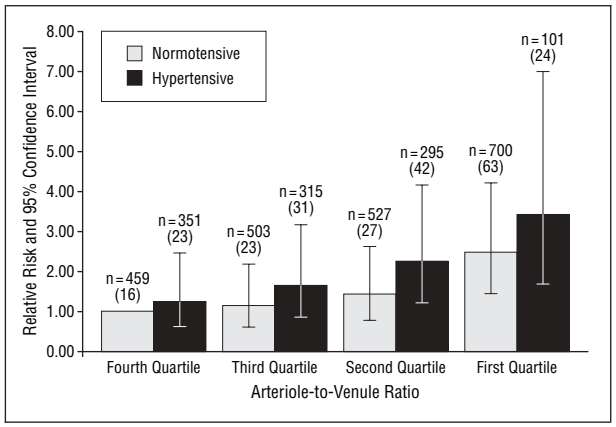

Figure. Joint effects of baseline retinal arteriole-to-venule ratio and hypertension status on the risk of diabetes mellitus among the 3251 study participants. Adjusted for age, sex, casual blood glucose level, glycosylated hemoglobin level, body mass index, physical activity status, total and high-density lipoprotein cholesterol levels, and cigarette smoking and alcohol consumption status. The n values represent number at risk (number of incident diabetes cases). The first bar is the reference group; hence, no confidence interval required.

tact with metabolically active, insulin-sensitive tissues such as skeletal muscles.[25] Endothelial dysfunction and impaired nitric oxide–mediated vasodilatation have been further hypothesized to directly lead to reduced insulin delivery to skeletal muscles, resulting in peripheral insulin resistance and hyperglycemia.[26] However, although an attractive hypothesis to explain our study findings, the role of skeletal blood flow as a pathophysiological factor in insulin resistance and diabetes pathogenesis has not been firmly established.[27-29] Furthermore, to our knowledge, there are no studies that have shown that the microvascular changes in the skin and skeletal muscles are similar to arteriolar narrowing in the eye.

Our study provides new insights into the relationship of hypertension and risk of type 2 diabetes. We demonstrated that elevated blood pressure was independently associated with risk of incident diabetes, consistent with findings of other studies.[7-9] Furthermore, preexisting hypertension and narrowed arterioles appear to be associated with a risk of diabetes that is greater than the effect of either factor alone. This is compatible with findings that functional microvascular changes (eg, increased arteriolar resistance and reduced blood flow in the skin) in persons with diabetes are accentuated in the presence of hypertension.[30] Therefore, arteriolar narrowing, possibly reflecting the effects of chronic hypertension, may provide the common link to diabetes development. In this regard, clinical trials have demonstrated that a reduction in blood pressure with certain antihypertensive agents is associated with a reduction in incident diabetes.[31,32] It is not clear whether one of the mechanisms for this finding is the vasodilating effect of these agents on the microvasculature.

The strengths of the present study include its population-based nature, quantitative evaluation of retinal arteriolar diameters, standardized identification of incident diabetes cases, and detailed information on risk factors. Study limitations should be highlighted. First, the loss to follow-up may have resulted in differential mortality, which may have masked or accentuated these associations. For example, if persons with reduced arteriolar diameters at risk of developing diabetes were more likely to die before the follow-up examinations, these associations could be falsely attenuated. Second, given the imprecision of casual glucose and glycosylated hemoglobin levels, misclassification of diabetes status may occur. This is especially worrisome in that those in the category of smallest arteriolar diameter had

high glucose and glycosylated hemoglobin levels. If there is selective misclassification of diabetes at baseline in which the diabetic participants are mislabeled as nondiabetic and have narrower arterioles, this might partly account for our findings.

In conclusion, data from this population-based study show a prospective association of retinal arteriolar narrowing and hypertension with incident diabetes , independent of known risk factors. These data suggest that arteriolar narrowing, possibly related to chronic hypertension, may be associated with the development of type 2 diabetes. If this finding is supported by further studies, microvascular disease may be a potential target for diabetes prevention.

Accepted for Publication: January 19, 2005.
Correspondence: Tien Yin Wong, MD, PhD, Centre for Eye Research Australia, University of Melbourne, 32 Gisborne St, East Melbourne 3002, Victoria, Australia (twong@unimelb.edu.au).
Funding/Support: This study was supported by the American Diabetes Association, Alexandria, Va (Drs Shankar and R. Klein); by grants EY06594 (Drs R. Klein and B. E. K. Klein) and HL66018 (Drs Wong and R. Klein) from the National Institutes of Health, Bethesda, Md; and by a Biomedical Council Young Investigator Award, Singapore (Dr Wong).

REFERENCES

1. Centers for Disease Control and Prevention. *National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2002*. Atlanta, Ga: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2003.
2. Tooke JE. Microvascular function in human diabetes: a physiological perspective. *Diabetes*. 1995;44:721-726.
3. Hsueh WA, Law RE. Diabetes is a vascular disease. *J Investig Med*. 1998;46:387-390.
4. Jaap AJ, Shore AC, Tooke JE. Relationship of insulin resistance to microvascular dysfunction in subjects with fasting hyperglycaemia. *Diabetologia*. 1997; 40:238-243.
5. Jaap AJ, Hammersley MS, Shore AC, Tooke JE. Reduced microvascular hyperaemia in subjects at risk of developing type 2 (non–insulin-dependent) diabetes mellitus. *Diabetologia*. 1994;37:214-216.
6. Caballero AE, Arora S, Saouaf R, et al. Microvascular and macrovascular reactivity is reduced in subjects at risk for type 2 diabetes. *Diabetes*. 1999;48:1856-1862.
7. Medalie JH, Papier CM, Goldbourt U, Herman JB. Major factors in the development of diabetes mellitus in 10,000 men. *Arch Intern Med*. 1975;135:811-817.
8. Haffner SM, Stern MP, Hazuda HP, Mitchell BD, Patterson JK. Cardiovascular risk factors in confirmed prediabetic individuals: does the clock for coronary heart disease start ticking before the onset of clinical diabetes? *JAMA*. 1990;263: 2893-2898.
9. Gress TW, Nieto FJ, Shahar E, Wofford MR, Brancati FL. Hypertension and antihypertensive therapy as risk factors for type 2 diabetes mellitus: Atherosclerosis Risk in Communities Study. *N Engl J Med*. 2000;342:905-912.
10. Sharrett AR, Hubbard LD, Cooper LS, et al. Retinal arteriolar diameters and elevated blood pressure: the Atherosclerosis Risk in Communities Study. *Am J Epidemiol*. 1999;150:263-270.
11. Klein R, Sharrett AR, Klein BE, et al. Are retinal arteriolar abnormalities related to atherosclerosis? the Atherosclerosis Risk in Communities Study. *Arterioscler Thromb Vasc Biol*. 2000;20:1644-1650.
12. Klein R, Klein BEK, Linton KLP, DeMets DL. The Beaver Dam Eye Study: visual acuity. *Ophthalmology*. 1991;98:1310-1315.
13. Klein R, Klein BEK, Lee KE. The changes in visual acuity in a population: the Beaver Dam Eye Study. *Ophthalmology*. 1996;103:1169-1178.
14. Klein R, Klein BE, Lee KE, Cruickshanks KJ, Chappell RJ. Changes in visual acuity in a population over a 10-year period: the Beaver Dam Eye Study. *Ophthalmology*. 2001;108:1757-1766.
15. Wong TY, Klein R, Klein BEK, Meuer SM, Hubbard LD. Retinal vessel diameters and their associations with age and blood pressure. *Invest Ophthalmol Vis Sci*. 2003;44:4644-4650.
16. Knudtson MD, Lee KE, Hubbard LD, Wong TY, Klein R, Klein BEK. A revised method for summarizing retinal vessel diameters. *Curr Eye Res*. 2003;27:143-149.
17. Hypertension Detection and Follow-up Program Cooperative Group. The Hypertension Detection and Follow-up Program. *Prev Med*. 1976;5:207-215.
18. Klein R, Klein BEK, Moss SE, Linton KLP. The Beaver Dam Eye Study: retinopathy in adults with newly discovered and previously diagnosed diabetes mellitus. *Ophthalmology*. 1992;99:58-62.
19. Klein R, Klein BEK. *Beaver Dam Eye Study: Manual of Operations*. Madison: Dept of Ophthalmology, University of Wisconsin–Madison; 1991.
20. Tso MO, Jampol LM. Pathophysiology of hypertensive retinopathy. *Ophthalmology*. 1982;89:1132-1145.
21. Wong TY, Hubbard LD, Klein R, et al. Retinal microvascular abnormalities and blood pressure in older people: the Cardiovascular Health Study. *Br J Ophthalmol*. 2002;86:1007-1013.
22. Wong TY, Klein R, Sharrett AR, et al. Retinal arteriolar narrowing and risk of diabetes in middle-aged persons. *JAMA*. 2002;287:2528-2533.
23. Morris SJ, Shore AC, Tooke JE. Responses of the skin microcirculation to acetylcholine and sodium nitroprusside in patients with NIDDM. *Diabetologia*. 1995; 38:1337-1344.
24. Laakso M, Edelman SV, Brechtel G, Baron AD. Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. *Diabetes*. 1992;41:1076-1083.
25. Hu FB, Stampfer MJ. Is type 2 diabetes mellitus a vascular condition? *Arterioscler Thromb Vasc Biol*. 2003;23:1715-1716.
26. Balletshofer BM, Rittig K, Enderle MD, et al. Endothelial dysfunction is detectable in young normotensive first-degree relatives of subjects with type 2 diabetes in association with insulin resistance. *Circulation*. 2000;101:1780-1784.
27. Clark MG, Wallis MG, Barrett EJ, et al. Blood flow and muscle metabolism: a focus on insulin action. *Am J Physiol Endocrinol Metab*. 2003;284:E241-E258. Available at: http://ajpendo.physiology.org/cgi/content/full/284/2/E241. Accessed February 14, 2005.
28. Laine H, Yki-Jarvinen H, Kirvela O, et al. Insulin resistance of glucose uptake in skeletal muscle cannot be ameliorated by enhancing endothelium-dependent blood flow in obesity. *J Clin Invest*. 1998;101:1156-1162.
29. Natali A, Bonadonna R, Santoro D, et al. Insulin resistance and vasodilation in essential hypertension: studies with adenosine. *J Clin Invest*. 1994;94:1570-1576.
30. Jaap AJ, Shore AC, Tooke JE. The influence of hypertension on microvascular blood flow and resistance to flow in the skin of patients with type 2 (non–insulin-dependent) diabetes. *Diabet Med*. 1994;11:883-887.
31. Yusuf S, Gerstein H, Hoogwerf B, et al; HOPE Study Investigators. Ramipril and the development of diabetes. *JAMA*. 2001;286:1882-1885.
32. Vermes E, Ducharme A, Bourassa MG, Lessard M, White M, Tardif JC; Studies of Left Ventricular Dysfunction. Enalapril reduces the incidence of diabetes in patients with chronic heart failure: insight from the Studies of Left Ventricular Dysfunction (SOLVD). *Circulation*. 2003;107:1291-1296.