Retinal Arteriolar Narrowing and Risk of Diabetes Mellitus in Middle-aged Persons

Tien Yin Wong, MD, MPH
Ronald Klein, MD, MPH
A. Richey Sharrett, MD, DrPH
Maria I. Schmidt, MD
James S. Pankow, PhD
David J. Couper, PhD
Barbara E. K. Klein, MD, MPH
Larry D. Hubbard, MAT
Bruce B. Duncan, MD, PhD
for the ARIC Investigators

Context Microvascular processes have been hypothesized to play a role in the pathogenesis of type 2 diabetes mellitus, but prospective clinical data regarding this hypothesis are unavailable.

Objective To examine the relation of retinal arteriolar narrowing, a marker of microvascular damage from aging, hypertension, and inflammation, to incident diabetes in healthy middle-aged persons.

Design, Setting, and Participants The Atherosclerosis Risk in Communities Study, an ongoing population-based, prospective cohort study in 4 US communities that began in 1987-1989. Included in this analysis were 7993 persons aged 49 to 73 years without diabetes, of whom retinal photographs were taken during the third examination (1993-1995).

Main Outcome Measures Incident diabetes (defined as fasting glucose levels of ≥126 mg/dL [7.0 mmol/L], casual levels of ≥200 mg/dL [11.1 mmol/L], diabetic medications use, or physician diagnosis of diabetes at the fourth examination) by quartile of retinal arteriole-to-venule ratio (AVR).

Results After a median follow-up of 3.5 years, 291 persons (3.6%) had incident diabetes. The incidence of diabetes was higher in persons with lower AVR at baseline (2.4%, 3.1%, 4.0%, and 5.2%, from highest to lowest AVR quartile; *P* for trend<.001). After controlling for fasting glucose and insulin levels, family history of diabetes, adiposity, physical activity, blood pressure, and other factors, persons in the lowest quartile of AVR were 71% more likely to develop diabetes than those in the highest quartile (odds ratio [OR], 1.71; 95% confidence interval [CI], 1.13-2.57; *P* for trend=.002). This association persisted with different diagnostic criteria (OR, 1.92; 95% CI, 1.10-3.36; *P* for trend=.01, using a fasting glucose level of ≥141 mg/dL [7.8 mmol/L] as a cutoff), and was seen even in people at lower risk of diabetes, including those without a family history of diabetes, without impaired fasting glucose, and with lower measures of adiposity.

Conclusions Retinal arteriolar narrowing is independently associated with risk of diabetes, supporting a microvascular role in the development of clinical diabetes.

JAMA. 2002;287:2528-2533 www.jama.com

TYPE 2 DIABETES MELLITUS AFfects up to 15 million persons in the United States and is a leading cause of morbidity and mortality in middle-aged persons.[1] Although the main physiological abnormalities are insulin resistance and hyperglycemia, the specific underlying mechanisms determining these changes remain uncertain.[2] Microvascular disease has been hypothesized to contribute to the development of diabetes.[2,3] This is based on studies that demonstrate microvascular abnormalities (eg, impaired microvascular reactivity and flow in the skin and skeletal muscles) in persons with type 2 diabetes[4,5] and in persons at high risk of developing diabetes, such as those with impaired glucose tolerance[6-8] and first-degree relatives of persons with diabetes.[8,9]

However, these studies are cross-sectional investigations among highly selected patient groups, often atypical of the general population.[4-9] Prospective or population-based data are unavailable, largely because changes in the microcirculation are difficult to evaluate outside of experimental settings.[10] The retinal arterioles offer an excellent opportunity to explore, noninvasively, the prognostic importance of microvascular disease.[11] In the Atherosclerosis Risk in Communities (ARIC) study, we developed a technique to quantify narrowing of the retinal arterioles, based on measuring their diameters on digitized photographs.[12] We have found retinal arteriolar narrowing to be strongly related to concurrent blood pressure and, independently, to past blood pressure,[13] markers of inflammation,[14] and risk of stroke.[15]

In this study, we examined the relation of retinal arteriolar narrowing to

Author Affiliations: Department of Ophthalmology, University of Wisconsin-Madison (Drs Wong, R. Klein, B. Klein, and Mr Hubbard); Singapore National Eye Center and Department of Ophthalmology, National University of Singapore (Dr Wong); National Heart, Lung, and Blood Institute, Bethesda, Md (Dr Sharrett); Social Medicine Department, School of Medicine, Federal University of Rio Grande do Sul, Porto Alegre RS, Brazil (Drs Schmidt and Duncan); Division of Epidemiology, University of Minnesota, Minneapolis (Dr Pankow); and Department of Biostatistics, University of North Carolina, Chapel Hill (Dr Couper). **A Complete Listing of the ARIC Investigators** was published previously (*Am J Epidemiol*. 1989;129:687-702). **Corresponding Author and Reprints:** Tien Yin Wong, MD, MPH, Department of Ophthalmology, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260 (e-mail: ophwty@nus.edu.sg).

incident diabetes in middle-aged persons free of this condition in the ARIC study.

METHODS

Study Population

The ARIC study[16] included 15 792 women and men 45 to 64 years of age at recruitment in 1987 through 1989. Population samples were selected from 4 US communities: Forsyth County, North Carolina; Jackson, Miss (black participants only); suburbs of Minneapolis, Minn; and Washington County, Maryland. Participants underwent 3 yearly follow-up examinations, in 1990 through 1992 (93% return rate), 1993 through 1995 (86% return rate), and 1996 through 1998 (81% return rate).

Retinal photographs were taken at the third examination (1993-1995).[12] Of the 12 887 participants who returned for this examination, we excluded 38 whose race was neither black nor white, 42 nonwhite residents in Minneapolis and Maryland (to permit stratification by race and field center), 2399 with prevalent diabetes, and 19 with retinal vascular occlusions, leaving 10 389 eligible for this study. Of these, 1372 had no retinal photographs or ungradable photographs and 1024 did not return for the fourth examination (1996-1998) or had incomplete data to confirm a new diagnosis of diabetes, leaving 7993 who provided data for this study. Comparisons of characteristics between participants included (n=7993) and excluded (n=2396) indicated that those included were younger and more likely to be white, had lower systolic and diastolic blood pressures, and lower fasting glucose levels, body mass indexes (BMIs), and waist-hip ratios (data not shown).

Measurement of Retinal Arteriolar Narrowing

The retinal photography procedure has been described previously.[12] Briefly, photographs of the retina were taken of 1 randomly selected eye after 5 minutes of dark adaptation. These photographs were digitized by a high-resolution scanner and the diameters of individual arterioles and venules coursing through a specified zone surrounding the optic disc were measured on the computer monitor by trained graders masked to subject identity.[12] The individual arteriolar and venular diameters were combined into summary measures and expressed as an arteriole-to-venule ratio (AVR).[12] The AVR accounts for magnification differences between photographs and is distributed normally in the general population.[12] An AVR of 1.0 indicates that, on average, retinal arteriolar diameters are the same as venular diameters, while a smaller AVR represents narrower arterioles, since venular diameters vary little.[12,13] The intragrader and intergrader reliability coefficients for AVR were 0.84 and 0.79, respectively.[12]

Trained graders also evaluated retinal photographic slides for focal lesions, including signs typical of diabetic retinopathy (eg, microaneurysms, retinal hemorrhages), arteriovenous nicking, and focal arteriolar narrowing, according to a standardized protocol.[12] These lesions were defined as present if graded as either definite or probable. Intragrader and intergrader κ statistics ranged from 0.61 to 1.00.[12]

Ascertainment of Diabetes Mellitus

Methods of ascertainment and diagnosis of diabetes in the ARIC study have been previously published.[17] Participants were asked to fast for at least 12 hours before morning blood collection. Glucose was processed via a modified hexokinase/glucose-6-phosphate dehydrogenase procedure.

Diabetes mellitus was defined if any of the following criteria, adapted from the 1997 American Diabetes Association guidelines,[18] were met: fasting ($\geq$8 hours) serum glucose levels of at least 126 mg/dL (7.0 mmol/L), casual (fasting <8 hours) glucose levels of at least 200 mg/dL (11.1 mmol/L), use of diabetic medications, or physician-diagnosed diabetes. Individuals were defined as having incident diabetes if they did not develop diabetes through the third examination but met any of these criteria at the fourth examination.

Definition of Other Variables

Participants underwent an extensive interview, physical examination, and laboratory investigations. Race was self-reported. A positive family history of diabetes was defined by participant report of diabetes in either biological parent. Physical activity was characterized by sports and leisure activity indexes (range, 0-5) described elsewhere.[19] Blood pressure was taken with a random-zero sphygmomanometer and the mean of the last 2 measurements was used. Mean arterial blood pressure was computed as two thirds of the diastolic value plus one third of the systolic value, and the average of this over the first 3 examinations (ie, 6-year mean arterial blood pressure) was included as a covariate in the assessment of the independence of retinal arteriolar narrowing with incident diabetes.[14,15] Height and weight were taken with participants in scrub suits and BMI was calculated. Waist-hip ratio was computed as the circumference of the waist (umbilical level) divided by the hips (maximum buttocks). Blood collection and processing for fasting insulin, total cholesterol, high-density lipoprotein cholesterol, triglycerides, white blood cell count (WBC), plasma fibrinogen, factor VIII, and von Willebrand factor (vWF) are described elsewhere.[20] Average internal carotid intima-media wall thickness (IMT) was obtained from standardized B-mode ultrasonograms.[21] All variables were measured at the third examination, except for insulin, WBC, fibrinogen, factor VIII, vWF, and carotid IMT, which were measured at the first examination, and mean arterial blood pressure, which was averaged over the first 3 examinations.

Statistical Methods

The AVR was categorized into quartiles (with the first quartile indicating the most severe arteriolar narrowing and the fourth the least) and also analyzed as a continuous variable (per 1-SD difference in AVR). We used analysis of covariance to compare the AVR and its components (summary measures of reti-

nal arteriolar and venular diameters) between persons who did and did not develop diabetes. We used logistic regression models to estimate the odds ratios (ORs) and 95% confidence intervals (CIs) of incident diabetes, comparing a given quartile of AVR vs the fourth quartile or a 1-SD difference in AVR. We initially adjusted for age (years), sex, race, and field center. In multivariable models, we additionally adjusted for 6-year mean arterial blood pressure, fasting glucose levels, fasting insulin levels, family history of diabetes, BMI, waist-hip ratio, sports and leisure activity indexes, high school education, pack-years of cigarette smoking, alcohol consumption status (ever, never), total and high-density lipoprotein cholesterol levels, and triglyceride levels. In a separate model, we also adjusted for WBC (1000 cells/mm^3), plasma fibrinogen, factor VIII, vWF, and carotid IMT, since these are possible confounders.[14]

We performed the following supplementary analyses. First, we used a higher cutoff (≥141 mg/dL [7.8 mmol/L]) for the fasting glucose value required for the diagnosis of diabetes (alternate diabetes definition). Second, we repeated analyses excluding persons with signs typical of diabetic retinopathy (eg, microaneurysms), since these persons may have preexisting diabetes. Third, we evaluated associations separately in persons with and without impaired fasting glucose levels (110-124 mg/dL [6.1-6.9 mmol/L]) at the third examination and tested interactions with other diabetes risk factors by stratification and by inclusion of cross-product terms in the logistic regression.

RESULTS

The baseline mean AVR in the population was 0.843 (SD, 0.08; median, 0.844; range, 0.57-1.22). TABLE 1 compares baseline characteristics of persons with retinal AVR falling in the first quartile (0.57-0.79) with those in the fourth (0.91-1.22). In general, persons in the first compared with the fourth AVR quartile were older, more likely to be men and to be black, and, after adjusting for age, sex, race, and field center, more likely to have a poorer diabetes risk profile.

Over a median follow-up of 3.5 years (range, 0.7-5.5 years), 291 (3.6%) persons developed diabetes. The incidence of diabetes increased from 2.4% to 5.2% with decreasing quartiles of AVR (TABLE 2). After adjustment for age, sex, race, and field center, persons in the lowest compared with the highest AVR quartile were twice as likely to develop diabetes (OR, 2.09; 95% CI, 1.47-2.98). This association was attenuated but still significant after additional adjustment for fasting glucose and insulin levels, family history of diabetes, and other risk factors (OR, 1.71; 95% CI, 1.13-2.57). These associations were somewhat stronger when we used an alternate definition of incident diabetes (fasting glucose ≥141 mg/dL [7.8 mmol/L] used as the cutoff) (Table 2).

When persons with signs of diabetic retinopathy (n=382) were excluded, the association was similar (OR, 1.75; 95% CI, 1.15-2.66, comparing the first with the fourth AVR quartile). Further adjustment for WBC, plasma fibrinogen, factor VIII, vWF, and carotid IMT in the multivariable model resulted in a slightly stronger association (OR, 1.98; 95% CI, 1.15-3.41, comparing the first with the fourth AVR quartile).

The results of AVR analyzed as a continuous variable are presented in TABLE 3. Each 1-SD decrease in the AVR (a decrease of 0.08) in the total sample

Table 1. Baseline Characteristics, by Quartile Extremes of AVR*

Characteristic	Crude	Adjusted†				
	Study Population (n = 7993)	First AVR Quartile (Range: 0.57-0.79) (n = 1998)	Second AVR Quartile (Range: 0.80-0.84) (n = 1998)	Third AVR Quartile (Range: 0.85-0.90) (n = 1999)	Fourth AVR Quartile (Range: 0.91-1.22) (n = 1998)	*P* Value‡
Age, mean (SE), y	59.4	59.7 (0.12)	59.5 (0.12)	59.4 (0.12)	59.1 (0.12)	.002
Men, %	43.3	51.8	44.8	41.6	35.2	<.001
Black, %	17.1	21.2	19.4	15.2	12.5	<.001
High school graduate, %	84.3	84.7	83.6	85.4	83.6	.30
Family history of diabetes, %	21.6	20.1	21.2	22.1	23.0	.16
Fasting glucose, mean (SE), mg/dL§	98.1	99.1 (0.22)	98.2 (0.22)	98.0 (0.22)	97.3 (0.22)	<.001
Fasting insulin, mean (SE), μU/mL	9.9	10.5 (0.16)	10.3 (0.16)	9.6 (0.16)	9.4 (0.16)	<.001
Blood pressure, mean (SE), mm Hg						
Systolic	122.2	128.5 (0.37)	123.9 (0.37)	120.4 (0.37)	116.1 (0.37)	<.001
Diastolic	71.6	75.2 (0.21)	72.6 (0.21)	70.7 (0.21)	68.0 (0.21)	<.001
Body mass index, mean (SE), kg/m^2	27.9	28.7 (0.11)	28.1 (0.11)	27.6 (0.11)	27.0 (0.11)	<.001
Waist-hip ratio, mean (SE)	0.93	0.94 (0.001)	0.94 (0.001)	0.93 (0.001)	0.92 (0.001)	<.001
Sports activity index, mean (SE)	2.57	2.53 (0.02)	2.53 (0.02)	2.63 (0.02)	2.62 (0.02)	<.001
Cigarette smoking, current, %	16.6	18.2	17.4	15.5	15.2	.03
Alcohol use, current, %	57.2	60.1	57.6	56.2	54.9	.003

*AVR indicates arteriole-to-venule ratio. See "Methods" section for definitions of characteristics.
†Values are adjusted for age, sex, race, and field center (except for age, men, and black, which are unadjusted for age, sex, and race, respectively) using analysis of covariance.
‡Represents overall difference among AVR quartiles.
§To convert values for fasting glucose to mmol/L, multiply values by 0.0555.

Table 2. Incidence and OR of Diabetes, by AVR Quartiles*

	Incident Diabetes					Incident Diabetes, Alternate Definition†				
	AVR Quartile				*P* Value for Trend	AVR Quartile				*P* Value for Trend
	1 (Range: 0.57-0.79)	2 (Range: 0.80-0.84)	3 (Range: 0.85-0.90)	4 (Range: 0.91-1.22)		1 (Range: 0.57-0.79)	2 (Range: 0.80-0.84)	3 (Range: 0.85-0.90)	4 (Range: 0.91-1.22)	
No. at risk	1998	1998	1999	1998		1998	1998	1999	1998	
Diabetes, No. (%)	104 (5.2)	79 (4.0)	61 (3.1)	47 (2.4)		57 (2.9)	42 (2.1)	41 (2.0)	21 (1.1)	
Diabetes OR (95% CI)										
Unadjusted‡	2.28 (1.61-3.23)	1.71 (1.18-2.46)	1.31 (0.89-1.92)	Reference	<.001	2.76 (1.67-4.58)	2.02 (1.19-3.43)	1.97 (1.16-3.26)	Reference	<.001
Age-, sex-, race-, center-adjusted	2.09 (1.47-2.98)	1.61 (1.11-2.32)	1.27 (0.86-1.87)	Reference	<.001	2.56 (1.54-4.26)	1.91 (1.13-3.25)	1.92 (1.13-3.26)	Reference	<.001
Multivariable-adjusted§	1.71 (1.13-2.57)	1.49 (0.98-2.27)	1.22 (0.79-1.88)	Reference	.002	1.92 (1.10-3.36)	1.66 (0.93-2.94)	1.71 (0.97-3.03)	Reference	.01

*AVR indicates arteriole-to-venule ratio; OR, odds ratio; and CI, confidence interval.
†Alternate incident diabetes definition based on fasting serum glucose level of 141 mg/dL (7.8 mmol/L), casual glucose level of 200 mg/dL (11.1 mmol/L), current use of diabetic medications, or physician diagnosis of diabetes.
‡Specific AVR quartile vs the fourth quartile.
§Multivariable-adjusted model includes adjustment for age, sex, race, and field center, plus further adjustment for fasting glucose and insulin, family history of diabetes, 6-year mean arterial blood pressure, body mass index, waist-hip ratio, sports and leisure activity indexes, education, pack-years of cigarette smoking, alcohol consumption, total and high-density lipoprotein cholesterol levels, and triglyceride levels.

was independently associated with a 26% increase in risk of diabetes (OR, 1.26; 95% CI, 1.09-1.46). This association was generally similar in people stratified into "high-risk" and "low-risk" baseline characteristics, being possibly stronger in black than in white participants and in persons with lower BMIs and waist-hip ratios. Analysis repeated using the logarithmic transformation of AVR did not improve the fit of the models presented (data not shown).

Focal signs of hypertensive retinopathy, such as arteriovenous nicking and focal arteriolar narrowing, were not related to incident diabetes (adjusted OR, 0.94; 95% CI, 0.65-1.35, and adjusted OR, 1.12; 95% CI, 0.78-1.59, respectively).

COMMENT

In this prospective cohort study of middle-aged persons without diabetes, retinal arterioles were significantly narrower in persons who subsequently developed diabetes during the ensuing 3.5 years compared with those who did not. After controlling for fasting glucose level and insulin level 6 years prior, family history of diabetes, blood pressure, adiposity, physical activity, and other known risk factors, retinal arteriolar narrowing (as reflected by a lower AVR) was independently associated with in-

Table 3. Risk of Incident Diabetes per 1-SD Decrease in AVR, Stratified by Diabetes Risk Factors*

Risk Factor	No. at Risk	Diabetes, No. (%)	OR (95% CI) of Diabetes per 1-SD Decrease in AVR†
Total	7993	291 (3.6)	1.26 (1.09-1.46)
Race			
White	6630	213 (3.2)	1.21 (1.02-1.43)
Black	1363	78 (5.7)	1.47 (1.05-2.02)
Family history of diabetes			
No	6266	203 (3.2)	1.28 (1.08-1.53)
Yes	1727	88 (5.1)	1.22 (0.93-1.62)
Fasting glucose, mg/dL‡			
Normal (<110)	6757	117 (1.7)	1.31 (1.05-1.63)
Impaired (≥110)	1054	163 (15.5)	1.24 (1.01-1.52)
Fasting insulin, μIU/L			
Low (<9)	4212	62 (1.5)	1.21 (0.94-1.46)
High (≥9)	3740	225 (6.0)	1.33 (1.13-1.61)
Carotid IMT, mm			
Low (<0.67)	2833	72 (2.5)	1.34 (0.99-1.81)
High (≥0.67)	2834	121 (4.3)	1.25 (0.98-1.55)
Six-year mean arterial blood pressure, mm Hg			
Low (<90)	4287	116 (2.7)	1.28 (1.00-1.57)
High (≥90)	3708	175 (4.7)	1.24 (1.02-1.51)
Body mass index, kg/m^2			
Low (<28)	3995	60 (1.5)	1.50 (1.09-2.07)
High (≥28)	3993	231 (5.8)	1.21 (1.02-1.42)
Waist-hip ratio			
Low (<0.94)	3994	56 (1.4)	1.54 (1.09-2.17)
High (≥0.94)	3993	235 (5.9)	1.20 (1.02-1.41)
Sports activity index (0-5)			
Low (<3)	2724	120 (4.4)	1.24 (0.99-1.58)
High (≥3)	5232	170 (3.2)	1.27 (1.05-1.53)

*AVR indicates arteriole-to-venule ratio; OR, odds ratio; CI, confidence interval; and IMT, intima-media thickness.
†See Table 2 footnote for list of covariates.
‡For fasting glucose, 110 mg/dL = 6.1 mmol/L.

creased risk of diabetes. This association persisted with different diabetes definitions, and was seen even among people at lower risk of developing this condition, including those without a family history of diabetes, those without impaired fasting glucose, those physically more active, and those with lower measures of adiposity.

Retinal arteriolar narrowing is a marker of microvascular damage from aging, hypertension, inflammation, and other processes.[11] It reflects intimal thickening and medial hyperplasia, hyalinization, and sclerosis seen histopathologically.[11] Because similar arteriolar changes associated with hypertension are well documented elsewhere in the body,[22,23] the retinal arterioles appear to offer insights into the state of the systemic arterioles in health and disease.

Our finding provides prospective clinical evidence to support a key hypothesis in the pathogenesis of diabetes. The microcirculation, estimated using measures of microvascular reactivity and blood flow in the skin and skeletal muscles, is known to be insulin sensitive (ie, insulin stimulates microvascular dilation and flow).[24] Several cross-sectional studies have demonstrated microvascular alterations in persons with type 2 diabetes[4,5] and in those at high risk of developing diabetes, including persons with impaired glucose tolerance,[6-8] first-degree relatives of persons with diabetes,[8,9] persons who are obese,[25] and persons with hypertension.[26,27] Because these microvascular alterations may result in a reduced ability of insulin to mediate glucose uptake in skeletal muscles, microvascular disease has been suggested to play a causal role in the development of diabetes.[2,3] Our study now suggests that arteriolar narrowing precedes the onset of diabetes, and may even play a role in its initial development. This relationship was independent of impaired fasting glucose, a family history of diabetes, and obesity and hypertension.

Our data also offer insights for a number of diverse observations regarding the epidemiology of diabetes. Although hypertension[28,29] and cigarette smoking[30,31] are related to the risk of diabetes, the underlying mechanisms are unclear. Microvascular alterations (eg, increased arteriolar resistance and reduced microvascular flow) have also been shown to precede hypertension[26,27] and have therefore been hypothesized to explain the excess risk of diabetes in persons with hypertension.[32] The risk of diabetes associated with cigarette smoking may be related to inflammation and consequent microvascular injury, since inflammation itself appears to play an important role in the development of diabetes.[33,34] We have previously demonstrated that retinal arteriolar narrowing is related to long-term average blood pressure levels[13] and independently related to cigarette smoking and markers of inflammation.[14] Thus, it is possible that arteriolar narrowing, resulting from hypertension, cigarette smoking, inflammation, and other unmeasured processes, may be a common pathophysiological link to diabetogenesis.

The strengths of the current study include its population-based design, the quantitative and masked evaluation of retinal arteriolar diameters, standardized identification of incident diabetes cases, and detailed information on risk factors. However, some limitations should be highlighted. First, given the imprecision of a single glucose determination and the relatively short follow-up, misclassification of diabetes may occur. Thus, arteriolar narrowing may be a marker of underlying diabetes in persons not yet meeting the diagnostic criteria. However, this association was independent of fasting glucose, insulin measured 6 years earlier, and other risk factors; persisted with a different diabetes definition; and was observed in persons without signs of diabetic retinopathy (a marker of underlying disease). Moreover, the fact that the associations were largely similar in those at higher and lower risk of diabetes probably minimizes the likelihood of misclassification biases. Second, selection bias may have masked some associations or accentuated others. Retinal photographs were taken 6 years into the ARIC study, and if persons with arteriolar narrowing at risk of developing diabetes were more likely to die prior to photography, these associations could be falsely attenuated. Third, we have only shown a short-term association between AVR and incident diabetes; further study is required to determine whether longer-term associations exist. Finally, no data on the use of different vasodilator medications were available.

In conclusion, this population-based study documents a prospective association of retinal arteriolar narrowing to incident diabetes mellitus in middle-aged persons, independent of known risk factors. This finding suggests that microvascular processes may play a role in the development of diabetes.

Author Contributions: *Study concept and design:* Wong, R. Klein, Hubbard, Duncan.
Acquisition of data: R. Klein, Couper.
Analysis and interpretation of data: Wong, Sharrett, Schmidt, Pankow, Couper, B. Klein, Hubbard, Duncan.
Drafting of the manuscript: Wong.
Critical revision of the manuscript for important intellectual content: Wong, R. Klein, Sharrett, Schmidt, Pankow, Couper, B. Klein, Hubbard, Duncan.
Statistical expertise: Couper.
Obtained funding: R. Klein.
Administrative, technical, or material support: Pankow.
Study supervision: R. Klein.
Funding/Support: This study was supported by contracts N01-HC-35125, N01-HC-35126, N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute, Bethesda, Md.
Acknowledgement: We thank the staff and participants in the ARIC study for their important contributions.

REFERENCES

1. Harris MI, Flegal KM, Cowie CC, et al. Prevalence of diabetes, impaired fasting glucose, and impaired glucose tolerance in US adults: the Third National Health and Nutrition Examination Survey, 1988-1994. *Diabetes Care*. 1998;21:518-524.
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. 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.
5. Laakso M, Edelman SV, Brechtel G, Baron AD. Impaired insulin-mediated skeletal muscle blood flow in patients with NIDDM. *Diabetes*. 1992;41:1076-1083.
6. Jaap AJ, Shore AC, Tooke JE. Relationship of insulin resistance to microvascular dysfunction in sub-

jects with fasting hyperglycaemia. *Diabetologia*. 1997; 40:238-243.
7. 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.
8. 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.
9. 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.
10. Tooke JE. Methodologies used in the study of the microcirculation in diabetes mellitus. *Diabetes Metab*. 1993;9:57-70.
11. Wong TY, Klein R, Klein BEK, Tielsch JM, Hubbard LD, Nieto FJ. Retinal microvascular abnormalities and their relations with hypertension, cardiovascular diseases and mortality. *Surv Ophthalmol*. 2001; 46:59-80.
12. Hubbard LD, Brothers RJ, King WN, et al, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Methods for evaluation of retinal microvascular abnormalities associated with hypertension/ sclerosis in the Atherosclerosis Risk in Communities (ARIC) Study. *Ophthalmology*. 1999;106:2269-2280.
13. 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.
14. 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.
15. Wong TY, Klein R, Couper DJ, et al. Retinal microvascular abnormalities and incident stroke: the Atherosclerosis Risk in Communities Study. *Lancet*. 2001; 358:1134-1140.
16. The ARIC Investigators. The Atherosclerosis Risk in Communities (ARIC) Study: design and objectives. *Am J Epidemiol*. 1989;129:687-702.
17. Brancati FL, Kao WH, Folsom AR, Watson RL, Szklo M. Incident type 2 diabetes mellitus in African American and white adults: the Atherosclerosis Risk in Communities Study. *JAMA*. 2000;283:2253-2259.
18. American Diabetes Association: Clinical Practice Recommendations 1997. *Diabetes Care*. 1997;20 (suppl 1):S1-S70.
19. Baecke JA, Burema J, Frijters JE. A short questionnaire for the measurement of habitual physical activity in epidemiological studies. *Am J Clin Nutr*. 1982; 36:936-942.
20. Papp AC, Hatzakis H, Bracey A, Wu KK. ARIC hemostasis study, I: development of a blood collection and processing system suitable for multicenter hemostatic studies. *Thromb Haemost*. 1989;61:15-19.
21. National Heart, Lung, and Blood Institute, University of North Carolina School of Public Health ARIC Coordinating Center. *Atherosclerosis Risk in Communities Study Operations Manual No. 2: Cohort Component Procedures*. Version 2.0. Chapel Hill: University of North Carolina; 1988.
22. Burchfiel CM, Tracy RE, Chyou PH, Strong JP. Cardiovascular risk factors and hyalinization of renal arterioles at autopsy: the Honolulu Heart Program. *Arterioscler Thromb Vasc Biol*. 1997;17:760-768.
23. Baumbach GL, Heistad DD. Remodeling of cerebral arterioles in chronic hypertension. *Hypertension*. 1989;13:968-972.
24. Baron AD, Clark MG. Role of blood flow in the regulation of muscle glucose uptake. *Annu Rev Nutr*. 1997;17:487-499.
25. Laakso M, Edelman SV, Brechtel G, Baron AD. Decreased effect of insulin to stimulate skeletal muscle blood flow in obese man: a novel mechanism for insulin resistance. *J Clin Invest*. 1990;85:1844-1852.
26. Hulthen UL, Endre T, Mattiasson I, Berglund G. Insulin and forearm vasodilation in hypertension-prone men. *Hypertension*. 1995;25:214-218.
27. Feldman RD, Bierbrier GS. Insulin-mediated vasodilation: impairment with increased blood pressure and body mass. *Lancet*. 1993;342:707-709.
28. Pell S, D'Alonzo CA. Some aspects of hypertension in diabetes mellitus. *JAMA*. 1967;202:104-110.
29. Morales PA, Mitchell BD, Valdez RA, Hazuda HP, Stern MP, Haffner SM. Incidence of NIDDM and impaired glucose tolerance in hypertensive subjects: the San Antonio Heart Study. *Diabetes*. 1993;42:154-161.
30. Manson JE, Ajani UA, Liu S, Nathan DM, Hennekens CH. A prospective study of cigarette smoking and the incidence of diabetes mellitus among US male physicians. *Am J Med*. 2000;109:538-542.
31. Rimm EB, Manson JE, Stampfer MJ, et al. Cigarette smoking and the risk of diabetes in women. *Am J Public Health*. 1993;83:211-214.
32. 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.
33. Schmidt MI, Duncan BB, Sharrett AR, et al. Markers of inflammation and prediction of diabetes mellitus in adults (Atherosclerosis Risk in Communities study): a cohort study. *Lancet*. 1999;353:1649-1652.
34. Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA*. 2001; 286:327-334.

Health and intellect are the two blessings of life.
—Menander (c 342-292 BCE)