

# The Relation of Retinal Vessel Caliber to the Incidence and Progression of Diabetic Retinopathy

## XIX: The Wisconsin Epidemiologic Study of Diabetic Retinopathy

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**Objective:** To describe the relation of retinal arteriolar and venular caliber to the incidence and progression of diabetic retinopathy in people with type 1 diabetes mellitus.

**Design:** Incidence findings in a population-based study of diabetic retinopathy in Wisconsin. Participants included 996 persons diagnosed as having diabetes mellitus before 30 years of age who took insulin and underwent the baseline examination, 891 in the 4-year follow-up, 765 in the 10-year follow-up, and 634 in the 14-year follow-up. Retinal photographs of 7 standard fields were taken at all examinations. Computer-assisted grading was performed from a digitized image of field 1 to determine the average diameter of retinal arterioles and venules and their ratio. Main outcome measures included incidence and progression of retinopathy, incidence of proliferative retinopathy, and macular edema.

**Results:** While adjusting for other factors, larger arteriolar (relative risk [RR] for the fourth vs first quartile range, 2.04; 95% confidence interval [CI], 1.20-3.47; test of trend,  $P = .008$ ) and venular diameters (RR, 2.33; 95% CI, 1.37-3.95; test of trend,  $P = .005$ ) were associated with

greater 4-year progression of retinopathy. Larger venular diameters (RR, 4.28; 95% CI, 1.50-12.19; test of trend,  $P = .006$ ) but not arteriolar diameters were associated with greater 4-year incidence of proliferative retinopathy. In multivariable analyses, arteriolar and venular calibers were not associated with the 4-year incidence of retinopathy. While adjusting for other factors, arteriolar and venular calibers were not associated with incidence of macular edema at 4 years. There were few associations of arteriolar or venular caliber with the 10- or 14-year incidence or the progression of retinopathy.

**Conclusions:** Larger arteriolar and venular caliber, independent of retinopathy severity level, is related to the progression of retinopathy, and larger venular caliber is associated with the 4-year incidence of proliferative retinopathy. Caliber of retinal vessels is not associated with incident retinopathy. These data suggest a quantitative measure of retinal vascular caliber provides additional information regarding risk for progression of retinopathy.

*Arch Ophthalmol.* 2004;122:76-83

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**D**ESPITE THE EFFICACY OF glycemic and blood pressure control and photocoagulation treatment in reducing visual loss in persons with diabetes, retinopathy remains an important cause of visual loss.<sup>1</sup> Early detection by means of dilated eye examinations and close follow-up of those with advanced retinopathy has been advocated to minimize visual loss in persons with diabetes.<sup>2</sup> Hyperglycemia, hypertension, microalbuminuria status, duration of diabetes, and pregnancy have been used to define increased risk for progression of retinopathy and to determine the frequency of such examinations.<sup>3</sup> Other than retinopathy severity, no ocular factors have been consistently associated with the risk for progression to proliferative retinopathy and incidence of macular edema. Dilated reti-

nal venules have been considered to be common in persons with diabetes, but were difficult to assess consistently and were not included in schemes classifying the severity of diabetic retinopathy.<sup>4</sup> Nevertheless, dilated retinal venules have been associated inconsistently with an increased risk for progression to proliferative retinopathy in persons with diabetes.<sup>5-12</sup> However, most of these observations have been made on selected small samples using ophthalmoscopy, and few have come from population-based studies.

In the Atherosclerosis Risk in Communities Study, we developed a technique to quantify vessel caliber in the retinal arterioles and venules based on measuring their diameters on digitized fundus photographs.<sup>13</sup> Using this technique, our group recently reported that narrowed retinal arterioles were associated

with 3-year incidence of diabetes in the Atherosclerosis Risk in Communities Study, suggesting that microvascular caliber changes occur in the preclinical stages of diabetes.<sup>14</sup> The purpose of this report is to describe the relation of retinal arteriolar and venular caliber and arteriole-venule ratio (AVR) with the incidence and progression of diabetic retinopathy and the incidence of macular edema in a large population-based study of persons with younger-onset (type 1) diabetes.

## METHODS

### STUDY POPULATION

The population, which has been described in previous reports, consisted of a probability sample selected from 10135 diabetic patients who received primary care in an 11-county area in southern Wisconsin from 1979 to 1980.<sup>15-20</sup> This sample was composed of a younger-onset group (all patients diagnosed as having diabetes before 30 years of age who took insulin [ $n=1210$ ]) and an older-onset group.

Data from participants in the younger-onset group who underwent at least 1 follow-up examination form the basis of this report. Of this group, 996 participated in the baseline examination (1980-1982),<sup>16</sup> 891 in the 4-year follow-up,<sup>17</sup> 765 in the 10-year follow-up,<sup>19</sup> and 634 in the 14-year follow-up.<sup>20</sup> Reasons for nonparticipation and comparisons between participants and nonparticipants at baseline and all the follow-up examinations have been presented elsewhere.<sup>15-20</sup> The principal reason for nonparticipation was death, accounting for 64 nonparticipants at the 4-year follow-up, an additional 86 at the 10-year follow-up, and an additional 64 at the 14-year follow-up.

### PROCEDURES

The baseline and follow-up examinations were performed in a mobile examination van in or near the cities where the participants resided. All examinations followed a similar protocol that was approved by the institutional human subjects committee of the University of Wisconsin-Madison. The pertinent parts of the ocular and physical examinations included measurement of blood pressure,<sup>21</sup> dilation of the pupil, 30° stereoscopic color fundus photography of 7 standard fields,<sup>22</sup> a semi-quantitative determination of protein levels in the urine using a urine chemistry test strip (Labstix; Ames, Elkhart, Ind), and determination of glycosylated hemoglobin A<sub>1</sub> levels from a capillary blood sample.<sup>23,24</sup>

A structured interview was conducted by the examiners and included questions about specific medications for control of hyperglycemia and blood pressure. Any question about medication use was verified by a physician's report.

### GRADING PROTOCOL

Grading protocols have been described in detail elsewhere<sup>17,25</sup> and are modifications of the Early Treatment Diabetic Retinopathy Study (ETDRS) adaptation of the modified Airlie House classification of diabetic retinopathy.<sup>26,27</sup> Interobserver and intraobserver variations and the validity of the systems have been evaluated, and the results have been presented elsewhere.<sup>17,25,27,28</sup>

### DEFINITIONS

For each eye, the maximum grade in any of the 7 standard photographic fields was determined for each of the lesions and used

in defining the retinopathy levels varying from level 10 (no retinopathy) to level 60 or greater (proliferative retinopathy); definitions have appeared elsewhere.<sup>19,27</sup> The retinopathy level for a participant was derived by concatenating the levels for the 2 eyes, giving the eye with the higher level greater weight. This scheme provided a 15-step scale. For purposes of classification, if the retinopathy severity could not be graded in an eye, it was considered to have a score equivalent to that of the other eye.

The incidence of any retinopathy was estimated from all persons who had no retinopathy at the baseline examination (severity level, 10/10) and who participated in the follow-up examination(s). Progression to proliferative retinopathy was estimated from all persons who were free of this complication at the baseline examination. For persons with nonproliferative or no retinopathy, progression was defined as the first instance of an increase in the severity of retinopathy by 2 steps or more from the baseline level at any of the follow-up examinations.

Macular edema was defined as thickening of the retina with or without partial loss of transparency within 1 disc diameter (DD) from the center of the macula<sup>29</sup> or the presence of focal photocoagulation scars in the macular area associated with a history of development of macular edema as documented by stereoscopic fundus photographs. Clinically significant macular edema was based on the detailed gradings and was defined as the presence of any one of the following: retinal thickening at or within 500  $\mu\text{m}$  of the center of the macula; hard exudates at or within 500  $\mu\text{m}$  of the center of the macula if associated with thickening of the adjacent retina; and/or a zone or zones of retinal thickening 1 disc area in size, at least part of which was within 1 DD of the center.<sup>29</sup> Whenever we found new signs of photocoagulation scars in the macular area in the absence of macular edema and we had not previously documented macular edema by grading fundus photographs taken at an earlier examination, we obtained fundus photographs from the participant's ophthalmologist. In the absence of fundus photographs, we obtained medical records documenting that macular edema due to diabetes had been present before the focal (or grid) photocoagulation. In situations where participants gave a history of laser photocoagulation but no signs of treatment burns were seen, we requested information from the treating ophthalmologist to verify that such treatment had been performed and to ascertain whether macular edema had been present before focal laser treatment. If macular edema could not be graded in an eye, the individual was assigned the score of the other eye. The incidence of macular edema was estimated from data for all persons who had no macular edema and had not been treated previously with photocoagulation at the baseline examination, and who participated in at least 1 follow-up examination.

Diameters of retinal vessels were measured after converting the photographs of field 1 to digital images. All arterioles and venules were measured in the area between 0.5 and 1 DD from the optic disc margin using a computer-assisted program. Computer-assisted measurements of individual arterioles and venules were each combined according to formulas developed by Parr and Spears<sup>30,31</sup> and Hubbard et al<sup>13</sup> to provide the average diameters of retinal arterioles (central retinal arteriolar equivalents [CRAE]) and venules (central retinal venular equivalents [CRVE]) in that eye. These were then expressed as an AVR. An AVR of 1.0 indicates that, on average, retinal arteriolar diameters are the same as venular diameters, whereas a smaller AVR represents narrower arterioles or larger venules. For the primary analyses, data from both eyes were combined by computing the mean if both eyes were gradable ( $n=754$ ) or by using the value of the single gradable eye ( $n=117$ ). The range of the CRAE was 117.1 to 306.6  $\mu\text{m}$ ; of the CRVE, 167.6 to 325.2  $\mu\text{m}$ ; and of the AVR, 0.587 to 1.119.

**Table 1. Characteristics of Younger-Onset Group at Baseline in the WESDR, 1980-1982**

Characteristic	Included		Excluded*		P
	No. of Participants	Finding	No. of Participants	Finding	
Age, mean (SD), y	871	27.9 (12.3)	125	39.1 (15.8)	<.001
Duration, mean (SD), y	871	13.3 (9.7)	125	24.5 (11.7)	<.001
Glycosylated hemoglobin, mean (SD), %	831	10.8 (2.1)	119	10.9 (2.1)	.55
Systolic blood pressure, mean (SD), mm Hg	865	122 (19)	122	143 (27)	<.001
Diastolic blood pressure, mean (SD), mm Hg	864	78 (11)	120	85 (14)	<.001
Male, %	871	50.3	125	59.2	.07
Hypertension, % present	865	16.9	123	56.9	<.001
Proteinuria, % present	838	16.6	117	60.7	<.001
Retinopathy					
% Absent	871	30.7	125	11.2	<.001
% Mild		42.7		9.6	
% Moderate		11.9		0.0	
% Proliferative		14.7		79.2	

Abbreviation: WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

\*Indicates did not participate in the 1984-1986 follow-up or did not have gradable retinal vessels at baseline.

### DEFINITION OF RELATED FACTORS

Age was defined as the age at the time of the baseline examination in 1980 to 1982. Age at diagnosis of diabetes mellitus was defined as the age at the time the diagnosis was first recorded by a physician on the patient's medical chart or in a hospital record. The duration of diabetes was the time from the age at diagnosis to the age at the baseline examination.

The mean systolic and diastolic blood pressures at baseline were the averages of the last 2 of 3 measurements obtained according to the protocol of the Hypertension Detection and Follow-up Program.<sup>21</sup> In individuals 25 years or older, hypertension at baseline was defined as a mean systolic blood pressure of at least 160 mm Hg, a mean diastolic blood pressure of at least 95 mm Hg, and/or a history of antihypertensive medication at the time of examination; in younger persons, it was defined as a mean systolic blood pressure of at least 140 mm Hg, a mean diastolic blood pressure of at least 90 mm Hg, and/or a history of antihypertensive medication at the time of examination. Pulse pressure at baseline was defined as the systolic minus the diastolic blood pressure. Mean arterial blood pressure at baseline was defined as diastolic blood pressure + (systolic blood pressure - diastolic blood pressure)/3. Body mass index at baseline was defined as weight in kilograms divided by the square of height in meters. Proteinuria was defined as a urine protein concentration of 0.03 g/dL or greater.

### STATISTICAL METHODS

We computed the 4-, 10- and 14-year cumulative incidences. Some participants who were observed at the 4- or 10-year examinations and were still at risk for development of an end point did not participate in the later examinations. Thus, these are censored observations. To compute cumulative 14-year rates while still using the information contained in these censored observations, the product-limit method was used.<sup>32</sup> To test for trends in the rates of incidence or progression and to compute relative risks, we used the Mantel-Haenszel method<sup>33</sup> stratified on the 3 follow-up periods. Multivariable analyses were based on logistic regression for 4-year end points and the discrete linear logistic model for 10- and 14-year end points.<sup>34,35</sup> Continuous variables were used as such. For the retinal vessel variables, the means of the eyes were used as the per person measurements. The variables used in all the models for the whole

cohort, except for macular edema as an end point, were duration of diabetes, sex, glycosylated hemoglobin level, mean arterial blood pressure, antihypertensive medication use, and severity of retinopathy at baseline. As the risk factors of interest (ie, the retinal vessel measurements) and the end points (ie, incidence and progression of retinopathy) are eye specific, we also performed analyses using the eye-specific data. We used generalized estimating equation models to evaluate these relationships.<sup>36</sup>

### RESULTS

Characteristics of the cohort at baseline are presented in **Table 1**. Persons were excluded if they did not participate in the 1984-1986 follow-up (n=105) or did not have gradable retinal vessels in at least 1 eye (n=20). Persons included in the study were younger, had shorter duration of diabetes and lower systolic and diastolic blood pressure, and were less likely to have hypertension, gross proteinuria, and proliferative retinopathy.

The 4-, 10-, and 14-year cumulative incidence and progression of retinopathy and incidence of macular edema appear in **Table 2**. The cumulative incidence and rates of progression of retinopathy were high and increased with longer follow-up. By the 14th year of follow-up, 85.7% of the cohort had had progression of their retinopathy, proliferative retinopathy had developed in 37.4%, and clinically significant macular edema had developed in 17.2%.

The crude associations of retinal vascular measures at baseline with incidence and progression of retinopathy at 4, 10, and 14 years are presented in **Figures 1, 2, 3, and 4**. Multivariable models controlling for factors previously shown to be related to the end points of interest are presented for the 4-year data in **Table 3**. The CRAE, CRVE, and AVR at baseline were not associated with incidence of retinopathy (Figure 1 and Table 3). There were few differences when the multivariable model was rerun excluding mean arterial blood pressure or antihypertensive medication use (data not shown).

**Table 2. Four-, 10-, and 14-Year Incidence of Ocular End Points in the WESDR**

End Point	No. at Risk	Incidence, %		
		4-Year Follow-up	10-Year Follow-up	14-Year Follow-up
Incidence of retinopathy	249	59.4	89.3	96.3
2-Step progression	691	44.7	76.0	85.7
Incidence of proliferative diabetic retinopathy	691	10.6	30.2	37.4
Incidence of proliferative diabetic retinopathy with high-risk characteristics	691	4.2	10.0	13.5
Incidence of macular edema	670	9.2	20.5	26.5
Incidence of clinically significant macular edema	670	4.0	13.8	17.2

Abbreviation: WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

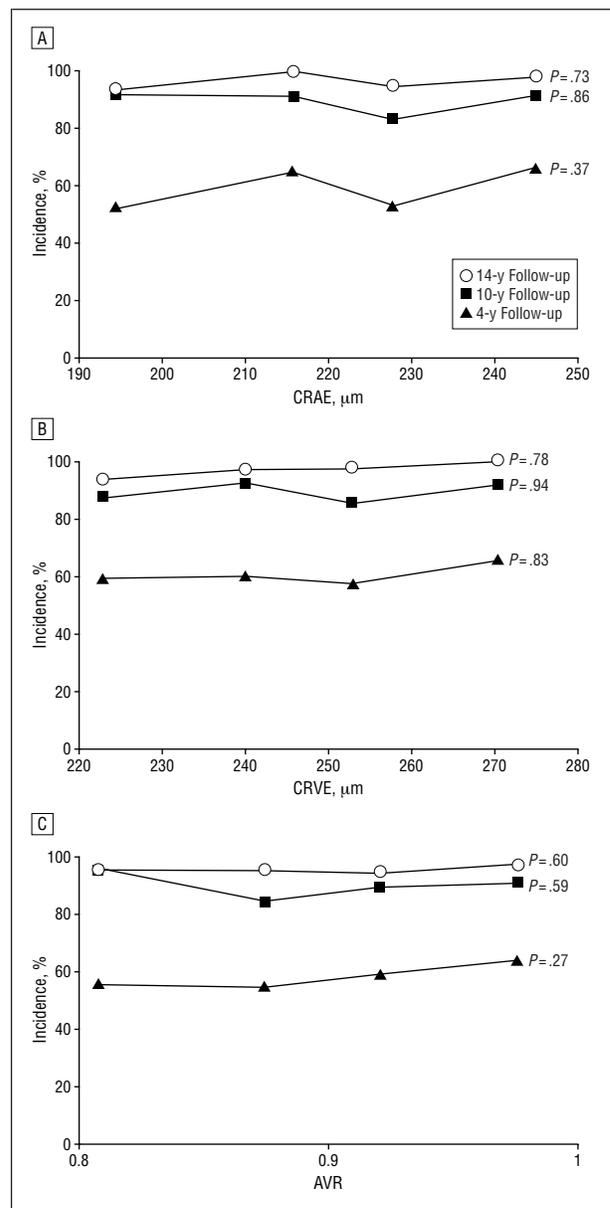
Larger CRAE and CRVE were associated with greater 4-year progression of retinopathy (Figure 2). The associations remained while controlling for sex, duration of diabetes, glycosylated hemoglobin level, mean arterial blood pressure, use of antihypertensive medications, and baseline retinopathy severity level (Table 3). Interactions of CRAE, CRVE, and AVR with baseline retinopathy level were examined. There was evidence of interactions between baseline retinopathy and CRVE ( $P = .06$ ) and AVR ( $P = .04$ ). The direction of this interaction between retinopathy and CRVE is such that at higher levels of retinopathy, the direct relationship between CRVE and progression is greater. For AVR, at higher levels of retinopathy, the inverse relationship between AVR and progression is greater. The associations were no longer statistically significant after 10 years of follow-up.

Larger CRVE and smaller AVR were strongly associated with greater 4-, 10-, and 14-year incidence of proliferative retinopathy (Figure 3). The CRAE was not associated. While controlling for sex, duration of diabetes, glycosylated hemoglobin level, mean arterial blood pressure, use of antihypertensive medications, and retinopathy severity level, proliferative retinopathy was 4 times as likely to develop at 4 years in participants in whom the CRVE was in the fourth quartile range at baseline (95% confidence interval [CI], 1.50-12.19) compared with participants in the first quartile range (Table 3).

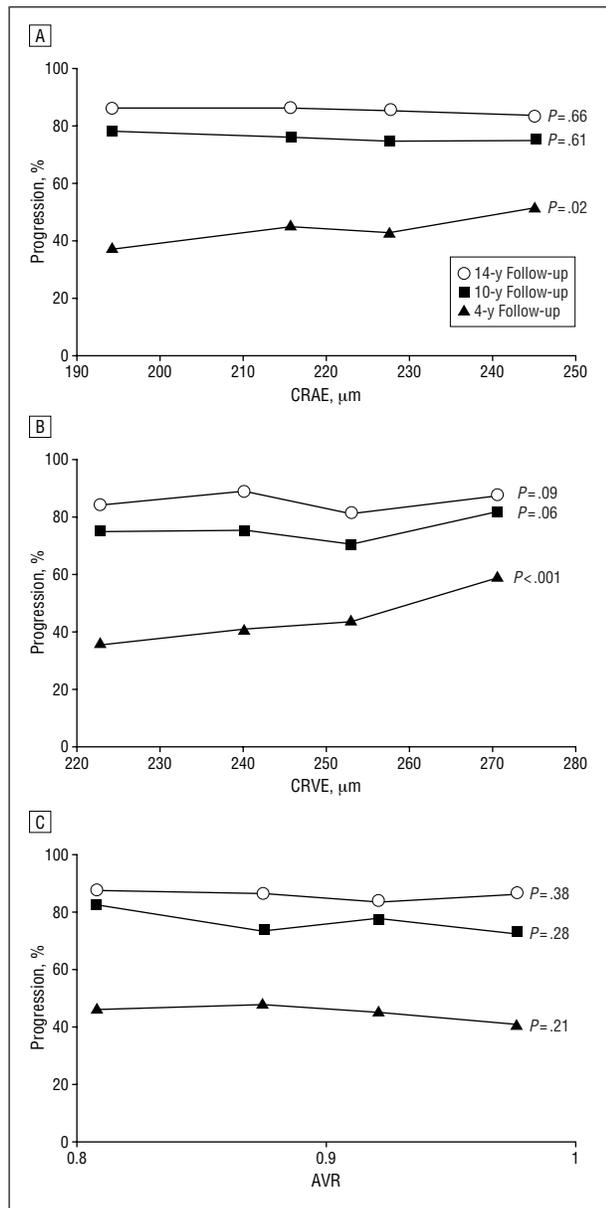
Larger CRVE and smaller CRAE at baseline were associated with greater 4-year and 14-year incidence of macular edema, respectively (Figure 4). Smaller AVR was associated with greater incidence of macular edema at 4 and 10 years but not at 14 years of follow-up. Multivariable analyses, controlling for glycosylated hemoglobin, gross proteinuria, and retinopathy severity level at baseline, showed that these relationships with incident macular edema were no longer statistically significant for CRAE, CRVE, and AVR (data not shown).

Findings were similar when we used generalized estimating equations (data not shown). There were no significant interactions with hypertensive status at baseline (data not shown).

Glycosylated hemoglobin and the retinal vessel variables are important variables with missing values (4.6% and 12.6%, respectively). To evaluate the effect this missing information has on the results, the multivariable models were rerun with these cases included with indicator



**Figure 1.** The incidence of retinopathy at 4, 10, and 14 years of follow-up by quartile of central retinal arteriolar equivalent (CRAE) (A), central retinal venular equivalent (CRVE) (B), and arteriole-venule ratio (AVR) (C) at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. P values are calculated using the test of trend.

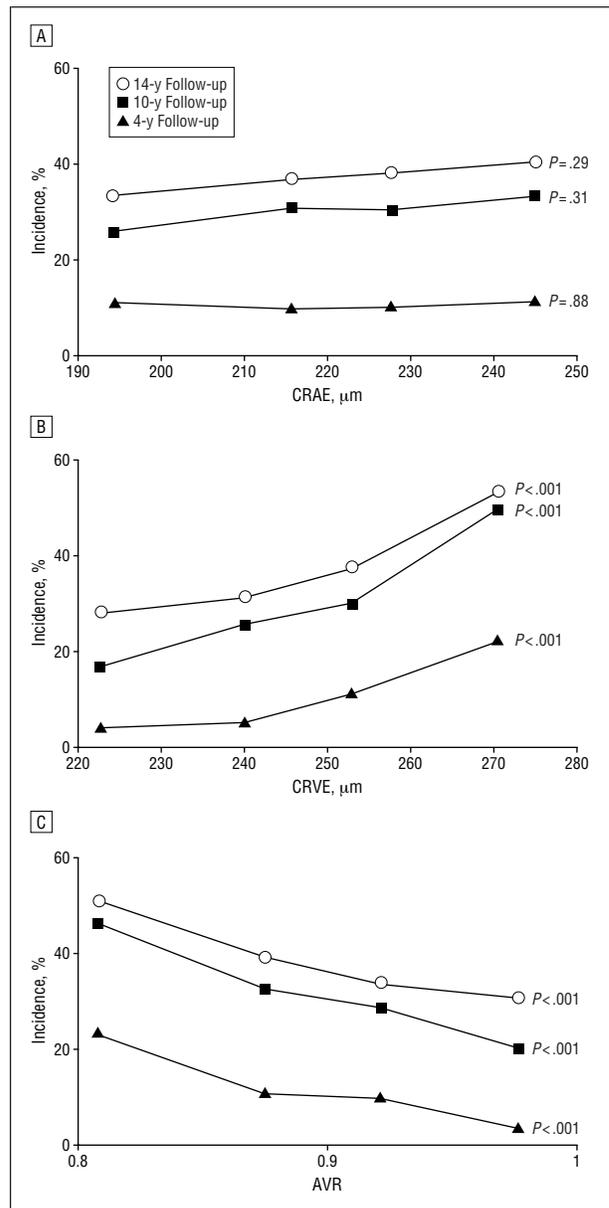


**Figure 2.** The progression of retinopathy at 4, 10, and 14 years of follow-up by quartile of central retinal arteriolar equivalent (CRAE) (A), central retinal venular equivalent (CRVE) (B), and arteriole-venule ratio (AVR) (C) at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *P* values are calculated using the test of trend.

variables to denote the state of the relevant variable being missing. This procedure resulted in no substantive changes in the associations between the retinal vessel variables and any of the end points (data not shown).

#### COMMENT

The data reported herein provide unique long-term population-based information regarding the relation of retinal vessel caliber to the incidence and progression of diabetic retinopathy and macular edema during a 14-year follow-up. Using a new computer-assisted technique to quantify measurement of the retinal arterioles and venules previously used in the Atherosclerosis Risk in Communities Study,<sup>13</sup> we report that, in persons with younger-



**Figure 3.** The incidence of proliferative diabetic retinopathy at 4, 10, and 14 years of follow-up by quartile of central retinal arteriolar equivalent (CRAE) (A), central retinal venular equivalent (CRVE) (B), and arteriole-venule ratio (AVR) (C) at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *P* values are calculated using the test of trend.

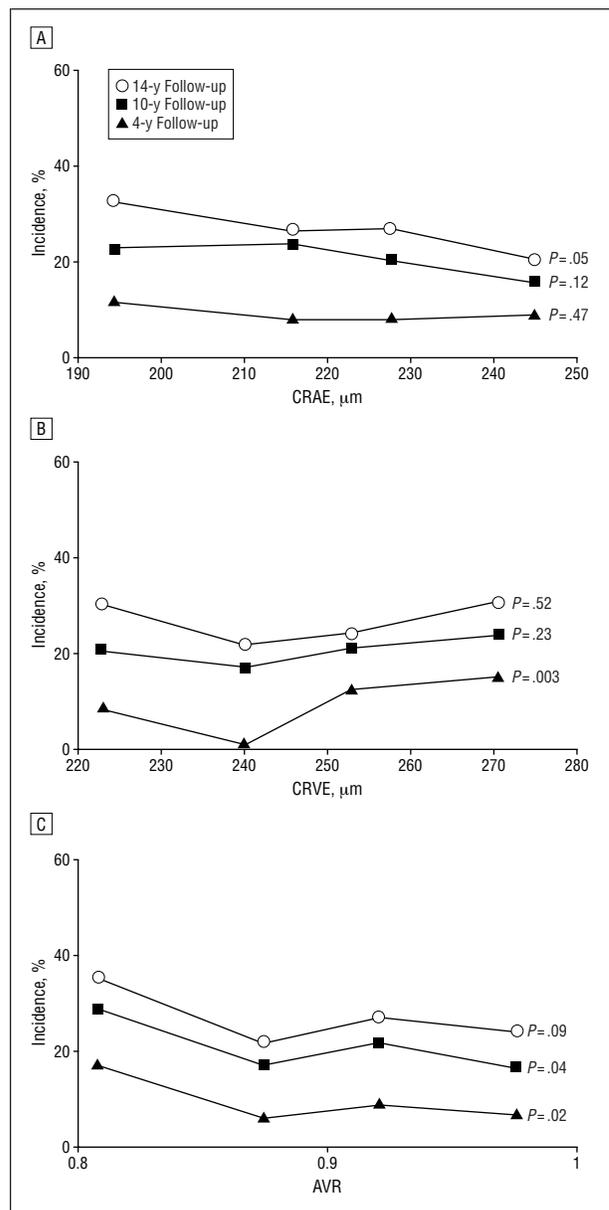
onset diabetes, greater vascular retinal caliber is not associated with incidence of retinopathy, larger arteriolar and venular diameters are associated with progression of retinopathy, and larger venular diameter at baseline is associated with the incidence of proliferative diabetic retinopathy.

The association in the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) of larger venular diameter with progression of retinopathy and incidence of proliferative retinopathy, independent of retinopathy severity, is consistent with data from earlier studies.<sup>4-12,37</sup> Retinal venous caliber abnormalities were important predictors of visual loss due to progression of retinopathy in the Diabetic Retinopathy Study (DRS).<sup>38</sup> Retinal venous beading, an irregular venular dilation, was

significantly associated with progression of proliferative disease in the DRS and ETDRS.<sup>26,27</sup> Based on these observations, the presence of venous beading was used to define severe nonproliferative retinopathy severity levels 47 and 53 in the ETDRS severity scale.<sup>27</sup> In the present study in the WESDR, the association of our measurements of venous caliber with progression of retinopathy remained independent of baseline retinopathy, hypertension status, and glycemic control, suggesting that larger venous caliber provides information independent of the current ETDRS system used to classify retinopathy severity level. Increase in venular diameter in eyes with retinopathy is thought to result from retinal hypoxia<sup>39</sup> and lactate accumulation resulting from hyperglycemia.<sup>40</sup> Successful treatment of proliferative diabetic retinopathy with panretinal photocoagulation has been shown to be accompanied by a reduction of venular caliber, thought to result from reduction of retinal hypoxia.<sup>10,41-43</sup>

We hypothesized that before the onset of retinopathy, eyes in diabetic subjects with narrower retinal arterioles, dilated venules, and smaller AVR would be associated with an increased risk for incident retinopathy. This was based on a number of observations. First, retinal arteriolar narrowing is associated with hypertensive and arteriosclerotic microvascular changes, endothelial dysfunction, and inflammatory changes, and these factors are thought to be involved in the pathogenesis of diabetic retinopathy.<sup>44-47</sup> Second, microvascular compliance is lower in diabetic subjects without retinopathy compared with nondiabetic subjects.<sup>48</sup> Third, retinal venular dilation had been observed in some studies in diabetic persons without retinopathy.<sup>49-52</sup> An alternative hypothesis was that before the onset of retinopathy, eyes in diabetic subjects with dilated arterioles would be at increased risk for incident retinopathy due to a breakdown in autoregulation.<sup>53</sup> However, we found no association of arteriolar or venular caliber with the incidence of retinopathy. Our findings regarding a lack of an association of incident retinopathy with venular caliber are consistent with data from earlier cross-sectional studies in which venular diameter was similar in the eyes of nondiabetic persons and diabetic persons without retinopathy.<sup>8,10,54,55</sup> In 45 children with type 1 diabetes mellitus, Falck and Laatikainen<sup>10</sup> reported higher but statistically nonsignificant venular diameter at baseline in eyes with incident retinopathy compared with eyes without incident retinopathy. They found that other signs of retinopathy developed in those eyes with greater than 10  $\mu\text{m}$  of venous dilation during the follow-up period more often than in patients with less or no change in the venous caliber. We have not measured change in venous caliber over time in our study. Our findings suggest that retinal vascular caliber measurements in those without retinopathy have little prognostic value before the development of retinopathy in persons with type 1 diabetes.

The strength of our study includes its large size, the broad distribution of severity of retinopathy at baseline, the defined and uniform follow-up intervals, and the low refusal rate. In addition, standardized protocols of measurement, including computer-assisted measurement of retinal vessel caliber and objective recording of diabetic



**Figure 4.** The incidence of macular edema at 4, 10, and 14 years of follow-up by quartile of central retinal arteriolar equivalent (CRAE) (A), central retinal venular equivalent (CRVE) (B), and arteriole-venule ratio (AVR) (C) at baseline in the Wisconsin Epidemiologic Study of Diabetic Retinopathy. *P* values are calculated using the test of trend.

retinopathy and macular edema using stereoscopic fundus photographs of 7 standard fields, were consistent over time. Grading of fundus photographs was performed in masked fashion using a standard classification system. However, caution must be observed in interpreting the findings in the present study. First, relationships may have been attenuated by selective survival. Retinopathy severity and retinal arteriolar narrowing have been shown to be related to mortality in persons in the diabetic population.<sup>56,57</sup> This would reduce the associations between arteriolar narrowing and progression of disease and incident proliferative retinopathy, especially in those followed up for a long time. Second, we did not control for variations in pulsatility associated with the cardiac cycle. This has been estimated to cause up to a 6% variation

**Table 3. The Relationship of CRAE, CRVE, and AVR to the 4-Year Incidence and Progression of Retinopathy and Incidence of Proliferative Retinopathy in the WESDR**

Baseline Retinal Vascular Measurements	4-y Incidence of Any Retinopathy*		4-y Progression of Retinopathy†		4-y Incidence of PDR‡	
	RR (95% CI)	P Value‡	RR (95% CI)	P Value‡	RR (95% CI)	P Value‡
<b>CRAE, <math>\mu</math>m</b>						
117.1-208.1	1.00	.25	1.00	.008	1.00	.50
208.2-221.1	1.53 (0.66-3.55)		1.35 (0.80-2.27)		0.73 (0.28-1.92)	
221.2-235.5	1.07 (0.46-2.49)		1.49 (0.87-2.52)		1.05 (0.40-2.73)	
235.6-306.6	2.03 (0.82-5.03)		2.04 (1.20-3.47)		1.18 (0.46-3.04)	
<b>CRVE, <math>\mu</math>m</b>						
167.6-233.1	1.00	.93	1.00	.005	1.00	.006
233.2-246.3	1.29 (0.60-2.75)		1.36 (0.83-2.24)		2.44 (0.71-8.41)	
246.4-260.6	0.83 (0.38-1.82)		1.24 (0.76-2.05)		2.96 (0.96-9.10)	
260.7-325.2	1.42 (0.47-4.24)		2.33 (1.37-3.95)		4.28 (1.50-12.19)	
<b>AVR</b>						
0.587-0.848	1.00	.23	1.00	.98	1.00	.03
0.849-0.897	0.68 (0.24-1.93)		1.13 (0.66-1.93)		0.57 (0.24-1.32)	
0.898-0.948	0.71 (0.26-1.94)		0.99 (0.58-1.67)		0.56 (0.25-1.28)	
0.949-1.119	1.41 (0.52-3.78)		1.06 (0.62-1.82)		0.29 (0.10-0.85)	

Abbreviations: AVR, arteriole-venule ratio; CI, confidence interval; CRAE, central retinal arteriolar equivalent; CRVE, central retinal venular equivalent; PDR, proliferative diabetic retinopathy; RR, relative risk; WESDR, Wisconsin Epidemiologic Study of Diabetic Retinopathy.

\*Multivariable adjusted, controlling for sex, duration of diabetes, glycosylated hemoglobin level, mean arterial blood pressure, and antihypertension medication use.

†Multivariable adjusted, controlling for sex, duration of diabetes, glycosylated hemoglobin level, mean arterial blood pressure, antihypertension medication use, and baseline retinopathy level.

‡Test of trend.

for arteriolar and venular diameters.<sup>58,59</sup> If we assume that the photographs were taken at random during the cardiac cycle, the resulting increase in variability of the gradings might result in an attenuation of our findings. Third, inability to find some associations of retinal vascular caliber width with incident or progressed retinopathy may be due, in part, to the limited area near the disc in which these blood vessels are measured.

## CONCLUSIONS

Measurement of venous caliber may provide additional information regarding progression of and risk for development of proliferative retinopathy than retinopathy severity itself in persons with type 1 diabetes mellitus. However, vessel caliber is not predictive of incident retinopathy. Further study is needed to examine whether retinal vessel caliber provides more information about systemic microvascular and macrovascular disease than severity of retinopathy in persons with type 1 diabetes.

Submitted for publication February 3, 2003; final revision received June 9, 2003; accepted September 10, 2003.

This study was supported by grants EY03083 and HL59259 from the National Institutes of Health, Bethesda, Md (Drs R. Klein and B. E. K. Klein), and in part by a Senior Scientific Investigator Award from Research to Prevent Blindness, New York, NY (Dr R. Klein).

We are grateful to the 452 Wisconsin physicians and their staffs who participated in and supported this study.

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