Retinal Microvascular Abnormalities and Renal Dysfunction: The Atherosclerosis Risk in Communities Study

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Abstract. Microvascular disease has been linked with renal dysfunction in patients with diabetes. The aim of this study was to examine the association of retinal microvascular abnormalities to renal dysfunction among participants of the Atherosclerosis Risk in Communities Study, a population-based investigation in four U.S. communities. At the third examination (1993 to 1995), retinal photography was performed and the presence of retinal microvascular abnormalities was documented using a standard grading protocol. Renal dysfunction was defined as an increase in serum creatinine of at least 0.4 mg/dl or a death or hospitalization as a result of chronic kidney disease between the second (1990 to 1992) and fourth (1996 to 1998) examinations. Among 10,056 people who were included in the study, 270 (2.7%) developed renal dysfunction. After controlling for age, gender, race, diabetes, BP, and other risk factors, individuals with retinopathy (odds ratio [OR], 2.0; 95% confidence interval [CI], 1.4 to 2.8), microaneurysms (OR, 2.0; 95% CI, 1.3 to 3.1), retinal hemorrhages (OR, 2.6; 95% CI, 1.6 to 4.0), soft exudates (OR, 2.7; 95% CI, 1.6 to 4.8), and arteriovenous nicking (OR, 1.4; 95% CI, 1.0 to 1.9) were more likely to develop renal dysfunction than individuals without these abnormalities. Retinal microvascular abnormalities are associated with renal dysfunction, suggesting that common systemic microvascular processes may underlie the development of microvascular damage in the eye and kidneys.

The pathogenesis of renal impairment in the general population is not well understood (1,2). A large proportion of patients with renal impairment do not have evidence of a primary renal disease (*e.g.*, nephritis). In these patients, vascular diseases involving the renal microcirculation have been hypothesized as one of the possible causes of early decline in renal function (3–5). Evidence to support such a hypothesis is derived from experimental studies of microvascular alterations in the renal circulation in chronic renal failure (6) and the strong link between kidney disease and vascular risk factors such as diabetes and hypertension, which are known to have major microvascular components (7–10).

The retinal microcirculation, accessible to direct noninvasive visualization, offers an opportunity to explore further the association of systemic microvascular disease, as seen in the eye, to renal dysfunction (11). Studies have found a correlation between pathologic changes in the retinal and renal microcirculation in spontaneously hypertensive rats (12), and the association between advanced retinopathy changes and nephropathy in people with diabetes is well known (13–18). In the general population, however, a possible association between retinal microvascular abnormalities and renal dysfunction has not been previously investigated. In the current study, we examined the relationship of retinal vascular abnormalities and renal dysfunction in a community-based sample of middle-aged people who lived in four U.S. communities.

Materials and Methods

Study Population

The Atherosclerosis Risk in Communities (ARIC) study examined 15,792 participants aged 45 to 64 yr at baseline in 1987 to 1989 (19). The study population was selected by probability sampling from four U.S. communities: Forsyth County, NC; Jackson, MS; suburbs of Minneapolis, MN; and Washington County, MD. The Jackson sample includes blacks only, and blacks were oversampled in Forsyth County, NC. Initial participation rates were 46% in Jackson and ~65% in the other communities. Participants were examined every 3 yr, with a second examination in 1990 to 1992 (n = 14,348; 93% of 15,440 survivors who returned for this examination), a third in 1993 to 1995 (n = 12,887; 86% of 14,944 survivors), and a fourth in 1996 to 1998 (n = 11,656; 80% of 14,485 survivors).

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Retinal photographs were taken only at the third examination (20,21), whereas serum creatinine was obtained at the second and fourth examinations (22,23). The current analysis therefore involved examining the association of retinal microvascular signs at the third examination with the 6-yr change in serum creatinine and the development of renal dysfunction between the second and fourth examinations.

The study population was derived as follows. Of the 11,656 who returned for the fourth examination, we excluded 31 whose race was neither black nor white, 38 black residents in Minneapolis and Maryland, 443 who had missing serum creatinine data or information of hospitalization or death from chronic renal disease at either the second or fourth examination, and 1,088 without retinal photographs or gradable photographs at the third examination, leaving 10,056 people for this study. Characteristics of participants with and without gradable retinal photographs have been previously reported; people with gradable photographs were generally younger and more likely to be white but did not differ by gender or smoking status (20).

Retinal Grading and Definitions

The retinal photography procedure and the assessment of the photographs in the ARIC study followed a standard protocol (20). Retinal photographs were taken of one randomly selected eye after 5 min of dark adaptation. Trained graders at the University of Wisconsin Fundus Reading Center, masked to participant characteristics, evaluated the photographic slides for presence of retinopathy and microvascular abnormalities using standardized protocols. Any retinopathy was defined as present when any of the following lesions were graded definite or probable: microaneurysms, retinal hemorrhages (blot or flame shaped), soft exudates, and other less common lesions (*e.g.*, hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere) (24). Arteriovenous nicking and focal arteriolar narrowing were defined separately as present when graded definite or probable. Retinal vessel diameters were measured using a computer-assisted technique. The photographs were digitized, and the diameters of all arterioles and venules coursing through a specified area one half to one-disc diameter from the optic disc margin were measured on the computer by graders who were masked to participant identity. The individual measurements were then combined into summary measures that reflected the average diameters of the arterioles and venules of that eye (μm). These measures were combined as the arteriole-to-venule ratio (AVR) (20). The AVR is a reflection of the relative diameter of the arterioles to venules, taking into account magnification differences between photographs (*e.g.*, an AVR of 1.0 indicates that retinal arteriolar diameters were, on average, the same as venular diameters). Quality control procedure of the retinal grading has been reported in detail elsewhere (20).

Definition of Developing Renal Dysfunction

Serum creatinine was measured at the second and the fourth examinations using a modified kinetic Jaffe method, described in detail in other reports (22,23). Assessment of the methodologic and day-to-day variability within ARIC participants revealed that 0.18 mg/dl (methodologic variability, SD = 0.05; within-person variability, SD = 0.04) was the minimal change in creatinine at which 95% confidence existed that a true change had occurred (25). We therefore defined a significant increase in serum creatinine as a change of at least twice this amount (0.4 mg/dl) (22,23).

We further defined the development of renal dysfunction as a significant increase in serum creatinine levels (of at least 0.4 mg/dl) or a hospitalization discharge or death coded for renal disease over the 6-yr period between the second and fourth examinations. Hospitalization discharge or death included the diagnosis of chronic renal disease (*International Classification of Diseases, Ninth Revision* [ICD-9] codes 581 to 583 or 585 to 588); hypertensive renal disease (ICD-9 code 403); hypertensive heart and renal disease (ICD-9 code 404); unspecified disorder of kidney and ureter (ICD-9 code 593.9); diabetes with renal manifestations (ICD-9 code 250.4); or kidney transplant, renal dialysis, or adjustment/fitting of catheter (ICD-9 codes V42.0, V45.1, or V56) through 1998. The primary outcomes of the study were the 6-yr change in serum creatinine and the development of renal dysfunction between the second and fourth examinations.

Definition of Other Variables

Participants underwent a standardized interview and examination at each visit (26). BP was taken with a random-zero sphygmomanometer, and the mean of the last two measurements was used. Mean arterial BP (MABP) was computed as two thirds of the diastolic plus one third of the systolic value, and MABP averaged over the first three examinations was included as a covariate in the assessment of the independence of the associations of retinal abnormalities with renal dysfunction. Hypertension was defined as systolic BP $\geq$140 mmHg, diastolic BP $\geq$90 mmHg, or use of antihypertensive medication during the previous 2 wk. Diabetes was defined as a fasting glucose $\geq$7.0 mmol/L, a nonfasting glucose $\geq$11.1 mmol/L, or a self-reported history of physician-diagnosed diabetes or treatment for diabetes. Height and weight were taken with participants in scrub suits, and body mass index was calculated in units of weight/height^2 (kg/m^2). Blood collection and processing for fasting total cholesterol, HDL cholesterol, triglycerides, and glucose are described elsewhere (25). Education, cigarette smoking, and alcohol consumption status were ascertained from interview. All covariates were based on data from the third examination, except for educational level (first examination) and MABP (average of the first three examinations).

Statistical Analyses

This analysis involved examining the association of retinal microvascular signs at the third ARIC examination (1993 to 1995) with the 6-yr change in serum creatinine and the development of renal dysfunction between the second (1990 to 1992) and fourth (1996 to 1998) examinations.

We compared participant characteristics among those who did and did not develop renal dysfunction using χ^2 tests (for proportions) and analysis of covariance (for means). We compared the mean serum creatinine level at the second examination and the 6-yr change in serum creatinine between the second and fourth examinations in people with and without a specific retinal lesion using analysis of covariance. We used logistic regression models to determine the odds of developing renal dysfunction associated with a specific retinal lesion. Models were initially adjusted for age, gender, race, and field center. In multivariable models, we further adjusted for diabetes (yes, no), fasting glucose (mg/dl), use of antihypertensive medication (yes, no), MABP (mmHg), fasting HDL cholesterol and triglyceride (mg/dl), body mass index (kg/m^2), and cigarette smoking and alcohol consumption (ever, never). These factors were considered potential confounders because of their known associations with retinopathy, renal dysfunction, or both (11,22,23).

To examine for possible interaction, we repeated these analyses by stratifying the population according to diabetes and hypertension status and by adding cross-product interaction terms (*e.g.*, diabetes $\times$ retinopathy) in logistic regression models of the entire sample. All

analyses were conducted with SPSS version 11.0 (SPSS Inc., Chicago, IL).

Results

Between the second and the fourth examinations, 270 (2.7%) participants developed renal dysfunction. This comprised 209 who had both a significant increase in serum creatinine levels and a hospitalization discharge or death coded for renal disease, 29 who developed a significant increase in serum creatinine levels only, and 32 who were hospitalized or died from renal disease only.

Participants who developed renal dysfunction were older and more likely to be men and black (Table 1). The development of renal dysfunction was associated with diabetes, higher fasting glucose levels, hypertension, higher mean systolic BP, lower HDL cholesterol levels, higher triglyceride levels, and current alcohol consumption, after adjusting for age, gender, race, and field center. A total of 687 (6.7%) participants had retinopathy at the third examination. Table 1 shows that participants with retinopathy were older and more likely black. Similarly, the presence of retinopathy was associated with diabetes, higher fasting glucose levels, hypertension, higher mean systolic BP, lower HDL cholesterol levels, higher triglyceride levels, and current alcohol consumption, after adjusting for age, gender, race, and field center.

The average serum creatinine level at the second examination was 0.901 mg/dl (SD, 0.30 mg/dl). Table 2 shows the serum creatinine levels at the second examination in the presence *versus* absence or quintile of each retinal vascular abnormality. Mean serum creatinine levels were generally similar in people with and without different retinal vascular lesions.

The mean serum creatinine level at the fourth examination was 0.928 mg/dl (SD, 0.30 mg/dl), and the mean change in serum creatinine between the second and fourth examinations was 0.027 mg/dl (SD, 0.31 mg/dl). Table 3 shows the 6-yr change in serum creatinine and the odds of developing renal dysfunction among participants with and without a specific retinal microvascular lesion. After controlling for age, gender, race, and field center, any retinopathy, microaneurysms, retinal hemorrhages, soft exudates, and arteriovenous nicking were associated with a larger 6-yr change in serum creatinine levels and a higher odds of developing renal dysfunction. Multivariable adjustment for diabetes, BP, and other factors attenuated these associations. Focal arteriolar narrowing was not significantly associated with either change in serum creatinine or development of renal dysfunction, whereas lower AVR was associated with a greater 6-yr change in serum creatinine but not related to the development of renal dysfunction. Analysis of the separate components of the AVR indicated that narrowed arteriolar diameters and narrowed venular diameters both were related to a greater 6-yr change in serum creatinine levels (data not shown).

Finally, we repeated these analyses by stratifying the population according to diabetes and hypertension status and by adding appropriate interaction terms in logistic regression models of the entire sample. Table 4 shows that people with diabetes, hypertension, and both diabetes and hypertension were more likely to have a larger 6-yr increase in serum creatinine levels and to develop renal dysfunction as compared with those without these conditions; the 6-yr increase in serum creatinine was 0.047 to 0.109 mg/dl in participants with hy-

Table 1. Characteristics of study population at the third examination (1993 to 1995), by absence/presence of renal dysfunction and retinopathy[a]

	Development of Renal Dysfunction[b]			Retinopathy		
	No (n = 9786)	Yes (n = 270)	P	No (n = 9491)	Yes (n = 687)	P
Age (yr)	59.7 ± 0.1	61.8 ± 0.3	<0.001	59.7 ± 0.1	60.3 ± 0.2	0.005
Men	43.9	58.5	<0.001	44.2	46.0	0.36
Black	19.1	25.9	0.005	18.7	34.2	<0.001
High school graduate[c]	82.4	77.8	0.04	82.3	78.5	0.009
Diabetes[c]	12.8	32.0	<0.001	11.6	39.6	<0.001
Fasting glucose (mg/dl)[c]	106.8 ± 0.4	128.5 ± 2.1	<0.001	107.0 ± 0.4	144.5 ± 1.4	<0.001
Hypertension[c]	37.6	63.9	<0.001	37.7	51.8	<0.001
Systolic BP (mm Hg)[c]	123.3 ± 0.2	129.9 ± 1.1	<0.001	123.3 ± 0.2	127.6 ± 0.7	<0.001
Diastolic BP (mmHg)[c]	71.6 ± 0.1	72.3 ± 5.9	0.274	71.7 ± 0.1	71.4 ± 0.4	0.38
Total plasma cholesterol (mg/dl)[c]	207.5 ± 0.4	211.5 ± 2.2	0.08	207.6 ± 0.4	206.5 ± 1.4	0.45
HDL cholesterol (mg/dl)[c]	52.4 ± 0.2	48.3 ± 1.0	<0.001	52.4 ± 0.2	49.9 ± 0.6	<0.001
Total triglyceride (mg/dl)[c]	141.2 ± 0.9	175.9 ± 5.3	<0.001	141.1 ± 0.9	155.0 ± 3.3	<0.001
Current cigarette smokers[c]	16.3	20.7	0.05	16.3	16.6	0.87
Current alcohol users[c]	55.0	44.2	<0.001	54.9	49.1	0.002

[a] Data are means (± SE) or proportions.
[b] Development of renal dysfunction defined as a 0.4-mg/dl increase in serum creatinine or deaths or hospitalizations for chronic renal diseases between the second and fourth examinations.
[c] Adjusted for age, gender, race, and field center.

Table 2. Serum creatinine levels at the second examination (1990 to 1992), by absence/presence of retinal microvascular abnormalities at the third examination (1993 to 1995)

		No. at Risk	Serum Creatinine	
			Age-Gender Race Adjusted (Mean [SE])[a]	*P*
Retinopathy	Absent	9491	0.900 (0.003)	0.43
	Present	687	0.909 (0.011)	
microaneurysm	Absent	9105	0.900 (0.003)	0.16
	Present	340	0.922 (0.015)	
retinal hemorrhage	Absent	9842	0.901 (0.003)	0.41
	Present	306	0.888 (0.016)	
soft exudates	Absent	9885	0.900 (0.003)	0.17
	Present	145	0.932 (0.023)	
Arteriovenous nicking	Absent	8631	0.901 (0.003)	0.82
	Present	1371	0.899 (0.007)	
Focal arteriolar narrowing	Absent	8392	0.900 (0.003)	0.30
	Present	1436	0.908 (0.007)	
Arteriole-to-venule ratio	Quintile 5	1894	0.899 (0.006)	0.73
	Quintile 4	1894	0.902 (0.006)	
	Quintile 3	1894	0.904 (0.006)	
	Quintile 2	1894	0.894 (0.006)	
	Quintile 1	1893	0.896 (0.006)	

[a] Mean serum creatinine (mg/dl) at the second examination, adjusted for age, gender, race, and field center in analysis of covariance models.

pertension and 0.063 to 0.172 mg/dl in participants with diabetes as compared with 0.008 to 0.013 mg/dl in nondiabetic and nonhypertensive participants. In general, the presence of retinopathy was associated with a greater increase in serum creatinine levels and renal dysfunction in subgroups with and without diabetes, with and without hypertension, and with and without both diabetes and hypertension, although some associations were not statistically significant. This association was stronger in participants with diabetes (odds ratio [OR], 2.6) than in those without diabetes (OR, 1.6; retinopathy × diabetes interaction term, $P = 0.24$) and in participants without hypertension (OR, 2.9) than in those with hypertension (OR, 1.6; retinopathy × hypertension interaction term, $P = 0.02$).

Discussion

In this community-based sample of middle-aged people, we examined the association of various manifestations of microvascular disease in the retina (microaneurysms, retinal hemorrhages, soft exudates, and arteriovenous nicking), documented from photographs at the third ARIC examination (1993 to 1995) with the 6-yr decline in renal function occurring between the second (1990 to 1992) and fourth (1996 to 1998) examinations. We demonstrated an association between retinopathy and renal dysfunction that was independent of age, gender, race, hypertension, diabetes, and other vascular risk factors. This association was largely similar in people with and without diabetes and hypertension.

These findings offer further insights into the pathophysiology of serum creatinine changes and the development of renal dysfunction. The retinal microvascular abnormalities evaluated here reflect small-vessel damage associated with increased age, diabetes, hypertension, inflammation, and other conditions (11,27). Thus, their associations with renal dysfunction suggest that systemic microvascular processes associated with these conditions may underlie the pathogenesis of both retinopathy and kidney glomerular dysfunction. This concept has been established most notably in people with diabetes, with studies showing a close link between diabetic retinopathy and nephropathy (13–18,28,29). For example, in participants with earlier onset diabetes in the Wisconsin Epidemiologic Study of Diabetic Retinopathy, retinopathy was reported to be associated with 10-yr incidence of renal impairment, independent of glycosylated hemoglobin levels, duration of diabetes, BP, and other risk factors (17). Our current study now extends these observations of other retinal vascular signs to the general population.

In subgroups of participants with and without diabetes, with and without hypertension, and with and without both conditions (Table 4), the presence of retinopathy was generally associated with a larger increase in serum creatinine levels and the development of renal dysfunction, although some of these associations were not statistically significant. These findings, coupled with the fact that retinopathy was associated with progressive renal disease independent of diabetes and hypertension in our overall analyses, suggest that susceptibility to microvascular disease (evidenced by retinopathy) is indicative of mechanisms that cause an impairment of kidney function other than those directly stemming from elevated BP or glucose.

A closer examination of these data may provide further clues

Table 3. Six-year change in serum creatinine and development of renal dysfunction, by absence/presence of retinal microvascular abnormalities[a]

		No. at Risk	Six-Year Change in Serum Creatinine				Development of Renal Dysfunction		
			Age-Gender-Race (Mean [SE])[b]	*P*	Multivariable (Mean [SE])[c]	*P*	%	Age-Gender-Race (OR [95% CI])[d]	Multivariable (OR [95% CI])[c]
Retinopathy	Absent	9491	0.023 (0.003)	<0.001	0.024 (0.003)	<0.001	2.3	1.0	1.0
	Present	687	0.085 (0.012)		0.072 (0.012)		7.7	3.1 (2.3 to 4.3)	2.0 (1.4 to 2.8)
microaneurysm	Absent	9105	0.023 (0.003)	<0.001	0.023 (0.003)	<0.001	2.3	1.0	1.0
	Present	340	0.133 (0.017)		0.118 (0.018)		9.9	4.0 (2.7 to 5.9)	2.0 (1.3 to 3.1)
retinal hemorrhage	Absent	9842	0.024 (0.003)	<0.001	0.024 (0.003)	<0.001	2.3	1.0	1.0
	Present	306	0.119 (0.018)		0.102 (0.019)		11.4	4.8 (3.2 to 7.1)	2.6 (1.6 to 4.0)
soft exudates	Absent	9885	0.024 (0.003)	<0.001	0.024 (0.003)	<0.001	2.5	1.0	1.0
	Present	145	0.169 (0.026)		0.153 (0.027)		14.2	5.5 (3.2 to 9.4)	2.7 (1.6 to 4.8)
Arteriovenous nicking	Absent	8631	0.023 (0.003)	0.001	0.023 (0.003)	0.004	2.4	1.0	1.0
	Present	1371	0.053 (0.008)		0.049 (0.008)		4.1	1.6 (1.2 to 2.1)	1.4 (1.0 to 1.9)
Focal arteriolar narrowing	Absent	8392	0.026 (0.003)	0.71	0.026 (0.003)	0.90	2.6	1.0	1.0
	Present	1436	0.029 (0.008)		0.025 (0.008)		2.9	1.0 (0.7 to 1.4)	0.9 (0.6 to 1.3)
Arteriole-to-venule ratio	Quintile 2–5	9469	0.019 (0.004)	0.001	0.020 (0.004)	0.006	2.5	1.0	1.0
	Quintile 1	1893	0.047 (0.007)		0.042 (0.007)		2.7	1.0 (0.7 to 1.4)	0.8 (0.6 to 1.1)

[a] OR, odds ratio; CI, confidence interval.

[b] Mean change (standard error) in serum creatinine (mg/dl) from the second to the fourth examinations associated with a specific retinal lesion, in analysis of covariance models adjusted for age, gender, race, and field center.

[c] Multivariable-adjusted for age, gender, race, field center, diabetes, fasting glucose levels, antihypertensive medication use, mean arterial BP averaged over 6 yr, body mass index, cigarette smoking, alcohol consumption, and fasting HDL cholesterol and triglyceride levels.

[d] OR (95% CI) of developing of renal dysfunction (0.4-mg/dl or more increase in serum creatinine or deaths or hospitalizations for renal diseases between the second and fourth examinations) associated with a specific retinal lesion, in logistic regression models adjusted for age, gender, race, and field center.

Table 4. Six-year change in serum creatinine and development of renal dysfunction, by presence/absence of retinopathy, stratified by diabetes and hypertension status

Diabetes and Hypertension Status	Retinopathy	No. at Risk	Six-Year Change in Serum Creatinine		Development of Renal Dysfunction	
			Multivariable-Adjusted (Mean [SE])[a]	P[b]	%	Multivariable-Adjusted (OR [95% CI])[c]
No diabetes	Absent	8287	0.017 (0.002)	0.32	2.0	1.0
	Present	396	0.028 (0.011)		3.5	1.6 (0.9 to 2.7)
Diabetes	Absent	1064	0.063 (0.020)	0.02	5.0	1.0
	Present	274	0.172 (0.040)		13.9	2.6 (1.6 to 4.3)
No hypertension	Absent	5881	0.009 (0.003)	0.05	1.2	1.0
	Present	295	0.032 (0.012)		5.4	2.9 (1.6 to 5.4)
Hypertension	Absent	3458	0.047 (0.007)	0.01	4.3	1.0
	Present	372	0.109 (0.023)		9.7	1.6 (1.1 to 2.5)
No diabetes or hypertension	Absent	5402	0.008 (0.003)	0.75	1.0	1.0
	Present	210	0.013 (0.013)		2.4	2.1 (0.8 to 5.5)
Both diabetes and hypertension	Absent	597	0.009 (0.034)	0.10	6.5	1.0
	Present	189	0.213 (0.061)		14.3	2.1 (1.2 to 3.8)

[a] Mean change (SE) in serum creatinine (mg/dl) from the second to the fourth examinations (6 yr) associated with retinopathy in analysis of covariance models.
[b] P value represents difference in mean change in serum creatinine comparing presence versus absence of retinopathy.
[c] OR (95% CI) of developing of renal dysfunction associated with retinopathy in logistic regression models. All models include adjustment for age, gender, race, field center, fasting glucose levels, antihypertensive medication use, mean arterial BP averaged over 6 yr, body mass index, cigarette smoking, alcohol consumption, and fasting HDL cholesterol and triglyceride levels. Models in the subgroups with "no hypertension" and with "hypertension" included additional adjustment for diabetes status.

to more specific microvascular mechanisms involved in the development of renal disease (1). The retinopathy lesions that were most strongly related to a larger increase in serum creatinine levels and renal dysfunction (microaneurysm, retinal hemorrhages, and soft exudates) are characteristic of retinal ischemia and reflect a breakdown of the blood-retina barrier in diabetic eyes and are caused by a combination of glucose-induced arteriolar endothelial dysfunction, inflammation characterized by leukocyte activation, reduced fibrinolysis, and increased platelet aggregability (30,31). We found significant, although weaker, associations between arteriovenous nicking with serum creatinine change and renal dysfunction and between lower AVR (reflecting relatively narrowed arteriolar diameters compared with venules) with serum creatinine change only. These two retinal vascular abnormalities have been suggested to reflect systemic inflammation and possibly endothelial dysfunction in the ARIC study (27). Thus, these data suggest that ischemic factors and disruption of the kidney's blood-renal barrier, related possibly to the effect of chronic mild systemic inflammation on dysfunction of the glomerular endothelial cells, may be important in the development of renal impairment in the general community (3,4,32–35).

Limitations of this study should be highlighted. First, the retinal and renal assessments were made at different study visits. We compared retinal data collected at the third examination with the change in serum creatinine levels and development of renal dysfunction between the second (3 yr earlier) and the fourth (3 yr later) examinations. Thus, we cannot distinguish clearly cause and effect in what is essentially a cross-sectional analysis. We note, for example, that there was no association between retinopathy and serum creatinine levels at the second examination. Second, a number of people were excluded, and selection biases, including selective mortality, may have obscured or accentuated some relevant associations. For example, exclusion of participants with retinal vascular abnormalities and renal impairment because of increased mortality before the third examination (when the retinal photographs were taken) may have attenuated some of the observed associations. However, we do not know which biases may have been introduced by excluding participants with missing serum creatinine data or ungradable retinal photographs. Finally, our diagnosis of diabetes was based predominantly on fasting glucose. Lacking a glucose tolerance test, we are unable to evaluate the effect of diabetes, diagnosed exclusively by 2-h levels. In addition, some individuals who were considered normal in fact have diabetes.

In summary, our study showed an association between retinopathy and renal dysfunction that was independent of age, diabetes, hypertension, and other risk factors. Our findings support the hypothesis that microvascular disease may be important in the pathogenesis of renal dysfunction in middle-aged people in the community. Further research may be useful in determining whether retinal changes predict the incidence of renal dysfunction.

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