Six-Year Incidence of Proteinuria in Type 1 Diabetic African Americans

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OBJECTIVE — We sought to report the 6-year incidence of proteinuria and associated risk factors in African Americans with type 1 diabetes.

RESEARCH DESIGN AND METHODS — African Americans (n = 483) with type 1 diabetes were reexamined in a 6-year follow-up study. Proteinuria and creatinuria were measured in 4-h timed urine specimens obtained at initial and follow-up visits. Other evaluations included a structured clinical interview, ocular examination, masked grading of seven stereoscopic fundus photographs, blood pressure measurements, blood assays, and administration of the Beck Depression Inventory (BDI).

RESULTS — Over the 6-year period, 117 (42.9%) of the 473 patients at risk developed "any" proteinuria, defined as either microalbuminuria (26.0%) or overt (16.9%) proteinuria; 87 (23.5%) progressed from micro- or no albuminuria to overt proteinuria and 39 (8.7%) to end-stage renal disease; and 40 (20.6%) regressed. Peak incidence of any proteinuria occurred for patients who were 10–14 years of age or had 5–10 years of diabetes duration at baseline. Multiple regression analysis showed that baseline albumin excretion rate (AER), systemic hypertension, blood cholesterol, and high BDI depression scores were significant and independent risk factors for incidence of any proteinuria.

CONCLUSIONS — In African Americans with type 1 diabetes, the 6-year incidence of proteinuria is high, particularly among young patients and those with a relatively short duration of diabetes at baseline. Baseline AER is the strongest predictor for incidence of any proteinuria.

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Renal disease represents a major complication for patients with both type 1 and type 2 diabetes. It is the leading cause of end-stage renal disease (ESRD) in the U.S., accounting for ~44% of all cases of ESRD (1). The presence of proteinuria, in particular microalbuminuria, is a sign of early diabetic nephropathy. The incidence of micro- or macroalbuminuria in type 1 and type 2 diabetic individuals varies greatly among different populations. Most studies of the incidence of proteinuria in type 1 diabetic patients have been of Caucasians (2–9). African Americans with diabetes are four times more likely to have ESRD compared with Caucasians (1,10,11). Only a few studies in African Americans with diabetes have been reported. However, these studies were mostly limited to type 2 diabetic subjects (12–14).

In a large cohort of African Americans with type 1 diabetes, the New Jersey 725, we have previously shown the frequency of proteinuria to be 49.8% (15,16). We further reported that microalbuminuria is a strong risk factor for mortality, particularly in men (17). Our study participants were re-examined as part of a 6-year follow-up, which provided a unique opportunity to examine the incidence of proteinuria in type 1 diabetic African Americans (18). Thus, the purpose of the present study is to investigate the 6-year incidence of, and risk factors for, proteinuria in type 1 diabetic African-American subjects.

RESEARCH DESIGN AND METHODS

— The original study comprised 725 type 1 diabetic African-American patients who participated in the New Jersey 725 study between 1993 and 1998 (15). Patients diagnosed with diabetes and treated with insulin before 30 years of age and currently on insulin were identified from a random review of 13,615 medical records. Of the 875 eligible patients, 725 (82.9%) were available for the initial baseline examination. Of the 725 patients, 508 (70.1%) participated in the 6-year follow-up examination (18). At follow-up, 25 of the 508 (4.9%) participants were no longer receiving insulin and had not received a pancreas transplant. Since these 25 patients may not truly be type 1 diabetic, they have been excluded, leaving 483 (95.1%) of the 508 patients available for analysis. Details regarding participants and nonparticipants have previously been reported (18). The mean ± SD time of follow-up was 6.1 ± 0.5 years and median follow-up 5.96 years.

Patients were examined in the eye clinic at University Hospital in Newark, New Jersey. On arrival, informed written consent was obtained. At both baseline and follow-up visits, a 4-h timed urine collection was obtained with the patient at rest.

Patient examination included the following: *1*) a structured clinical interview, the purpose of which was to obtain detailed medical and ophthalmologic histories as well as sociodemographic factors and lifestyle variables (i.e., self-reported measures of cigarette smoking, alcohol consumption, and illicit drug abuse); *2*) a dilated retinal examination; *3*) stereoscopic color retinal photographs of the seven standard fields; *4*) weight and

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Abbreviations: AER, albumin excretion rate; BDI, Beck Depression Inventory; ESRD, end-stage renal disease.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

height; and 5) blood pressure measurements repeated twice (using a random-zero sphygmomanometer according to the Hypertension Detection and Follow-up Program protocol) and using the average of both measurements (19). The Beck Depression Inventory (BDI) was administered to patients >18 years of age on both visits.

Urine specimens (4-h timed) were assayed for albumin (using a radioimmunoassay) and for creatinine (using the alkaline picrate method) (SmithKline & Beecham Clinical Laboratory). The inter- and intra-assay coefficients of variation (CVs) for the urine albumin assay were 7.0% for concentration <20 μg/min and 5.0% for concentration ≥20 μg/min. Urine collection was considered adequate if the creatinine concentration in the 4-h urine collection was at least 15–30 mg/dl for men and 10–15 mg/dl for women. Chemstrip regent (Boehringer Mannheim) was used to exclude patients with urinary tract infections.

Venous blood was drawn for measurement of total glycated hemoglobin (using high-pressure liquid chromatography; Bio-Rad, Labcorp Laboratory, Hercules, CA); blood creatinine (using the alkaline picrate method); and HDL, LDL, and total cholesterol (using an enzymatic assay and separation spectrophotometry; Genzyme Diagnostics, Cambridge, MA). The normal range for total glycated hemoglobin is 4.2–7.0% and the intra-assay CV 0.38–1.47%.

The institutional review board of the University of Medicine and Dentistry of New Jersey, New Jersey Medical School, Newark, New Jersey, approved the study.

Definitions

Of the 483 patients, 12 did not have a 4-h urine collection at baseline, and an additional 6 patients did not have a 4-h urine collection at the 6-year follow-up. Two patients with known systemic lupus were excluded.

The 6-year incidence of any proteinuria (either microalbuminuria or overt proteinuria) was calculated for all patients ($n = 273$) who, at baseline, had an AER <20 μg/min, were not on dialysis, and had not received a kidney transplant. Patients who developed any proteinuria were those of this group who, at follow-up, had microalbuminuria (AER 20–200 μg/min) or overt proteinuria (AER >200 μg/min), were on dialysis, or had received a kidney transplant. Patients who developed microalbuminuria were those of this group who, at follow-up, had microalbuminuria (AER 20–200 μg/min). Patients who developed overt proteinuria were those of this group who, at follow-up, either had overt proteinuria, were on dialysis, or had received a kidney transplant.

The 6-year progression to overt proteinuria was calculated for all patients ($n = 370$) who, at baseline, either had no albuminuria or no microalbuminuria. Patients who progressed to overt proteinuria were those of this group who, at follow-up, had overt proteinuria, were on dialysis, or had received a kidney transplant.

The 6-year incidence of ESRD was calculated for all patients ($n = 448$) who did not have dialysis or kidney transplant at baseline. Patients who developed ESRD were those of this group who, at follow-up, either were on dialysis or had received a kidney transplant.

The 6-year incidence of regression of proteinuria was calculated for all patients ($n = 194$) who, at baseline, had any proteinuria. Excluded were patients who were on dialysis or had received a kidney transplant. Patients who regressed were those of this group who, at follow-up, had regressed from microproteinuria to no proteinuria or from overt proteinuria to either micro- or no proteinuria.

Patient age was defined as age at baseline examination. Age at diagnosis of diabetes was defined as the age at which the diagnosis of diabetes was first recorded (by a physician) in the patient's hospital record. Duration of diabetes was the interval between age at diagnosis and age at baseline. Systemic hypertension was defined as present if, at baseline, either systolic blood pressure was ≥140 mmHg or diastolic blood pressure ≥90 mmHg or the patient was taking antihypertensive medication. Macroangiopathy was considered present if, at baseline, *1*) the patient reported having undergone toe, foot, or leg amputation for a circulatory problem (excluding amputation secondary to an infection) or had a myocardial infarction, coronary angioplasty, or a stroke; and 2) any of these were diagnosed by the treating physician following review by one of the investigators (M.R.) of the medical records of either previous hospital admissions or office visits.

Color fundus photographs were graded for diabetic retinopathy severity by the Wisconsin Fundus Photography Reading Center in Madison, Wisconsin. This was done in a masked fashion using the modified Early Treatment of Diabetic Retinopathy Study Airlie House classification of diabetic retinopathy (20–21). Level 10 indicates no diabetic retinopathy, levels 20–53 indicate nonproliferative diabetic retinopathy of increasing severity, and levels 61–85 indicate proliferative diabetic retinopathy of increasing severity or past history of laser photocoagulation or pars plana vitrectomy for proliferative diabetic retinopathy. Retinopathy level for a participant was determined using the severity levels in right and left eyes, giving greater weight to the worse eye.

Patients were considered depressed if, at both visits, the BDI score was ≥14. Baseline socioeconomic factors recorded included patient's level of education (for those ≥25 years of age), personal income (for those ≥18 years of age), and family income. Patient socioeconomic status was classified according to the Goldthorpe and Hope social grading of occupations (22). Smoking was defined as "pack years smoked," obtained by dividing the number of cigarettes smoked per day by 20, multiplied by the number of years smoked until baseline examination.

Statistical analyses

Statistical analyses were performed using the statistical software package SAS, version 9.1. Incidence rates with 95% binomial CIs were calculated for the following end points: any proteinuria, microalbuminuria, overt proteinuria, regression of proteinuria, and ESRD. The criterion for statistical significance was $P < 0.05$.

The proportions of patients who either developed any proteinuria or progressed to overt proteinuria are reported in relation to baseline age at examination, duration of diabetes, and sex. Cochran-Mantel-Haenszel statistics were used to test for trends in incidence of proteinuria among subgroups. For analysis of risk factors, 6-year incidence of any proteinuria was used, since it had the largest number of cases available for analysis. Strengths of the association between the incidence of any proteinuria and various baseline characteristics were tested using logistic regression. For dichotomous variables, odds ratios (ORs) and 95% CIs were used to quantify the association between any proteinuria and each risk factor. The statistical significance of the associations was based on Wald test. For categorical variables with more than two categories, the ORs are presented for each level of the risk factor, com-

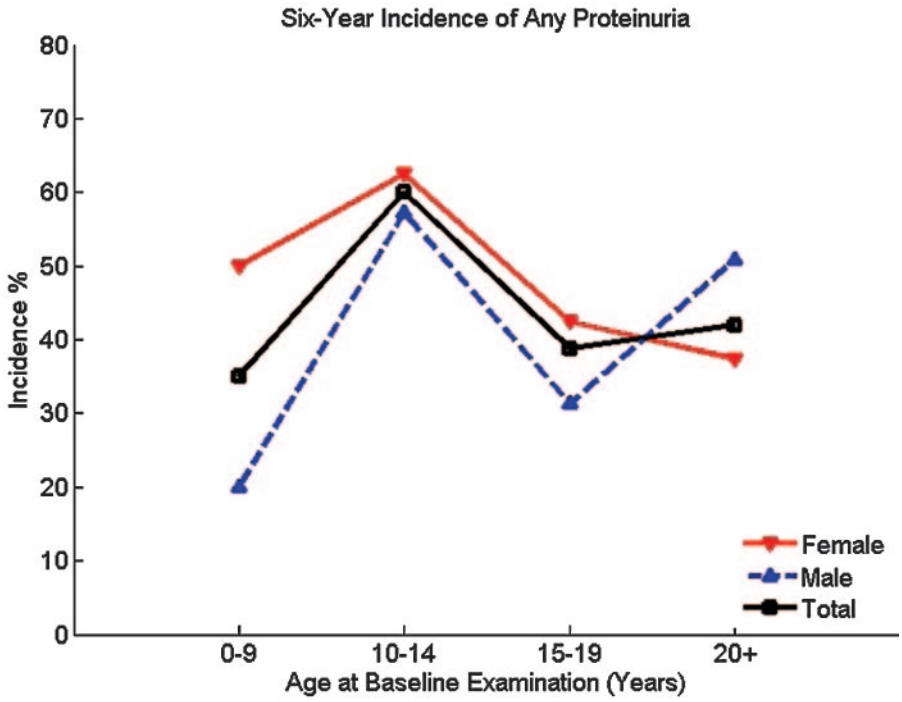

Figure 1—*The 6-year incidence of any proteinuria in type 1 diabetic African-American men and women by age at the baseline examination.*

pared with a reference level thought to represent the lowest risk. All tests are two sided and use a 0.05 significance level. Multiple logistic regression was used to isolate the impact of specific risk factors in relation to incidence of any proteinuria, controlling for the effect of potential confounders. The dependent variable in this regression is any proteinuria. Models were run including baseline characteristics either significant on univariate analysis or likely to contribute to the incidence risk. Because AER and hypertension were highly correlated with each other, alternative models including and excluding AER were also used.

RESULTS — Online appendix Table 1 (available at http://dx.doi.org/10.2337/dc06-2534) shows the baseline characteristics of the 483 patients who had a 6-year follow-up examination.

Six-year incidence of proteinuria

Over the 6-year period, 117 (42.9% [95% CI 36.9–50.0]) of 273 patients with no albuminuria at baseline developed any proteinuria. Of those 273 patients, 71 (26.0% [20.9–31.6]) developed microalbuminuria and 46 (16.9% [12.6–21.8]) overt proteinuria. Of the 370 patients who had either micro- or no albuminuria at baseline, 87 (23.5% [19.3–28.2]) progressed to overt proteinuria. Thirty-nine (8.7% [6.3–11.7]) patients developed ESRD, and 40 (20.6% [15.2–27.0]) regressed (online appendix Table 2). Among the 40 patients who regressed, 9 regressed from overt proteinuria to microalbuminuria, 1 from overt to no proteinuria, and 30 from microalbuminuria to no proteinuria.

Relationship of proteinuria to baseline age, duration of diabetes, and sex

The 6-year incidence of any proteinuria increased sharply from 35% (in patients <10 years of age at baseline) to 60% (in those 10–14 years of age). In patients >20 years of age at baseline, the incidence declined to 37.0% in women while increasing to 51.0% in men (Fig. 1). Among patients with 0–4 years of duration of diabetes at baseline, the 6-year incidence of any proteinuria was 36.1% and increased to 52.3% in those with 5–10 years of diabetes duration at baseline. In patients with 15–30 years of diabetes duration at baseline, the incidence of any proteinuria decreased, except for men, who exhibited a sharp increase in incidence (Fig. 2). There was no significant association between incidence of any proteinuria with either baseline age (P = 0.65) or duration of diabetes (P = 0.51). There was no significant sex difference for incidence of any proteinuria.

The 6-year incidence of microalbuminuria and progression to overt proteinuria showed early and late peaks for both men and women aged 10–14 and ≥20 years at baseline (online appendix Table 3 and online appendix Figs. 3 and 4). The 6-year progression to overt proteinuria increased significantly and positively in men with increasing baseline age (P = 0.03) and duration of diabetes (P = 0.001) and, in women, tended to increase

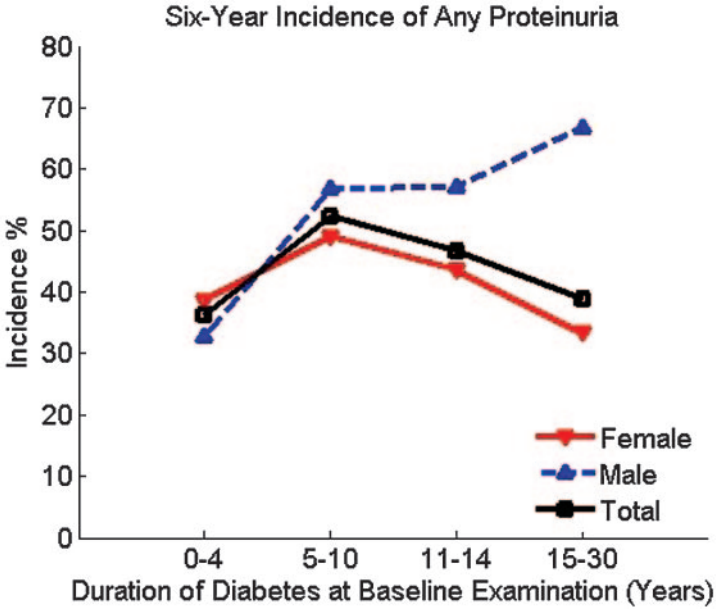

Figure 2—*The 6-year incidence of any proteinuria in type 1 diabetic African-American men and women by duration of diabetes at the baseline examination.*

Table 1—*Multivariate analysis* of 6-year incidence of any proteinuria by baseline characteristics in African Americans with type 1 diabetes*

Baseline characteristics	OR (95% CI)	*P*†
Model 1		
AER (μg/min)	1.14 (1.05–1.23)	<0.0001
Total cholesterol (mg/dl)‡	—	0.03
≤169.49	1.0	—
169.50–198.79	1.04 (0.43–2.48)	—
198.80–236.69	3.09 (1.10–8.72)	—
≥236.70	0.46 (0.16–1.35)	—
Depression	—	0.03
No	1.0	—
Yes	3.01 (1.14–7.99)	—
Model 2		
Systemic hypertension	—	0.01
No	1.0	—
Yes	2.13 (1.20–3.76)	—

*Model 1 includes all variables significant on univariate analysis, and model 2 excludes AER; †overall *P* values; ‡quartiles.

with increasing baseline duration of diabetes ($P = 0.05$).

Baseline risk factors for 6-year incidence of any proteinuria

Univariate analysis

Patients who developed any proteinuria over the 6-year period were more likely, at baseline, to *1*) have higher AER (OR 1.12 [95% CI 1.06–1.18], $P < 0.0001$); systemic hypertension (2.01[1.17–3.47], $P = 0.01$); higher glycated hemoglobin values (1.06 [1.003–1.12], $P = 0.04$); and higher blood cholesterol ($P = 0.04$); *2*) be of lower socioeconomic status (1.67 [1.03–2.71], $P = 0.04$); and *3*) be depressed (2.43 [1.02–5.78], $P = 0.045$) (online appendix Table 4). There was no significant association between incidence of any proteinuria and age at diagnosis, BMI, education, family history of hypertension, insulin dose, peripheral neuropathy, smoking, use of diuretics or ACE inhibitors, macroangiopathy, or diabetic retinopathy severity.

Multivariate analysis

When baseline characteristics, which were significant on univariate analysis, were included in the model, 6-year incidence of any proteinuria was significantly and independently associated with higher baseline AER (OR 1.14 [95% CI 1.05–1.23], $P < 0.001$); higher blood cholesterol levels (3.01 [1.14–7.99], $P = 0.03$); and depression (3.1 [1.10–8.72], $P = 0.03$) (Table 1). When AER was excluded from this model, systemic hypertension was the only baseline characteristic significantly and independently associated with the 6-year incidence of any proteinuria (Table 1). Higher systolic blood pressure was associated with an increased risk of any proteinuria (1.03 [1.008–1.05]).

When baseline duration of diabetes, AER, total glycated hemoglobin, systemic hypertension, and total cholesterol were entered into the model, only AER ($P < 0.0001$) and total cholesterol ($P = 0.02$) were significantly and independently associated with 6-year incidence of any proteinuria. When baseline duration of diabetes, ACE inhibitor use, and AER were entered into the model, AER was the only significant characteristic associated with 6-year incidence of any proteinuria ($P < 0.0001$).

CONCLUSIONS — The results of the present study indicate that the 6-year incidence of any proteinuria (42.9% [microalbuminuria 26.0% and overt proteinuria 16.9%]), progression to overt proteinuria (27.5%), and ESRD (8.7%) are high for African Americans with type 1 diabetes. Baseline AER, systemic hypertension, blood cholesterol, and depression were significant and independent risk factors for incidence of any proteinuria in this population.

Most previously published studies with a similar length of follow-up have reported incidence of proteinuria in predominantly Caucasian type 1 diabetic individuals (6,8,9,23). These studies indicated a lower incidence of proteinuria than that found for our African-American patients. For instance, in the European Diabetes Epidemiology Study, the 7-year incidence of microalbuminuria was 12.6% compared with 26.0% in our African-American patients and that of overt proteinuria 1.7% compared with 16.9% in the present study (9). In our African-American patients, the 6-year incidence of ESRD (8.7%) is also much higher than the 2.2% incidence reported for type 1 diabetic Caucasians by both Klein et al. (7) at 10 years and Finne et al. at 20 years (24). However, we cannot exclude that patient selection may explain differences between studies.

It has been previously reported that in type 1 diabetic Caucasians, there may be peaks of incidence of proteinuria, early and late (2–4). In our African-American patients, the first peak of incidence of microalbuminuria occurs among younger (10–14 years of age) patients at baseline than that which has been previously reported (2). A second peak of incidence of microalbuminuria, contributed mostly by men, is seen in older (≥20 years of age) patients with longer (>15 years) duration of diabetes at baseline (online appendix Table 3 and online appendix Figs. 3 and 4). It has been suggested that the early peak incidence of microalbuminuria may reflect pubertal hormonal changes or that both peaks represent selective susceptibility, possibly genetic (4).

In our African-American male subjects, the risk of progression to overt proteinuria increases significantly with increasing age (online appendix Fig. 3), while the sharp decline seen in those with long duration of diabetes probably reflects selective mortality, since proteinuria is a risk for mortality in this population, particularly in African-American men (17). Thus, our incidence data suggest that type 1 diabetic African-American patients should be evaluated for proteinuria not only at the time of diagnosis of diabetes, but also, importantly, annually thereafter.

An AER, even in the normal range, has been previously reported to be the strongest predictor of incidence of overt proteinuria among type 1 diabetic Caucasians, as found in the present study (rev. in 25). For instance, in the Microalbuminuria Collaborative Study, any AER >10 μg/min was associated with progression to microalbuminuria (6). This is consistent with our data, which show that 70% of patients with AER >11 μg/min developed any proteinuria. It is also noteworthy that, as in other studies, proteinuria

regressed in 40 (20.6%) of our African-American patients (26). In 14 (35%) of these 40 (20.6%) patients, regression may have been due to the institution of either ACE inhibitors or antihypertensive medication. Regression may also be related to lack of either sensitivity or precision of the urine collection methods, since only one single 4-h urine specimen was obtained, or to fluctuations in measurements (25). Thus, it has been suggested that the annual increase in AER should be evaluated, as opposed to one single measurement, to assess progression of renal disease in diabetic patients (25).

In the present study, systemic hypertension, particularly systolic hypertension, was shown to be an independent risk factor for incidence of any proteinuria only when AER was removed from the multiple regression model. The Microalbuminuria Collaborative Study Group reported similar findings (6). Klein et al. (7) have shown that diastolic blood pressure—even in the normal range—is an independent risk factor for overt proteinuria in type 1 diabetic Caucasians. While both AER and systemic hypertension have been found to be risk factors for incidence of proteinuria, it is unclear whether they are markers for, or are involved in, the pathogenesis of the disease (27). In the present study, the lack of association between incidence of any proteinuria and the use of ACE inhibitors may be explained either by the small number of patients taking these medications ($n = 43$) or by the fact that all patients were African American.

In the present study, glycemic control was a significant risk factor for incidence of proteinuria in the univariate analysis only. Similarly, in the Microalbuminuria Collaborative Study, glycemic control was no longer a significant risk factor for incidence of microalbuminuria when AER was excluded from the model (6). This led the authors to suggest that it is the interaction of hyperglycemia with hypertension that may be the important factor in the development of diabetic nephropathy (6). However, previously published studies have shown that poor glycemic control is an independent risk factor for incidence of proteinuria (4,5,7–9,28,29). For instance, in the Diabetes Control and Complications Trial, intensive glycemic control reduced the 9-year incidence of microalbuminuria by 37% (28).

In our African-American patients, high blood cholesterol was an independent risk factor for any proteinuria, as also found in other studies (5,9). For example, data from the European Diabetes Epidemiology Study show that measures of insulin resistance (e.g., increased fasting triglycerides and waist-to-hip ratio) are risk factors for incidence of microalbuminuria (9). Since insulin resistance is present in type 1 diabetes and may precede microalbuminuria, it has been suggested that hypercholesterolemia may act through direct endothelial injury, resulting in capillary leakage of albumin (30). In support of this are *1*) the similarities between the pathology of glomerulosclerosis and that of atherosclerosis and 2) animal study data, which indicate that increased blood lipids may damage glomeruli (31).

A new and intriguing finding of the present study was that depression was an independent risk factor for incidence of any proteinuria. We have previously shown that depression in our African-American patients is significantly associated with higher baseline total glycated hemoglobin, as reported by others for Caucasian diabetic patients (32,33). However, the finding that depression is associated with incidence of proteinuria independently of glycemic control raises the possibility that the depression-hyperglycemia relationship may not be mediated by diabetes self-care behavior and that other pathways should be studied (33). Thus, it is noteworthy that similar pathophysiological changes have been described both for patients with depression and for patients with diabetic renal disease. These include abnormalities in coagulation factors and vascular endothelial function, alteration of immune and inflammatory responses, and insulin resistance (34). Thus, our data suggest that, in addition to blood pressure and glycemic control and lipid-lowering agents, screening for depression might be considered in the management of this population.

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