Diabetes in Urban African-Americans

II. High prevalence of microalbuminuria and nephropathy in African-Americans with diabetes

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OBJECTIVE — African-Americans with diabetes have an increased risk of end-stage renal disease, but underlying mechanisms are poorly understood. We undertook this study to evaluate prevalence and risk factors for renal disease in an African-American population with diabetes.

RESEARCH DESIGN AND METHODS — We measured urine albumin excretion in 578 consecutive patients presenting for the first time to the Grady Memorial Hospital Diabetes Unit in Atlanta, GA. The unit serves an urban population that is predominantly African-American; 85% of patients have non-insulin-dependent diabetes mellitus (NIDDM). Subjects provided 24-h and/or ~3-h urine collections for measurement of albumin and creatinine.

RESULTS — Correlation of the albumin/creatinine ratio (μg/mg) with the 24-h albumin excretion rate was 0.89 ($P < 0.001$, $n = 123$). Although the median duration of diabetes was only 1 year, among all subjects, the estimated prevalence of microalbuminuria (30–300 mg albumin/24 h) was 25% and that of nephropathy (>300 mg albumin/24 h) was 11%. Among African-Americans with NIDDM ($n = 466$), the estimated prevalence of microalbuminuria was 24% and that of nephropathy was 12%; prevalence remained high (25 and 5%, respectively) among 219 patients with <1 year known duration of diabetes. Metabolic control was not associated with disease. However, among all subjects with NIDDM, the odds ratio for nephropathy among subjects with disease duration >5 years compared with those with disease duration <1 year was 4.65 (95% confidence interval [CI] 2.24–9.79), and the odds ratio for nephropathy among subjects with hypertension compared with those without hypertension was 2.64 (CI 1.42–4.93). Odds ratios were comparable among African-Americans with NIDDM. Trends were similar but less significant for subjects with microalbuminuria.

CONCLUSIONS — Albuminuria can be identified reliably and conveniently by the albumin/creatinine ratio in brief urine collections. In our patients, clinically significant albuminuria occurred in 36% of persons at first presentation. Since increased risk was associated with hypertension and control of hypertension can slow progression of renal disease, screening for albuminuria and treatment of hypertension should be aggressive in urban populations of African-Americans with diabetes.

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AER, albumin excretion rate; Alb/Cr, albumin/creatinine; BMI, body mass index; CI, 95% confidence interval; ESRD, end-stage renal disease; GMH, Grady Memorial Hospital; HDL, high-density lipoprotein; IDDM, insulin-dependent diabetes mellitus; LDL, low-density lipoprotein; NIDDM, non-insulin-dependent diabetes mellitus.

While diabetes is the single most frequent cause of end-stage renal disease (ESRD) in the U.S., the risk of ESRD related to non-insulin-dependent diabetes mellitus (NIDDM) is four to five times greater among African-Americans than among Caucasians, even after adjustment for the higher prevalence of diabetes and hypertension among African-Americans (1–3). Although the risk of diabetes-related ESRD is greater among people with insulin-dependent diabetes mellitus (IDDM), NIDDM accounts for most cases of diabetes and thus most cases of diabetes-related ESRD. Specifically, the U.S. Renal Data System has reported that NIDDM causes at least 60% of all treated cases of ESRD (2,4).

In studies examining NIDDM patients of European descent, the association between microalbuminuria and ESRD has been weaker than that in IDDM (5,6). This has been attributed to competing mortality from atherosclerosis in the older NIDDM population. However, in ethnic groups with a high incidence of diabetic nephropathy, including Mexican-Americans, Pima Indians, and Asians, microalbuminuria has been a strong predictor of eventual renal disease (7–10). Whether a similar association exists among African-Americans with NIDDM has not been established.

Information regarding the prevalence and associated risks of renal disease among African-Americans with NIDDM should help to identify groups at highest risk, permitting targeted screening and prevention efforts. Since such information is largely unavailable, particularly in patients with a relatively short duration of diabetes (11), we have measured the prevalence of microalbuminuria and nephropathy in an urban population of African-Americans with diabetes and attempted to identify associated risks for renal disease.

RESEARCH DESIGN AND METHODS

— Between 18 October 1992 and 7 July 1993, 578 patients pre-

senting to the Grady Memorial Hospital (GMH) Diabetes Unit in Atlanta, GA, were examined for proteinuria. Of the 578 subjects, 466 were African-Americans with NIDDM.

The GMH Diabetes Unit serves an urban, economically disadvantaged population that is predominantly African-American; <10% of patients have commercial health insurance, and about 50% have no third-party coverage at all (12). Of patients who say they can read, average literacy is at the sixth grade level (K. Dobberstein, personal communication). To receive subsidized care at GMH, patients must submit proof of income. In a recent financial survey of new patients seen in the Diabetes Unit, 54% of attendees had incomes below the Federal Poverty Guideline, and 69% did not exceed 125% of the Guideline (K. Dobberstein, personal communication).

All patients seen for the first time undergo physical examination, in-depth interview, and laboratory testing. NIDDM is defined by absence of ketosis history, management of diabetes without insulin, presence of obesity (defined by weight >120% ideal body weight) and/or family history of diabetes in at least one first-degree relative, and absence of recurrent pancreatitis or use of diabetogenic medications. Duration of diabetes is estimated by asking patients when a health-care provider first told them they had diabetes. For this study, hypertension is defined as systolic blood pressure >160 mm/Hg, diastolic blood pressure >90 mmHg, and/or use of antihypertensive medication. Body mass index (BMI) is calculated as weight in kilograms per height in meters squared. Laboratory examination includes determinations of fasting serum glucose and routine blood chemistry measurements, HbA_{1c}, cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, and C-peptide. Total cholesterol and triglyceride levels are measured by enzymatic assay (Hitachi 747/717, Boehringer Mannheim, Indianapolis, IN). HDL cholesterol is measured using a precipitation technique (Reagent set HDL-C, Boehringer Mannheim). Low-density lipoprotein (LDL) cholesterol is estimated by Friedewald's formula: LDL = (Total cholesterol − [0.20 * triglycerides + HDL cholesterol]), except when triglyceride levels exceed 300 mg/dl (15). C-peptide is measured by radioimmunoassay (INCSTAR, Stillwater, MN), and HbA_{1c} is measured by high-performance liquid chromatography (DIAMAT glycosylated hemoglobin analyzer, Bio-Rad, Hercules, CA). All patients were asked to produce a urine specimen upon arrival. Patients with ≥2+ protein by standard dipstick were presumed to have clinical nephropathy. Patients with <2+ protein were asked to begin a timed urine collection, generally lasting about 3 h. Activity was limited to ambulation in the clinic area during the collection. The duration and volume of collection were recorded, and microalbumin content was determined using a Boehringer-Mannheim nephelometric technique with a sensitivity of 0.18 mg/dl (16). All patients were asked to bring a 24-h urine collection upon return, for measurement of albumin content. By convention, a normal albumin excretion rate (AER) was defined as <30 mg/24 h, microalbuminuria was defined as 30–300 mg/24 h, and clinical nephropathy was defined as >300 mg/24 h (17).

The validity of the timed collections for identifying clinically important albuminuria was determined by correlating the ratio of albumin (μg) to creatinine (mg) with the 24-h AER. Because of skewness in the AER and ratio data, correlations were also examined after logarithmic transformation (base 10). Only 24-h collections that contained at least 70% of predicted creatinine excretion, based on the equations of Cockcroft and Gault, were included in these analyses (18).

Validity was examined further by calculating sensitivity, specificity, predictive value positive, and predictive value negative of different cutoff points of the albumin/creatinine (Alb/Cr) ratios relative to the 24-h collection results. Based on these results, the Alb/Cr ratios from ~3-h collections were subsequently used as a surrogate for the 24-h albumin excretion rate.

For statistical analysis, Student's *t* test was used to determine differences in group means among men and women from the entire population and from African-Americans with NIDDM. Among subjects with NIDDM, Pearson's correlation coefficients were computed to examine associations between albuminuria and age, hypertension, duration of disease, BMI, lipid and lipoprotein levels, and glycemic control based on HbA_{1c}. Stepwise regression analysis was used to assess the change in the albumin excretion rate by age, sex, diabetes duration, BMI, hypertensive status, and glycemic control as measured by HbA_{1c}. The magnitude of associations was also examined using odds ratios, with categorization of continuous variables for the latter. Significance for all tests was indicated by $P < 0.05$. Data are presented as means + SD.

RESULTS

Subjects

The characteristics of all 578 individuals and the 466 African-Americans with NIDDM are shown in Table 1. Of the 112 patients who were not African-American with NIDDM, 52 were African-American with IDDM, 17 were Caucasian with IDDM, 40 were Caucasian with NIDDM, and the remaining 13 included Hispanics and Asians with NIDDM. In the entire population, a similar proportion of men and women (86.5 and 86.6%) were African-American, but the prevalence of NIDDM was significantly lower among men than among women (75.5% vs. 81.8%, $P < 0.05$). Characteristics of all subjects and African-Americans with NIDDM were similar, mean age was about 50 years, mean diabetes duration was about 5 years, and mean HbA_{1c} was about 10%. In both groups, men tended to have lower BMI than women did. The median duration of diabetes was much shorter than the mean, 1.2 years among women and 1.3 years among men for the

Table 1—*Population characteristics, GMH Diabetes Clinic, October 1992–July 1993*

	All subjects	Men	Women
All subjects			
n	578	245	333
Age (years)	51.6 ± 13.2	49.5 ± 12.8	52.0 ± 8.0
Duration of diabetes (years)	5.7 ± 8.0	5.1 ± 7.0	5.5 ± 8.0
HbA_{1c} (%)	10.0 ± 2.8	10.2 ± 3.0	9.7 ± 2.7
BMI	31.3 ± 7.4	28.4 ± 3.3	32.9 ± 8.1
African-American	496 (85.8)	212 (86.5)	284 (86.6)
NIDDM	473 (81.8)	185 (75.5)*	288 (86.6)*
Hypertension	260 (45.0)	89 (36.3)*	174 (52.3)*
African-American subjects with NIDDM			
n	466	170	265
Age (years)	52.7 ± 12.6	50.9 ± 12.6	54.0 ± 13.5
Duration of diabetes (years)	5.3 ± 7.6	4.8 ± 7.1	5.3 ± 7.9
HbA_{1c} (%)	10.0 ± 2.7	10.3 ± 3.0	9.9 ± 2.6
BMI	32.2 ± 7.1	30.2 ± 5.7	33.7 ± 7.9
Hypertension	221 (47.4)	71 (38.3)	149 (53.0)

Data are means ± SD or number (%). * $P < 0.05$ for men vs. women.

Table 2—*Prevalence of microalbuminuric and clinical nephropathy using the Alb/Cr ratio and 24-h AER, GMH Diabetes Clinic, October 1992–July 1993*

	All subjects	African-American subjects with IDDM
Ratio		
n	543	443
<25 μg/mg	64.4	65.3
25–250 μg/mg	24.4	24.0
>250 μg/mg	11.0	11.9
24-h AER		
n	137	122
<30 mg	57.7	57.0
30–300 mg	24.8	25.9
>300 mg	17.5	17.0

Data are *n* or %.

entire population and 1.2 years for both men and women among African-Americans with NIDDM.

Urine collections

Of the 578 subjects, 33 had ≥2+ protein by standard dipstick in their initial urine specimen and were not asked to produce a timed specimen. Six of these individuals returned adequate 24-h specimens. Albumin excretion was normal in one, one had microalbuminuria, and four had clinical nephropathy. Of the 545 remaining patients, complete data for calculation of an Alb/Cr ratio were available for 537. Urine specimens collected for 24 h were returned by 168 of the 578 subjects (31% of women and 27% of men). About 80% of specimens in both men and women contained at least 70% of the predicted creatinine content, resulting in 137 specimens for analysis, 54 from men and 83 from women.

Of the 466 African-Americans with NIDDM, 23 had ≥2+ protein by standard dipstick, and 5 of them returned adequate 24-h specimens; 1 had microalbuminuria and 4 had clinical nephropathy. Of the 443 remaining African-Americans with NIDDM, complete data for calculation of an Alb/Cr ratio were available for 438; 122 individuals returned adequate 24-h specimens.

Validation of timed collections

The Pearson correlation coefficients between the measured 24-h AERs and Alb/Cr ratios and the measured 24-h AERs and the log-transformed Alb/Cr ratios were 0.89 ($n = 123$, $P < 0.001$) and 0.82 ($n = 123$, $P < 0.001$), respectively. Numbers are less than the total number of 24-h collections because not all individuals who had 24-h collections had 3-h collections, a few subjects had missing data for either 3- or 24-h calculations, and albumin values of zero could not be log-transformed. When values for the Alb/Cr ratios were compared with the measured 24-h AERs, a cutoff point of 25 μg/mg provided reliable identification of AERs >30 mg/24 h, with a sensitivity and specificity of 81 and 89%, respectively. Predictive value positive and predictive value negative were both 86%. Nephropathy, or an AER of >300 mg/24 h, was identified by a ratio cutoff point of 250 μg/mg, with a sensitivity and specificity of 70 and 97%, respectively, and a predictive values positive and negative of 82 and 94%, respectively.

Prevalence of albuminuria

Using the Alb/Cr ratios, the prevalences of microalbuminuria (ratio 25–250 μg/mg) and clinical nephropathy (ratio >250 μg/mg) among all dipstick-negative subjects were 25 and 10%, respectively. Inclusion of the six subjects with gross protein on initial urinalysis who also returned adequate 24-h urine collections increased the prevalence of clinical nephropathy to 11% but did not affect the prevalence of microalbuminuria (Table 1); if albuminuria had been similar in all 33 subjects with gross proteinuria, the prevalence of nephropathy would have been 15%. Analysis of the available 24-h collections yielded similar results; except for a greater tendency to identify nephropathy, microalbuminuria was present in 25% and nephropathy in 18%.

Because albumin excretion at microalbuminuric levels is known to vary from day to day, depending upon level of activity and other parameters (19), we also calculated the prevalence of disease using the higher cutoffs of 30 μg/mg for the ratio and 60 mg for the 24-h AER (Table 2). Using these definitions, the preva-

lence of microalbuminuria was 22% based on the Alb/Cr ratios and 16% based on the 24-h collections. Whether the timed or 24-h urine collections were used for calculation, however, total prevalence of abnormal albuminuria remained over 30%, because of the high prevalence of nephropathy identified on 24-h collections.

Among the African-Americans with NIDDM, and including the dipstick-positive patients with 24-h urine collections, the Alb/Cr ratio identified microalbuminuria in 24% and nephropathy in 12%, while the 24-h collections revealed microalbuminuria in 26% and nephropathy in 16% (Fig. 1). Even among subjects with duration of diabetes of <1 year, the prevalence of significant albuminuria remained high among the African-Americans with NIDDM: microalbuminuria was identified in 25% and nephropathy in 5% by Alb/Cr ratio (n = 219) and in 26 and 10% by 24-h collection (n = 70).

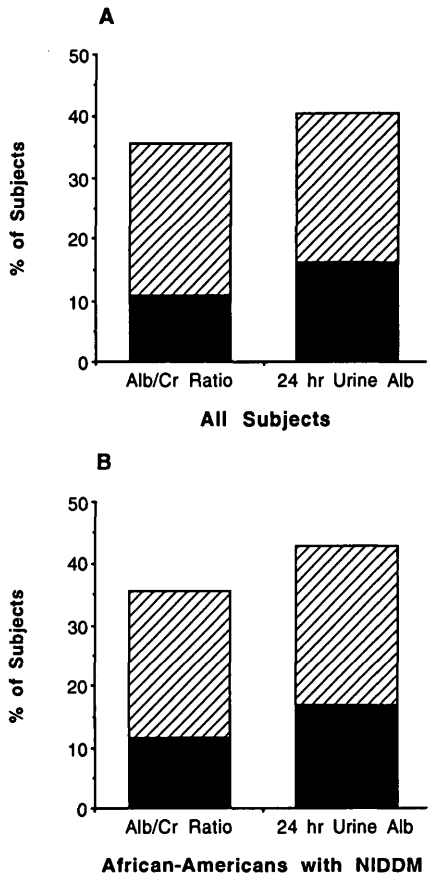

Figure 1—*Prevalence of microalbuminuria (▨) and nephropathy (■) based on ~3-h and 24-h urine collections among all subjects (A) and African-American subjects (B) with NIDDM; GMH Diabetes Clinic; July 1992–October 1993. Microalbuminuria = Alb/Cr ratios 25–250 μg/mg by ~3-h collection and >30 mg by 24-h collection. Nephropathy = Alb/Cr ratios >250 μg/mg by ~3-h collection and >300 mg by 24-h collection.*

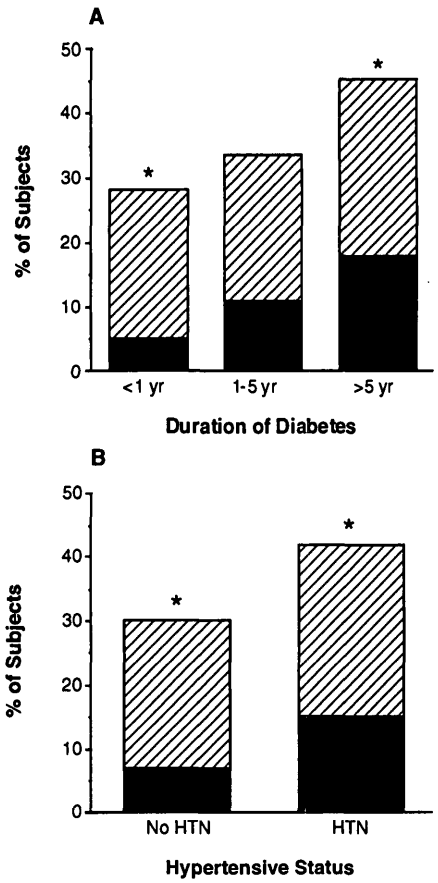

Figure 2—*Proportion of subjects with microalbuminuria (▨; Alb/Cr ratios 25–250 μg/mg) and nephropathy (■; Alb/Cr ratios >250 μg/mg) by duration of diabetes <1 year, 1–5 years, or >5 years (A) and by hypertensive status (B); GMH Diabetes Clinic; July 1992–October 1993. Odds ratio was significantly different for nephropathy, *P < 0.05. HTN, hypertension.*

Risk factors for albuminuria

In additional analyses, we examined associations between microalbuminuria and potential risk factors for disease among subjects with NIDDM. In simple correlation analysis, the log-transformed Alb/Cr ratio was modestly but significantly associated with age (r = 0.14, P < 0.001), duration of diabetes (r = 0.21, P < 0.001), total cholesterol (r = 0.14, P < 0.01), log (triglycerides) (r = 0.14, P < 0.01), and C-peptide level (r = 0.13, P < 0.01). Categorizing the variables and examining odds ratios revealed that the odds of having clinical nephropathy (Alb/Cr ratio >250 μg/mg) were 4.65 (95% confidence interval [CI] 2.24–9.79) times greater among people with disease duration >5 years compared to those with disease duration <1 year (Fig. 2*A*). People with hypertension were 2.64 (CI 1.42–4.93) times more likely to have clinical nephropathy than those without hypertension (Fig. 2*B*). Trends toward an increased prevalence of microalbuminuria (Alb/Cr ratio 25–250 μg/mg) among individuals with hypertension and longer duration of disease were similar but did not reach statistical significance (Fig. 2*A* and *B*). The impact of duration and hypertension on albumin excretion was unchanged (odds ratios 4.60 [CI 2.06–10.47] and 2.96 [CI 1.47–5.99], respectively) when analysis was limited to African-Americans. In stepwise regression analysis examining the relative contributions of all variables (age, duration of diabetes, hypertensive status, HbA_{1c}, BMI, lipids, and C-peptide) to the $\log_{10}$(Alb/Cr ratio), hypertension (P = 0.0015), duration of diabetes (P = 0.0001), C-peptide (P = 0.0005), cholesterol (P = 0.016), and LDL cholesterol (P = 0.0013) remained significant predictors of albuminuria. When this analysis was limited to African-Americans, C-peptide no longer contributed significantly.

CONCLUSIONS— Epidemiological studies have shown a substantially increased risk for ESRD among African-Americans with NIDDM that is not ex-

plained by increased prevalence of diabetes or hypertension (2,3). However, relatively little is known about predialysis renal disease in this population, particularly in patients with diabetes of short duration (11). To approach this problem, we first established the reliability of brief urine collections for identification of microalbuminuria and clinical nephropathy in an urban, predominantly African-American population with diabetes; the Alb/Cr ratio was slightly better than the timed (~3 h) AER in identifying increased 24-h albumin excretion. Other investigators have found similar reliability of the Alb/Cr ratio in different clinic populations (18,20,21). Demonstrating the utility of brief urine collections in our population was essential, because we were able to obtain adequate 24-h urine collections in only 137 subjects. In our population, the prevalence of clinically important albuminuria was 35% based on Alb/Cr ratios and 42% based on 24-h urine collections. The high prevalence of albuminuria in our population of urban African-Americans appears to be substantially greater than that in many other patient populations, although comparison with previous reports is difficult because of differences in methodology, patient selection, and baseline population characteristics. In Caucasian populations with NIDDM, the prevalence of albuminuria (microalbuminuria and nephropathy combined) has been reported by Haffner et al. (7) to be 20% in 44 subjects, by Neil et al. (22) to be 19% in 236 subjects, and by Klein et al. (23) to be 42% in 798 subjects. Mean duration of diabetes (~14 years) was much higher in the study by Klein et al. (23) and may have contributed to their finding of a high prevalence of albuminuria.

The prevalence of albuminuria appears to be higher in non-Caucasian racial groups than in Caucasians. In previous reports, 43% of Mexican-Americans, 32% of Pima Indians, and 75% of Nauruans have been reported to have clinically significant albuminuria. Similar to African-Americans, these groups have a high prevalence of NIDDM and an increased risk of ESRD (7,8,10). Dasmahapatra et al. (11) recently reported a 50% prevalence of albuminuria in African-Americans with NIDDM. Their findings were based on 24-h urine collections and may be compared with the 42% prevalence in our study. However, mean BMI (~34) and duration of diabetes (~14 years) were much greater in their population than in ours, and information on the prevalence of albuminuria in patients with recently diagnosed NIDDM was not available, making it difficult to compare the two patient populations.

In populations with recent onset of NIDDM, there has been relatively little investigation of albuminuria. Several studies in Caucasians with NIDDM have examined individuals with diabetes for <1 year, Uusitupa et al. (24) identified a 20% prevalence of albuminuria in 132 subjects, Standl and Stiegler (25) identified a 24% prevalence in 68 subjects, and Damsgaard and Mogensen (26) identified a 26% prevalence in 81 subjects. The age of the patients was somewhat greater in the latter two studies (61 and 67 years, respectively) than in the first (56 years), which may have contributed to the higher prevalence of disease. In our population, the combined prevalence of microalbuminuria and nephropathy was 30% among African-Americans with NIDDM of <1-year duration, despite an average age of only 50 years.

Possible explanations for the higher prevalence of disease in our patient population include a unique susceptibility of the diabetic kidney in African-Americans, the presence of concomitant hypertension or other risk factors, longer duration of undiagnosed diabetes, and/or delayed access to care (27). An increased prevalence of hypertension in our population relative to other groups of African-Americans with NIDDM could have contributed to the high prevalence of albuminuria identified, but few data are available for comparison. In one study that examined lipids in African-Americans with NIDDM, the prevalence of hypertension was 45%, similar to the 47% prevalence that we report (28). This suggests that the impact of hypertension in our population may be similar to that in other groups of African-Americans with NIDDM. As is the case with many studies of patients with NIDDM, an important limitation of our findings is determining the duration of diabetes accurately; the duration of undiagnosed diabetes may have been substantial in our patients and could have contributed to the high prevalence of albuminuria noted even among subjects with recently diagnosed diabetes. Poverty, low rates of insurance coverage, and low levels of literacy in our population represent barriers to care that are difficult to quantify, and other data regarding access to care in our patients are not yet available. However, data from other African-American populations indicate that access to care is more limited than for other groups and that this contributes to poorer outcomes (27). Finally, it is possible that patients attending a clinic caring only for individuals with diabetes have more severe disease than people with diabetes receiving care elsewhere. However, HbA_{1c} at presentation in 1,494 patients attending our Diabetes Unit (14) was comparable to that in 1,373 people with diabetes attending primary care clinics that serve the same population (M.P. Rafferty, unpublished observations).

In our population, hypertension and longer duration of disease increased the odds of albuminuria among subjects with NIDDM, as has been reported in studies of Caucasian subjects (5,6,30) and one study in African-Americans (11). However, in contrast with studies of Caucasian populations with either IDDM or NIDDM (31–33), we did not find an association between albuminuria and levels of HbA_{1c}. It seems unlikely that pathogenetic mechanisms for nephropathy should be different in our patient population, and it is of interest that Dasmahapatra et al. (11) also failed to identify an association between albuminuria and diabetic control in African-Americans. The

minor contributions of LDL cholesterol and total cholesterol levels to albuminuria in the multivariate analysis could reflect an association with insulin resistance. Insulin resistance and its associated lipid abnormalities have been correlated with microalbuminuria in studies of people with both IDDM and NIDDM (34,35).

Albuminuria has been demonstrated in older populations without diabetes, and it has been suggested that a higher cutoff for disease should be used in persons with NIDDM, to avoid misclassification due to what may be an expected event of aging (36,37). In our cohort, the prevalence of disease remained high (34%) even when an AER of 60 mg/24 h was used to define disease. A number of studies have implicated albuminuria in NIDDM as a greater risk factor for mortality than for ESRD, attributing both the albuminuria and the mortality to generalized vascular disease. Because of the weaker association with ESRD, some authors have argued against screening for albuminuria in NIDDM (35). However, in other racial groups at increased risk for diabetes-related ESRD, antecedent nephropathy has been shown to be a reliable predictor of subsequent renal failure (9,10). Prospective follow-up of our population would be necessary to determine whether the same may be true among African-Americans.

Our study provides new information about a very high prevalence for potentially treatable renal disease in a population of urban African-Americans with diabetes. These observations may have important implications for implementation of screening and preventive strategies in similar populations.

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