Changes in Albumin Excretion in the Diabetes Prevention Program

DIABETES PREVENTION PROGRAM RESEARCH GROUP*

OBJECTIVE — Increased urinary albumin excretion rates have been linked to nephropathy and macrovascular disease. We here describe the baseline prevalence and effect of Diabetes Prevention Program (DPP) interventions on the development and reversal of elevated albumin excretion.

RESEARCH DESIGN AND METHODS — Urine albumin-to-creatinine ratios (ACRs) were calculated from untimed urine collections. Analyses compared participants by treatment group, diabetes and hypertension status, and use of ACE inhibitors or angiotensin II receptor blockers (ARBs).

RESULTS — Elevated ACR levels (≥30 mg/g creatinine) were present at baseline in 198 (6.2%) of 3,188 participants: placebo 5.3%, metformin 6.5%, and intensive lifestyle (ILS) 6.8%. Of the 2,802 with ACR measurements at baseline and at the end of the study, the percentage with elevated levels declined (incident and regression) from 6.2 to 6.1%, with no significant differences between the groups even with adjustment for ACE inhibitor and ARB use. The odds of developing an elevated ACR were 59% higher for a participant who developed diabetes compared with one who did not.

CONCLUSIONS — At entry into the DPP, an elevated ACR was present in 6.2%. Despite the marked decrease in progression to diabetes and the improvement in insulin resistance and other cardiovascular risk markers in the ILS and metformin groups, there was no improvement in ACR, on average, in those two groups. However, the frequency of an elevated ACR was higher in participants who developed diabetes. An increased ACR may have multiple causes, thus obscuring the improvements that might have been expected with the reduction in insulin resistance seen in the DPP.

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Increased urinary albumin excretion rates (AERs) have been linked to the development of diabetic nephropathy and macrovascular disease in patients with type 1 and type 2 diabetes (1,2). The development of increased AER is associated not only with hyperglycemia but also with blood pressure elevations (3–6). Because of difficulties in precisely timing the onset of type 2 diabetes, the duration and degree of glucose intolerance necessary for the development of elevations of AER have been addressed in large, cross-sectional, and longitudinal studies. In cross-sectional studies of Pima Indians, microalbuminuria was found in 8% of those with normal glucose tolerance, 15% of those with impaired glucose tolerance (IGT), and 47% of those with type 2 diabetes (7). These studies have also shown that microalbuminuria was correlated with insulin resistance (8), rising glucose levels (9,10), and the presence of the metabolic syndrome (11).

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Representatives of the National Institutes of Health and the Centers for Disease Control and Prevention participated in the design of the study and in the reporting of the results. Although additional funding was provided by a variety of other sources, as listed in the ACKNOWLEDGMENTS, these sources had no role in the design or conduct of the study or in the reporting of results.

The Diabetes Prevention Program (DPP) was a randomized, prospective, clinical trial that tested strategies to prevent or delay the development of type 2 diabetes in overweight or obese participants aged ≥25 years with elevated fasting glucose and IGT (12,13). We have previously reported that 28% of the 3,819 participants initially entered into the study had hypertension, that the mean urine albumin was 14 mg/g creatinine, and that the albumin-to-creatinine ratio (ACR) had a weak ($r = 0.09$) but statistically significant correlation with systolic blood pressure (SBP) at baseline (14). Both lifestyle modification and metformin treatment resulted in significant decreases in the development of diabetes during the DPP (13). We now analyze the development of elevations in ACR as a function of time and treatment group during the DPP.

RESEARCH DESIGN AND METHODS

— Full details of the protocol, recruitment, and outcomes have been published (5,6). The current report includes 3,188 of the 3,234 participants entering the study who had urine ACR measurements before randomization. This number does not include participants from the troglitazone arm, which was discontinued.

Inclusion and exclusion criteria have been published previously (12,13). Pertinent to the current analysis, the following exclusions should be noted: serum creatinine ≥1.4 mg/dl (124 μmol/l) for men or ≥1.3 mg/dl (115 μmol/l) for women; urine protein ≥2+ on one occasion (dipstick) in the absence of infection or vaginal contamination; and in individuals who were or would become 80 years of age during the study, a direct measure of creatinine clearance <75 ml/min, based on a 24-h urine collection.

Standardized interviewer-administered questionnaires were used to obtain self-reported data on personal medical history, medications, diet, and other factors. Overall, adiposity was assessed by BMI. All anthropometric measures reflected the average of two measurements. Blood pressure was measured with a standard mercury manometer with the participant seated in a chair for 5 minutes

before the first of two measures separated by 30 s. The mean of the two readings were used in the analyses. Hypertension is defined as meeting any of three criteria: SBP ≥140 mmHg, diastolic blood pressure (DBP) ≥90 mmHg, or taking medications that lower blood pressure. Further details have been published elsewhere (5,6,12,13).

Laboratory methods

All of the analytical measurements were performed at the Central Biochemistry Laboratory (Northwest Lipid Research Laboratories, University of Washington, Seattle, WA) as described previously (12,13). Pertinent to the current analyses, creatinine concentrations in the serum and urine were measured by a variation of the Jaffe method and urine albumin concentration was measured by a fluoroimmunoassay. Albuminuria was assessed using a spot urine test of albumin and creatinine. The ACR was used to define categories of albuminuria: normal (<30 mg/g creatinine), microalbuminuria (30-<300 mg/g creatinine), and macroalbuminuria (≥300 mg/g creatinine). In this report, the term "elevated ACR" indicates the combined categories of microalbuminuria and macroalbuminuria.

Statistical analyses

For this analysis, participants were followed for an average of 3.4 years with the end of study assessment ranging from 2.4 to 5.4 years, a period 4 months longer than that reported previously (13) to maximize the available data that were collected during the masked phase of the DPP. Nominal (unadjusted) *P* values and confidence intervals are reported. Logistic regression was used to compare the prevalence of elevated ACR at baseline and end of study. Wilcoxon's signed-rank test was used to assess whether the paired ACR levels changed between baseline and the end of study within groups, whereas the Kruskal-Wallis test was used to compare the ACR levels at the end of the study among the three treatment groups.

RESULTS

Baseline assessments (*n* = 3,188)

The baseline prevalence of elevated albuminuria by baseline characteristics and treatment group are displayed in Fig. 1. Elevated ACR levels were present in 198 participants (6.2%), with similar percentages in the three groups: placebo 5.3%, metformin 6.5%, and intensive lifestyle (ILS) 6.8%. Only 14 participants in the entire study had an ACR ≥300 mg/g creatinine at baseline. ACE inhibitors or angiotensin II receptor blockers (ARBs) were used at baseline in 8.2, 9.9, and 8.6% of the participants in the placebo, metformin, and ILS groups, respectively. At baseline there were no treatment group differences, including systolic and diastolic blood pressure, the presence of hypertension, mean urine ACR, or serum creatinine.

When the baseline ACR measurements were broken down by quartiles (≤3.7, >3.7–5.5, >5.5–9.7, and >9.7 mg/g), those with higher ACR levels had higher BMIs, greater waist circumferences, higher fasting insulin level, higher SBP and DBP levels, and greater frequencies of hypertension (Table 1).

Paired baseline and end of study assessments (*n* = 2,802)

Of the participants with baseline evaluations, 2,802 had measurements performed at the end of the study. In these 2,802 participants the total number with elevated ACR levels did not change significantly, going from 174 (6.2%) to 171 (6.1%) participants, after a mean of 3.4 years in the study. These numbers comprise both a regression to normal from prior elevated levels plus incident cases (Table 2). The net change in individuals moving from normal to elevated ACR (numbers worsening minus numbers regressing) were 9 (placebo), 0 (metformin) and −12 (ILS). Overall, there were more improvements in the ILS group and more individuals who worsened in the placebo group, although this difference was not statistically significant ($P = 0.07$) (Table 2). Despite the significant decrease in the incidence of diabetes among the ILS and metformin groups compared with the placebo group, there were only minimal and not statistically significant differences in the frequency of elevated ACR levels between the groups (placebo 6.3%, metformin 6.7%, and ILS 5.4%) at the end of the study. The median ACR levels in all three groups did not change significantly and the changes did not differ significantly among the treatment groups: placebo 0.10 mg/g creatinine, metformin 0.12 mg/g creatinine, and ILS 0.06 mg/g creatinine. Although at the end of the study, the frequency of SBP ≥140 mmHg was lower in the ILS group (10.1%) than in the other two groups (placebo 12.2% and metformin 12.6%), this difference was not significantly different. The differences in frequencies of DBP ≥90 mmHg at the end of the study approached significance ($P = 0.056$) among the three groups: ILS 5.7%, metformin 8.5%, and placebo 6.7%.

The frequency of ACE inhibitor or ARB use increased in all three groups, from 8.3 to 23% in the placebo group, from 9.6 to 23.3% in the metformin group, and from 8.7 to 17.9% in the ILS group. The increase in the ILS group was significantly less than that in the other two groups ($P = 0.023$), possibly because of the slightly lower frequency of hypertension at the end of the study in this group. We performed detailed analyses to determine incident new cases of elevated ACR levels versus regression to normal, with and without use of ACE inhibitors or ARBs, because the use of these drugs at baseline might have prevented the detection of a possible elevated level and the institution of therapy with these drugs might either cause regression to normal of preexisting elevated levels or prevent the development of abnormal levels. For example, of the 931 ILS participants who had a baseline and end-of-study assessment for ACR, 62 (6.7%) had elevated levels at baseline. However, there were an additional 71 (7.6%) participants who were taking ACE inhibitors or ARBs. Thus, the prevalence of elevated ACR at baseline, when unmasked by concurrent use of ACE inhibitors or ARBs, could have been between 6.7 and 14.3%. Among the 869 ILS participants who did not have elevated ACR levels at baseline, 28 (3.2%) had elevated ACR levels at the end of study examination and an additional 70 (8.1%) participants initiated treatment with ACE inhibitors or ARBs after baseline, so the incidence of an increased ACR ranged from 3.0 to 11.3%. Conversely, 40 of the 62 participants (64.5%) with elevated ACR levels at baseline no longer had elevated levels at the end of study; however, 18 of these 40 were taking ACE inhibitors or ARBs so the resolution of an elevated ACR level ranges from 35.5 to 64.5%. When the overall prevalence (new incidence cases and reversal of elevated ACR levels) for the three groups was analyzed in this way, the estimates of elevated ACR levels at the end of the study were not significantly different among the three treatment groups, even adjusted for ACE inhibitor and ARB use. In addition, the treatment assignments had no significant effect on log ACR at the end of the study whether or not adjustments were made for the baseline covariates: log-

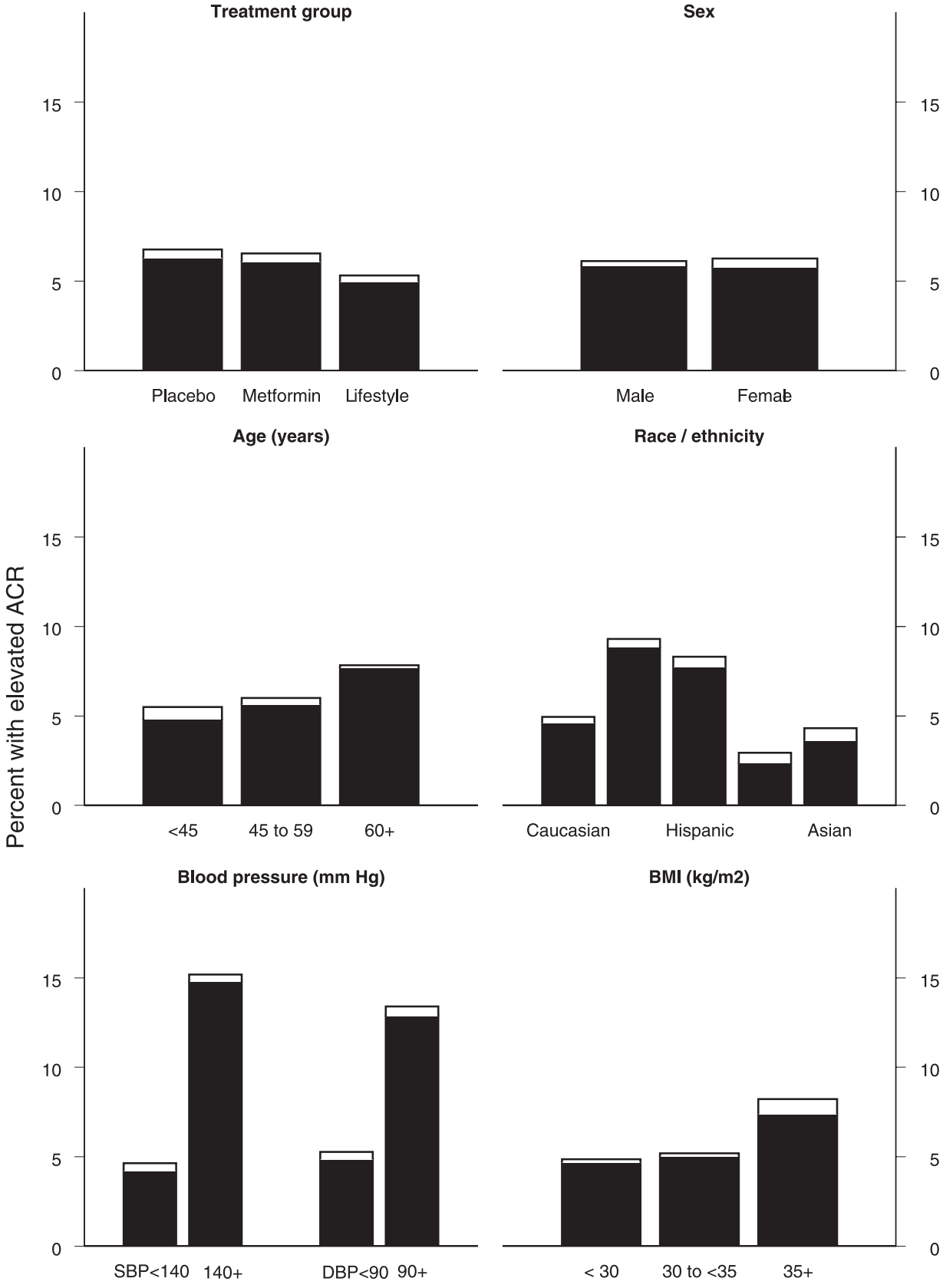

Figure 1—*Prevalence of elevated ACR levels at baseline by subgroups. The height of the bars represents the percentage of subjects with an elevated ACR (≥30 mg/g), ■ represents microalbuminuria (ACR between 30 and <300), and □ represents macroalbuminuria (ACR ≥300). The prevalence of albuminuria differed among subgroups for age, race/ethnicity, SBP, DBP, and BMI* ($P < 0.05$).

Table 1—*Baseline characteristics by ACR quartiles*

	Overall (mg/g)	ACR quartiles ≤3.7 mg/g	3.7 to ≤5.5 mg/g	5.5 to ≤9.7 mg/g	>9.7 mg/g	*P*
n	3,188	772	818	798	800	
Sex (% female)	2,158 (68)	453 (59)	536 (66)	595 (75)	574 (72)	<0.001
Age (years)	50.6 ± 10.7	50.0 ± 10.6	50.3 ± 10.4	50.6 ± 10.5	51.6 ± 11.1	0.02
BMI (kg/m^2)	32.5 ± 8.5	31.8 ± 7.2	32.4 ± 7.1	32.3 ± 7.1	33.5 ± 7.2	<0.001
Waist circumference (cm)	103 ± 19	102 ± 16	103 ± 16	103 ± 16	106 ± 16	<0.001
Fasting glucose (mg/dl)	106 ± 11	106 ± 9	106 ± 9	106 ± 9	107 ± 9	0.12
120-min glucose (mg/dl)	165 ± 24	165 ± 20	164 ± 20	164 ± 20	166 ± 20	0.10
A1C (%)	5.98 ± 0.65	5.94 ± 0.55	5.99 ± 0.54	6.00 ± 0.54	6.00 ± 0.54	0.04
Fasting insulin (μU/ml)	23.7 ± 2.1	22.1 ± 1.8	23.6 ± 1.8	23.8 ± 1.8	25.6 ± 1.8	<0.001
Systolic blood pressure (mmHg)	124 ± 19	120 ± 16	122 ± 16	124 ± 16	128 ± 16	<0.001
Diastolic blood pressure (mmHg)	79 ± 13	77 ± 11	78 ± 10	79 ± 10	81 ± 10	<0.001

Data are *n* (%) for categories and means ± SD for continuous variables except for fasting insulin represented as geometric mean. All variables except female sex and age are adjusted for baseline age, sex, and race/ethnicity.

transformed ACR, systolic and diastolic blood pressures, use of ACE inhibitors/ARBs, age, sex, and race/ethnicity.

The odds of developing an elevated ACR level were 59% higher for a participant who developed diabetes compared with one who did not, and there was no difference among the three treatment groups in this regard (Fig. 2). Participants in the placebo group who developed diabetes experienced a significantly greater change in ACR compared with those without diabetes ($P = 0.036$; median 0.02 vs. 0.34 mg/g creatinine) (Fig. 3), although these changes were so small as to be of little clinical importance. The presence of hypertension also increased the median ACR in diabetic and nondiabetic participants in each treatment group (Fig. 3).

CONCLUSIONS — In participants entering the DPP, the frequency of an elevated ACR level was 5.8%, a proportion considerably lower than that found in other comparable populations. In the Third National Health and Nutrition Examination Survey (1988–1994), microalbuminuria was present overall in 7.8% of women and 5.0% of men but in those with the metabolic syndrome, microalbuminuria was found in 12% of men and 13% of women (11). As mentioned previously, 15% of Pima Indians with IGT have microalbuminuria (7). In other studies in subjects with IGT, 9.9% of Australians (15), 14 (16) and 24% (17) of Japanese, 11.8% of Koreans (18), and 19% of Indians had microalbuminuria (19).

The reasons that our participants had such low rates of elevated ACR levels are not clear. Blood pressure was particularly well controlled (mean SBP 123.7 ± 14.7 and mean DBP 78.3 ± 9.3 mmHg). These blood pressures are substantially lower than those found in the patients with microalbuminuria in the Australian Diabetes, Obesity, and Lifestyle (AusDiab) Study (151 ± 23/78 ± 13 mmHg) (15). Furthermore, entry exclusion criteria (creatinine ≥1.4 mg/dl in men, ≥1.3 mg/dl in women, creatinine clearance <75 ml/min in subjects aged >80 years, and ≥2+ proteinuria on dipstick) may have removed many with or at high risk for developing elevated ACR. Another issue is the use of ACE inhibitors or ARBs, which may lower urinary albumin excretion; these drugs were used in 6.7, 8.3, and 6.1% in the ILS, metformin, and placebo groups, respectively. As these drugs were often used for hypertension treatment without knowing baseline albuminuria status, the frequency of elevated ACR levels could have been as high as 13.0, 14.4, and 11.1% in the ILS, metformin, and placebo groups, respectively, making these percentages more in line with the frequencies found in other studies.

Table 2—*Change in classification between normal and elevated ACR from baseline to end of study by treatment group*

Baseline	End-of-study status	Placebo	Metformin	ILS
Normal ACR		890 (95)	869 (93)	869 (93)
	Developed elevated ACR	33 (4)	35 (4)	28 (3)
	Remained without elevated ACR	857 (96)	834 (96)	841 (95)
Elevated ACR		50 (5)	62 (7)	62 (7)
	Resolved elevated ACR	24 (48.0)	35 (56)	40 (64)
	Remained with elevated ACR	26 (52)	27 (44)	22 (35)
Total		940	931	931
	Stable status	883 (93.9)	861 (92.5)	863 (92.7)
	Worsened albuminuria	33 (3.5)	35 (3.8)	28 (3.0)
	Improved albuminuria	24 (2.6)	35 (3.8)	40 (4.3)
	Net increase in elevated ACR	9 (1.0)	0 (0.0)	−12 (−1.3)*

Data are *n* (%). Elevated ACR is defined as ACR ≥30 mg/g. *$P_{trend} = 0.07$ for test of linear trend between treatment group (placebo to metformin to ILS) and change in category (worsened to stable to improved).

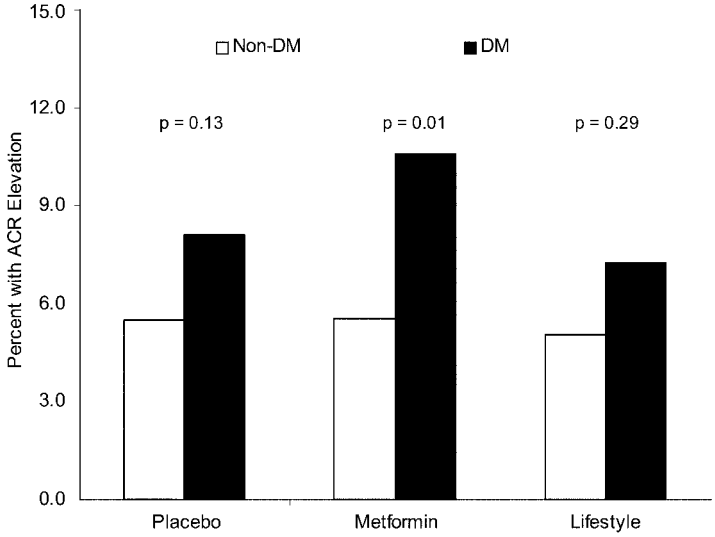

Figure 2—*Prevalence of elevated ACR (≥30 mg/g) at end of study by treatment group and diabetes (DM) status.* P *value indicates the difference in rates between the diabetic and nondiabetic treatment groups.*

Elevated ACR correlated with insulin resistance in the DPP, and this has also been shown in other studies of individuals with normal and IGT (8). Therefore, it would have been expected that the interventions with ILS and metformin, which decreased the development of diabetes and decreased the degree of insulin resistance (20,21), would similarly decrease albumin excretion and the frequency of microalbuminuria. Furthermore, metformin has previously been shown to decrease urinary albumin excretion in patients with type 2 diabetes (22). However, this was not the case in the DPP cohorts. One possible reason is that although this is the largest study to have addressed this issue, we still did not have enough power to detect such changes, as there were relatively small numbers who had microalbuminuria at baseline and there was only a short time to detect incident cases of microalbuminuria.

The presence of micro- and macroalbuminuria in patients with IGT and diabetes has been thought to be a marker of increased cardiovascular risk (2,23,24). However, despite the improvement in insulin resistance and other cardiovascular risk markers in the ILS and metformin groups (21,22), there was no improvement in ACR in those two groups.

Obesity has been associated with glomerular hypertrophy, increased urinary albumin excretion, and even decreased glomerular filtration rate in the absence of diabetes in some patients (25). It may be that the increased ACR found in the DPP participants has multiple causes, including insulin resistance, endothelial dysfunction, early diabetic nephropathy related to hyperglycemia, hypertensive nephropathy, and focal sclerosis related to obesity. We did not adjust for antihypertensive drug use other than ACE inhibitors and ARBs, and this may also be a shortcoming. Thus, the modest changes in insulin resistance and weight loss that occurred with active intervention in the DPP over the relatively short period of time of 3.4 years may be only one set of factors that need to be corrected to affect the kidney disease in this patient population.

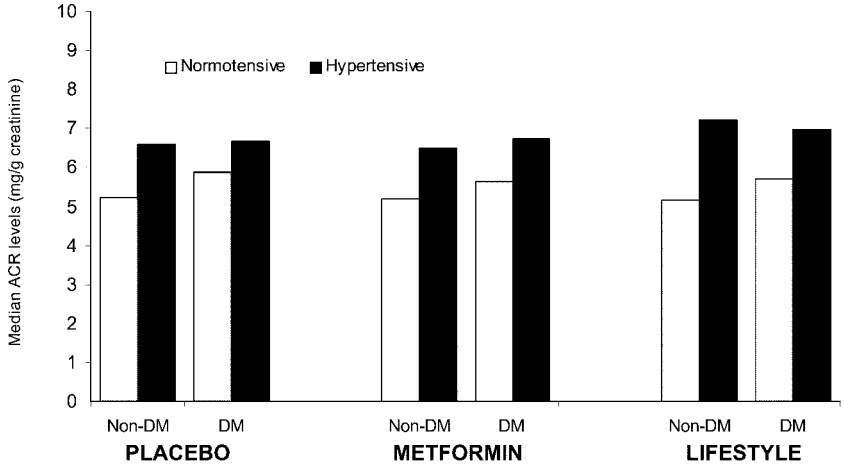

Figure 3—*Median ACR (milligrams per gram) by diabetes (DM) and hypertension status at end of study.*

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No potential conflicts of interest relevant to this article were reported.

APPENDIX

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