Does Microalbuminuria Predict Diabetic Nephropathy?

BAHMAN P. TABAEI, MPH
ABDUL S. AL-KASSAB, MD, PHD
LIZA L. ILAG, MD
CATHERINE M. ZAWACKI, RN, BSN, BS
WILLIAM H. HERMAN, MD, MPH

OBJECTIVE — To describe risk factors associated with microalbuminuria (MA) in subjects with diabetes, investigate the predictive value of MA as a marker of risk for diabetic nephropathy (DN), and define risk factors associated with the development and progression of MA.

RESEARCH DESIGN AND METHODS — We conducted a prospective longitudinal study of 23 diabetic subjects with persistent MA and 209 diabetic subjects without MA who attended diabetes clinics at the University of Michigan Medical Center in 1989 and 1990. Both groups were examined at baseline and after 7 years. At baseline, urinary albumin–to–creatinine ratios were studied in random, first morning, and 24-h urine samples. At follow-up, a 12-h overnight urine sample was collected and analyzed for albumin and creatinine. At baseline, MA was defined by at least two separate urine specimens with albumin–to–creatinine ratios between 30 and 299 μg albumin per milligram of creatinine.

RESULTS — MA regressed in 56% of subjects with baseline MA without systematic application of corrective measures and developed in 16% of subjects without baseline MA. The predictive value positive of MA as a marker of risk for DN was 43%, and the predictive value negative was 77%. In the combined cohort, the incidence and progression of MA were significantly associated with poor glycemic control and duration of diabetes between 10 and 14 years.

CONCLUSIONS — MA may not be as sensitive and specific a predictor of DN as previously suggested. Other markers of risk for DN are needed for optimal clinical management.

Diabetes Care 24:1560–1566, 2001

Microalbuminuria (MA) is considered to be a risk factor for diabetic nephropathy (DN) and progressive renal insufficiency in diabetes (1–5). Primary prevention of DN is feasible if the factors that initiate the change from normal urinary albumin excretion to MA and from MA to DN can be identified and treated (6). Cross-sectional and longitudinal studies conducted in type 1 and type 2 diabetic patients have identified risk factors associated with the development of MA and with the progression of MA to DN. These include lower BMI, longer duration of diabetes, hyperglycemia, hypertension, dyslipidemia, cigarette smoking, and family history of hypertension (4,7–12). Although MA has been considered to reflect an early stage in an irreversible process, recent investigations have cast doubt on this by demonstrating that MA often regresses to normal (4,13,14). This has raised questions about the predictive value of MA.

This prospective longitudinal study was conducted to investigate the predictive value of MA as a marker of risk for DN and to define risk factors associated with the development and progression of MA in subjects with type 1 and type 2 diabetes.

RESEARCH DESIGN AND METHODS

— We conducted a prospective longitudinal study of patients with type 1 and type 2 diabetes with and without MA. The study population was drawn from a cross-sectional study of 554 diabetic patients who attended pediatric and adult diabetes clinics at the University of Michigan Medical Center in 1989 and 1990. A total of 347 subjects with negative or trace leukocytes, blood, and protein by urine dipstick provided two or more random first-morning or 24-h urine specimens for quantitative microalbumin and creatinine testing over a 1-year period. Of the 347 subjects eligible for the follow-up study, 4 provided one random urine sample, 62 provided two random urine samples, 104 provided three random urine samples, and 177 provided four random urine samples. In addition, 49 provided a 24-h urine only, 27 provided a first-morning urine only, and 172 provided both a 24-h urine and a first-morning urine sample. Based on the results of these tests, diabetic patients were classified as normoalbuminuric or microalbuminuric. At baseline, normoalbuminuria was defined as urinary albumin–to–creatinine ratio <30 μg/mg in two or more urine samples and no more than one value ≥30 μg/mg. MA was defined as urinary albumin–to–creatinine ratio 30–299 μg/mg in at least two urine samples. At follow-up, DN was defined by albumin–to–creatinine ratio >300 μg albumin per milligram creatinine. A total of 232 diabetic subjects from the initial cohort were included in the 7-year follow-up study. These included all 23 microalbuminuric subjects at baseline and 209 normoalbuminuric subjects matched to the microalbuminuric group on the basis of age (±5 years), type of diabetes, and duration of diabetes (±5 years) using frequency matching.

Protocol

At both baseline and follow-up, the study was reviewed and approved by the Insti-

From the Departments of Internal Medicine and Epidemiology, University of Michigan Health System, Ann Arbor, Michigan.

Address correspondence and reprint requests to William H. Herman, University of Michigan Medical Center, Division of Endocrinology and Metabolism, 1500 East Medical Center Drive, 3920 Taubman Center, Ann Arbor, MI 48109-0354. E-mail: wherman@umich.edu.

Received for publication 19 January 2001 and accepted in revised form 23 May 2001.

Abbreviations: DN, diabetic nephropathy; IQR, interquartile range; MA, microalbuminuria; OR, odds ratio; PVN, predictive value negative; PVP, predictive value positive.

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

tutional Review Board of the University of Michigan Medical Center, and all subjects provided written informed consent.

Baseline. During the initial visits (1989–1990), age, race, sex, type and known duration of diabetes, height, weight, blood pressure, tobacco use, and family history of hypertension were recorded. Laboratory evaluations included serial measurements of total GHb and total cholesterol, HDL cholesterol, and triglycerides over a 12-month period. Urinary albumin–to–creatinine ratios were assessed in two or more random first-morning and 24-h urine samples.

Follow-up. During the 7-year follow-up period, patients received usual clinical care. Between 1996 and 1998, subjects were recontacted and invited to participate in the follow-up study. Participants were admitted to the General Clinical Research Center in the evening for a 14-h overnight stay. A standardized questionnaire was administered. ACE inhibitor use was determined for each participant and verified by a health care professional. A urine dipstick test was performed to rule out leukocytes and blood, and a 12-h overnight urine sample was collected and analyzed for albumin and creatinine.

Measurements

All laboratory measurements were performed in the Michigan Diabetes Research and Training Center Chemistry Laboratory. Urinary albumin concentration was measured by enzyme-linked immunosorbent assay with an Albuwell kit produced by Exocell (Philadelphia, PA). Urinary creatinine was measured by a standard dry slide enzymatic method based on the creatinine amidohydrolase assay, adapted for automated analysis using a Kodak Ektachem 700 analyzer (Rochester, NY). Total GHb was measured by affinity chromatography, followed by spectrophotometry using a Glyc-Affin GHb kit manufactured by Isolab (Akron, OH). Serum total cholesterol and serum triglycerides were measured with a Singlevial kit from Boehringer Mannheim (Indianapolis, IN). HDL cholesterol was determined with a kit manufactured by Roche (Nutley, NJ). Mean GHb, total cholesterol, HDL, and triglyceride values were calculated as the mean of all determinations obtained during the baseline period.

BMI was calculated as weight in kilograms divided by height in meters squared. Arterial blood pressure was measured with a sphygmomanometer to the nearest 2 mmHg in the right arm with the patient in sitting position. Reported values are the average of all readings obtained during the baseline period.

Data analysis

Descriptive statistics were obtained for all variables using medians and 25th and 75th interquartile ranges (IQRs) for continuous variables and using frequencies and proportions for categorical variables. Differences between groups were assessed with the Cochran-Mantel-Haenszel χ^2 test (15–17) and Mantel-Haenszel test-based confidence limits (18) controlling for age, type, and known duration of diabetes.

The frequency of progression from normoalbuminuria to MA/DN and from MA to DN as well as the statistical significance of differences between progressors and nonprogressors were assessed with the Wilcoxon's rank-sum test for continuous variables and Fisher's exact test for categorical variables. Tests for linear trend in risk were carried out with Mantel-Haenszel χ^2 test for trend.

The predictive value positive (PVP) for MA as a marker of DN was defined as the probability of remaining microalbuminuric or developing DN given MA at baseline. The predictive value negative (PVN) for MA as a marker of DN was defined as the probability of remaining normoalbuminuric given an absence of MA at baseline. They were calculated as follows:

$$\text{PVP} = \text{true}\ [+]/(\text{true}\ [+] + \text{false}\ [+]) = a/(a + b), \text{ and}$$

$$\text{PVN} = \text{true}\ [-]/(\text{true}\ [-] + \text{false}\ [-]) = d/(c + d),$$

where a is the number of individuals with MA who remained microalbuminuric or developed DN (true [+]); b is the number of individuals with MA who regressed to normoalbuminuria (false [+]); c is the number of individuals with normoalbuminuria who progressed to MA or developed DN (false [−]); and d is the number of individuals with normoalbuminuria who remained normoalbuminuric (true [−]).

Bivariate and multivariate logistic regression analysis was performed to evaluate the strength of the association between the predictor variables and the probability of progression adjusted for type of diabetes and baseline MA status. Odds ratios (ORs) were estimated for duration of diabetes (0–4, 5–9, 10–14, +15 years), GHb (<10; ≥10%), total cholesterol (continuous, in milligrams per deciliter), triglycerides (continuous, in milligrams per deciliter) and ACE inhibitor use at follow-up (1 = yes, 0 = no). The significance of variables in the models was assessed by the Wald χ^2 test. The −2 log likelihood ratio test and the score statistic were used to test the overall significance of the models. The fit of the models was assessed by the Pearson χ^2 test and the deviance statistic. The possible interactions between variables were assessed using the Breslow and Day χ^2 test. All variables were modeled as continuous and categorical, and smoothed plots of the probabilities predicted by fitting a generalized additive model were examined to select the appropriate form of the final bivariate and multivariate models. To measure the relative risks of the predictor variables on the outcome, ORs and their 95% CIs were calculated. All continuous variables were categorized to the 50th percentile of their distribution for the χ^2 and logistic regression analyses.

$P < 0.05$ was defined as the limit of statistical significance. All statistical analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC).

RESULTS

From the original cohort, 232 diabetic subjects were selected for study, including 23 with MA and 209 with normoalbuminuria (Fig. 1). All subjects had follow-up for 7 years after their baseline evaluation. During the course of the study, 120 subjects were lost to follow-up or refused to participate, and 2 subjects died. Thus, a total of 110 (48%) diabetic subjects completed the longitudinal study (83% of the cases and 44% of the control subjects). Of this group, 11 subjects were excluded from the analysis because the criteria for frequency matching were not met. Comparisons between participants and those lost to follow-up showed no differences between the two groups with respect to their baseline characteristics (data not shown).

Baseline variables associated with MA

Table 1 describes the clinical and metabolic characteristics of diabetic subjects at

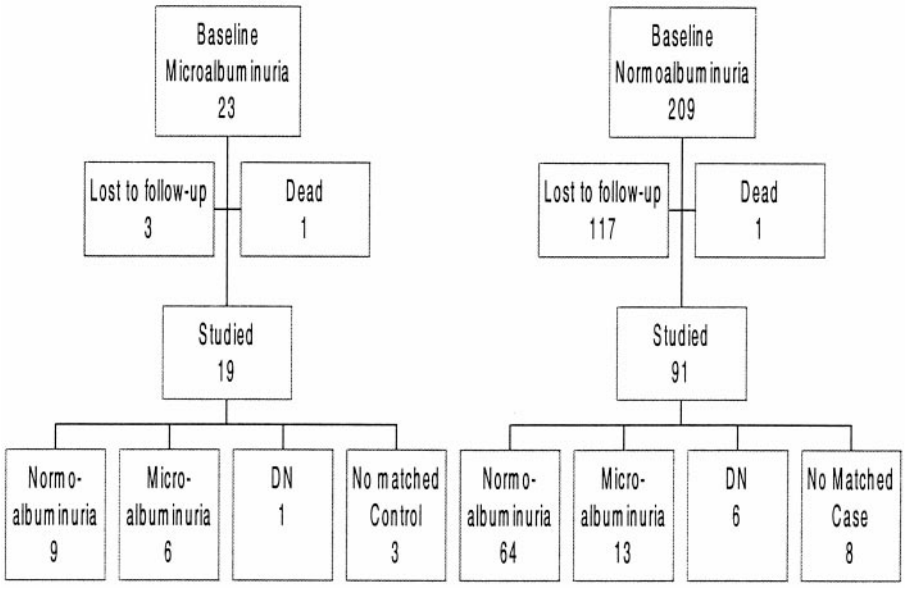

Figure 1—*Outcome of diabetic subjects with normoalbuminuria and MA after 7 years of follow-up.*

baseline by type of diabetes and group. In the groups with type 1 and type 2 diabetes, the normoalbuminuric and microalbuminuric subjects did not differ with respect to BMI, blood pressure, GHb, lipids, smoking, or family history of hypertension. In both types of diabetes, more female subjects had MA at baseline, and the overall difference was statistically significant.

Risk of progression to MA and DN

Over the 7-year observation period, five (56%) of the microalbuminuric subjects with type 1 diabetes became normoalbuminuric, three (33%) remained microalbuminuric, and one (11%) developed DN. Among the normoalbuminuric subjects with type 1 diabetes, six (11%) developed MA and one (2%) progressed to DN. Of the subjects with type 2 diabetes, four (57%) of the microalbuminuric subjects became normoalbuminuric, three (43%) remained microalbuminuric, and none progressed to DN. Among the normoalbuminuric subjects with type 2 diabetes, seven (24%) developed MA and five (17%) progressed to DN.

Thus, of the subjects with MA at baseline, 56% regressed to normoalbuminuria. No statistically significant association was found between age and regression (data not shown). In the microalbuminuric subjects who regressed to normoalbuminuria, baseline GHb levels were significantly lower compared with nonregressors. No significant association was found between ACE inhibitor use at follow-up and regression to normoalbuminuria. Only three (33%) of regressors (all with type 2 diabetes) were on ACE inhibitor treatment at follow-up compared with five (71%) of the nonregressors (two [50%] with type 1 and three [100%] with type 2 diabetes).

Predictors of progression to MA and DN

Table 2 presents the baseline clinical and metabolic characteristics of the subjects who progressed from normoalbuminuria to MA or from MA to DN and those who did not progress by type of diabetes. Because the baseline characteristics of nonprogressors with normoalbuminuria or MA did not differ significantly (data not shown), they were combined as one group.

In the type 1 diabetic subjects, systolic blood pressure, GHb, and triglycerides were significantly higher in progressors compared with nonprogressors. In this group, more progressors were treated with ACE inhibitors at follow-up compared with nonprogressors (88 vs. 6%). In the type 2 diabetic subjects, GHb and triglycerides were significantly higher in progressors compared with nonprogressors. ACE inhibitor use at follow-up did

Table 1—*Characteristics of subjects at baseline*

	Type 1 diabetes		Type 2 diabetes	
Variable	Normal	MA	Normal	MA
n	54	9	29	7
Age (years)	19 (15–23)	19 (11–26)	55 (52–59)	55 (48–62)
Sex				
Female	20 (37)	8 (89)*	12 (41)	4 (57)
Male	34 (63)	1 (11)	17 (59)	3 (43)
Race				
White	50 (94)	8 (89)	23 (79)	6 (86)
Black	3 (6)	1 (11)	6 (21)	1 (14)
Duration (years)	8.7 (6.2–11.1)	8.7 (4.0–14.0)	9.4 (7.3–11.5)	9.4 (3.0–16.7)
BMI (kg/m^2)	25.4 (20.2–29.0)	23.2 (18.9–26.7)	30.0 (26.8–33.3)	34.0 (30.2–35.1)
GHb (%)	10.8 (9.6–12.0)	11.2 (10.4–15.3)	11.7 (9.7–12.7)	11.2 (9.4–12.8)
SBP (mmHg)	125 (116–135)	120 (116–127)	133 (125–139)	117 (112–125)
DBP (mmHg)	75 (68–82)	75 (68–78)	76 (71–81)	68 (61–73)
TCHOL (mg/dl)	180 (156–232)	178 (160–203)	203 (166–242)	175 (148–204)
TRIG (mg/dl)	168 (113–221)	99 (80–178)	195 (107–298)	106 (71–168)
HDL cholesterol (mg/dl)	37 (29–43)	45 (40–48)	36 (31–42)	44 (38–61)
Family history of hypertension				
Yes	19 (35)	3 (38)	17 (66)	2 (50)
No	35 (65)	5 (63)	9 (35)	2 (50)
Smoking				
Yes	10 (19)	2 (25)	17 (68)	4 (67)
No	43 (81)	6 (75)	8 (32)	2 (33)

Data are median (25 and 75% IQR) for continuous variables and frequency (%) for categorical variables. *Microalbuminuria vs. normal; the Cochran-Mantel-Haenszel χ^2 and test-based confidence limits controlling for age, type of diabetes, and duration of diabetes. Statistically significant at $P < 0.05$. DBP, diastolic blood pressure; SBP, systolic blood pressure; TCHOL, total cholesterol; TRIG, triglycerides.

Table 2—*Characteristics associated with the progression to microalbuminuria and DN by type of diabetes*

	Type 1 diabetes		Type 2 diabetes	
Variable	Nonprogressors	Progressors	Nonprogressors	Progressors
n	55	8	23	12
Age (years)	16 (10–28)	15 (13–17)	57 (48–63)	58 (53–63)
Sex				
Female	25 (46)	3 (38)	9 (39)	5 (42)
Male	30 (54)	5 (62)	14 (61)	7 (58)
Race				
White	52 (96)	6 (75)*	19 (86)	9 (75)
Black	2 (4)	2 (25)	3 (14)	3 (25)
Duration (years)	6 (3–13)	7 (3–12)	8 (5–15)	10 (7–13)
BMI (kg/m^2)	21.1 (18.2–24.2)	19.1 (16.3–20.4)	31.2 (27.2–33.9)	30.4 (26.8–33.2)
GHb (%)	10.8 (9.4–12.3)	17.9 (11.5–18.9)*	9.9 (9.3–12.0)	12.5 (10.9–13.6)†
SBP (mmHg)	116 (111–125)	126 (119–132)*	135 (126–141)	131 (117–136)
DBP (mmHg)	68 (61–75)	71 (64–79)	76 (72–82)	76 (70–80)
TCHOL (mg/dl)	176 (150–202)	166 (152–222)	176 (156–241)	209 (173–258)
TRIG (mg/dl)	105 (71–157)	216 (158–234)*	182 (103–265)	279 (120–371)†
HDL (mg/dl)	44 (38–58)	45 (41–56)	36 (31–43)	31 (29–38)
ACE inhibitor at follow-up				
Yes	3 (6)	7 (88)*	18 (78)	9 (75)
No	51 (94)	1 (12)	6 (22)	3 (25)
Family history of hypertension				
Yes	20 (37)	2 (25)	11 (65)	7 (64)
No	34 (63)	6 (75)	6 (35)	4 (36)
Smoking				
Yes	10 (21)	1 (13)	11 (65)	8 (80)
No	38 (79)	7 (87)	6 (35)	2 (20)

Data are median (25 and 75% IQR) for continuous variables and frequency (%) for categorical variables. *Statistically significant at $P < 0.05$ progressors vs. nonprogressors, type 1 diabetes; †statistically significant at $P < 0.05$ progressors vs. nonprogressors, type 2 diabetes. DBP, diastolic blood pressure; SBP, systolic blood pressure; TCHOL, total cholesterol; TRIG, triglycerides.

not differ between the two groups. In both types of diabetes, progressors and nonprogressors did not differ with respect to age, sex, BMI, diastolic blood pressure, total cholesterol, HDL, smoking, or family history of hypertension. Duration of diabetes did not differ among groups, but it tended to be lower in nonprogressors.

Table 3 shows the simple logistic regression analysis of baseline variables associated with the progression to MA/DN after adjusting for type of diabetes and baseline MA status. There was a statistically significant association between 10 and 14 years duration of diabetes, GHb, total cholesterol, and triglycerides at baseline and both ACE inhibitor use at follow-up and the development of MA. The risk of developing MA in subjects with known duration of diabetes 10–14 years was 4.11 times higher compared with subjects with known duration of diabetes 0–4 years. The risk of developing MA was 7.22 times higher in subjects with GHb ≥10% compared with subjects with GHb <10%. With a 1-mg/dl increase in total cholesterol and triglycerides, the risk of developing MA increased by 1.01 and 1.10 times, respectively. The risk of MA was 14.40 times higher in diabetic subjects treated with ACE inhibitors at follow-up compared with those not treated with ACE inhibitors at follow-up.

To test the independent effects of risk factors on the risk of progression to MA/DN, we developed a multiple logistic model. The overall significance of the final logistic regression model, estimated by −2 log likelihood test statistic and χ^2 test score was 32.4 ($P = 0.0001$) and 26.0 ($P = 0.0005$), respectively. Variables independently associated with progression to MA/DN were duration of diabetes (OR 10.5, 95%CI 1.12–15.4 for duration 10–14 years) and GHb (1.63, 1.18–2.53 for GHb ≥ 10%). Total cholesterol, triglycerides, and ACE inhibitor use at follow-up were no longer significant, and no interaction term was significant in the model.

CONCLUSIONS

The predictive value of MA

This prospective longitudinal study revealed that over a 7-year follow-up period, only 6% of subjects with persistent MA at baseline progressed to DN. Among subjects with persistent MA at baseline, 38% did not progress, and 56% regressed to normoalbuminuria. In contrast, 16% of age-, type-, and duration of diabetes–matched normoalbuminuric subjects progressed to MA, and 7% progressed to DN. These results are in contrast to those of earlier studies, which have reported that ~85% of the patients with MA develop DN (5,19). These earlier studies may have been biased by overestimation of risk because of different definitions of MA, a single urine collection at baseline, higher levels of MA at baseline, and post hoc analyses. In addition, there may be changes in the natural history of DN resulting from secular trends in glucose and blood pressure control. Our findings are in agreement with more recent studies of the natural history of DN, which have reported that 19–24% of the patients with MA develop DN, and approximately one-third of the subjects with MA return to normoalbuminuria. These studies have concluded that MA may often regress or improve in diabetic subjects (1,14,20–22).

The PVP of MA as a marker of risk for DN was 43%, and the PVN was 77%. The PVP of a screening test is determined not only by factors that determine the validity of the test, but also by the prevalence of disease in the population. The prevalence of MA among the subjects in our study was only 16%. This may be due in part to the fact that only those subjects whose urine was determined by dipstick to be trace or negative for protein were enrolled. When the prevalence of preclinical disease is this low, the PVP will be low even when using a test with high sensitivity and specificity. Nevertheless, MA is far from ideal as a risk marker or predictor of DN, especially in populations prescreened with urine dipsticks.

The reasons for the regression of MA to normoalbuminuria are not clear. The

Table 3—*Characteristics associated with progression to microalbuminuria and DN; controlling for type of diabetes and baseline microalbuminuria status*

Variable	OR	95% CI
Age (years)		
0–19	1.00	—
20–39	0.28	0.03–2.47
40–59	1.68	0.54–5.18
≥60	3.97	0.67–23.6
Sex		
Male	1.00	—
Female	0.99	0.34–2.85
Race		
White	1.00	—
Black	0.28	0.07–1.20
Duration (years)		
0–4	1.00	—
5–9	1.27	0.31–5.18
10–14	4.11	1.00–7.07*
+ 15	0.27	0.03–2.69
BMI (kg/m^2)		
<25	1.00	—
≥25	0.57	0.05–6.42
GHb		
<10	1.00	—
≥10	7.22	1.41–16.8*
SBP (mmHg)		
<123	1.00	—
≥123	1.28	0.40–4.08
DBP (mmHg)		
<71	1.00	—
≥71	0.99	0.29–3.32
TCHOL (mg/dl)	1.01	1.00–1.02*
TRIG (mg/dl)	1.10	1.01–1.17*
HDL (mg/dl)		
<41	1.00	—
≥41	0.97	0.26–3.71
ACE Inhibitor at follow-up		
No	1.00	—
Yes	14.40	3.27–36.10*
Family history of hypertension		
No	1.00	—
Yes	0.73	0.24–2.28
Smoking		
No	1.00	—
Yes	1.40	0.41–4.79

*Statistically significant at $P < 0.05$. DBP, diastolic blood pressure; SBP, systolic blood pressure; TCHOL, total cholesterol; TRIG, triglycerides.

lack of association between MA and the usual clinical and metabolic risk factors at baseline suggests that increased urine albumin–to–creatinine ratios may have represented false positive tests. Some have suggested that MA is more likely to regress in younger subjects (23). Others speculate that MA detected in diabetic adolescents is less predictive of progression than has been reported in adults (24). We did not find any statistically significant difference between progressors and nonprogressors with respect to age. Others have suggested that better glycemic control and the use of ACE inhibitors may account for regression of MA (25,26). We found that lower GHb levels were significantly associated with regression to normoalbuminuria. However, we did not find an association between ACE inhibitor therapy and regression. In our diabetic subjects, nonregressors were as likely to receive ACE inhibitors as were regressors. Our result is in agreement with Sikka et al. (27), who reported an inverse association between MA and ACE inhibitor use and demonstrated that 61% of the diabetic patients use ACE inhibitors for the treatment of conditions other than abnormal albuminuria.

Two criteria must be met if MA is to be a useful clinical test. First, a measurable rise in MA must occur early enough to permit clinical intervention. Second, this rise should correlate with outcomes (28). In our study population, MA did not meet these two criteria because *1*) more normoalbuminuric subjects progressed to MA/DN compared with microalbuminuric subjects (23 vs. 6%) and 2) 56% of the microalbuminuric subjects regressed to normoalbuminuria.

Determinants of progression to MA and DN

To prevent or reverse the course of DN, risk factors involved in the etiology of disease must be defined. Studies investigating determinants of MA have identified poor glycemic control, elevated blood pressure, dyslipidemia, cigarette smoking, and family history of hypertension as initiating factors (1,9–11). In some studies, race, duration of diabetes, and male sex also have been associated with increased risk of MA (7,8,29). Age and BMI have been shown to exert little or no influence on the development of MA (30). Research dealing with ACE inhibitors in both types of diabetes have reported a beneficial effect on both the development and progression of MA to DN (26).

In our study, subjects with both type 1 and type 2 diabetes and progressive disease were characterized by duration of diabetes between 10 and 14 years, higher GHb levels, higher total cholesterol and triglycerides, and ACE inhibitor use at follow-up. In multiple regression analysis, only duration of diabetes between 10 and 14 years and GHb were independent predictors of progression to MA/DN. The risk of progression to MA/DN decreased with duration of diabetes >14 years. The decrease in risk after 14 years likely reflects the well-described genetic susceptibility to DN. Those who did not develop DN by 14 years were at decreased risk. In randomized controlled clinical trials, hyperglycemia has been shown to cause the development and progression of microvascular complications in type 1 and type 2 diabetes (31,32). Others have also reported the association of MA/DN and the duration of diabetes (33–35) and suggested that both exposure to glycemia and individual susceptibility factors are critical for the pathogenesis of DN.

There are a number of potential limitations to our study. First, ~50% of subjects in this prospective observational study were lost to follow-up over 7 years (17% of the cases and 56% of the control subjects). However, those lost to follow-up did not differ from those who were followed with regard to baseline clinical variables. We therefore consider it unlikely that, had they been available, those lost to follow-up would have changed the outcome of the study.

Second, we studied only 19 subjects with persistent MA at baseline. Based on the literature, we had anticipated a higher prevalence of MA at baseline and a higher rate of progression over 7 years. Nevertheless, when we consider all 19 subjects with persistent MA (including the 3 with no matched control subject), only 2 of 19 (11%) progressed to DN. This observation is consistent with a true underlying probability of <30% based on the upper 95% confidence limit calculated from the exact probability. This probability of progression was similar to that observed among all 91 subjects with normoalbuminuria at baseline. In the latter group, the upper 95% confidence limit calculated from the exact probability was 29%. The observed lack of difference between groups is a function of not only the small sample size but also the similarity of the two proportions.

A third limitation to the study was the use of different methods for assignment of exposure and assessment of outcome. We chose a single 12-h overnight urine collection for follow-up because we needed

to weigh respondent burden with reliability and precision of the measurement. Many of the subjects no longer received their medical care at the University of Michigan Medical Center, and it was not feasible to ask them to provide multiple specimens over a prolonged period of time. In addition, we wanted to optimize the reliability of the test by ensuring that patients did not have leukocytes or blood in their urine, by ensuring accurate timing of the collection, and by reducing variation in physical activity.

In summary, our data indicate that persistent MA, defined as an albumin–to–creatinine ratio of 30–299 μg/mg in at least two urine samples, progressed to DN in only 6% of the individuals with type 1 and type 2 diabetes (95% upper confidence limit = 30%) and regressed in 56% of the individuals with diabetes without systematic application of corrective measures. Therefore, we conclude that the predictive precision of MA as a risk marker for DN is less strong and that MA is a less sensitive and less specific predictor of DN than previously reported. In this study, we demonstrate a positive independent relation between the progression to MA/DN and both duration of diabetes between 10 and 14 years and poor glycemic control in subjects with type 1 and type 2 diabetes.

Acknowledgments— This work was supported by the Endocrine Fellows Foundation, the Centers for Disease Control and Prevention, and grants from the National Institutes of Health to the Michigan Diabetes Research and Training Center (DK-20572) and the General Clinical Research Center (M-01-RR-00042) at the University of Michigan.

References

1. Ritz E: Nephropathy in type 2 diabetes. *Journal of Internal Medicine* 245:111–126, 1999
2. Alzaid AA: Microalbuminuria in patients with NIDDM: an overview (Review). *Diabetes Care* 19:79–89, 1996
3. American Diabetes Association: Diabetic nephropathy (Position Statement). *Diabetes Care* 23 (Suppl. 1):S69–S72, 2000
4. Mogensen CE: Microalbuminuria, blood pressure and diabetic renal disease: origin and development of ideas. *Diabetologia* 42:263–285, 1999
5. Viberti GC, Jarrett RJ, Mahmud U, Hill RD, Argyropoulus A, Keen H: Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* i:1430–1432, 1982
6. Powrie JK, Watts GF, Ingham NA, Talmud PJ, Shaw KM: Role of glycaemic control in development of microalbuminuria in patients with insulin dependent diabetes. *BMJ* 309:1608–1612, 1994
7. Ritz E, Reinhold O: Nephropathy in patients with type 2 diabetes mellitus. *N Engl J Med* 341:1127–1133, 1999
8. Niskanen LK, Penttila I, Parviainen M, Uusitupa MIJ: Evolution, risk factors, and prognostic implications of albuminuria in NIDDM. *Diabetes Care* 19:486–493, 1996
9. The Microalbuminuria Collaborative Study Group: Predictors of the development of microalbuminuria in patients with type 1 diabetes mellitus: a seven-year prospective study. *Diabet Med* 16: 918–925, 1999
10. Klein R, Klein BE, Moss SE: Relation of glycemic control to diabetic microvascular complications in diabetes mellitus. *Ann Intern Med* 124:90–96, 1996
11. Villar G, Garcia Y, Goicolea I, Vazquez JA: Determinants of development of microalbuminuria in normotensive patients with type 1 and type 2 diabetes. *Diabet Metab* 25:246–254, 1999
12. Warram JH, Scott LJ, Hanna LS, Wantman M, Cohen SE, Laffel LMB, Ryan L, Krolewski AS: Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 49:94–100, 2000
13. Ismail N, Beckner B, Strtzelczyk P, Ritz E: Renal disease and hypertension in non-insulin-dependent diabetes mellitus. *Kidney Int* 55:1–28, 1999
14. Caramori ML, Fioretto P, Mauer M: The need for early predictors of diabetic nephropathy risk: Is albumin excretion rate sufficient? *Diabetes* 49:1399–1408, 2000
15. Mentel N, Haenszel W: Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst* 22: 719–748, 1959
16. Cochran WG: Some methods for strengthening the χ^2 test. *Biometrics* 10:417–451, 1954
17. Lachin JM: *Biostatistical Methods: The Assessment of Relative Risks*. New York, John Wiley and Sons, 2000
18. Miettinen OS: Estimability and estimation in case-reference studies. *Am J Epidemiol* 103:226–235, 1976
19. Mogensen CE, Christensen CK: Predicting diabetic nephropathy in insulin-dependent diabetes. *N Engl J Med* 311: 89–93, 1984
20. Ellis D, LIoyd C, Becker DJ, Forrest KYZ, Orchard TJ: The changing course of diabetic nephropathy: low-density lipoprotein cholesterol and blood pressure correlate with regression of proteinuria. *Am J Kidney Dis* 27:809–818, 1996
21. Bojestig M, Arnqvist HJ, Karlberg BE, Ludvigsson J: Glycemic control and progression in type 1 diabetic patients with microalbuminuria. *Diabetes Care* 19:313–317, 1996
22. Almdal T, Norgaard K, Feldt-Rasmussen B, Deckert T: The predictive value of microalbuminuria in IDDM: a five-year follow-up study. *Diabetes Care* 17:120–125, 1994
23. Rudberg S, Dahlquist G: Determinants of progression of microalbuminuria in adolescents with IDDM. *Diabetes Care* 19: 369–371, 1996
24. Gorman D, Sochett E, Daneman D: The natural history of microalbuminuria in adolescents with type 1 diabetes. *J Pediatr* 134:333–337, 1999
25. Levin SR, Coburn JW, Abraira C, Henderson WG, Colwell JA, Emanuele NV, Nuttall FQ, Sawin CT, Comstock JP, Silbert CK, for the Veterans Affairs Cooperative Study on Glycemic Control and Complications in Type 2 Diabetes Feasibility Trial Investigators: Effect of intensive glycemic control on microalbuminuria in type 2 diabetes. *Diabetes Care* 23:1478–1485, 2000
26. Rossing P: Promotion, prediction and prevention of progression of nephropathy in type 1 diabetes mellitus. *Diabet Med* 15:900–919, 1998
27. Sikka R, Waters J, Moore W, Sutton DR, Herman WH, Aubert RE: Renal assessment practices and the effect of nurse case management of health maintenance organization patients with diabetes. *Diabetes Care* 22:1–6, 1999
28. Evans G, Greaves I: Microalbuminuria as predictor of outcome: shows promise but large prospective trials are needed. *BMJ* 318:207–208, 1999
29. Forsblom CM, Groop PH, Ekstrand A, Totterman KJ, Sane T, Saloranta C, Groop L: Predictors of progression from normoalbuminuria to microalbuminuria in NIDDM. *Diabetes Care* 21:1932–1938, 1998
30. Mathiesen ER, Ronn B, Storm B, Foght H, Deckert T: The natural course of microalbuminuria in insulin-dependent diabetes: a 10-year prospective study. *Diabet Med* 12:482–487, 1995
31. The Diabetes Control and Complications Trial Research Group: The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329: 977–986, 1993
32. UK Prospective Diabetes Study Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
33. Sobngwi E, Mbanya JC, Moukouri EN,

Ngu KB: Microalbuminuria and retinopathy in a diabetic population of Cameroon. *Diabetes Res Clin Pract* 44:191–196, 1999
34. Bruno G, Cavallo-Perin P, Bargero G, Borra M, Calvi V, D'Errico N, Deambrogio P, Pagano G: Prevalence and risk factors for micro-and macroalbuminuria in an Italian population-based cohort of NIDDM subjects. *Diabetes Care* 19:43–47, 1996
35. Campos-Pastor MM, Escobar-Jimenez F, Mezquita P, Herrera-Pombo JL, Hawkins-Carranza F, Luna JD, Azriel S, Serraclara A, Rigopoulos M: Factors associated with microalbuminuria in type 1 diabetes mellitus: a cross-sectional study. *Diabetes Res Clin Pract* 48:43–49, 2000