Progression of Microalbuminuria to Proteinuria in Type 1 Diabetes

Nonlinear Relationship With Hyperglycemia

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While small clinical trials have shown that improved glycemic control reduces the risk of progression of microalbuminuria to proteinuria, two recent clinical trials did not confirm this finding. We sought to reconcile the contradictory evidence by examining the dose-response relationship between hyperglycemia and progression of microalbuminuria to proteinuria in individuals with type 1 diabetes and microalbuminuria (n = 312) who were followed for 4 years with repeated assessments of urinary albumin excretion. Since 33 patients did not participate in follow-up (10.6%), data for 279 patients were analyzed. Urinary albumin excretion level worsened to proteinuria in 40 (4.1 per 100 person-years). To examine the dose-response relationship, baseline HbA_{1c} was divided into four roughly equal groups using the cut points 8, 9, and 10%. The incidence rate varied significantly among the four groups (P = 0.008). Among those with HbA_{1c} <8.0%, the incidence rate of progression was only 1.3 per 100 person-years, while it was 5.1, 4.2, and 6.7 per 100 person-years in the three other groups. We used generalized additive models to examine the dose-response curve using HbA_{1c} as a continuous variable and found that the risk of progression rises steeply between an HbA_{1c} of 7.5–8.5% and then remains approximately constant across higher levels. In conclusion, the results of this study suggest that, in patients with microalbuminuria, the risk of progression to overt proteinuria can be reduced by improved glycemic control only if the HbA_{1c} is maintained below 8.5%. Moreover, below that value, the risk declines as the level of HbA_{1c} decreases. *Diabetes* 49:94–100, 2000

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Received for publication 11 February 1999 and accepted in revised form 28 September 1999.

ACR, albumin/creatinine ratio; DCCT, Diabetes Control and Complications Trial; GAM, generalized additive model; UAE, urinary albumin excretion.

In patients with type 1 diabetes, the development of kidney complications, known as diabetic nephropathy, consists of several stages: the onset of microalbuminuria, its progression to overt proteinuria, and progression of the proteinuria to end-stage renal disease (1,2). Several recent studies clearly demonstrated that the onset of microalbuminuria is determined by the level of glycemic control and can be retarded by intensive diabetes treatment (3,4). The risk rises exponentially with increasing hyperglycemia (5).

The role of hyperglycemia in the progression of microalbuminuria to the more advanced stages of nephropathy is unclear, however. Several follow-up studies have demonstrated association between progression of microalbuminuria and the level of glycemic control (6–9). Moreover, a few small clinical trials of intensive insulin therapy indicated that intensive therapy reduces the risk of progression of nephropathy (10). However, the results of two recent clinical trials did not confirm this conclusion (11,12).

The present study sought to reconcile the contradictory evidence from the earlier studies by examining the dose-response relationship between exposure to hyperglycemia and progression of microalbuminuria to overt proteinuria in the largest cohort studied so far.

RESEARCH DESIGN AND METHODS

Selection of study subjects. Between 1 January 1991 and 31 March 1992, a 50% sample of the patients aged 15–44 years attending the Internal Medicine or Pediatrics departments of the Joslin Diabetes Center was screened for microalbuminuria in a random urine specimen. By 31 March 1992, 1,602 patients with type 1 diabetes had been screened at least once for microalbuminuria. Subsequently, whenever members of the cohort returned to the clinic, their random urine specimens were examined for microalbuminuria. Details of the selection criteria and methods were published with the results of the screening study (5,13), and an abbreviated description is included here. The study protocol was approved by the Committee on Human Studies of the Joslin Diabetes Center.

Evaluation of urinary albumin excretion with albumin/creatinine ratio. The ratio of urinary concentrations of albumin and creatinine (ACR) measured in random urine samples has become a widely accepted tool for assessing urinary albumin excretion (UAE) (14–20). Therefore, we used the ACR for both the diagnosis and follow-up of UAE in this study. Urinary albumin concentration was measured by immunonephelometry (Behring, Somerville, NJ), and urinary creatinine concentration was measured by colorimetry (modified Jaffe reaction) on an Astra-7 automated system (Beckman Instruments, Brea, CA). A detailed description of laboratory methods has been published (5,13).

Three levels of UAE were distinguished: normal, microalbuminuria, and overt proteinuria. Sex-specific criteria for these levels in terms of the ACR were published previously (13). For men, the lower limits of microalbuminuria and overt

proteinuria are 17 and 250 µg/mg (1.9 and 28 mg/mmol), respectively. For women, they are 25 and 355 µg/mg (2.8 and 40 mg/mmol).

Definition of microalbuminuria at baseline. Of the 1,602 patients screened, 38 began dialysis during the baseline period or were found to have a kidney transplant. They were classified as having overt proteinuria on clinical grounds, while the remaining 1,564 patients were classified on the basis of ACR measurements. In a clinical setting, it has been customary to define a patient's level of UAE according to a consensus of the last three measurements. A category of UAE is assigned if the level is confirmed by at least two out of three consecutive measurements. In this study, we sought to improve on the customary definition by imposing time constraints on the intervals between measurements. Short-term episodes of microalbuminuria (lasting a few weeks) occur in some patients. In order to detect persistent microalbuminuria instead of these transient episodes, we required that the measurements of ACR be separated by a longer period; the median interval was 5 months (minimum 8 weeks). Furthermore, to define the level of UAE, we used a fixed interval of two years, by which time the majority of patients (61%) had at least three ACR determinations. This protocol made the elapsed time for obtaining a classification consistent for all patients and the starting date for follow-up less dependent on visit frequency. It also improved our confidence in the baseline classification by incorporating additional information when more than three tests were available.

Beginning with the date of the initial urine specimen screened for microalbuminuria, a 2-year baseline period was defined. The median of all ACR measurements within the 2-year baseline was used to assign each patient to one of the levels of UAE defined above. For 953 patients (61%), the median was based on 3–12 samples. Classification of 283 (18%) patients was based on two ACR measurements that agreed, so a third determination was not necessary to establish a consensus. Another 58 patients (4%) with two samples in different categories were classified by the geometric mean of the two. The remaining 270 patients (17%) were classified on the basis of the single value available. To test whether the classification of patients on the basis of a single baseline ACR determination or two discordant ones had any effect on the results described in this report, we repeated the analyses after eliminating them. The results of that analysis are described below under "Robustness of the analysis."

Follow-up. Out of the 1,602 patients enrolled in the study, 312 had microalbuminuria by the above criteria. Urine samples were collected whenever patients returned for clinic visits. Patients who had not returned to the clinic by the anniversary of their last visit were asked to send a urine sample by mail. The 2-year interval following the baseline evaluation was considered the first follow-up interval, and the subsequent 2-year interval was considered the second follow-up interval. Of the 312 patients with persistent microalbuminuria by the above criteria, 33 (10.6%) provided no follow-up urine specimen; therefore, this analysis is based on the remaining 279 patients who provided a median of 5 follow-up measurements.

Definition of progression of microalbuminuria. Determination of nephropathy status during each 2-year follow-up interval was based on the same algorithm as the baseline interval. The classification of 74% of the intervals was based on ≥2 ACR determinations, while the remaining were classified on the basis of a single ACR. A classification as proteinuria in either follow-up interval was considered as an end point. In most patients, proteinuria is progressive and leads to loss of renal function (21). However, regression of proteinuria even into the normoalbuminuria range has been documented in a small proportion of cases (22,23).

A total of 19 subjects progressed to proteinuria during the first follow-up interval, and another 21 progressed in the second. For none of the progressors was the classification as proteinuria based on a pair of ACR determinations that did not agree. For 11 of them, however, it was based on a single ACR. Four who progressed in the first follow-up interval regressed to microalbuminuria in the second; three of the four were treated with ACE inhibitors.

Examinations and medical record review. Out of the 279 patients, 201 (72%) were examined by a trained examiner for the purpose of this study (53% during baseline, and the remaining 19% during the first follow-up interval before any had progressed to proteinuria). Blood pressure was measured with a Dinamap Monitor (Critikon, Tampa, FL). Sitting blood pressure was measured three times separated by 2 min and the three measurements were averaged for this analysis. For the 78 (28%) patients who were not examined by the trained examiner, the medical records during the baseline period were reviewed, and the first three blood pressure measurements in the clinic by sphygmomanometer were abstracted and averaged. For three of these patients, no blood pressures were recorded during the baseline period.

Baseline height and weight were abstracted from the medical records. BMI was calculated by the formula: weight (in kilograms) divided by height (in meters) squared. Ideal body weight (%) was calculated by multiplying the BMI by 4.3 for men and 4.7 for women (24).

Measurements of glycosylated hemoglobin. We extracted from the records of the clinical laboratory of the Joslin Diabetes Center all measurements of glycosylated hemoglobin performed on members of the cohort during the 2-year baseline period. All baseline determinations of glycosylated hemoglobin were measured electrophoretically as HbA_1 (Corning Medical and Scientific, Corning, NY.). Since that time, HbA_{1c}, rather than total HbA_1, has become the preferred measure of glycemic control. Conversion of our archived HbA_1 measurements to HbA_{1c} values was validated in the following manner. When the laboratory method was changed to ion-exchange high performance liquid chromatography (Variant; Bio-Rad Laboratories, Hercules, CA) in 1995, both methods were run in parallel for 4 months. The correlation coefficient for duplicate determinations on the same specimens was 0.98, so we converted all HbA_1 values in our data files to HbA_{1c} values ($HbA_{1c} = [HbA_1 - 0.14]/1.23$) (5). In this analysis, we expressed the data as the HbA_{1c} values to be consistent with current clinical practice. The normal range in this laboratory is 4.0–6.0%.

The median number of HbA_{1c} measurements during the two-year baseline period was four. Three or more measurements of HbA_{1c} were obtained for 73% of the patients; two measurements were available for 15%, only one measurement for 11%, and none was available for 2%. The geometric mean of all values available within the two-year baseline interval was used as the index of glycemic exposure.

Treatment with antihypertensive agents. Through a review of medical records and interviews with patients with microalbuminuria, we identified those treated with ACE inhibitors or other antihypertensive agents, either during the baseline interval or subsequently during follow-up.

Statistical analysis. Group differences for quantitative variables were tested by ANOVA and for qualitative variables by χ^2 analysis (SAS 6.12 for Windows; SAS Institute, Cary, NC). To estimate the incidence rates of proteinuria, a person was credited with 2 person-years of follow up for each interval in which they did not progress, and 1 person-year in the interval in which they progressed (25).

The use of follow-up intervals instead of specific dates to define progression to proteinuria suggested a discrete failure time approach to the analysis of the follow-up data (26). This effectively means that people could enter the analysis two times if they did not have an event in the first interval. The independent effects of blood pressure and HbA_{1c} on the progression to proteinuria were examined in a multiple logistic model that included diastolic blood pressure, HbA_{1c}, and potential confounders (26). As a measure of the level of UAE within the microalbuminuria range, the median of the baseline ACR determinations was used. For 70 patients with two baseline ACRs, the geometric mean of the two was used as the median. The median ACR was transformed to the logarithm for statistical analysis. Using the same discrete failure time approach, a generalized additive model (GAM) was constructed to examine further the relationship between baseline HbA_{1c} and progression to proteinuria. A GAM replaces the usual assumption of linearity with a flexible smooth term, in this case the loess option, to fit a smooth curve to the ungrouped data (27). The analyses were performed in S-Plus (StatSci Division, MathSoft, Seattle, WA). We examined a range of spans and found a value of 0.7 captured the shape of the curve with a minimum of oscillations (confirmed by Akaike's Information Criterion). The results are presented as predicted incidence rates with the shaded region representing the pointwise ±2 SE band (Fig. 1).

Robustness of the analysis. Due to variability of UAE, the patients whose diagnosis of microalbuminuria was based on a single determination of the ACR or two discordant determinations may have been misclassified (see "Definition of microalbuminuria at baseline" above). To determine whether the inclusion of such patients affected the results, the analysis was repeated after excluding them. Not only was the overall incidence rate of progression to proteinuria (4.0 per 100 person-years; 33 progressors during 835 person-years of follow-up) the same as in the total group (40 progressors during 964 person-years), but the dose-response relationship with HbA_{1c} was unchanged. Moreover, the nature and statistical significance of the other comparisons in Tables 1–3 were unaffected except the relative odds for the highest diastolic blood pressure group in Table 3 no longer reached significance with the reduced sample size.

We also repeated the analyses after deleting the 11 patients classified as proteinuric on the basis of a single ACR determination. This reduced the incidence rate to 3.1 per 100 person-years but did not affect the pattern of associations shown in Tables 1–3.

RESULTS

Characteristics of those who progressed to proteinuria and those who did not are compared in Table 1. Progressors and nonprogressors were similar with regard to sex, age, duration of diabetes, and insulin dose. Percent ideal body weight was the same in the two groups (data not shown). Serum creatinine was similar in the two groups, but the mean of the baseline ACR determinations (analyzed in the logarithmic scale) was significantly higher in those who progressed to proteinuria. This is an expected result; the risk of progression into

TABLE 1
Characteristics of the study group according to whether microalbuminuria progressed to proteinuria during follow-up

Characteristic	Nonprogressors	Progressors	*P* value
n	239	40	
Sex (% male)	48	58	NS
Age (years)	30 ± 8	30 ± 6	NS
Age at diagnosis (years)	12 ± 7	12 ± 8	NS
Diabetes duration (years)	18 ± 9	17 ± 8	NS
Insulin dose (U/kg)	0.72 ± 0.31	0.72 ± 0.25	NS
Serum creatinine (mg/dl)	0.86 ± 0.23	0.87 ± 0.27	NS
Baseline ACR (µg/mg)	70 ± 60	132 ± 80	0.0001
HbA_{1c} (%)	8.8 ± 1.6	9.6 ± 1.4	0.007
Baseline treatment with ACE inhibitors or other antihypertensive agent (%)	30.1	40.0	NS
Blood pressure (mmHg)			
Systolic	124 ± 16	126 ± 15	NS
Diastolic	73 ± 9	78 ± 7	0.005

Data are means ± SD, unless otherwise indicated. For baseline ACR, individuals were characterized by the median of their ACR determinations except the 70 patients with two determinations, for whom the geometric mean was used as the median. The significance test was performed after logarithmic transformation. HbA_{1c} was not measured during baseline on five patients, including two progressors. Blood pressure measurements were not available for three patients (see RESEARCH DESIGN AND METHODS). To convert serum creatinine from mg/dl to µmol/l multiply by 88.4. To convert ACR from µg/mg to mg/mmol, multiply by 0.112.

the proteinuric range during a four-year follow-up interval is greatest for those closest to proteinuria at baseline. Aside from this result, the most significant difference was in the level of HbA_{1c} during baseline.

More of the progressors were treated with antihypertensive agents during the baseline interval (40 vs. 30%), but the difference was not statistically significant. In both groups, 85% (75 out of 88) of those treated were receiving an ACE inhibitor. The blood pressures reported in Table 1 include measurements on those treated with antihypertensive agents as well as those not treated. Systolic blood pressure was the same in the two groups, but diastolic blood pressure was significantly higher in progressors than in nonprogressors despite the slightly higher proportion treated with antihypertensive agents. When the group was stratified by treatment with antihypertensive agents, diastolic pressure was slightly higher in those treated, but the difference between progressors and nonprogressors was the same.

To examine the dose-response relationship between the measure of glycemic control and risk of proteinuria, we divided the range of HbA_{1c} at 8, 9, and 10% to yield four approximately equal groups (Table 2). The incidence rate of proteinuria varied significantly among the four groups (P = 0.008). The variability was entirely due to the low rate in patients with HbA_{1c} <8% (1.3 per 100 person-years), while the rate was similar in the other three groups.

To see if the nonlinearity of the dose response might have been the consequence of some other variable that was associated with progression (baseline ACR and blood pressure variables), the four HbA_{1c} groups were compared with respect to these variables (Table 2). Baseline ACR level did not vary significantly among the four groups. The proportion of patients on antihypertensive treatment varied significantly among the groups, but this was primarily due to the low proportion treated in the group of patients with the poorest glycemic control, the proportion being similar in the other three groups. Finally, both systolic and diastolic blood pressures were similar in all groups. Thus, the low incidence rate of proteinuria in the group of patients with HbA_{1c} <8% cannot be attributed to an initially lower UAE, more treatment with ACE inhibitors or other antihypertensive agents, or lower blood pressures.

To test the independent effects of glycemic exposure and diastolic blood pressure on the risk of progression to proteinuria, we developed a multiple logistic model of determinants of the incidence rate of proteinuria (see RESEARCH DESIGN ANDMETHODS). In addition to HbA_{1c} and diastolic blood pressure, each divided into four approximately equal groups, the model included sex, age, duration of diabetes, baseline

TABLE 2
Characteristics of study group according to level of HbA_{1c}

Characteristic	HbA_{1c} (%)			
	5.1–7.9	8.0–8.9	9.0–9.9	10.0–13.1
n	85	57	64	68
Incidence rate (%)	1.3	5.1	4.2	6.7
Cases/person-years	4/317	10/196	9/212	15/224
Baseline ACR (µg/mg)	78 ± 73	76 ± 57	87 ± 72	74 ± 57
Baseline treatment with ACE inhibitors or other antihypertensive agent (%)	41	28	39	18
Blood pressure (mmHg)				
Systolic	124 ± 15	129 ± 16	124 ± 16	122 ± 17
Diastolic	73 ± 8	76 ± 9	74 ± 9	74 ± 8

Data are means ± SD, unless otherwise indicated. For baseline ACR, individuals were characterized by the median of their ACR determinations except the 70 patients with two determinations, for whom the geometric mean was used as the median. To convert ACR from µg/mg to mg/mmol, multiply by 0.112.

TABLE 3
Multiple logistic analysis of the joint effects of HbA_{1c} and diastolic blood pressure on the progression of microalbuminuria to proteinuria

	Odds ratio (95% CI)
HbA_{1c} (%)	
5.1–7.9	1.0 (reference)
8.0–8.9	4.2 (1.2–14.4)
9.0–9.9	3.2 (0.9–11.2)
10.0–13.1	5.5 (1.6–18.7)
Diastolic blood pressure (mmHg)	
53–69	1.0 (reference)
70–74	3.4 (0.9–12.4)
75-79	3.3 (0.9–12.2)
80–105	3.8 (1.2–12.6)

The analysis is adjusted for sex, age, duration of diabetes, treatment with antihypertensive agents, and median baseline ACR.

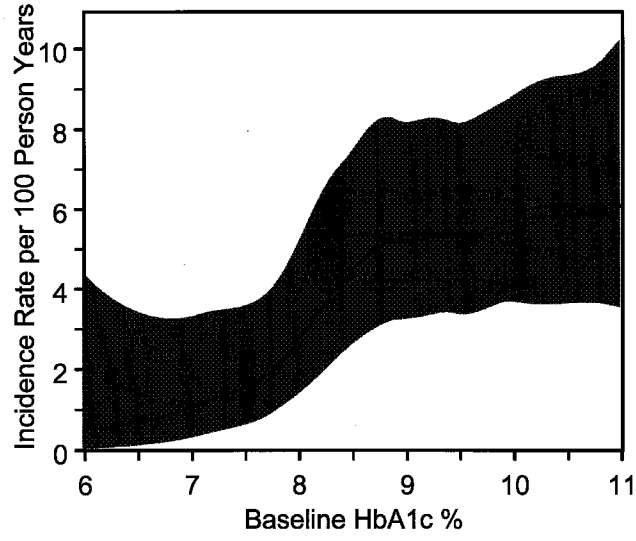

FIG. 1. Predicted incidence rate of progression of microalbuminuria to proteinuria according to level of HbA_{1c} during the baseline period. Using a discrete failure time approach, a GAM was constructed that fitted a smooth curve to the data using the loess option with span = 0.7 (see RESEARCHDESIGN AND METHODS). The shaded region represents the pointwise ±2 SE band.

treatment with antihypertensive agents, and level of ACR at baseline (Table 3). The estimates of the effects for the HbA_{1c} groups were consistent with the incidence rates in Table 2. Relative to the group with HbA_{1c} <8%, the odds ratios for each of the groups with progressively higher HbA_{1c} were 4.2,3.2, and 5.5 (P values 0.023, 0.066, and 0.006, respectively). A similar pattern was seen for diastolic blood pressure. Compared with those with a diastolic blood pressure <70 mmHg, the relative risks for each of the groups with progressively higher diastolic blood pressure were 3.4, 3.3, and 3.8 (P values 0.065, 0.067, and 0.028, respectively). The estimates of the effects of HbA_{1c} and diastolic blood pressure in this multivariate model are essentially the same as those obtained when HbA_{1c} or diastolic blood pressure were examined separately in univariate models. This indicates that the effects of these two variables are independent.

In addition to the 75 patients who began treatment with an ACE inhibitor before or during the baseline period, an additional 36 patients began treatment with an ACE inhibitor during the first follow-up interval, and 33 more during the second follow-up interval. To test whether initiation of ACE inhibition after the baseline interval could have affected the pattern of results, we excluded all patients treated with an ACE inhibitor and repeated the analysis. The overall incidence of proteinuria in those never treated with an ACE inhibitor was 2.3 per 100 person-years (11 progressors in 469 person-years) as compared with 4.1 per 100 person-years in the total group. However, the pattern according to level of HbA_{1c} remained the same as in the total group (data not shown).

The low incidence rate among those never treated with ACE inhibitors is a consequence of the appearance of clinical indications for placing patients on antihypertensive treatment. As noted above, those on antihypertensive treatment had higher blood pressures than those not treated. The patients' clinical condition prompted their physicians to begin treatment with ACE inhibitors. Thus, exclusion of patients who began ACE inhibition during follow-up preferentially removed those at greatest risk of progression to proteinuria.

To examine in more detail the shape of the dose-response relationships between these two exposures (HbA_{1c} and diastolic blood pressure) and the incidence of progression of microalbuminuria, these exposures were analyzed as continuous variables with GAM (see RESEARCH DESIGN AND METHODS). The fit of a loess curve to the HbA_{1c} data produced a predicted incidence rate that follows a smooth curve (Fig. 1) closely resembling the incidence rate in the grouped data in Table 3. The curve rises gradually up to a HbA_{1c} of ~7.5% and then steeply up to a HbA_{1c} of ~8.5%. Above that value, the predicted incidence rate is fairly constant. While the modest number of cases available for this analysis leaves some uncertainty about the shape of the curve in this range (as indicated by the width of the shaded ±2 SE confidence band), the height of the smoothed curve does not seem to continue to rise as it did in the middle range of HbA_{1c}. This departure from linearity is almost statistically significant (P = 0.08). Using the same approach to analyze diastolic blood pressure, we found no evidence of nonlinearity (data not shown); therefore, we conclude that these data are consistent with a linear effect of diastolic blood pressure on risk.

DISCUSSION

We have examined the determinants of progression of microalbuminuria to proteinuria in a large cohort of patients with type 1 diabetes who were followed for 4 years. The incidence rate of progression of microalbuminuria to persistent proteinuria was 4.1/100 person-years. A cohort of prevalent cases of microalbuminuria such as this includes a heterogeneous mixture of subjects in whom microalbuminuria may progress or regress (28) or possibly persist for a very long time (13). The process is dynamic, and subjects whose microalbuminuria regresses are at greatly increased risk of the subsequent development of persistent microalbuminuria (29). With only 4 years of follow-up in this study, analyses of the determinants of regression or long-term persistence would be incomplete, and these issues have been postponed until longer follow-up has accumulated.

A progression rate of 4.1/100 person-years translates into a cumulative incidence of 34–47% after 10–15 years of obser-

vation. This value is lower than those from earlier observations in much smaller studies in which 75–85% of type 1 diabetic patients with microalbuminuria progressed to overt proteinuria during 10–14 years of follow-up (30–32). In part this difference may be due to imprecise estimates from small study samples, increased use of ACE inhibitors in this study, or other changes in patient management.

Among the patients with microalbuminuria, the risk of progression to proteinuria was significantly influenced by level of glycemic control and diastolic blood pressure. Whereas the dose-response relationship for diastolic blood pressure appears to be linear, the dose-response relationship for glycemia seems to be nonlinear. The risk of progression increases with increasing baseline HbA_{1c} up to a level of ~8.5%, where the rise in risk is interrupted. Across all higher levels of HbA_{1c}, the risk remains fairly constant. This dose-response relationship was not confounded by age, duration of diabetes, baseline level of ACR, blood pressure, or treatment with antihypertensive agents, including ACE inhibitors.

Several follow-up studies have demonstrated an association between progression of microalbuminuria to overt proteinuria and level of glycemic control (6–9). None was large enough, however, to characterize the shape of the relationship. Several clinical trials of intensive insulin therapy, albeit small ones, reported significantly reduced risk of progression of microalbuminuria (10). Inconclusive results, however, were subsequently obtained in the two largest clinical trials conducted so far. Investigators in the U.K. studied 70 patients with microalbuminuria and concluded that improved glycemic control for three years had no significant impact on the risk of progression to overt proteinuria (11). Similar findings were reported for the 73 patients with microalbuminuria who participated in the Diabetes Control and Complications Trial (DCCT) and were followed for 6.5 years (12).

The results of the current study shed light on these negative clinical trials. Based on the dose-response relationship found in the current study, only the patients whose intensified glycemic control reduced their HbA_{1c} level to <8.5% would be expected to benefit. In that range, the magnitude of the benefit would be a function of how far below 8.5% they were able to get and whether they could sustain it for a prolonged time. Therefore, the power of those studies to detect an effect of improved glycemic control was determined by the proportion of patients achieving a level <8.5%, not the reduction in the overall mean HbA_{1c} for the group. What fraction of the patients in these studies achieved that result is unknown. However, the suggestion of a reduced risk in the DCCT intensive therapy group might be more impressive if the results were stratified according to HbA_{1c} levels at baseline and while in the study (12). The point regarding the need to achieve an HbA_{1c} <8.5%, and preferably close to 7.5%, should be considered in the design of any future trials, and it should be a benchmark for the clinical management of these patients.

The mechanisms responsible for a nonlinear effect of hyperglycemia on the progression of microalbuminuria to overt proteinuria are not clear. The effect of hyperglycemia on size selectivity has been investigated in patients with overt proteinuria (33). Hyperglycemia increased the clearance of small molecules (28–40 ± in radius) but not large macromolecules (>44 ± in radius). Whether these findings can be extrapolated to patients with microalbuminuria is open to speculation. The effect of hyperglycemia on renal hemodynamics has been investigated in several studies (34–36). A recent study in humans showed that raising blood glucose from normoglycemia to 180 mg/dl (10 mmol/l)—a level corresponding to an HbA_{1c} of ~8% (37)—for a 12-h period increases systemic blood pressure, plasma renin activity, and filtration fraction (36). These findings suggest that hyperglycemia, in addition to raising systemic blood pressure, may increase intraglomerular pressure via the renin-angiotensin system. Consistent with this hypothesis are results reported by Jenkins et al. (35). They demonstrated that the level of glycosylated hemoglobin in individuals with type 1 diabetes is negatively correlated with renal blood flow and positively correlated with filtration fraction, abnormalities that were eliminated by ACE inhibitors (35). The relevance of these observations, however, is uncertain. Whereas the renal vascular constriction reported by Jenkins et al. increased linearly with level of glycosylated hemoglobin, the risk of progression of microalbuminuria to proteinuria in our study leveled off when hyperglycemia reached approximately the neighborhood of the renal threshold for glucose.

The importance of increased intraglomerular pressure in the progression is supported by observations of an association between the rate of progression of microalbuminuria to proteinuria and systemic blood pressure, as well as the effectiveness of antihypertensive treatment in slowing progression (8,38–41). In the present study, progressors to proteinuria had higher baseline diastolic (but not systolic) blood pressure than nonprogressors, and evidence of this association persisted after adjustment for the level of glycemic control, baseline ACR level, and antihypertensive treatment. The shape of this dose-response relationship remains uncertain, however. The possibility of a nonlinear effect was suggested by the stratified analysis, but the data were not strong enough to reject the hypothesis of a linear effect. Systemic blood pressure was evaluated at a single examination for most patients, whereas the median number of ACR evaluations was three. Stronger evidence regarding the effect of blood pressure (systolic as well as diastolic) might have emerged if multiple measurements over time were available. Interestingly, lower blood pressure was among the determinants of regression of proteinuria to microalbuminuria in a study documenting the reversibility of nephropathy (23). This may be indirect evidence supporting a role for higher blood pressure in the progression of microalbuminuria to proteinuria.

Some issues related to the generalizability of our findings must be acknowledged. The study population was predominantly (92%) Caucasians with type 1 diabetes, so the findings may not be applicable to diabetic patients in minority populations or to patients with type 2 diabetes. Moreover, our estimates of the rate of progression refer to a group of patients almost half of whom were not treated with ACE inhibitors. Currently, all such patients should be treated with ACE inhibitors, and this is expected to reduce the rate of progress by half (8). However, since the effect of ACE inhibition is unrelated to the level of glycemic control (8), one may assume that the shape of the dose-response relationship between glycemic level and progression would be unchanged.

Finally, some of the patients in this study who progressed to overt proteinuria may have declining renal function as well (8). Recent observational studies indicate that the rate

of decline of renal function bears a similar nonlinear relationship with prolonged hyperglycemia as the progression of microalbuminuria to overt proteinuria (42–44). Whether the mechanisms underlying the progression of these two processes are the same is unclear. However, reduction of HbA_{1c} to the lowest level possible may be a very effective way of retarding not only the rate of progression of microalbuminuria to proteinuria but also the rate of decline of renal function.

ACKNOWLEDGMENTS

This research was supported by National Institutes of Health Grant RO1-DK41526 and the Joslin Diabetes Center. L.J.S. was supported by training grant T32BK072-21/22.

We are indebted to the clinic staff and patients of the Joslin Diabetes Center for their assistance and cooperation in conducting this study and to the following members of the department: F. Denry, M. Davidson, M. Pezzolesi, K. Weeks, D. Butler, and E. Hart.

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