Determinants of Progression from Microalbuminuria to Proteinuria in Patients Who Have Type 1 Diabetes and Are Treated with Angiotensin-Converting Enzyme Inhibitors

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The aims of this study were to assess the frequency and determinants of (*1*) treatment with angiotensin-converting enzyme inhibitors (ACE-I) and (2) progression to proteinuria in the presence of ACE-I treatment in patients with type 1 diabetes and microalbuminuria. A clinic-based cohort study of patients with type 1 diabetes was begun in 1991. The patients who were included in this study ($n = 373$) are the cohort members who received a diagnosis of microalbuminuria during a 2-yr baseline observation and were followed for 10 yr with frequent assessments of urinary albumin excretion and biennial examinations. Progression to proteinuria occurred when the median urinary albumin excretion during a 2-yr interval exceeded 299 μg/min. During the decade-long study, the proportion of patients who had a history of microalbuminuria and were treated with ACE-I rose from 17 to 67%. Patients who started this treatment had (on average) higher BP, higher urinary albumin excretion, and longer diabetes duration than those who did not. Microalbuminuria often progressed to proteinuria (6.3/100 person-years) in those who were treated. Poor glycemic control and elevated serum cholesterol were the major determinants/predictors of this progression. Although treatment with ACE-I increased during the past decade, it was not completely effective, because microalbuminuria progressed to proteinuria in many treated patients. Poor glycemic control and elevated serum cholesterol were the major determinants/predictors for progression while on ACE-I treatment. The mechanisms that are responsible for the frequent failure of ACE-I to prevent progression of microalbuminuria to proteinuria in a clinical setting are not clear.

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Small elevation in urinary albumin excretion rate (AER) marks a distinct early stage of diabetic nephropathy termed microalbuminuria. When first described, this stage was believed to be the first step in an inevitable progression to proteinuria and ESRD (1–3). Recent studies demonstrated that microalbuminuria returns to normoalbuminuria in at least half of patients (4–7). Nevertheless, microalbuminuria can still be considered a marker of increased risk for advanced diabetic nephropathy and a justification for medical intervention (8).

During the past decade, several clinical trials demonstrated the effectiveness of angiotensin-converting enzyme inhibitors (ACE-I) in retarding the progression of microalbuminuria to proteinuria and slowing the rate of renal function decline in patients with proteinuria (9–13). However, a subset of the ACE-I-treated patients still progressed to more advanced stages of diabetic nephropathy (9–13).

The Joslin Study of the Natural History of Microalbuminuria in Type 1 Diabetes is an observational study that was begun in 1991 (6,14). The study spans a time when prescription of ACE-I for microalbuminuria was infrequent (early 1990s) to the present, when it is recommended practice (8). Therefore, the Joslin cohort provides an opportunity to examine the frequency and determinants of initiation of treatment with ACE-I and, more important, the frequency and determinants of progression to proteinuria while taking ACE-I. Previous reports based on the Joslin cohort described the determinants of the onset of microalbuminuria (15) and its regression to normoalbuminuria (6) and determinants of progression to proteinuria in the absence of treatment with ACE-I (16).

Materials and Methods

The study group for this report comprises the patients who had microalbuminuria and were enrolled in the Joslin Study of the Natural History of Microalbuminuria in Type 1 Diabetes (14). It is further follow-up of the same study group described previously for the examination of the regression of microalbuminuria (6).

Between January 1, 1991, and March 31, 1992, a 50% sample of Joslin

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Clinic patients who had type 1 diabetes and were aged 15 to 44 yr had their urine specimens screened for microalbuminuria (Figure 1). These 1602 patients with type 1 diabetes received a diagnosis of diabetes before age 41 yr, lived in Massachusetts at screening, and attended the Joslin Clinic for at least 1 yr before screening. The Committee on Human Studies of the Joslin Diabetes Center approved study procedures and the informed consent process.

Participants continued to provide urine for measurement of AER over the next decade during routine clinic visits or, if not attending clinic, by mail or a visit to their home. Biennial examinations were performed at clinic visits or at home to obtain medical history regarding current and past medications (particularly ACE-I and other antihypertensive drugs, BP measurements, and urine and blood specimens.

From participants' Joslin Clinic records, we obtained information on BP, medication history (prescription of ACE-I and other antihypertensive drugs), glycosylated hemoglobin (HbA_{1c}), serum cholesterol, and albumin-to-creatinine ratios. Details of the HbA_{1c} assays and the protocols for measuring the urinary albumin-to-creatinine ratio and its conversion to AER were described previously (17). Serum cholesterol was measured by an enzymatic timed end point method (Synchron CX 9ALX; Beckman Coulter, Fullerton, CA).

For analysis, the duration of the 10-yr study beginning with the first measurement of AER was divided into a 2-yr initial interval followed by four 2-yr follow-up intervals. The stage of diabetic nephropathy during the initial and all subsequent 2-yr intervals was determined by the median of all AER measurements in the interval (three on average). Medians in the range of 30 to 299 μg/min were considered microalbuminuria. Microalbuminuria was present in 312 patients in the initial 2-yr interval (prevalent cohort) (14) and developed during the first 4 yr of follow-up in 109 of the 1080 patients with normoalbuminuria (median AER <30 μg/min) in the initial interval (incident cohort) (15). For the prevalent cohort, the initial 2-yr interval was considered their baseline evaluation. For the incident cohort, baseline was the interval in which microalbuminuria developed. The remainder of the cohort had ESRD or proteinuria in the initial interval and was not included in the follow-up ($n = 210$). Figure 1 provides an outline of our study.

Progression to proteinuria during follow-up was defined as the first interval in which the median AER exceeded the upper limit of microalbuminuria (AER >299 μg/min). For facilitation of the study of progression to proteinuria while on ACE-I treatment, the starting dates of the 2-yr intervals for patients who were treated with ACE-I were realigned to coincide with the starting date of treatment. After the interval dates were realigned, 373 (89%) of the 421 patients remained assessable. Of these, 313 were followed to study completion (the last follow-up interval for which they were eligible), and for the remaining 60, median follow-up time was 4 yr. During follow-up, 73 patients progressed to proteinuria and 11 died before reaching the study end point.

For evaluation of the effectiveness of treatment with ACE-I on serum ACE activity, two groups of patients were examined at the end of the follow-up in 2003 to 2005: A random group of 24 patients who had never been treated with ACE-I and a random group of 21 patients who had been treated with ACE-I for >4 yr. From both groups of patients, serum was obtained for measurements of serum ACE activity using a previously described method (18). In brief, this method is based on the determination of hippuric acid, generated *in vitro* during cleavage of synthetic substrate Hippuryl-His-Leu by ACE in serum, incubated under controlled condition. Concentration of hippuric acid is measured after extraction by a spectrophotometric method at 228 nm (18). ACE activity is expressed in international milliunits as nanomoles of hippuric acid generated during 1 min at 37°C per 1 ml of serum (mU/ml). Normal values are in the range of 14.7 to 35.9 mU/ml. Intra- and interassay coefficients of variation were 7 and 14%, respectively. Sensitivity of the method is 0.1 mU/ml.

All analyses were done in SAS (V8.02 for Windows; SAS Institute, Cary, NC). Two analytical approaches were used. In the first approach, patients' characteristics in specific intervals were compared. Prescription of ACE-I was not randomly assigned; instead, treatment was based on the clinical judgment of participants' physicians. To identify determinants of the initiation of treatment with ACE-I, we used the interval preceding its initiation to characterize a patient who began treatment during follow-up ($n = 153$). Patients who were treated at baseline ($n = 63$) could not be included in this analysis because they were not studied before its initiation. To characterize patients who were never treated with ACE-I, we used stratified random sampling to yield the same distribution of follow-up intervals (follow-up 1, follow-up 2, *etc.*) in both groups. This balanced any effect of temporal trends in characteristics.

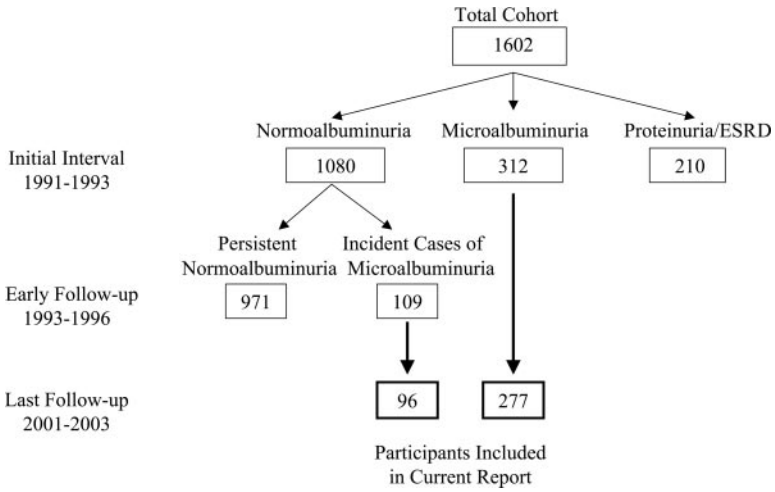

Figure 1. An outline of the first Joslin Study on the Natural History of Microalbuminuria in Type 1 Diabetes. Only patients with microalbuminuria diagnosed during the initial interval (prevalent MA; $n = 312$) and patients who developed new microalbuminuria during the early follow-up (incident MA; $n = 109$) were included in this study; 277 were followed from the first group and 96 from the second group.

In the second approach, we calculated incidence rates of progression to proteinuria as the measure of disease occurrence. The 2-yr intervals of observation time for a patient were considered in pairs. The first, or "exposure," interval characterized the patient at risk for progression during the second, or "outcome," interval. If progression did not occur, then the outcome interval contributed 2 yr of person time. If progression occurred, then the outcome interval contributed 1 yr of person time (event assumed to occur at midpoint), and all subsequent time was censored.

The total observation time was 2753 person-years. The 2-yr baseline intervals, during which each individual's nephropathy status was determined, accounted for 746 person-years, and the remaining 2007 person-years compose the observation time during which the individuals were at risk for progression to proteinuria. The 2007 person-years included 905 person-years of observation during ACE-I treatment (355 contributed by patients who were already treated at baseline and 550 by patients who started treatment during follow-up) and 1102 person-years of observation without ACE-I treatment (789 contributed by patients who were never treated during follow-up with ACE-I and 313 by patients who began treatment during follow-up).

For the analysis of determinants/predictors of progression of microalbuminuria to proteinuria while on treatment with ACE-I, microalbuminuria had to be present in the exposure interval and treatment with ACE-I present in the outcome interval. If microalbuminuria regressed to normoalbuminuria during an outcome interval, then subsequent intervals could not be included in the analysis unless microalbuminuria returned. As previously reported (6), regression of microalbuminuria to normoalbuminuria was frequent in this cohort. Subsequent progression from normoalbuminuria to proteinuria was rare, regardless of treatment with ACE-I: None during 348 person-years of observation without treatment with ACE-I and only two during 192 person-years of observation with treatment. Exclusion of the intervals with normoalbuminuria from the analysis left 713 person-years of microalbuminuria with ACE-I treatment and 754 person-years of microalbuminuria without ACE-I treatment.

Patient characteristics during the exposure interval were considered potential determinants/predictors for the outcome interval. For each laboratory measure (other than AER), the average of all measurements within the exposure interval was used. The percentage of intervals with missing data on determinants/predictors were 4% for HbA_{1c}, 12% for cholesterol, and 18% for BP. For each of these determinants/predictors, the high correlation between successive pairs of intervals justified carrying the last value forward for missing data (19). We used pooled logistic regression to estimate their effects on progression from microalbuminuria to proteinuria and likelihood ratio tests to determine statistical significance (20).

Results

Characteristics of the Study Group

Baseline characteristics of the study group of patients with microalbuminuria are summarized in Table 1 according to membership in the incident or prevalent cohort. The two cohorts had similar distributions of gender, age, postpubertal duration of diabetes, HbA_{1c}, cholesterol, triglycerides, and BP. They also had similar proportions of people who had never smoked, but the incident cohort had more current smokers and fewer former smokers. As expected, the level of AER was lower in the incident cohort than in the prevalent cohort. At baseline, prevalent cohort members were more frequently treated with an ACE-I (20%) than incident cohort members (7%).

Table 1. Baseline characteristics of the incident and prevalent cohorts[a]

Baseline Characteristics	Prevalent Cohort (n = 277)	Incident Cohort (n = 96)	P
Male gender (%)	50	47	0.62
Smoking status (%)			0.006
current	29	46	
former	19	10	
never	52	44	
Age (yr)	30 ± 8	31 ± 8	0.12
Diabetes duration (yr)	17 ± 9	16 ± 8	0.31
BMI (kg/m^2)	24.6 ± 3.5	24.7 ± 4.9	0.96
HbA_{1c} (%)	9.0 ± 1.6	9.2 ± 1.6	0.24
Cholesterol (mg/dl)	196 ± 41	197 ± 41	0.73
SBP (mmHg)	123 ± 15	124 ± 17	0.69
DBP (mmHg)	75 ± 9	75 ± 8	0.93
AER ($\mu g/min$)[b]	74.3 (46.1 to 135.1)	48.8 (37.8 to 72.3)	<0.0001
Treated with a lipid-lowering medication (%)	2	0	0.33
Treated with an ACE-I (%)[c]	20	7	0.003
Treated with an antihypertensive medication not an ACE-I (%)	10	6	0.23

[a]ACE-I, angiotensin-converting enzyme inhibitor; AER, albumin excretion rate; BMI, body mass index; DBP, diastolic BP; HbA_{1c}, glycosylated hemoglobin; SBP, systolic BP.

[b]Data are median and interquartile range and transformed to logarithmic scale for significance testing.

[c]Patients who were treated with an ACE-I for at least 3 mo. Only one patient was treated for >3 mo and discontinued ACE-I during the study. This person did so after 6 yr of treatment and then contributed to non–ACE-I–treated person time after discontinuation.

Maximum follow-up after the 2-yr baseline was 8 yr for the prevalent cohort and 6 yr for the incident cohort. The 6-yr cumulative incidence of progression to proteinuria was similar in the incident and prevalent cohorts: 16.0% (95% confidence interval 7.9 to 24.1%) and 18.9% (95% confidence interval 14.2 to 23.7%), respectively.

Treatment with ACE-I

Treatment with ACE-I increased during the span of the study. In the combined incident and prevalent cohorts, 17% were treated at baseline, 31% at follow-up 1, 43% at follow-up 2, 53% at follow-up 3, and 67% at follow-up 4. The most frequently used ACE-I were enalapril, lisinopril, captopril, and quinapril. By the end of the study, 75% of patients who were using one of these agents were prescribed dosages that commonly are used in clinical trials. A subset of patients ($n = 50$) were interviewed in 2004 about compliance with ACE-I. Of these patients, 94% reported that they always took their prescribed dose, and 6% reported taking their prescribed dose 75% of the time.

Characteristics of the 153 patients who had microalbuminuria and began treatment with ACE-I during follow-up are compared with untreated patients in Table 2 (see the Materials and Methods section for details of the selection of the sample of untreated patients for this comparison). Unlike the clinical trials of ACE-I, treated patients in this study differed systematically from those who were untreated. They had higher systolic and diastolic BP, higher AER, higher cholesterol, and longer diabetes duration than treated patients. Nonsmokers were somewhat more likely to be treated with ACE-I than smokers.

Determinants of Progression to Proteinuria in the Presence of ACE-I Treatment

The incidence rate of progression from microalbuminuria to proteinuria was 6.3 per 100 person-years (45 events in 713 person-years) during treatment with ACE-I and 3.5 per 100 person-years (26 events during 752 person-years) in the absence of treatment. The reason for lower incidence of progression in the absence of ACE-I treatment is unclear and it is not the subject of this study.

Univariate Analysis. The incidence rate of progression to proteinuria in the presence of ACE-I treatment is shown in Table 3 according to various determinants/predictors. The incidence rate varied little with gender, membership in the incident or prevalent cohort, and smoking status. However, it declined significantly with increasing duration of diabetes from 11.5 per 100 person-years for duration <16 yr to 3.2 per 100 person-years for duration >30 yr ($P = 0.009$). Conversely, it increased significantly with HbA_{1c} value ($P < 0.0001$). Only nine events of progression occurred during 351 person-years of exposure to HbA_{1c} values below the median 8.6%, resulting in an incidence rate of 2.6 per 100 person-years. The rate increased to 6.1 per 100 person-years in the third quartile (8.6 to 9.6%) and 14.5 per 100 person-years in the fourth. Higher serum cholesterol was also associated with a higher rate of progression ($P = 0.002$). The incidence rate increased from 3.0 per 100 person-years for serum cholesterol less than the median 199 mg/dl to 6.4 per 100 person-years for concentrations between 199 and 223 mg/dl, and then to 12.6 per 100 person-years for higher concentrations. The incidence rate of progression to proteinuria did not vary significantly with either systolic or diastolic BP; however, it increased at higher levels of AER ($P < 0.0001$), rising sharply in the fourth quartile (>159 μg/min). The incidence rate of progression did not vary significantly with duration of treatment with ACE-I ($P = 0.38$) or trend in one direction. The incidence of progression was 6.3 per 100 person-years during the first two yr, 8.1 per 100 person-years during the third and fourth years, and 4.6 per 100 person-years during the sixth through tenth years.

Multivariate Analysis. The independent effects of these exposures on the risk for progression of microalbuminuria to proteinuria in the presence of ACE-I treatment were evaluated with multiple logistic models. Overall, the multivariate results for all of the significant determinants/predictors were unchanged from their univariate effects, indicating the independence of their effects. The only exception was the decreasing risk for progression with increasing duration of diabetes, which was no longer significant when AER and HbA_{1c} were included in the model.

Table 2. Characteristics of patients according to treatment with ACE-I[a]

Clinical Characteristics	Not Treated ($n = 153$)	Treated ($n = 153$)	*P*
Male gender (%)	48	52	0.57
Current smoker (%)	39	28	0.05
Age (yr)	32	33	0.06
Diabetes duration (yr)	17	21	0.0001
HbA_{1c} (%)	9.3	9.1	0.25
Cholesterol (mg/dl)	187	202	0.0007
SBP (mmHg)	119	128	<0.0001
DBP (mmHg)	73	77	<0.0001
AER (μg/min)[b]	37.8	98.7	<0.0001

[a]For selection of intervals for comparison between the two groups, see Materials and Methods.
[b]Data are median and transformed to logarithmic scale for significance testing.

Table 3. Incidence rates of progression of microalbuminuria to proteinuria in patients who were treated with ACE-I according to selected characteristics

Characteristics	Person-Years (*n*)	Progressed to Proteinuria (*n*)	Incidence Rate (per 100 person-years)	*P*[a]
Gender				0.92
men	354	22	6.2	
women	359	23	6.4	
Cohort				0.26
incidence	127	11	8.7	
prevalence	586	34	5.8	
Smoking status				0.24
current	155	13	8.4	
former or never	553	31	5.6	
Duration of diabetes (yr)[b]				0.009
<16	165	19	11.5	
16 to 30	362	20	5.5	
>30	186	6	3.2	
BMI (kg/m^2)[b]				0.84
<22.3	151	11	7.3	
22.3 to 27.5	310	18	5.8	
>27.5	157	5	3.2	
HbA_{1c} (%)[c]				<0.0001
<8.6	351	9	2.6	
8.6 to 9.6	198	12	6.1	
>9.6	159	23	14.5	
Cholesterol (mg/dl)[c]				0.002
<199	363	11	3.0	
199 to 223	171	11	6.4	
>223	167	21	12.6	
SBP (mmHg)[b,d]				0.13
<118	165	15	9.1	
118 to 137	340	22	6.5	
>137	186	6	3.2	
DBP (mmHg)[b]				0.58
<70	128	10	7.8	
70 to 80	370	20	5.4	
>80	193	13	6.7	
AER ($\mu g/min$)[c]				<0.0001
<91.7	372	6	1.6	
91.7 to 158.9	183	9	4.9	
>158.9	158	30	19.0	
Treatment with lipid-lowering drugs during outcome interval				0.46
no	606	40	6.6	
yes	107	5	4.7	
Treatment with antihypertensive medications other than ACE-I during outcome interval[e]				0.19
no	510	36	7.1	
yes	203	9	4.4	
Years of treatment with ACE-I by the end of outcome interval				0.38
2	318	20	6.3	
4	198	16	8.1	
>4	197	9	4.6	

[a]Testing overall significance of the exposure using likelihood ratio test.
[b]Second and third quartiles collapsed.
[c]First and second quartiles collapsed.
[d]Using American Diabetes Association BP goals of SBP <130 mmHg and DBP <80 mmHg, 57% did not meet that target and 43% did. This was not related to progression to proteinuria, however. Of those who met the goal, 13% progressed to proteinuria, and of those who did not meet the goal, 11% progressed to proteinuria.
[e]The introduction of angiotensin II receptor blockers (ARB) as a treatment option occurred near the end of the study and was infrequent. Two patients were treated with an ARB in addition to their existing ACE-I treatment during two follow-up intervals and three patients for one follow-up interval. Three patients switched to an ARB after long-term treatment with an ACE-I and were still counted in the ACE-I–treated group.

Additivity of the Effects of Risk Factors on Progression

The incidence rate of progression to proteinuria in the presence of ACE-I treatment is shown in Figure 2 according to combinations of the two modifiable determinants/predictors (HbA_{1c} and serum cholesterol), separately for patients with low and high AER. In individuals with AER <159 μg/min, the incidence rate was 1.1 per 100 person-years when HbA_{1c} was <9.6% and serum cholesterol was <223 mg/dl. It increased to 3.3 per 100 person-years when either risk factor exceeded those values and increased further to 12.8 per 100 person years when both did. In individuals with AER ≥159 μg/min, the incidence rate was 8.8 per 100 person-years when both HbA_{1c} and serum cholesterol were below those values. It increased to 20.5 per 100 person-years when either determinants/predictors exceeded those values and increased further to 63.6 per 100 person-years when both did. The pattern across groups was similar at both levels of AER, but the rate was magnified five-fold in those with AER ≥159 μg/min. A test for trend across risk factor combinations was statistically significant in low ($P = 0.0005$) and high ($P = 0.005$) AER groups.

To estimate the fraction of progressions to proteinuria that are attributable to these exposures, assume that clinical interventions could eliminate the effect of these modifiable determinants/predictors (elevated HbA_{1c} and serum cholesterol). In the low AER group, the incidence rate collapsing one and two risk factors together was 5.2 per 100 and 1.1 per 100 person-years for zero risk factors; therefore, the interventions could prevent 79% of the progressions to proteinuria. In the high AER group, the incidence rate collapsing one and two risk factors together was 14.1 per 100 and 8.8 per 100 person-years for zero risk factors; therefore, the interventions could prevent 38% of the progressions to proteinuria.

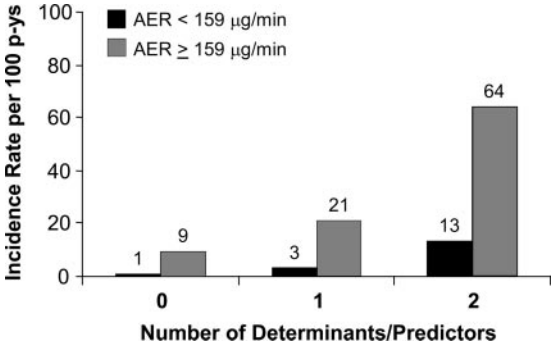

Figure 2. Incidence rates of progression from microalbuminuria to proteinuria according to number of determinants/predictors present. The results are shown separately by level of albumin excretion rate (AER): Low AER is defined as the first three quartiles of AER (AER <159 μg/min), and high AER is defined as the fourth quartile AER (AER ≥159 μg/min). The determinants/predictors are fourth quartile of glycosylated hemoglobin (HbA_{1c}; >9.6%) and fourth quartile of cholesterol (>223 mg/dl). Controlling for duration and gender, there was a statistically significant test for trend in low AER ($P = 0.0005$) and high AER ($P = 0.0051$). Person-time and sample size for low AER: 0 determinants/predictors 352 person-years ($n = 103$), 1 determinant/predictor 153 person-years ($n = 57$), and 2 determinants/predictors 39 person-years ($n = 17$). Person-time and sample size for high AER: 0 determinants/predictors 68 person-years ($n = 34$), 1 determinant/predictor 78 person-years ($n = 40$), and 2 determinants/predictors 11 person-years ($n = 8$).

Effectiveness of ACE-I Treatment Measured by Serum ACE Activity

For evaluation of the effectiveness of treatment with ACE-I on serum ACE activity in a clinical setting, two groups of patients were examined at the end of follow-up in 2003 to 2005. We selected a random group of 24 patients who had never been treated with ACE-I and a random group of 21 patients who had been treated with ACE-I for >4 yr. From both groups of patients, serum was obtained for measurements of serum ACE activity (Figure 3). Patients who were treated with ACE-I had profoundly reduced serum ACE activity in comparison with patients without treatment ($P < 0.0001$). On average, there was a >60% reduction in serum ACE activity comparing patients who were treated with ACE-I (mean 13.6 mU/ml) to those who were not treated (mean 34.5 mU/ml). However, serum ACE activity was not blocked completely in those who were treated.

Discussion

During the past decade, treatment of microalbuminuria with ACE-I has become very common in patients with type 1 diabetes. Currently, almost two thirds are treated with ACE-I in a clinic that specializes in diabetes care. However, despite American Diabetes Association recommendations (8), clinical practice tends to favor the initiation of treatment in patients with more advanced microalbuminuria. Patients who are given ACE-I have higher BP, higher AER, and longer diabetes dura-

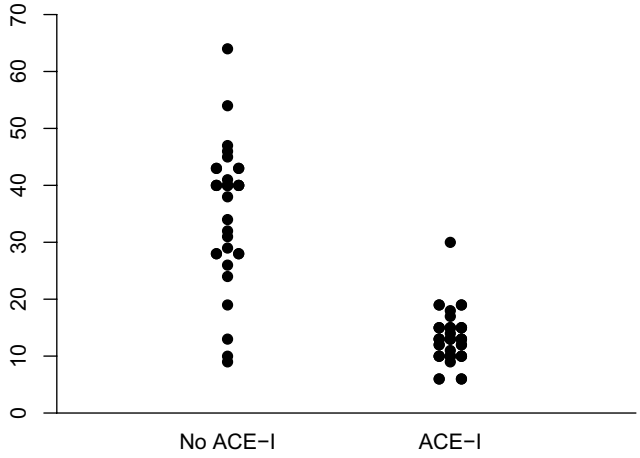

Figure 3. Levels of serum angiotensin-converting enzyme (ACE) activity in patients who were not treated with ACE inhibitors (ACE-I) and patients who were treated with ACE-I. The mean level (SD) of serum ACE activity in patients who were not treated with ACE-I was 34.5 (13.5) mU/ml and in patients who were treated with ACE-I was 13.6 (5.3) mU/ml. The difference between the two groups was statistically significant ($P < 0.0001$).

tion than those who are not treated. This "treatment bias" most likely accounts for the higher risk for progression to proteinuria in those who were treated than in those who were not treated with ACE-I in this study. Also, despite the proven efficacy of ACE-I in short-term clinical trials (21), our data indicate that they are inadequate as the sole component of long-term clinical management. The progression of microalbuminuria occurs frequently despite ACE-I treatment, and its major determinants/predictors are poor glycemic control and elevated serum cholesterol.

To compare the incidence rate of progression from microalbuminuria to proteinuria in this study with three clinical trials, we converted the cumulative incidence rates of progression reported for the ACE-I treated arms of the double-blinded, randomized trials (12,13) and open, randomized, controlled study (9,10) to incidence rates and obtained 1.3 per 100 person-years (9,10), 3 per 100 person-years (13) and 5 per 100 person-years (12), all lower than our incidence rate of 6.3 per 100 person-years. The difference most likely reflects the self-motivation found in patients who qualify for participation in clinical trials (particularly their glycemic control), which is not as diverse as that of our clinic patients. Our incidence rates do not include time when microalbuminuria has regressed to normoalbuminuria. When these intervals are included in the calculation of the incidence rate of progression to proteinuria, the estimated rate decreases from 6.3 per 100 person-years to 5.2 per 100 person-years.

It is unclear from these trials whether the effectiveness of ACE-I increases, decreases, or stays the same over a long period of time. The finding in our 10-yr follow-up study of an unchanging risk for progression from microalbuminuria to proteinuria as the duration of treatment with ACE-I was prolonged is consistent with an interpretation that ACE-I postpone or prevent proteinuria or ESRD in a small subset of patients, whereas other factors determine progression in the majority of patients.

Progression from microalbuminuria to proteinuria despite ACE-I therapy may result from incomplete patient adherence to therapy or from insufficient biologic efficacy of these medications as prescribed. In this study, self-reported adherence to therapy was good. We also showed that patients who were treated with ACE-I had significantly lower serum ACE activity, although still present, than patients who were not treated with these drugs. Consistent with other reports, on average, there was a >60% reduction in serum ACE activity comparing patients who were treated with ACE-I and not treated (22). It is not clear whether effectiveness of ACE-I in preventing progression to proteinuria would increase with high-dosage ACE-I (23). However, a study on imidapril found no increase in renin-angiotensin-aldosterone system blockade when dosages from 2.5 to 10 mg were compared (22). It is possible that alternative approaches to renin-angiotensin-aldosterone system blockade may be required (24). Such approaches may include the combination of ACE-I agents with angiotensin II receptor blockers (24–26) or the use of aldosterone blockade agents such as spironolactone (27,28). The results of this study justify further research into these alternative approaches in type 1 diabetes. In addition, because in our study ACE-I was prescribed to patients with more advanced microalbuminuria, it is still possible that treatment of microalbuminuria soon after its onset with ACE-I or dual therapy might be more effective.

This study provides strong support for the role of chronic hyperglycemia as a major determinant/predictor of glomerular damage even in the presence of treatment with ACE-I. Its role in the presence of treatment with ACE-I recapitulates its role in the absence of treatment, as reported previously from an analysis of the first 4 yr of follow-up of this cohort when few were treated with ACE-I (16). In the secondary prevention arm of the Diabetes Control and Complications Trial of intensive diabetes management, the effect of HbA_{1c} on the risk for progression of microalbuminuria to proteinuria was NS (29). This was most likely due to the group's low level of microalbuminuria and low HbA_{1c} (two determinants of low risk) and its small size (73 patients with microalbuminuria). Other studies support an effect of hyperglycemia on progression from microalbuminuria to proteinuria (5,7,30,31).

Low serum cholesterol favors regression of microalbuminuria to normoalbuminuria, as previously shown in this same cohort of patients (6). Conversely, higher serum cholesterol increases the risk for progression to proteinuria, in a dose-dependent manner. The question of whether serum cholesterol causes progression or is only a predictor cannot be determined from the results of this study.

On the basis of these results, a reduction of HbA_{1c} below 9.6% and serum cholesterol below 223 mg/dl can be projected to reduce the number of individuals who progress to proteinuria during follow-up by 79% for the low AER group and by 38% for the high AER group. Although these therapeutic goals are feasible, the true effect of interventions to achieve them can only be determined in a clinical trial. A meta-analysis of trials of lipid-lowering therapy and progression of renal disease found a trend toward decreasing AER with treatment (32). Of the six studies of patients with type 1 or type 2 diabetes analyzed, AER was reduced, although not significantly, in all. Lack of significance was most likely due to the small sample size.

Higher diastolic BP within normal ranges was associated in our previous study with progression of microalbuminuria to proteinuria (16). Consistent with other reports (5,7,30,31), in this study, which focused on patients who were treated with ACE-I, we found no association of progression to proteinuria with BP.

The risk for progression increased as the baseline level of AER increased and approached the value that defined proteinuria. To determine whether this was an artifact, we repeated the analysis defining progression as a 50% increase, which avoids the imposition of an arbitrary boundary. With this criterion, the number of progressions increased from 45 to 68, and the effect of most covariates was present but weakened (data not shown). We found that most of the additional progressions were among patients with very low levels of AER. A 50% increase in those small values falls within the range of assay variation, so the additional progressions might represent nonspecific variation of AER rather than progressive disease.

Some limitations of our study deserve mention. The first is the generalizability of patient outcomes that were obtained at the Joslin Clinic to settings that place less emphasis on glycemic control or screen less frequently for microalbuminuria. Less attention to either of these may result in a higher rate of progression from microalbuminuria to proteinuria in patients who are treated with ACE-I. A second limitation is that, to conduct the study within the normal operation of Joslin Clinic, we followed standard clinic procedures and collected random daytime urine samples (not first morning) rather than timed urine collections. Previous studies have shown that results that are based on random urine collections correlate very closely to results that are based on daytime timed urine collections (17,33). Another limitation of this study is that readers who are accustomed to microalbuminuria defined as 20 to 200 μg/min will wonder whether our findings that were based on 30 to 300 μg/min will apply to their experience. The 20- to 200-μg/min criteria were developed in settings that measure urinary albumin in overnight urine or first voided morning samples. In such samples, albumin concentrations are lower than those found in random urine collected during daytime activities. Our findings based on 30 to 300 μg/min in daytime samples should be very close to what would be obtained if the 20- to 200-μg/min criteria are applied to first-voided samples (34). Conversely, a reader who applies the 20- to 200-μg/min criteria to daytime collections can expect to see a lower frequency of progression than we report because the high-risk individual in the range 200 to 299 has already been classified as having proteinuria. The final limitation of our study is the modest number of events of progressions to proteinuria. Although the number of person-years of observation of patients who had microalbuminuria and were being treated with ACE-I (n = 713) exceeds that in any published clinical trials (21), our number of events was sufficient to detect only determinants with strong effects. We were not able to examine, for example, a possibility that ACE-I might have different effectiveness according to level of glycemic control or the role of other weaker determinants of progression to proteinuria such as smoking or duration of diabetes.

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Disclosures

None.

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See the related editorial, "Treating Diabetic Nephropathy: Unfinished Success Is Not Failure," on pages 407–409.

Ficociello *et al*. and the editorial by Lewis in this month's *CJASN* (pages 407–409) point to the fact that high urinary albumin excretion and high blood pressure, as well as the duration of diabetes, are major factors allowing microalbuminuria to evolve into overt proteinuria despite ACE inhibitors. The article in this month's *JASN* by Eijkelkamp *et al*. (pages 1540–1546) emphasizes the importance of albuminuria as a target for renoprotective therapies independent of blood pressure control. Obviously, this is a continuum that needs to be appreciated by all nephrologists caring for patients with diabetes.