

# The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812

JUNE 5, 2003

VOL. 348 NO. 23

## Regression of Microalbuminuria in Type 1 Diabetes

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### ABSTRACT

#### BACKGROUND

In the present study, we aimed to determine the frequency of a significant reduction in urinary albumin excretion and factors affecting such reduction in patients with type 1 diabetes and microalbuminuria.

#### METHODS

The study included 386 patients with persistent microalbuminuria, indicated by repeated measurements of urinary albumin excretion (estimated on the basis of albumin-to-creatinine ratios) in the range of 30 to 299  $\mu\text{g}$  per minute during an initial two-year evaluation period. Subsequent measurements during the next six years were grouped into two-year periods, averaged, and analyzed for regression of microalbuminuria, which was defined as a 50 percent reduction in urinary albumin excretion from one two-year period to the next.

#### RESULTS

Regression of microalbuminuria was frequent, with a six-year cumulative incidence of 58 percent (95 percent confidence interval, 52 to 64 percent). The use of angiotensin-converting-enzyme inhibitors was not associated with the regression of microalbuminuria. However, microalbuminuria of short duration, salutary levels of glycosylated hemoglobin (less than 8 percent), low systolic blood pressure (less than 115 mm Hg), and low levels of both cholesterol and triglycerides (less than 198 mg per deciliter [5.12 mmol per liter] and 145 mg per deciliter [1.64 mmol per liter], respectively) were independently associated with the regression of microalbuminuria. Patients with salutary levels of all modifiable factors had a hazard ratio for regression of 3.0 (95 percent confidence interval, 1.5 to 6.0), as compared with patients with no salutary levels of any modifiable factor.

#### CONCLUSIONS

Frequent regression of microalbuminuria in patients with type 1 diabetes indicates that elevated urinary albumin excretion does not imply inexorably progressive nephropathy. Identification of the multiple determinants of the regression of microalbuminuria has implications for current theories about the mechanisms of early diabetic nephropathy.

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N Engl J Med 2003;348:2285-93.

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**I**N THE EARLY 1980S, THREE LANDMARK studies of patients with type 1 diabetes suggested an ominous prognosis for those with minute elevations of urinary albumin excretion, designated as microalbuminuria. Microalbuminuria was said to confer a 60 to 85 percent risk of the development of overt proteinuria within 6 to 14 years.<sup>1-3</sup> Although derived from small studies, this model of diabetic nephropathy held that microalbuminuria in type 1 diabetes heralded an inexorable process leading to overt proteinuria.

Other prospective studies challenged this model, suggesting a considerably lower risk of progression to proteinuria<sup>4-7</sup>; in some patients microalbuminuria remained stable, whereas in others microalbuminuria abated transiently or even permanently.<sup>8-10</sup> If the factors determining regression could be identified, they might provide clues to effective strategies for preventing advanced diabetic nephropathy.

The Joslin Study of the Natural History of Microalbuminuria was designed to identify the determinants of the early stages of diabetic nephropathy in type 1 diabetes. Previously published results described factors affecting the incidence of microalbuminuria<sup>11,12</sup> and its progression to overt proteinuria.<sup>6</sup> In the current study, we aimed to determine the frequency of a significant reduction in urinary albumin excretion and the factors affecting such reduction in patients with microalbuminuria.

## METHODS

### SELECTION OF STUDY PARTICIPANTS

All patients with type 1 diabetes and microalbuminuria who were enrolled in the Joslin Study of the Natural History of Microalbuminuria<sup>6,11,12</sup> were eligible. Urine specimens from every second patient with type 1 diabetes who was 15 to 44 years of age, seen at the Joslin Clinic in Boston between January 1991 and April 1992, were examined for urinary albumin excretion (1602 patients). The patients whose urine specimens were examined were observed for the next eight years. For analysis, observation was divided into two-year periods, consisting of an initial evaluation period and a first, second, and third follow-up period. Microalbuminuria was present initially in 312 patients (the prevalence cohort) and developed later in another 109 patients during the first or second follow-up period (the incidence cohort).<sup>12</sup> Only 25 patients from the prevalence cohort (8 percent) and 10 from the

incidence cohort (9 percent) were lost to follow-up, leaving 386 for analysis. The study protocol and consent procedures were approved by the committee on human studies of the Joslin Diabetes Center. Written informed consent was obtained from all patients.

### ASSESSMENT OF URINARY ALBUMIN EXCRETION

The albumin excretion rate was estimated on the basis of the albumin-to-creatinine ratio in random urine samples, as previously described.<sup>11-13</sup> The participants provided an average of 3.3 urine samples per two-year period. Individual values for the albumin-to-creatinine ratio (measured in milligrams per gram) were transformed to a (base-10) logarithmic scale for analysis and converted to albumin excretion rates (in micrograms per minute) by the formula  $\log(\text{AER}) = 0.44 + (0.85)\log(\text{ACR}) - (0.13)\text{sex}$ , where AER is the albumin excretion rate, ACR is the albumin-to-creatinine ratio, and sex is assigned a value of 1 for female patients and 0 for male patients.<sup>13</sup> This conversion formula was derived from an independent sample of patients with type 1 diabetes who underwent simultaneous determinations of the albumin-to-creatinine ratio and the albumin excretion rate based on a three-hour daytime collection (Pearson correlation coefficient, 0.97).<sup>13</sup>

At the end of each two-year period, the participants were classified according to their nephropathy status (normal levels of albumin excretion, microalbuminuria, or proteinuria) on the basis of the median of all urinary measurements within the two years.<sup>12,13</sup> Microalbuminuria was defined by an albumin excretion rate of 30 to 299  $\mu\text{g}$  per minute (43 to 430 mg per 24 hours). This definition was similar to that used in the Diabetes Control and Complications Trial, which was 40 mg per 24 hours estimated from a daytime, timed urine collection (4 hours) converted to 24-hour values.<sup>14</sup>

### DEFINITION OF REGRESSION OF MICROALBUMINURIA

The lower threshold for the above definition of microalbuminuria, if used as the basis for defining decreasing albumin excretion during follow-up, has inherent problems as a result of regression toward the mean and the propensity for participants with albumin excretion rates close to the lower boundary for microalbuminuria to cross the boundary because of random measurement error. These problems were minimized by our basing the estimate

of a patient's albumin excretion on the geometric mean of several measurements (mean, 3.3 per period) and defining regression of microalbuminuria as a 50 percent reduction in albumin excretion from one two-year period to the next. Given the standard deviation of 38 percent for the albumin excretion rate in an individual subject,<sup>13</sup> the critical value for a significant decrease in the average of three measurements (in a one-tailed test) is 46 percent, which we rounded to 50 percent. Figure 1 illustrates the method of determining the time and occurrence of the outcome.

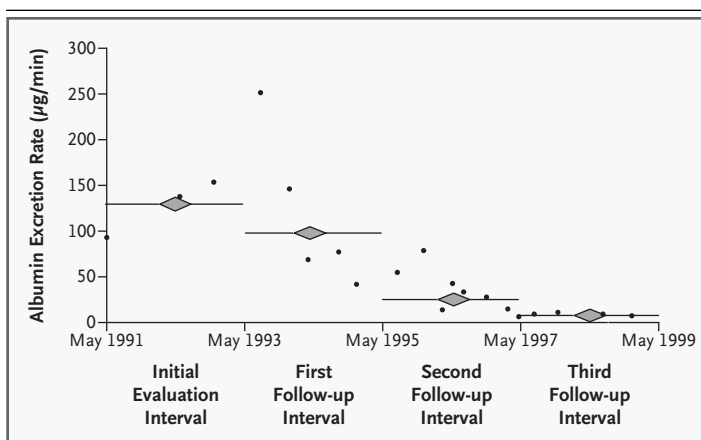
#### MEASUREMENT OF EXPOSURE VARIABLES

The examination for exposure variables included a medical-history interview, with emphasis on the use of angiotensin-converting-enzyme (ACE) inhibitors and non-ACE-inhibitor antihypertensive medications; measurement of blood pressure; and blood sampling for determination of biochemical values. All laboratory variables measured within a two-year period were averaged (the mean number of measurements per two-year period was 4.0 for glycosylated hemoglobin, 2.0 for total cholesterol, 1.9 for triglycerides, and 1.7 for high-density lipoprotein). Glycosylated hemoglobin was measured as hemoglobin A<sub>1c</sub>.<sup>11</sup> Lipid concentrations were measured by an enzymatic timed-end-point method (Synchron CX 9ALX, Beckman Coulter). Blood-pressure measurements for the first three clinic visits in each period were averaged. The use of ACE inhibitors or non-ACE-inhibitor antihypertensive medications and exposure to cigarette smoking were recorded if they occurred for at least three months in a given two-year period.

#### STATISTICAL ANALYSIS

The data were examined first by a case-control analysis, in which the participants were classified according to whether regression of microalbuminuria occurred during follow-up. Next, the data were examined by a failure-time (Cox regression) analysis, in which the predictor variables were permitted to vary over time. The level of the predictor variables in the preceding two-year period was used in this analysis, since events bore the strongest temporal relation to exposures in that period (data not shown). Follow-up time was censored if regression of microalbuminuria occurred or if the patient was unavailable for follow-up in the next period.

Descriptive statistics were calculated and analy-



**Figure 1. Albumin Excretion Rate over Time for a Patient with Regression of Microalbuminuria.**

Individual albumin excretion measurements estimated on the basis of the albumin-to-creatinine ratio are shown as solid circles, and geometric means of all measurements made during each two-year period are shown as diamonds; bars indicate the duration of the measurement periods. The participant was a woman who was 28 years old at the beginning of study enrollment and who did not use angiotensin-converting-enzyme inhibitors at any point during the eight years of the study. In the majority of the patients, the individual measurements of the albumin excretion rate changed in a nonlinear fashion during follow-up. Division of follow-up into two-year periods captured the significant directional changes in sequential measurements. In this example, the mean albumin excretion rate decreased by 23 percent from the initial evaluation period to the first follow-up period, and by 74 percent from the first to the second follow-up period. The albumin excretion rate decreased by more than 50 percent in the latter period. Since the second period corresponds to four years of follow-up, the time of the event for this patient was four years. Only the first occurrence of regression was included in the analysis, and therefore the further decrease in the third follow-up period was ignored.

ses of univariate and multivariate regression models were performed with use of SAS software (version 8.02 for Windows). Cumulative incidence rates were estimated by life-table methods. The selection of exposure variables for the multivariate analyses was based on preliminary univariate Cox regression analyses. All variables with an alpha level of less than 5 percent according to the Wald test were retained for the multivariate analysis. Indicator variables were created to represent continuous variables with a nonlinear association with survival time. A manual backward stepwise procedure was used to select explanatory variables with statistically significant effects on the time to regression (alpha, <5 percent). This multivariate Cox regression model was associated with 25 events per independent variable and a  $\chi^2$  in a log-likelihood test of 55 ( $P < 0.001$ ).

## RESULTS

Table 1 shows the distribution of the patients according to their nephropathy status for each two-year study period. During the three follow-up periods, the prevalence of proteinuria increased to 7 percent, 13 percent, and then 15 percent. The six-year cumulative incidence of an increase in urinary albumin excretion into the range defined as proteinuria was 19 percent (95 percent confidence interval, 14 to 23). This estimate is higher than the prevalence in the third follow-up period because the level of albumin excretion decreased in some of the patients with proteinuria. An analysis of the frequency of the progression of microalbuminuria to proteinuria and the factors associated with such progression has been previously reported.<sup>6</sup>

The most striking finding was that at six years the cumulative proportion of subjects whose albumin-excretion rate had decreased into the normal range was 59 percent (95 percent confidence interval, 54 to 64). The prevalence of normal albumin excretion remained constant after the first follow-up period because microalbuminuria recurred in some patients, whereas others had albumin excretion that became normal in the second or third follow-up period (Table 1). To make the analysis independent of the boundary between normal albumin excretion and microalbuminuria, however, we defined regression of microalbuminuria as a reduction of 50 per-

cent or more in the albumin excretion rate from one two-year period to the next.

Regression of microalbuminuria occurred in 196 patients, a six-year cumulative incidence of 58 percent (95 percent confidence interval, 52 to 64). The characteristics of the patients at base line are summarized in Table 2 according to whether or not regression of microalbuminuria occurred. Those in whom regression occurred were younger and were more likely to be female (the first difference, but not the second, was statistically significant). There were no base-line differences in the mean albumin excretion rate or the mean serum creatinine level between those who did and those who did not later have a regression of microalbuminuria. There were also no base-line differences between these groups in the rate of smoking, the use of non-ACE-inhibitor antihypertensive medications, or the proportion of patients with membership in the incidence cohort. The number of subjects whose microalbuminuria regressed was slightly lower among those taking ACE inhibitors than among those not taking such drugs during follow-up. Subjects with regression of microalbuminuria had lower systolic blood pressure and lower levels of glycosylated hemoglobin, total cholesterol, and triglycerides, although the difference in systolic blood pressure was not significant.

Factors associated with regression of microalbuminuria in the follow-up analysis are shown in Table 3. Among the nonmodifiable factors, the hazard ratios for regression of microalbuminuria were significant for younger age and for membership in the incidence cohort — that is, for microalbuminuria of shorter duration.

The strongest modifiable factors associated with regression of microalbuminuria were lipid levels and glycemic exposure. In preliminary analyses, the effects of total cholesterol and triglycerides were nonlinear. The likelihood of the regression of microalbuminuria appeared greatest among patients in the two lowest quartiles of cholesterol level and the three lowest quartiles of triglyceride level (Table 3). Although these factors were correlated, their effects were independent. Therefore, lipid levels in the multivariate model were represented by four groups defined by both cholesterol and triglycerides (Table 3). A low level of either cholesterol or triglycerides alone approximately doubled the chance of the regression of microalbuminuria, but low levels of both cholesterol and triglycerides had little effect beyond that of either alone. The hazard

**Table 1. Nephropathy Status According to Two-Year Study Period.**

| Status*                  | Initial Evaluation Period† | 1st Follow-up Period | 2nd Follow-up Period | 3rd Follow-up Period |
|--------------------------|----------------------------|----------------------|----------------------|----------------------|
|                          |                            |                      |                      |                      |
| Proteinuria              | —                          | 24 (7)               | 37 (13)              | 33 (15)              |
| Microalbuminuria         | 386 (100)                  | 191 (54)             | 141 (49)             | 99 (45)              |
| Normal albumin excretion | —                          | 136 (39)             | 110 (38)             | 88 (40)              |
| Total                    | 386 (100)                  | 351 (100)‡           | 288 (100)‡           | 220 (100)‡           |

\* The lower limits of the albumin excretion rate for microalbuminuria and proteinuria were 30 and 300  $\mu\text{g}$  per minute, respectively.

† The initial evaluation period was the first two-year period during which microalbuminuria was present. Microalbuminuria was present initially in 287 patients (the prevalence cohort) and developed during a later period in 99 (the incidence cohort). In the incidence cohort, the initial evaluation period took place after two years in 62 patients and after four years in 37.

‡ After adjustment for the shorter length of potential follow-up in the incidence cohort, the completeness of follow-up was 91 percent, 83 percent, and 77 percent in the first, second, and third periods, respectively.

**Table 2. Clinical Characteristics of the Study Participants According to the Presence or Absence of Regression of Microalbuminuria during Follow-up.\***

| Characteristic†   | Regression (N=196) | No Regression (N=190) | P Value‡ |
|---|--------------------|-----------------------|----------|
| Female sex (%)  | 55                 | 47                    | 0.16     |
| Age (yr)  | 29±8               | 31±8                  | 0.02     |
| Duration of diabetes (yr)§                                | 17±9               | 18±9                  | 0.41     |
| Albumin excretion rate (µg/min)                           |                    |                       |          |
| Initial   |                    |                       | 0.64     |
| Median  | 59                 | 57                    |          |
| Interquartile range                                       | 41–122             | 37–110                |          |
| At end of study¶  |                    |                       | <0.001   |
| Median  | 17                 | 87                    |          |
| Interquartile range                                       | 11–34              | 38–262                |          |
| Microalbuminuria of short duration (incidence cohort) (%) | 26                 | 25                    | 0.86     |
| Use of non-ACE-inhibitor antihypertensive drugs (%)       |                    |                       |          |
| Initial   | 8                  | 10                    | 0.52     |
| At end of study   | 15                 | 16                    | 0.68     |
| Use of ACE inhibitors (%)                                 |                    |                       |          |
| Initial   | 23                 | 28                    | 0.22     |
| At end of study   | 41                 | 53                    | 0.02     |
| Systolic blood pressure (mm Hg)                           | 121±16             | 124±14                | 0.07     |
| Diastolic blood pressure (mm Hg)                          | 74±9               | 76±8                  | 0.11     |
| Glycosylated hemoglobin (%)                               | 8.8±1.5            | 9.3±1.6               | 0.001    |
| Total cholesterol (mg/dl)**                               | 193±40             | 203±40                | 0.01     |
| HDL cholesterol (mg/dl)**                                 | 53±13              | 53±16                 | 0.59     |
| Triglycerides (mg/dl)††                                   | 109±57             | 146±134               | <0.001   |
| Current smoking (%)                                       | 33                 | 34                    | 0.25     |
| Mean follow-up time (yr)¶                                 | 4.3±1.7            | 4.6±1.5               | 0.12     |

\* Plus-minus values are means ±SD. Base-line creatinine levels did not differ between those who did and those who did not subsequently have regression of microalbuminuria (0.9±0.2 mg per deciliter [80±18 µmol per liter] and 0.9±0.3 mg per deciliter [80±27 µmol per liter], respectively; P=0.89). The mean number of individual urinary albumin excretion measurements per two-year period was 3.2±1.8 for those who had microalbuminuria regression and 3.3±1.8 for those who did not (P=0.40). ACE denotes angiotensin-converting enzyme, and HDL high-density lipoprotein.

† Characteristics are given for the initial evaluation period unless otherwise stated.

‡ P values for categorical variables were calculated with the  $\chi^2$  test statistic, and those for continuous variables were calculated by analysis of variance, both without ordering.

§ For subjects with prepubertal onset of diabetes, the duration of diabetes was calculated from the age of 11 years.

¶ For this analysis, data from subjects in whom regression occurred were not censored at the time of the event, and thus the end of the study for both groups is the last follow-up period during which the subject was evaluated.

|| The most frequently used ACE inhibitor was lisinopril (34 percent). Eighty percent of ACE-inhibitor users were taking one of the following four agents (median daily dose in parentheses): lisinopril (20 mg), enalapril (10 mg), captopril (75 mg), and quinapril (20 mg). Of the participants using one of these four agents, 37 percent did not report the dose.

\*\* To convert values for total cholesterol and HDL cholesterol to millimoles per liter, multiply by 0.02586.

†† To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

ratio for the regression of microalbuminuria increased progressively as glycosylated hemoglobin decreased, with by far the strongest effect in the lowest quartile (glycosylated hemoglobin level, <8 percent).

Systolic blood pressure was the third modifiable

determinant of the regression of microalbuminuria. It was initially examined in three categories together with a fourth group (those treated with non-ACE-inhibitor antihypertensive medications). The hazard ratio for the regression of microalbuminuria increased only in the lowest category (those with

**Table 3. Results of the Cox Regression Analysis of Regression of Microalbuminuria with the Use of Time-Dependent Factors.\***

| Factor  | Adjusted Hazard Ratio (95% CI) | P Value† |
|---|--------------------------------|----------|
| <b>Nonmodifiable</b>                              |                                |          |
| Age (≤26 vs. >26 yr)                              | 1.6 (1.2–2.2)                  | 0.004    |
| Incidence cohort (vs. prevalence cohort)‡         | 1.8 (1.2–2.6)                  | 0.003    |
| <b>Modifiable</b>                                 |                                |          |
| Lipid status§                                     |                                | 0.002    |
| Cholesterol <198 mg/dl, triglycerides <145 mg/dl  | 2.4 (1.4–4.0)                  |          |
| Cholesterol <198 mg/dl, triglycerides ≥145 mg/dl  | 1.9 (1.0–3.8)                  |          |
| Cholesterol ≥198 mg/dl, triglycerides <145 mg/dl  | 2.1 (1.2–3.5)                  |          |
| Cholesterol ≥198 mg/dl, triglycerides ≥145 mg/dl¶ | 1.0                            |          |
| Glycosylated hemoglobin                           |                                | 0.02     |
| <8.0 %  | 1.9 (1.2–2.9)                  |          |
| 8.0–8.9 %   | 1.5 (1.0–2.3)                  |          |
| 9.0–9.9 %   | 1.2 (0.8–1.9)                  |          |
| ≥10.0 %¶  | 1.0                            |          |
| Systolic blood pressure                           |                                | 0.02     |
| <115 mm Hg  | 1.4 (1.0–1.9)                  |          |
| ≥115 mm Hg¶**                                     | 1.0                            |          |

\* The multivariate model was adjusted for sex, ACE-inhibitor status (hazard ratio for use, 0.9; 95 percent confidence interval, 0.7 to 1.3), and mean urinary albumin excretion in the initial evaluation period. Sixteen (8 percent) of the instances of regression were preceded by a period during which the mean albumin excretion rate had already subsided to the normal range (less than 30 μg per minute). The complete data analysis produced estimates for all predictor variables within 10 percent of the presented model with the use of a simple imputation method. CI denotes confidence interval.

† P values were derived from the Wald test, representing the contribution of each independent predictor variable.

‡ Those in the incidence cohort (in whom microalbuminuria developed after the beginning of the study) had microalbuminuria of shorter duration than those in the prevalence cohort (in whom microalbuminuria was present during the initial two years).

§ Cholesterol and triglyceride levels were significantly associated with the regression of microalbuminuria in the multivariate model (hazard ratio for total cholesterol below the median of 198 mg per deciliter, 1.4; 95 percent confidence interval, 1.1 to 1.9; hazard ratio for triglycerides below the third quartile of 145 mg per deciliter, 1.9; 95 percent confidence interval, 1.3 to 2.8). A total cholesterol value of 198 mg per deciliter is equivalent to 5.12 mmol per liter, and a triglyceride value of 145 mg per deciliter is equivalent to 1.64 mmol per liter.

¶ This served as the reference category.

|| Diastolic blood pressure and mean arterial pressure were not significantly associated with the regression of microalbuminuria in these analyses.

\*\* Intervals in which the patients used antihypertensive agents other than ACE inhibitors are included.

systolic blood pressure of less than 115 mm Hg). Because the hazard ratio for the group with treated hypertension was the same as that for those with systolic blood pressure at or above 115 mm Hg, these groups were combined.

To investigate the combined effect of the three

modifiable factors on the regression of microalbuminuria, we first dichotomized the level of each determinant as salutary or nonsalutary. The salutary level was defined as the first category of the factor, as listed in Table 3, and the remaining categories were combined as nonsalutary. We then coded each follow-up period of observation on a scale of 0 to 3, according to the number of modifiable factors at a salutary level. The hazard ratio for the regression of microalbuminuria increased significantly with each increment in the number of factors at a salutary level (Fig. 2). If all three factors, as compared with none, were at salutary levels, the hazard ratio for the regression of microalbuminuria was 3.0 (95 percent confidence interval, 1.5 to 6.0).

## DISCUSSION

Microalbuminuria in patients with type 1 diabetes has been considered the first step toward proteinuria and renal failure, yet our results indicate that microalbuminuria is more likely to subside to normal levels than to progress to overt proteinuria. Therefore, the evolution of early diabetic nephropathy may not be confined to a single pathway leading to progression to proteinuria.

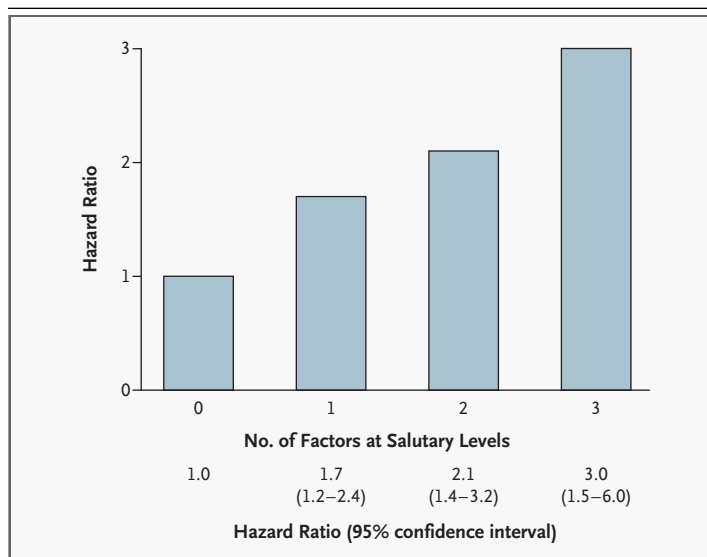
Persistent elevation of urinary albumin excretion above 30 μg per minute is rare in the general population,<sup>13,15</sup> but in patients with type 1 diabetes the lifetime risk of such elevation is approximately 60 percent.<sup>13,16</sup> Early landmark studies of microalbuminuria indicated that the risk of a progressive increase in albumin excretion to overt proteinuria within 6 to 14 years was 60 to 85 percent.<sup>1–3</sup> This finding implied that microalbuminuria heralds the onset of an inexorable process leading to overt proteinuria. However, our six-year follow-up of almost 400 persons with well-documented microalbuminuria found that a minority (19 percent) went on to have overt proteinuria, whereas in the majority (approximately 60 percent) there was regression to normal albumin excretion levels. The same frequency of regression of microalbuminuria was observed when microalbuminuria was defined as a 50 percent reduction in albumin excretion. The reason for the low risk of progression to proteinuria in our study, in comparison with the early studies, is unclear, but two possibilities might be considered. First, the three landmark studies,<sup>1–3</sup> which involved a total of only 30 patients, may have overestimated the true risk. Second, there may have been a true decrease in the frequency of progression to protein-

uria during the past 20 to 30 years. For example, if the frequency of regression of microalbuminuria had increased during this time, the proportion of patients with progression to proteinuria would have decreased, given the pool of persons remaining at risk. Other studies have reported regression of overt proteinuria,<sup>17,18</sup> even independently of the use of ACE inhibitors.<sup>19</sup> Neither these studies nor the present prospective study of regression of microalbuminuria demonstrates which alternative is the more plausible.

These considerations suggest a model of early diabetic nephropathy in which elevated urinary albumin excretion is a marker of dynamic, rather than fixed, renal injury. According to this model, when elevated urinary albumin excretion develops in persons with type 1 diabetes, it can remain static, advance toward overt proteinuria, or regress toward normal levels, as it did in a large proportion of the patients in this study. Factors associated with the regression pathway may provide clues to interventions that may promote the diminution of microalbuminuria to normal levels of albumin excretion.

Given the well-established role of hyperglycemia as a risk factor for the onset<sup>9,10,12,20-23</sup> and progression<sup>6,10,23,24</sup> of microalbuminuria, it is not surprising that levels of glycosylated hemoglobin below 8.0 percent are associated with the regression of microalbuminuria. The fact that the frequency of regression does not decline with further increases in glycosylated hemoglobin presents an interesting contrast to the dose-response pattern for the onset of microalbuminuria, which is infrequent at glycosylated hemoglobin levels below 8.0 percent. However, the frequency of microalbuminuria rises steeply at higher levels and is exaggerated in cigarette smokers.<sup>11,12</sup> Perhaps the mechanisms underlying the regression of microalbuminuria are most effective in the low range of glycosylated hemoglobin levels, at which they are not overwhelmed by the opposing effects of high levels of glycosylated hemoglobin and its interaction with smoking. Thus, glycosylated hemoglobin levels below 8.0 percent may be considered salutary, permitting resolution or repair of functional aberrations in the glomerulus<sup>25-27</sup> or proximal tubule<sup>28</sup> that commonly lead to increased urinary albumin excretion.

Earlier clinical trials did not support an association between interventions to enhance glycemic control and favorable outcome in patients with type 1 diabetes and microalbuminuria.<sup>29</sup> Inadequate sample size<sup>30</sup> and insufficient follow-up time<sup>31</sup>



**Figure 2. Additive Effects of Factors at Salutary Levels on Regression of Microalbuminuria.**

Salutary levels of the various factors were defined as less than 8 percent for glycosylated hemoglobin, less than 115 mm Hg for systolic blood pressure, and a combination of less than 198 mg of total cholesterol per deciliter (5.12 mmol per liter) and less than 145 mg of triglycerides per deciliter (1.64 mmol per liter). Absence of a salutary level of any of the three factors was considered the reference category. In separate analyses, no specific combination of factors was identified for which salutary levels were more predictive of regression of microalbuminuria (data not shown). The estimates were adjusted for age, sex, membership in the microalbuminuria incidence or prevalence cohort, mean urinary albumin excretion in the initial evaluation period, use or nonuse of angiotensin-converting-enzyme inhibitor therapy, and missing values for each variable. The numbers of person-years during which patients had 0, 1, 2, and 3 factors at salutary levels were 536 (31 percent), 692 (41 percent), 398 (23 percent), and 80 (5 percent), respectively.

appear to be responsible for such negative findings, emphasizing the need for long-term clinical studies involving a large number of subjects. Moreover, trials should be designed with multifactorial interventions, as has been done in comparable studies of patients with type 2 diabetes.<sup>32</sup>

Regression of microalbuminuria was associated with low systolic blood pressure (below 115 mm Hg). Since microalbuminuria is associated with impairment of renal hemodynamic autoregulation,<sup>33,34</sup> we hypothesize that very low systemic blood pressure attenuates shear stress and may permit the recovery of glomerular integrity. However, it remains to be determined whether pharmacologic intervention resulting in a very low systemic blood pressure will be effective in reducing urinary albumin excretion.

The association between low levels of total se-

rum cholesterol and triglycerides and the regression of microalbuminuria provides a rationale for pharmacologic intervention with lipid-lowering agents, even in patients with type 1 diabetes who do not have overt dyslipidemia. Although data implicating lipid abnormalities in the development and evolution of early diabetic nephropathy are limited,<sup>22</sup> extensive experimental data in animal models support the concept that lipids have a pathogenic role in progressive glomerular and tubulointerstitial injury.<sup>33,35-38</sup>

Microalbuminuria of short duration (regardless of the duration of diabetes) is more likely to regress than microalbuminuria of long duration. Although more research is required to explain this finding, we suggest that frequent screening for microalbuminuria, even at low levels, may lead to more effective intervention. The practice<sup>39</sup> of delaying the follow-up confirmation of microalbuminuria detected in a single urine sample or of delaying intervention until high levels of urinary albumin excretion are reached may not be prudent in the light of the current results.

The use of ACE inhibitors retarded the increase in urinary albumin excretion in short-term clinical trials. ACE inhibitors are now well established for prevention of the progression of microalbuminuria to proteinuria.<sup>40</sup> However, in the present study, the use of ACE inhibitors was not associated with the regression of microalbuminuria. Moreover, detailed analysis found that the effect of low blood pressure in this study was independent of the use or nonuse of ACE inhibitors. Rather than a contradiction, it is possible that the beneficial pharmacologic effects of ACE inhibitors that prevent the progression of microalbuminuria do not influence the biologic mechanisms that underlie the regression of microalbuminuria.

Our findings have limitations. First, despite the common features in the natural history and biology of early diabetic nephropathy in type 1 and type 2 diabetes, further study will be required to determine the relevance of our results to type 2 diabetes. Second, although the present study identified important clinical determinants of regression, other factors, including genetic factors,<sup>41</sup> should be examined. Third, although our findings support a new model of early diabetic nephropathy, the contributing variables are not known with precision. Salutary values for glycemic control, systolic blood pressure, and serum lipids have additive effects on the regression of microalbuminuria, but the sample size and measurement errors limit the precision of these values. Finally, our statistical analysis incorporated certain arbitrary definitions, such as the designation of a 50 percent reduction in urinary albumin excretion as significant regression of microalbuminuria. Such definitions served the purposes of this analysis, but a different target, such as normal albumin excretion, might be more effective in preventing the progression of diabetic nephropathy. Clinical trials that assess the optimal target level of albumin excretion — in terms of the regression of microalbuminuria — as well as the optimal levels of other factors are warranted.

Supported by a grant (RO1-DK41526) from the National Institutes of Health, by the Joslin Diabetes Center, and by a Juvenile Diabetes Foundation International fellowship grant (3-2001-829, to Dr. Perkins) and a William Randolph Hearst Fellowship provided by the William Randolph Hearst Foundation (to Dr. Perkins).

We are indebted to the patients of the Joslin Clinic and to the staff of the Joslin Diabetes Center, particularly the Reception Desk, Clinical Laboratory, Management Information Systems, and Medical Records Department, for their assistance and cooperation in conducting this study; and to the following members of the Section on Genetics and Epidemiology: K. Anderson, J. Bonner, D. Butler, N. Castronuovo, M. Davidson, F. Denry, E. Hart, M. Hisatomi, C.A. Jones, M.D., L.M.B. Laffel, M.D., J. Nititham, B. Palecek, M. Pezolesi, M. O'Keefe, D. Sheehan, and M. Wantman.

#### REFERENCES

- Viberti GC, Hill RD, Jarrett RJ, Argyropoulos A, Mahmud U, Keen H. Microalbuminuria as a predictor of clinical nephropathy in insulin-dependent diabetes mellitus. *Lancet* 1982;1:1430-2.
- Parving H-H, Oxenbøll B, Svendsen PA, Christiansen JS, Andersen AR. Early detection of patients at risk of developing diabetic nephropathy: a longitudinal study of urinary albumin excretion. *Acta Endocrinol (Copenh)* 1982;100:550-5.
- Mogensen CE, Christensen CK. Predicting diabetic nephropathy in insulin-dependent patients. *N Engl J Med* 1984;311:89-93.
- Forsblom CM, Groop P-H, Ekstrand A, Groop LC. Predictive value of microalbuminuria in patients with insulin-dependent diabetes of long duration. *BMJ* 1992;305:1051-3.
- Rudberg S, Persson B, Dahlquist G. Increased glomerular filtration rate as a predictor of diabetic nephropathy — an 8-year prospective study. *Kidney Int* 1992;41:822-8.
- Warram JH, Scott LJ, Hanna LS, et al. Progression of microalbuminuria to proteinuria in type 1 diabetes: nonlinear relationship with hyperglycemia. *Diabetes* 2000;49:94-100.
- Caramori ML, Fioretto P, Mauer M. The need for early predictors of diabetic nephropathy risk: is albumin excretion rate sufficient? *Diabetes* 2000;49:1399-408.
- Cooper ME, Frauman A, O'Brien RC, Seeman E, Murray RM, Jerums G. Progression of proteinuria in type 1 and type 2 diabetes. *Diabet Med* 1988;5:361-8. [Erratum, *Diabet Med* 1988;5:422.]
- 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* 1999;16:918-25.
- The Diabetes Control and Complications (DCCT) Research Group. Effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995;47:1703-20.

11. Krolewski AS, Laffel LMB, Krolewski M, Quinn M, Warram JH. Glycosylated hemoglobin and the risk of microalbuminuria in patients with insulin-dependent diabetes mellitus. *N Engl J Med* 1995;332:1251-5.
12. Scott LJ, Warram JH, Hanna LS, Laffel LM, Ryan L, Krolewski AS. A nonlinear effect of hyperglycemia and current cigarette smoking are major determinants of the onset of microalbuminuria in type 1 diabetes. *Diabetes* 2001;50:2842-9.
13. Warram JH, Gearin G, Laffel L, Krolewski AS. Effect of duration of type 1 diabetes on the prevalence of stages of diabetic nephropathy defined by urinary albumin/creatinine ratio. *J Am Soc Nephrol* 1996;7:930-7.
14. The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): results of feasibility study. *Diabetes Care* 1987;10:1-19.
15. Garg AX, Kiberd BA, Clark WF, Haynes RB, Clouse CM. Albuminuria and renal insufficiency prevalence guides population screening: results from the NHANES III. *Kidney Int* 2002;61:2165-75.
16. Orchard TJ, Dorman JS, Maser RE, et al. Prevalence of complications in IDDM by sex and duration: Pittsburgh Epidemiology of Diabetes Complications Study II. *Diabetes* 1990;39:1116-24.
17. Wilmer WA, Hebert LA, Lewis EJ, et al. Remission of nephrotic syndrome in type 1 diabetes: long-term follow-up of patients in the Captopril Study. *Am J Kidney Dis* 1999;34:308-14.
18. Hovind P, Rossing P, Tarnow L, Toft H, Parving J, Parving HH. Remission of nephrotic-range albuminuria in type 1 diabetic patients. *Diabetes Care* 2001;24:1972-7.
19. Ellis D, Lloyd C, Becker DJ, Forrest KY, Orchard TJ. The changing course of diabetic nephropathy: low-density lipoprotein cholesterol and blood pressure correlate with regression of proteinuria. *Am J Kidney Dis* 1996;27:809-18.
20. Coonrod BA, Ellis D, Becker DJ, et al. Predictors of microalbuminuria in individuals with IDDM: Pittsburgh Epidemiology of Diabetes Complications Study. *Diabetes Care* 1993;16:1376-83.
21. 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* 1995;12:482-7.
22. Chaturvedi N, Bandinelli S, Mangili R, Penno G, Rottiers RE, Fuller JH. Microalbuminuria in type 1 diabetes: rates, risk factors and glycaemic threshold. *Kidney Int* 2001;60:219-27.
23. The Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Effect of intensive therapy on the microvascular complications of type 1 diabetes mellitus. *JAMA* 2002;287:2563-9.
24. Wang PH, Lau J, Chalmers TC. Meta-analysis of effects of intensive blood-glucose control on late complications of type 1 diabetes. *Lancet* 1993;341:1306-9.
25. Stockand JD, Sansom SC. Regulation of filtration rate by glomerular mesangial cells in health and diabetic renal disease. *Am J Kidney Dis* 1997;29:971-81.
26. Kitamura M, Fine LG. The concept of glomerular self-defense. *Kidney Int* 1999;55:1639-71.
27. Raats CJ, Van Den Born J, Berden JH. Glomerular heparan sulfate alterations: mechanisms and relevance for proteinuria. *Kidney Int* 2000;57:385-400.
28. Oldfield MD, Bach LA, Forbes JM, et al. Advanced glycation end products cause epithelial-myofibroblast transdifferentiation via the receptor for advanced glycation end products (RAGE). *J Clin Invest* 2001;108:1853-63.
29. Microalbuminuria Collaborative Study Group, United Kingdom. Intensive therapy and progression to clinical albuminuria in patients with insulin dependent diabetes mellitus and microalbuminuria. *BMJ* 1995;311:973-7.
30. Chaturvedi N, Fuller JH. Effect of intensive treatment in insulin dependent diabetes mellitus with microalbuminuria: sample size was too small. *BMJ* 1996;312:253.
31. Feldt-Rasmussen B, Mathiesen ER, Jensen T, Lauritzen T, Deckert T. Effect of improved metabolic control on loss of kidney function in type 1 (insulin-dependent) diabetic patients: an update of the Steno studies. *Diabetologia* 1991;34:164-70.
32. Gaede P, Vedel P, Parving HH, Pedersen O. Intensified multifactorial intervention in patients with type 2 diabetes mellitus and microalbuminuria: the Steno type 2 randomised study. *Lancet* 1999;353:617-22.
33. Remuzzi G, Ruggenenti P, Benigni A. Understanding the nature of renal disease progression. *Kidney Int* 1997;51:2-15.
34. Raptis AE, Viberti G. Pathogenesis of diabetic nephropathy. *Exp Clin Endocrinol Diabetes* 2001;109:Suppl 2:S424-S437.
35. Humes HD, Nguyen VD, Cieslinski DA, Messana JM. The role of free fatty acids in hypoxia-induced injury to renal proximal tubule cells. *Am J Physiol* 1989;256:F688-F696.
36. Zoja C, Morigi M, Figliuzzi M, et al. Proximal tubular cell synthesis and secretion of endothelin-1 on challenge with albumin and other proteins. *Am J Kidney Dis* 1995;26:934-41.
37. Osicka TM, Comper WD. Protein degradation during renal passage in normal kidneys is inhibited in experimental albuminuria. *Clin Sci (Lond)* 1997;93:65-72.
38. Schreiner GF. Renal toxicity of albumin and other lipoproteins. *Curr Opin Nephrol Hypertens* 1995;4:369-73.
39. Wong T, Foote EF, Lefavour GS, Cody RP, Brown CJ, Sherman RA. Physician knowledge and practice patterns relating to diabetic nephropathy. *J Am Pharm Assoc (Wash)* 1999;39:785-90.
40. The ACE Inhibitors in Diabetic Nephropathy Trialist Group. Should all patients with type 1 diabetes mellitus and microalbuminuria receive angiotensin-converting enzyme inhibitors? A meta-analysis of individual patient data. *Ann Intern Med* 2001;134:370-9.
41. Krolewski AS. Genetics of diabetic nephropathy: evidence for major and minor gene effects. *Kidney Int* 1999;55:1582-96.

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