Effect of Duration of Type I Diabetes on the Prevalence of Stages of Diabetic Nephropathy Defined by Urinary Albumin/Creatinine Ratio

James H. Warram, Gary Gearin, Lori Laffel, and Andrzej S. Krolewski

ABSTRACT

The objective of this study was to determine the prevalence of stages of diabetic nephropathy, defined by the albumin/creatinine ratio (AC ratio) in repeated measurements in random urine samples. Over a 30-month interval, 1613 patients with Type I diabetes (IDDM) (aged 15 to 44 yr, IDDM duration 1 to 39 yr), and 218 healthy control subjects provided multiple urine specimens. AC ratios measured in urine samples taken 5 months apart were highly reproducible (Spearman \( r = 0.83 \)). A criterion for the boundary between normoalbuminuria and microalbuminuria was obtained by searching for a cutpoint that optimized agreement between serial specimens on individuals. The result was lower in men than women: 17 as compared with 25 \( \mu g/mg \). These two values corresponded to the 95th percentiles of the respective distributions of the AC ratio in healthy control subjects. Also these sex-specific cutpoints, when converted to albumin excretion rates, became almost equal: 30 and 31 \( \mu g/min \). Microalbuminuria appeared early in the course of IDDM (6% of those with only 1 to 3 yr of diabetes) and then increased rapidly during two intervals, the first and third decades, before leveling off at 52%. By that time the cumulative risk of overt proteinuria had risen to 27%. Determinations of the AC ratio in random urine samples are easily obtained and are reliable indices of elevated urinary albumin excretion (microalbuminuria) in IDDM. The pattern of occurrence of microalbuminuria according to duration of IDDM suggests that there may be two subsets of diabetic nephropathy, one appearing early and the other late. Patients with microalbuminuria and 25 yr of postpubertal IDDM have low risk of progression to advanced diabetic nephropathy.

Key Words: Microalbuminuria, proteinuria, IDDM, albumin/creatinine ratio, serum creatinine

Elevated urinary albumin excretion (microalbuminuria) in patients with Type I diabetes (IDDM) is an early warning sign of impending diabetic nephropathy (1). Its diagnosis is critical for the implementation of intervention programs to prevent advanced stages of diabetic nephropathy (2).

A variety of protocols with timed urine collections have been developed to diagnose microalbuminuria (3–6). All of these protocols, however, are impractical in clinical settings and epidemiologic studies because their execution demands extra time from patients and providers, and urine collections are frequently incomplete due to omission of one or more voids. A convenient alternative for assessing albumin excretion is the ratio of concentrations of albumin and creatinine (AC ratio) measured in random voids (7–10). So far, in patients with diabetes, the AC ratio has been widely used only in the studies conducted among the Pima (10). The recent Consensus Statement on the Prevention of Diabetic Nephropathy, however, proposed screening for microalbuminuria by using the AC ratio in random urine samples with values \( \geq 30 \mu g/mg \) considered abnormal (11).

In this report, we examine the characteristics of the AC ratio distribution in 1613 patients with IDDM and 218 healthy control subjects and identify AC ratio values for the lower and upper boundaries for microalbuminuria. On the basis of these boundaries, we determine the prevalence of stages of diabetic nephropathy in a large cohort of patients with IDDM according to the duration of diabetes.

STUDY POPULATION AND METHODS

Eligibility Criteria

Between January 1, 1991, and March 31, 1992, we screened for microalbuminuria in a 50% random sample (\( N = 1795 \)) of the patients with diabetes, aged 15 to 44 yr, who visited the Internal Medicine or Pediatrics Departments at the Joslin Clinic. Additional eligibility requirements were that diabetes had been diagnosed before the age of 40 and that the patient was a Massachusetts resident who had been registered at the clinic for at least 1 yr before screening. The screening protocol was approved by the Committee on Human Subjects at the Joslin Diabetes Center. A more detailed description of the selection of patients and the collection of urine specimens has been published elsewhere (12).
random, daytime urine samples submitted for routine urinalysis were used. Assays for urinary albumin and creatinine were performed within 7 days of urine collection. Urine from these 1795 patients was collected whenever they returned to the clinic, and the analyses presented here are based on the results available as of June 30, 1993.

Microalbuminuria Determination

Albumin concentration in each urine sample was first assessed by Multistix (Ames, Miles Laboratories, Elkhart, IN), which was read by an optical scanner. Urine samples with a 2+ or greater reading (albumin ≥100 mg/dL) were considered overtly albuminuric and were not examined for microalbuminuria. All others were assayed for albumin and creatinine concentrations. Albumin concentration was measured by immunonephelometry on a BN100 with the N Albumin Kit (Behring, Somerville, NJ) for serum albumin and a manufacturer-supplied protocol designed specifically for the low concentrations of albumin found in urine (13). Urine samples were centrifuged and, if no albumin was detected by dipstick, the urine was assayed undiluted (lower limit of detection, 2 µg/mL). If the dipstick detected a trace of albumin, the urine was diluted accordingly. The coefficient of variation was <2% intra-assay, and <4% interassay. Urine creatinine concentrations were performed by alkaline picric colorimetry (modified Jaffe reaction) on an Astra7 (Beckman Instruments, Brea, CA).

The ratio of concentrations of albumin (µg) to creatinine (mg) in random urine specimens (AC ratio) was used as an index of urinary albumin excretion (UAE). The AC ratio in µg/mg can be converted to SI units (mg/mmol) by dividing by 8.84; however, the AC ratio is usually expressed in µg/mg because the numeric value in these units happens to approximate the numeric value of the corresponding albumin excretion rate expressed in µg/min. To have a more precise means to convert an AC ratio to an AER (µg/min), such as would be determined on a timed urine collection, we estimated a conversion formula. In an independent sample of 58 patients with 15 to 20 yr duration of IDDM, simultaneous determinations of the AC ratio and AER were obtained by the same laboratory methods described above for assaying albumin and creatinine. Patients were examined in the morning between 9 and 12 a.m. After voiding, each patient drank 250 mL of water every half-hour for 3 h and collected all urine. The AER was determined in the timed urine collection, and the AC ratio was determined in the urine voided at the beginning of the timed collection. The regression equation (r² = 0.935) was as follows: Log(AER) = 0.44 + (0.85)Log(AC ratio) (0.13)sex, where sex = 1 for women, 0 for men. AER in this sample ranged from 5 to 6000 µg/min, with a geometric mean of 77 µg/min.

Serum Creatinine Determination

For 79% of the patients with elevated urinary albumin excretion (412/521) and a 50% random sample of individuals with normal albumin excretion (546/1092), we obtained serum for determination of creatinine. The serum creatinine level was measured in the same way as that of the urine creatinine (see above).

Study Population

The date of diagnosis of diabetes was abstracted from the medical record at the Joslin Clinic. Diabetes was classified as insulin dependent if it was diagnosed before the 21st birthday. For all patients diagnosed after the 21st birthday, the medical record was reviewed by a physician. Insulin dependence was confirmed if the medical record documented the beginning of insulin therapy within 1 yr of the diagnosis of diabetes and continuous insulin usage up to the present time.

Of 1795 patients screened, 177 (10%) had non-insulin-dependent diabetes and were not used in the present analysis. Another five individuals were excluded because they had noninsulin-dependent renal disease, such as an unclassified nondiabetic renal histology, membranoproliferative glomerulonephritis, polycystic kidney disease, and two with documented proteinuria (etiologies unknown) predicting the diagnosis of diabetes. Of the remaining 1613, 92% reported their racial or ethnic origin as non-Hispanic white. The remaining 8% of the group was composed of nearly equal proportions of blacks, Hispanics, and Asians. Because none of these small groups was distinctly different from the total, all racial/ethnic groups were analyzed as one group.

As a comparison group, 218 nondiabetic individuals aged 15 to 60 yr, without diagnosed kidney disease were recruited. The albumin and creatinine levels in their urine samples were measured in the same manner as the patients with IDDM. Half of this group were employees of the Joslin Diabetes Center and the rest were nondiabetic members of families participating in genetic studies in this department.

Data Analysis

Age and duration of diabetes were calculated by subtracting from the screening date the dates of birth and diabetes diagnosis, respectively. To describe the distributions of the measurements in urine, the 75th and 90th percentiles were used to reflect shifts in the upper tail. The size of the within-individual variability increased in proportion with the albumin excretion, so the analysis was done in the logarithms so that similar percentage differences would be equal regardless of the level of excretion. As the boundary between normal albumin excretion and microalbuminuria, we sought to identify the value that optimized reproducibility of the diagnosis in sequential urine samples. For this analysis individuals with an AC ratio in the overt proteinuria range (≥300 µg/mg) were omitted. The search procedure was conducted separately for women and men. Values of the AC ratio in the boundary range were systematically searched for the cutpoint that maximized concordance (measured as the relative odds) of the classifications of the first and second specimens.

Multiple linear regression was used to examine the relationship between the logarithm of the AC ratio and renal function (measured as the reciprocal of serum creatinine). The data suggested that the AC ratio had to exceed a threshold before there was a trend. Regression methods for determining the threshold in a linear relation were used to test the slope and estimate the threshold (14).

RESULTS

The final study group included 1613 patients aged 15 to 44 yr with IDDM duration 1 to 39 yr and 218 nondiabetic control subjects. Table 1 shows characteristics of the study groups. Almost half (47%) of the diabetic patients had IDDM for 15 or more years, and their average age was 33. The average age of the nondiabetic control subjects was 34 yr, and their ages spanned a wider range (15 to 60 yr). Men and women were equal in number in all duration groups and in
Prevalence of Nephropathy in IDDM

TABLE 1. Characteristics of the study group according to duration of diabetes

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nondiabetic Control Subjects (N = 218)</th>
<th>Diabetic Patients Duration of Diabetes (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>1 to 4 (N = 238)</td>
</tr>
<tr>
<td>Percent Women</td>
<td>48</td>
<td>48</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>34 ± 12</td>
<td>26 ± 8</td>
</tr>
<tr>
<td>Number of Screening Visits</td>
<td>1.4</td>
<td>2.3</td>
</tr>
<tr>
<td>Median Screening Interval in Months</td>
<td>-</td>
<td>14</td>
</tr>
</tbody>
</table>

nondiabetic control subjects. The results were analyzed as a collection of urine samples to examine the shape of distributions. For all other analyses results were grouped by individual.

Distributions of Urinary Albumin, Urinary Creatinine, and AC Ratio

The median urinary creatinine concentration was about 50% higher for men than women, regardless of diabetes status, and was 25% lower among patients with IDDM than nondiabetic control subjects, regardless of gender and duration of diabetes. The same pattern was present in the upper tail as reflected in the 75th and 90th percentiles in Table 2. For albumin concentrations, the pattern was quite different. The distribution was similar for patients with short-duration IDDM (1 to 4 yr) and nondiabetic control subjects, regardless of gender, but with increasing duration of diabetes, there was an upward shift of the whole distribution and increasing skewness to the right: the median doubled and the 90th percentile increased 20-fold for women and 100-fold for men.

In patients with short-duration IDDM, the 75th percentile of the AC ratio distribution was 45% higher than in nondiabetics, and the 90th percentile more than doubled in both men and women, evidence that a substantial increase in albumin excretion had occurred in a subset of patients within the first years of diabetes. Comparison of the percentiles of the AC ratio for men and women (Table 2) reveals that percentiles for men were about 20% lower than the comparable percentiles for women, indicating that different criteria are necessary for evaluating the AC ratio in women and men.

In the urine samples from nondiabetic control subjects, almost all of the AC ratios were clustered below 16 μg/mg for women and below 12 μg/mg for men. The 95th percentiles were 25 μg/mg and 17 μg/mg, respectively. The few samples (5%) with ratios above these values were widely scattered, up to 69 μg/mg for women and 88 μg/mg for men. A characteristic of the AC ratio distribution in patients with IDDM was the suggestion of a shallow valley dividing the distribution into two modes. In specimens from each duration group a valley in the interval 16 to 19 μg/mg separated a secondary distribution from the main distribution. This interval coincided with the upper edge of the AC ratio distribution in nondiabetic control subjects. This feature of the distribution was not prominent enough to be statistically significant, but it persisted regardless of how the data were stratified (data not shown).

TABLE 2. Percentiles of the distributions of the concentrations of albumin (μg/mL) and creatinine (mg/dL) and the albumin to creatinine ratio (μg/mg) in 3984 random urine samples according to duration of diabetes, separately for men and women (males/females)

<table>
<thead>
<tr>
<th></th>
<th>Nondiabetic Control Subjects (N = 155/155)</th>
<th>Diabetic Patients Duration of Diabetes (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 to 4 (N = 282/260)</td>
<td>5 to 14 (N = 680/743)</td>
</tr>
<tr>
<td>Creatinine Percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75th</td>
<td>184/158</td>
<td>147/124</td>
</tr>
<tr>
<td>90th</td>
<td>233/204</td>
<td>199/170</td>
</tr>
<tr>
<td>Albumin Percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75th</td>
<td>11.1/11.7</td>
<td>12.0/13.0</td>
</tr>
<tr>
<td>90th</td>
<td>21.4/21.5</td>
<td>25.0/29.0</td>
</tr>
<tr>
<td>AC Ratio Percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>75th</td>
<td>7.1/9.0</td>
<td>10.2/13.2</td>
</tr>
<tr>
<td>90th</td>
<td>14.2/14.9</td>
<td>23.4/30.9</td>
</tr>
</tbody>
</table>
Variability of Albumin to Creatinine Ratio

In the 1263 patients who supplied a second specimen of urine (median interval was 5 months), the variability of AC ratio was examined. There was no net change in the albumin concentration, creatinine concentration, or the AC ratio between measurements. The correlation between serial measurements was modest for albumin concentration (0.68, \( P < 0.0001 \)) and was actually rather low for creatinine concentration (0.39, \( P < 0.0001 \)). However, the correlation between successive determinations of their AC ratio was very high (0.83, \( P < 0.0001 \)). Much of the variability in urinary albumin concentration over time, therefore, was presumably the result of differences in hydration status, and this source of variability was largely removed by adjusting for urinary creatinine concentration. The individual averages for a pair of AC ratio determinations ranged from a low of 2 pg/mg to a high of 7778 pg/mg with an overall mean of 237 pg/mg and standard deviation of 697 pg/mg. Despite the inclusion of such diverse urinary albumin excretion levels, the average within individual coefficient of variation for the AC ratio was only 38%.

Lower Boundary of Microalbuminuria

The criterion for dividing normoalbuminuria from microalbuminuria that maximized the concordance of classifications of repeat samples from an individual was 25 μg/mg for women and 17 μg/mg for men (see Study Population and Methods). Among women, even after exclusion of those in the overt proteinuria range, if the AC ratio in the first specimen was above ≥25 μg/mg, the second specimen was 16 times more likely to be ≥25 than if the first was <25 μg/mg. Among men, the concordance at the optimum cutpoint was even higher; if the first specimen was ≥17 μg/mg, the second was 28 times more likely to be elevated as well. These sex-specific criteria for the lower boundary of microalbuminuria converge almost to a single value when converted to albumin excretion rates (30 and 31 μg/min, respectively) (see Microalbuminuria Determination for details of the conversion formula).

Upper Boundary of Microalbuminuria

Of the 3697 urine specimens assayed for microalbuminuria, there were 3412 (92%) with simultaneous readings by dipstick. The dipstick readings are summarized according to AC ratio categories in Figure 1. A majority of specimens in the low range of microalbuminuria had negative dipstick readings. However, almost half of patients in the high range of microalbuminuria had positive dipstick values. The proportion increased to 75% for AC ratios corresponding to an AER of 300 to 499 μg/min and, finally, to 100% for AER >700 μg/min. The implication of these findings is that a dipstick, which measures albumin concentration without adjusting for hydration, is not an accurate test for the upper boundary of microalbuminuria (or lower boundary of overt proteinuria). A patient with early overt proteinuria may be dipstick negative if well hydrated, whereas a patient with microalbuminuria may be dipstick positive if dehydrated.

Another approach to identifying the upper boundary of microalbuminuria was to search for an AC ratio value above which there is evidence of declining renal function. Because the serum creatinine concentration was determined for more than half of the study patients (910/1613 = 59%) while we were screening the AC ratio, we sought to use this large data set to identify the lowest albumin excretion level associated with declining renal function. With a regression model for determining the breakpoint in the linear relationship between two continuous variables, we looked for a threshold effect of the AC ratio (geometric mean of an individual’s three screening determinations) on the reciprocal of serum creatinine as a measure of renal function (18). We found that a breakpoint model fit the data significantly better than a single line (\( P < 0.005 \) for women and \( P < 0.0005 \) for men). The estimated thresholds were 63 μg/mg for women and 58 μg/mg for men. Below the thresholds, the estimated slopes were nearly zero, whereas significant negative slopes were estimated above the thresholds, \( P < 0.0001 \) for both women and men. The threshold in this model, therefore, corresponds to the level of urinary albumin excretion which marks the beginning of renal function loss.

To relate the data visually to this model, grouped data are plotted in Figure 2. Patients were grouped separately by sex into approximately equally sized groups according to the geometric mean of their AC ratio determinations, and the mean AC ratio was
Volume 7 • Number 6 • 1996

Prevalence of Nephropathy in IDDM

Figure 2. Regression model of the breakpoint in the linear relationship between the reciprocal serum creatinine (100 \times \text{serum creatinine}^{-1}) and the geometric mean of the albumin to creatinine ratios (AC ratio) in random urine samples according to sex (solid line for women; dashed line for men). Below the breakpoint (63 and 58 \mu g/mg for women and men, respectively), the reciprocal serum creatinine did not vary significantly, but above the breakpoint it declined significantly. For a doubling of the AC ratio, the slopes (±SE) were -11.9 (±1.4; \(P < 0.0001\)) and -8.4 (±1.0; \(P < 0.0001\)). The low microalbuminuria range of the AC ratio is indicated by a shaded rectangle. To illustrate the data in relation to the model, individuals were grouped according to the geometric mean of their AC ratio determinations into five equally sized groups within each phase of the model and plotted at the mean of their reciprocal creatinines.

plotted against the mean reciprocal creatinine for the group. Below the threshold, reciprocal creatinine concentration was higher for women than men, but it declined more steeply above the threshold so that it was nearly equal for the sexes when the AC ratio reached the range 2000 to 6000 \mu g/mg.

On the basis of these analyses, the following criteria were adopted for distinguishing stages of diabetic nephropathy on the basis of AC ratios determined in random urine samples. The lower and upper boundaries of microalbuminuria were set at the values 25 and 355 \mu g/mg for women and the values 17 and 250 \mu g/mg for men. Higher values were considered as indicative of overt proteinuria. These sex-specific criteria for the AC ratio correspond to albumin excretion rates of 30 and 300 \mu g/min, respectively (see conversion formula in Microalbuminuria Determination). Having evidence of renal function loss in the upper range of microalbuminuria, we distinguished low and high microalbuminuria by dividing it, arbitrarily, at the midpoint. The midpoint was defined as the geometric mean of the lower and upper boundaries: 92 for women and 65 for men. With these criteria, patients with IDDM were classified according to the prevailing classification of their AC ratios.

Prevalence of Stages of Diabetic Nephropathy According to Duration of IDDM

To examine the influence of diabetes duration on the prevalence of these stages of nephropathy, the group was divided according to age (in decades) of diabetes diagnosis. The pattern in the 445 patients diagnosed before age 10 yr was distinctly different from that in patients diagnosed at older ages; the appearance of overt nephropathy was delayed about 8 yr. However, when duration was calculated from puberty (assumed to be age 12) for those with a prepubertal onset of diabetes, the pattern became quite consistent across all ages of onset of diabetes. Therefore, the prevalence of stages of diabetic nephropathy was determined according to postpubertal duration of IDDM (Figure 3).

The height of the top curve represents the prevalence of all stages of diabetic nephropathy. To develop more advanced nephropathy, patients must first have developed microalbuminuria, so the prevalence of all stages of diabetic nephropathy can be considered as an estimate of the cumulative incidence of microalbuminuria according to postpubertal duration of IDDM. Similarly, the height of the lowest curve indicates the prevalence (cumulative incidence) of persistent proteinuria (including patients on hemodialysis and those with renal transplant).

In patients with IDDM, the cumulative incidence of persistent microalbuminuria increased with duration of IDDM with distinct variations in the rate of in-

Figure 3. Prevalence of persistent elevation of urinary albumin excretion according to postpubertal duration of IDDM. Urinary albumin excretion was measured in random urine samples as the albumin to creatinine ratio (A/C ratio in \mu g/mg). Postpubertal duration is the total duration less the number of years of IDDM before the 10th birthday. Solid line represents prevalence AC ratios ≥17 for men and 25 for women; dashed line represents prevalence of AC ratios ≥65 for men and 92 for women; and dotted line represents prevalence of overt proteinuria, AC ratio ≥250 for men and ≥355 for women.
crease. A particularly notable feature was the very early appearance of significant numbers of patients with microalbuminuria: 6.4% of patients with IDDM for only 1 to 3 yr, a value eight times the 0.8% prevalence found in the sample of nondiabetics. The cumulative incidence of microalbuminuria leveled off around 20% after 10 yr of diabetes and then resumed its steep climb in the second decade, reaching a new plateau around 52% after 30 yr of postpubertal duration of diabetes.

The first case of overt proteinuria occurred after 7 yr of IDDM. Beginning with the 9th yr, there was an abrupt increase in the cumulative incidence of overt proteinuria as duration of diabetes increased, reaching a plateau during the third decade of IDDM, a feature similar to microalbuminuria. After 30 yr of postpubertal IDDM, the cumulative incidence of overt proteinuria leveled off around 27%.

The difference between the two cumulative incidence curves reflects the prevalence of persistent microalbuminuria. Interestingly, when the microalbuminuria range was divided at its midpoint into low and high microalbuminuria, very different patterns of variation with duration emerged. The prevalence of low microalbuminuria grew rapidly to 12% within the first decade, waned to 6% in the middle of the second decade, and then returned to 14% by the beginning of the third decade where it remained thereafter. High microalbuminuria, on the other hand, grew slowly through the first two decades and then declined very gradually thereafter. This latter pattern paralleled the rate of growth in the prevalence of overt proteinuria.

DISCUSSION

Elevated UAE in patients with IDDM indicates the existence of functional as well as morphologic abnormalities in the kidney (15–20). The albumin excretion rate (AER) obtained from timed urine collections is the most direct measure of UAE (1). However, because of the demands of the protocol and imperfect patient adherence, the AER is not practical for epidemiologic studies or clinical settings. A simple index, the ratio of urinary concentrations of albumin and creatinine (AC ratio), measured in a random sample of urine has become tool for assessing UAE (7–10, 21–23). In the present study, the large number of albumin and creatinine determinations on urine samples from patients with IDDM and nondiabetic control subjects enabled us to evaluate the AC ratio as a tool for diagnosing microalbuminuria. For discussion, the results will be grouped into three topics: (1) comparison of the AC ratio with the AER, (2) definition of lower and upper boundaries of microalbuminuria, and (3) description of the prevalence of early and advanced stages of diabetic nephropathy using criteria based on the AC ratio.

We found a very close relationship, \( r^2 = 0.94 \), between an AC ratio determined in a random urine sample and the AER determined during a 3-h urine collection immediately after the random void. Other authors have also reported high correlations between the AC ratio in random urine samples and the AER (or protein excretion rate) determined in 24-h or timed urine collections (8, 20, 21). Moreover, the correlation between measurements of AC ratios in random urine samples obtained at quarterly or semiannual visits (Spearman \( r = 0.83 \)) is at least as good as that reported for AER measurements based on timed urine collections (23–25). In this study, the coefficient of variation for the AC ratio (38%) was slightly lower than has been reported in other studies for the AER (45% to 60%) (23–25). Interestingly, the coefficient of variation in one study was lower for the AC ratio than for the AER when both were calculated in the same timed urine collections (26).

The AC ratio can be used to diagnose early stages of diabetic nephropathy in IDDM (1, 3–6). Because a small amount of albumin is present in the urine of most individuals who have no renal abnormality, a boundary between normal and abnormal UAE (microalbuminuria) must be determined. This can be approached from three different perspectives. For example, the criterion could be set arbitrarily as the 95th percentile of the distribution of the AC ratio in nondiabetic individuals. Alternatively, the criterion could be based on the ability of a value of the AC ratio to predict progression to overt proteinuria. The lowest value that has high specificity as a predictor of progression, however, may represent a stage of the disease so advanced that intervention is ineffective. The third alternative is to restrict consideration to the range of AC ratio where intervention is still effective and select that value which minimizes the cost of screening and intervention (2). The data required to define the lower boundary of microalbuminuria on a cost-effective basis do not exist for the AER or the AC ratio, and various attempts to identify a predictive criterion based on the AER have given discrepant results (3–6). Therefore, the first approach, a criterion based on the upper tail of the distribution in normals, is generally used.

Using this approach, we found that almost all AC ratios in urine samples from nondiabetic control subjects are below 16 \( \mu \)g of albumin/mg of creatinine. The 95th percentile is 17 for men and 25 for women. Evidence that these values may have a biological basis was obtained from an examination of the reproducibility of the AC ratio. Agreement between repeat determinations of the AC ratio in patients with IDDM was maximized when the distribution was dichotomized at 25 \( \mu \)g/mg for women and 17 \( \mu \)g/mg for men. Furthermore, if these cutpoints for the AC ratio are converted into AER, with the sex-specific conversion formula described in Microalbuminuria Determination, they converge to the same value: 30 \( \mu \)g/min. These additional characteristics of the selected cutpoints suggest that they have a biological basis, although they provide no clue as to its nature.

In contrast to the varieties of evidence supporting a
choice of the lower boundary for microalbuminuria, there is little basis for pinpointing an upper boundary. Traditionally, an albumin excretion rate above 200 \(\mu g/\text{min}\) in overnight urine collection and 300 \(\mu g/\text{min}\) in 24-h urine has been considered as the cut point separating microalbuminuria from overt proteinuria (1). This cut point, however, is arbitrary and was chosen on the assumption that higher values of the AER are usually recognized by dipstick methods. Data supporting that assumption are nonexistent, and this study, which had a sufficient number of samples to examine this issue, documented a significant lack of precision in the dipstick method when used to discriminate between microalbuminuria and proteinuria. A patient with early overt proteinuria may be dipstick-negative if well hydrated, whereas a patient with microalbuminuria may be dipstick-positive if dehydrated. The net effect is that the dipstick method misclassifies a large proportion of patients with microalbuminuria as overt proteinuria.

The prevalence of stages of diabetic nephropathy according to duration of IDDM was determined using AC ratio-based criteria. In agreement with other studies, we found that duration of IDDM before age 10 did not have an impact on the occurrence of nephropathy after age 10 (27). Thereafter, the prevalence of persistently elevated UAE (total microalbuminuria which includes low and high microalbuminuria and overt proteinuria) is much higher than in nondiabetics, and it increases with duration of IDDM. A particularly important finding is the very early appearance of significant numbers of patients with microalbuminuria. Six percent of patients with IDDM for only 1 to 3 yr had persistently elevated AC ratios, a value 8 times the 0.8% prevalence among nondiabetics. A similarly high prevalence of microalbuminuria in patients with IDDM with short duration of diabetes has been found in other studies (28). Another interesting observation is that the rising prevalence of microalbuminuria leveled off twice: after 10 yr of diabetes it remained for a while around 20%, and during the third decade of IDDM remained around 52%. These findings indicate that there may be two subsets of microalbuminuria occurring in IDDM (29). They may have different etiologies and may have different risks of progression to advanced nephropathy.

Patients with IDDM and microalbuminuria are at risk of developing overt proteinuria. In our study the first cases of overt proteinuria occurred after 7 yr duration of IDDM. Beginning in the ninth year, there was an abrupt increase in the prevalence of overt proteinuria as duration of diabetes increased, reaching a plateau during the third decade of IDDM. After 30 yr of postpubertal IDDM, the prevalence of overt proteinuria was 27%, whereas the prevalence of total nephropathy was 52%. The large difference, 25%, is the residual of cases of persistent microalbuminuria that have not yet progressed to proteinuria. The Pittsburgh Epidemiology of Diabetes Complications Study found a similar excess prevalence of microalbuminuria over that for overt proteinuria (30). Because follow-up studies have shown that after 30 yr of IDDM, the incidence rate of overt proteinuria is very low (31,32), one can conclude that few of these remaining cases of microalbuminuria will progress to overt proteinuria. To some extent, this lack of progression may be due to competing risk of death due to cardiovascular disease among those who develop microalbuminuria. However, this hypothesis cannot explain entirely the apparent lack of progression of microalbuminuria because much of the cardiovascular mortality in fourth decade of diabetes occurs among those with overt proteinuria rather than microalbuminuria (33).

With stochastic models, it was possible to simulate data that mimic quite well the prevalence data from this study (29). In the process, it became clear that certain model characteristics were necessary to achieve this close fit. For example, patients who develop microalbuminuria during the first 10 years of postpubertal IDDM must, in almost all cases, progress to overt proteinuria. Moreover, their median transition time from onset of microalbuminuria to onset of overt proteinuria seems to be 9 yr. Without these characteristics, the model could not generate the observed prevalence of overt proteinuria at 20 yr of IDDM. Otherwise, one must postulate that a large number of patients progress from normal to overt proteinuria quite suddenly, a phenomenon which is not seen clinically. Patients who develop microalbuminuria after the first decade of diabetes, on the other hand, have a different prognosis. Only half can progress or else the prevalence of overt proteinuria would exceed the level observed after 30 yr of IDDM (31,32).

These findings are in agreement with several long-term studies on the progression from microalbuminuria to more advanced stages of nephropathy. These studies showed that 75 to 85% of the patients with an albumin excretion rate above 15 to 70 \(\mu g/\text{min}\) progressed to overt proteinuria over a period of 10 to 14 yr (3–6). However, in the most recent long-term follow-up study, the proportion was only 50% (34). Interestingly, the first studies included patients with relatively short-duration diabetes, whereas the last study had patients with an average duration of 26 yr at entry. Thus, while these studies seem discrepant, they are consistent with our prevalence data and the results of the stochastic modeling (29). IDDM patients who develop microalbuminuria early in the course of IDDM have a higher risk of progression to overt proteinuria than patients who develop microalbuminuria late in the course of IDDM.

Finally, limitations in the generalizability of our findings should be considered. First, because our study is based on AC ratio measurements performed on urine samples obtained during the daytime, the cut points for the diagnosis of low and high microalbuminuria may be different (most likely they will be lower) if the measurements are based on first voided
urine specimens obtained after an overnight rest. Second, we studied only patients with IDDM, so the extent to which findings in patients with NIDDM will be similar is unknown. Third, our findings about two distinct levels of microalbuminuria and the hypotheses regarding clinical and etiologic implications are based on cross-sectional data and a short follow-up study. Therefore, generalization of them should be qualified until they have been confirmed in further follow-up.

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