Spectrum of Proteinuria in Type I and Type II Diabetes

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We prospectively investigated the evolution of proteinuria in 52 type I diabetics over 7.8 ± 0.3 (mean ± SE) yr and in 61 type II diabetics over 6.4 ± 0.3 yr. Measurements of renal protein clearance were performed serially, and the time course of proteinuria was classified in each subject based on a threshold albumin clearance of 11 nl/s, equivalent to a urinary albumin excretion rate of 30 μg/min. The classification based on this threshold yielded four distinct patterns of albuminuria: minimal, intermittent, progressing, and established. These patterns occurred in both type I and type II diabetics independently of the duration of follow-up. This study has identified a pattern of intermittent microalbuminuria that is also associated with transient elevations of transferrin and IgG clearances.

The relationship of clinical and biochemical parameters to proteinuria patterns was evaluated. No relationship was detected between proteinuria patterns and glycemic control in either type I or type II diabetics. In type I but not type II diabetics, established proteinuria was associated with higher systolic blood pressure and decreased creatinine clearance.

The phase of intermittent proteinuria detected in this study may represent a reversible stage in the development of diabetic nephropathy, but the factors that trigger the transition to progressing proteinuria remain obscure. *Diabetes Care* 10:419–27, 1987

In recent years it has been suggested that a state of preclinical microalbuminuria exists in diabetes (1,2) and that it may predict the later onset of Albustix-positive proteinuria. These predictions have generally been based on analyses of urinary albumin excretion rates in insulin-dependent (type I) diabetics at two points 6–14 yr apart (3–5). Microalbuminuria has also been used as a prognostic index in non-insulin-dependent (type II) diabetes, although its relationship to overt diabetic nephropathy is not as clearly defined in this group of diabetics (6,7).

Intermittent increases in proteinuria have been described in type I diabetes (8–10). However, it is not known if these episodes cause sufficient variability of protein excretion to diminish the predictive value of single measurements for the onset of overt diabetic nephropathy (11,12). Variability of protein excretion from day to day has already been studied (12), but this is the first study that has examined this aspect of proteinuria in type I and type II diabetics over several years. The aim of this prospective study was to describe the natural history of evolving diabetic proteinuria and its association with glycemic control, blood pressure, and other clinical parameters in type I and type II diabetics. Therefore, serial measurements of protein handling and renal function were performed in each subject over several years.

MATERIALS AND METHODS

Subjects. The Austin Hospital Diabetes Clinic was set up in 1971 to provide both a referral service and primary medical care for adult diabetic subjects. Between 1973 and 1979, regular clinic attenders were recruited to an open-ended study of evolving diabetic nephropathy. At recruitment, patients were asked to attend every 3 mo for at least 3 yr. Patients were enrolled independently of the type, age of onset, and duration of diabetes. Patients were excluded if they already had established renal impairment (serum creatinine >0.2 mM), known nondiabetic renal disease, or uncontrolled cardiac failure. The presence of other medical illness or therapy unrelated to diabetes was not a reason for exclusion. Patients were designated as type I diabetics if they had persistent

ketonuria, weight loss on presentation, and insulin dependency within 1 mo of diagnosis. All other diabetic patients were classified as type II diabetics. All insulin-treated patients were receiving subcutaneous insulin once or twice daily.

Twenty-four-hour urine samples were collected at 3-mo intervals at home in the absence of severe or prolonged exercise, and blood was sampled at the end of each collection. Urine microscopy and culture were performed in each subject to exclude infection.

Methods. The renal clearances of albumin, transferrin, and IgG were determined after measurement of the individual protein concentrations in urine and plasma. Transferrin, IgG, and urinary albumin assays were performed by a coated-tube radio immunoassay on dialyzed urine and plasma (13). Serum albumin was measured by an autoanalyzer technique. Antibodies to individual proteins were obtained from Silenus (Melbourne, Australia), and ^{125}I-labeled tracers were prepared by the chloramine-T method (14). The interassay coefficients of variation were 10.9% for albumin clearance (n = 14), 14.6% for transferrin clearance (n = 15), and 15.5% for IgG clearance (n = 14). Total proteinuria was measured in 24-h urine samples by the fluorescamine method with an interassay coefficient of variation of 8.8% (n = 14) (15). Albustix measurements were performed on the same specimens, with a positive test equaling an albumin clearance of ~55 nl/s (equivalent to a urinary albumin excretion rate of 150 μg/min).

Plasma glucose was measured by a glucose oxidase technique (16), and stable HbA_1 was measured by the thiobarbituric acid technique from 1978 to 1981 (17) and by column chromatography preceded by a dialysis step after 1981 (18). There was a close correlation between the two methods (r = .90, $P < .01$, n = 35). Urinary and serum creatinine concentrations were measured by an autoanalyzer technique (Beckman Astra 8). The calculation of creatinine clearance, based on this autoanalyzer method, correlates closely with inulin clearance methods for the estimation of glomerular filtration rate in patients without significant renal impairment (19–21). It was considered unethical to perform radioisotopic measurements of glomerular filtration rate at 3-mo intervals. However, glomerular filtration rate measured by the diethylenetriamine pentaacetic acid method correlated closely with creatinine clearance (r = .80, $P < .01$, n = 35). All patients had at least six measurements of creatinine clearance. Supine blood pressure was measured every 3 mo.

Statistical analysis. The criterion for inclusion in the data analysis was completion of at least six separate tests of proteinuria and renal function spanning at least 36 mo of follow-up. Of the 144 patients recruited initially, 113 fulfilled this criterion.

Comparisons of patient characteristics among the four defined proteinuria groups were performed by Student's t test assuming unequal variances for variables that were normally distributed (22). Differences in sex ratio and proportions of patients with antihypertensive therapy and Albustix-positive proteinuria were compared with the χ^2-test. Creatinine clearance was adjusted for surface area (23). The rate of decline of creatinine clearance was calculated by dividing the difference of the mean of the initial three and final three values for creatinine clearance by the duration of follow-up (ml · min^{-1} · yr^{-1}). Because parameters of proteinuria were distributed nonparametrically, logarithmic transformation of protein clearances was performed; therefore, geometric means are shown (22). The relationships of individual protein clearances to each other and to total proteinuria were evaluated by linear regression analysis (22). Blood pressure and glycemic control did not change significantly during the study. This justified the use of mean data from individual subjects in the analysis of the relationship between these parameters and proteinuria groups.

Because duration of follow-up was not equal in all patients in the study, stepwise multiple regression analysis (22) was performed to determine if the levels of the specific protein clearances were related to the duration of follow-up. The specific protein clearance was the independent variable, and the dependent variables included age, duration of disease, and duration of follow-up.

RESULTS

Clinical characteristics of study population. Fifty-two type I and 61 type II diabetics were studied for intervals of 7.8 ± 0.3 yr (mean ± SE, range 3.4–11.8) and 6.4 ± 0.3 yr (range 3.0–10.3), respectively (Table 1). Thus, a total of 796 patient-yr of observations were made. At the start of the study, 20 type I and 6 type II diabetics were newly diagnosed and

TABLE 1
Clinical characteristics

	Type I	Type II
Number of subjects	52	61
Age at diagnosis (yr)	22 ± 2	49 ± 1*
Age at start of study (yr)	30 ± 2	57 ± 1*
Disease duration at end of study (yr)	15.0 ± 1.3	13.7 ± 1.0
Duration of study (yr)	7.8 ± 0.3	6.4 ± 0.3*
Number of observations	22 ± 1	20 ± 1
Sex (M/F)	35/17	36/25
Weight (kg)	73 ± 2	76 ± 2
Systolic blood pressure (mmHg)	132 ± 2	148 ± 2*
Diastolic blood pressure (mmHg)	82 ± 1	86 ± 1*
Antihypertensive treatment	10	27*
HbA_1 (%)	10.6 ± 0.2	10.2 ± 0.2
Fasting plasma glucose (mM)	12.3 ± 0.4	12.0 ± 0.4
Urinary glucose (mmol/24 h)	199 ± 19	112 ± 16*
Number of subjects with Albustix-positive (>0.3 g/L) proteinuria	5	10
Creatinine clearance (ml · min^{-1} · 1.73 m^{-2})	93.0 ± 3.3	86.2 ± 3.1
Rate of decline of creatinine clearance (ml · min^{-1} · yr^{-1})	2.4 ± 0.4	1.1 ± 0.3*

Means ± SE are shown based on data collected over entire study period.
*$P < .01$, type I vs. type II.

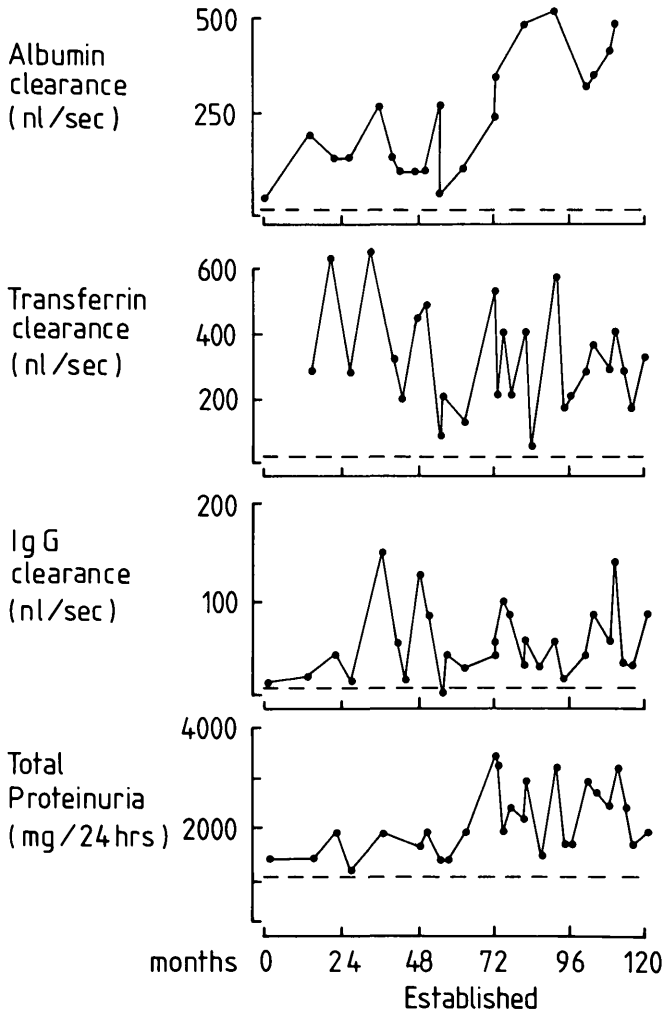

FIG. 1. Established proteinuria (patient D.G.). Initial and final albumin clearance values >11 nl/s. *Dashed lines* represent twice upper limit of normal range, equal to lower limit of microalbuminuric range. Albumin clearance of 11 nl/s = albumin excretion rate of 30 μg/min.

12 type I and 10 type II had diabetes for a duration of >15 yr. At the end of the study, only 2 type I and 6 type II diabetics had a disease duration of <5 yr, whereas 23 type I and 22 type II diabetics had a disease duration of >15 yr. Type I and type II diabetics had similar durations of disease and glycemic control. However, type II diabetics were older and had higher blood pressures and marginally shorter follow-ups. Type I diabetics had similar levels but greater rates of decline of creatinine clearance than type II diabetics.

Thirty-one (10 type I, 21 type II) patients failed to meet the inclusion criteria for the study. Two patients had serum creatinine >0.2 mM, 22 were followed for <3 yr (3 died, 3 shifted), and 7 had <6 renal protein-clearance measurements, despite a duration of follow-up of >3 yr.

Classification of proteinuria groups. The protein-excretion pattern of each of the 113 subjects was analyzed by examining the initial three and final three levels of albumin clearance in each subject. Because it has been suggested that the lower limit of microalbuminuria in type I and type II diabetes is an albumin excretion rate of 30 μg/min and that this level has significant prognostic implications for the development of diabetic nephropathy (3,6), the classification of patterns of albuminuria was based on this threshold level. A urinary albumin excretion rate of 30 μg/min performed on a 24-h urine specimen corresponds to an albumin clearance of 11 nl/s. Samples were not used for classification of proteinuria pattern if they were infected or if they had been collected within 2 wk of an episode of ketoacidosis.

Four type I and 10 type II diabetics had elevated albumin clearance at entry into the study, and these patients were defined as having established proteinuria (Fig. 1). Of the 48

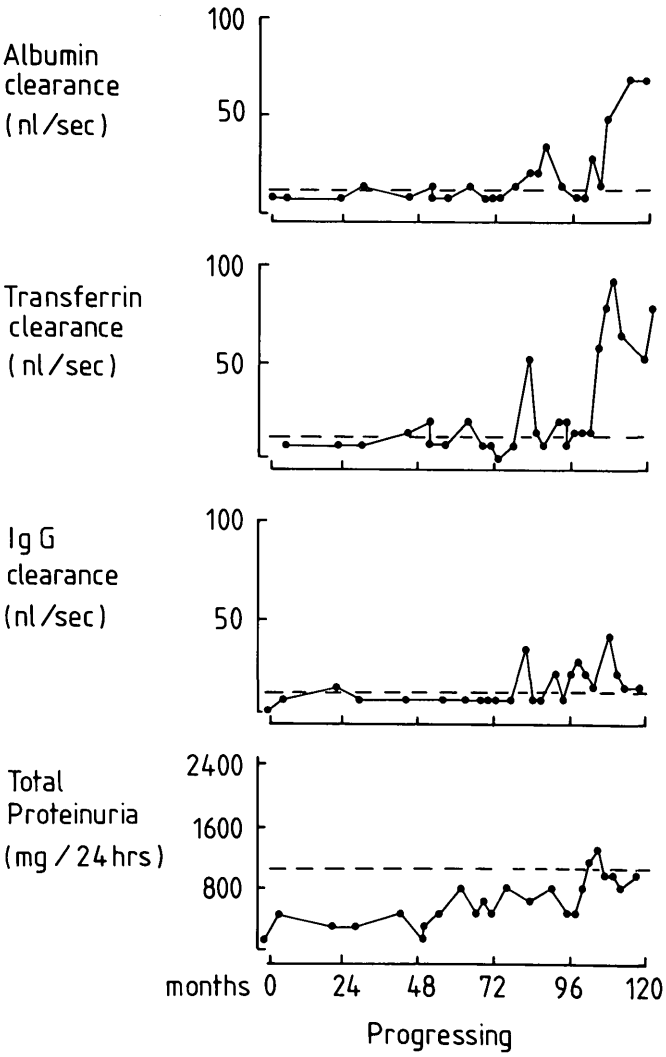

FIG. 2. Progressing proteinuria (patient N.K.). Albumin clearance initially <11 nl/s with last 3 values >11 nl/s (spanning at least 12 mo). *Dashed lines* represent twice upper limit of normal range, equal to lower limit of microalbuminuric range. Albumin clearance of 11 nl/s = albumin excretion rate of 30 μg/min.

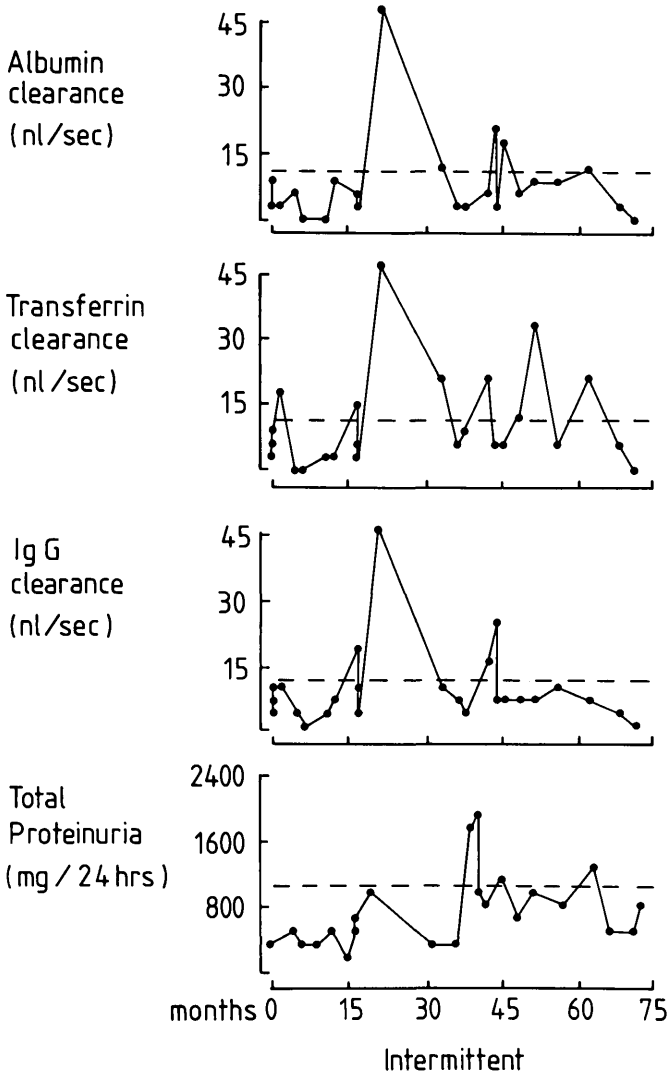

FIG. 3. Intermittent proteinuria (patient W.D.). Initial and final albumin clearances <11 nl/s with at least 2 values >11 nl/s. *Dashed lines* represent twice upper limit of normal range, equal to lower limit of microalbuminuric range. Albumin clearance of 11 nl/s = albumin excretion rate of 30 μg/min.

type I and 51 type II diabetics with initially normal albumin clearance, only 4 type I and 9 type II subjects showed a progressive rise in albumin clearance, with the final three albumin clearances, spanning at least 12 mo, exceeding 11 nl/s. This subgroup was defined as having progressing proteinuria (Fig. 2). The remaining 44 type I and 42 type II diabetics whose initial and final albumin clearances did not exceed 11 nl/s were then further classified by analyzing the longitudinal pattern of albumin clearance. This revealed a subgroup of 14 type I and 13 type II diabetics who had at least two episodes of elevated albumin clearance (>11 nl/s); these subjects were classified as having intermittent proteinuria (Fig. 3). The remaining diabetics were defined as having minimal proteinuria (Fig. 4). Therefore, the analysis yielded four separate patterns of evolution of proteinuria occurring in both type I and type II diabetics. Figures 1–4 indicate the time course of proteinuria in a representative subject from each proteinuria group.

Albumin clearance correlated closely with transferrin clearance ($r = .63$, $P < .001$), IgG clearance ($r = .44$, $P < .01$), and total proteinuria ($r = .71$, $P < .001$) when all individual data were analyzed ($n = 1851$) and when these parameters were analyzed within each individual. Albumin clearance levels in the four proteinuria groups were closely reflected by transferrin and IgG clearances and, to a lesser degree, by total proteinuria (Figs. 1–4). In subjects with intermittent and progressing proteinuria, most increases in albumin clearance were associated with rises in transferrin

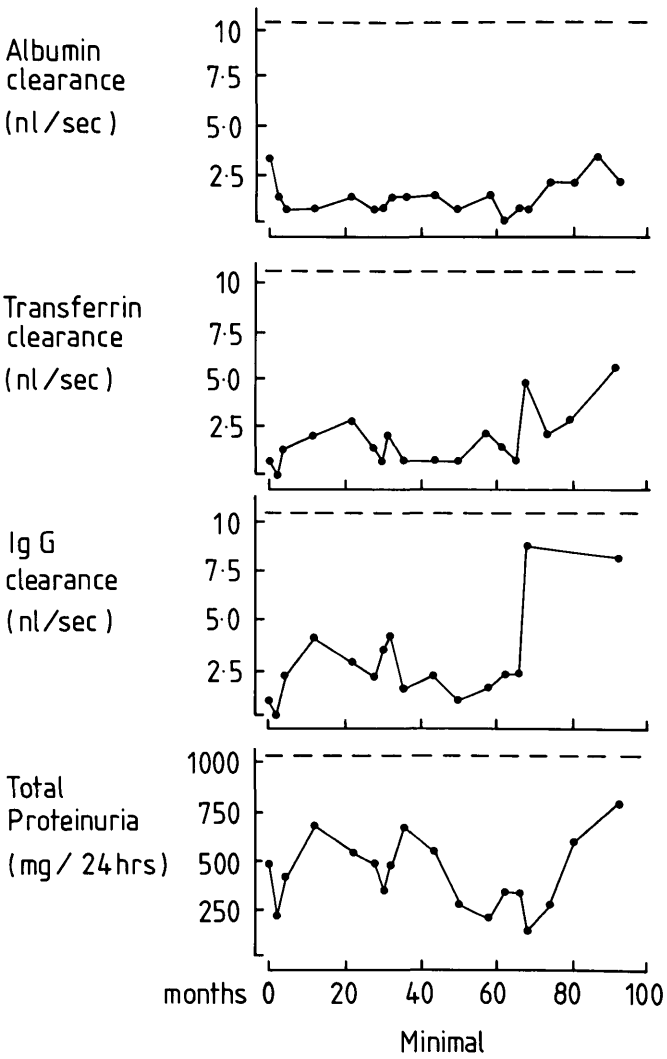

FIG. 4. Minimal proteinuria (patient S.M.). All albumin clearance values <11 nl/s. *Dashed lines* represent twice upper limit of normal range, equal to lower limit of microalbuminuric range. Albumin clearance of 11 nl/s = albumin excretion rate of 30 μg/min.

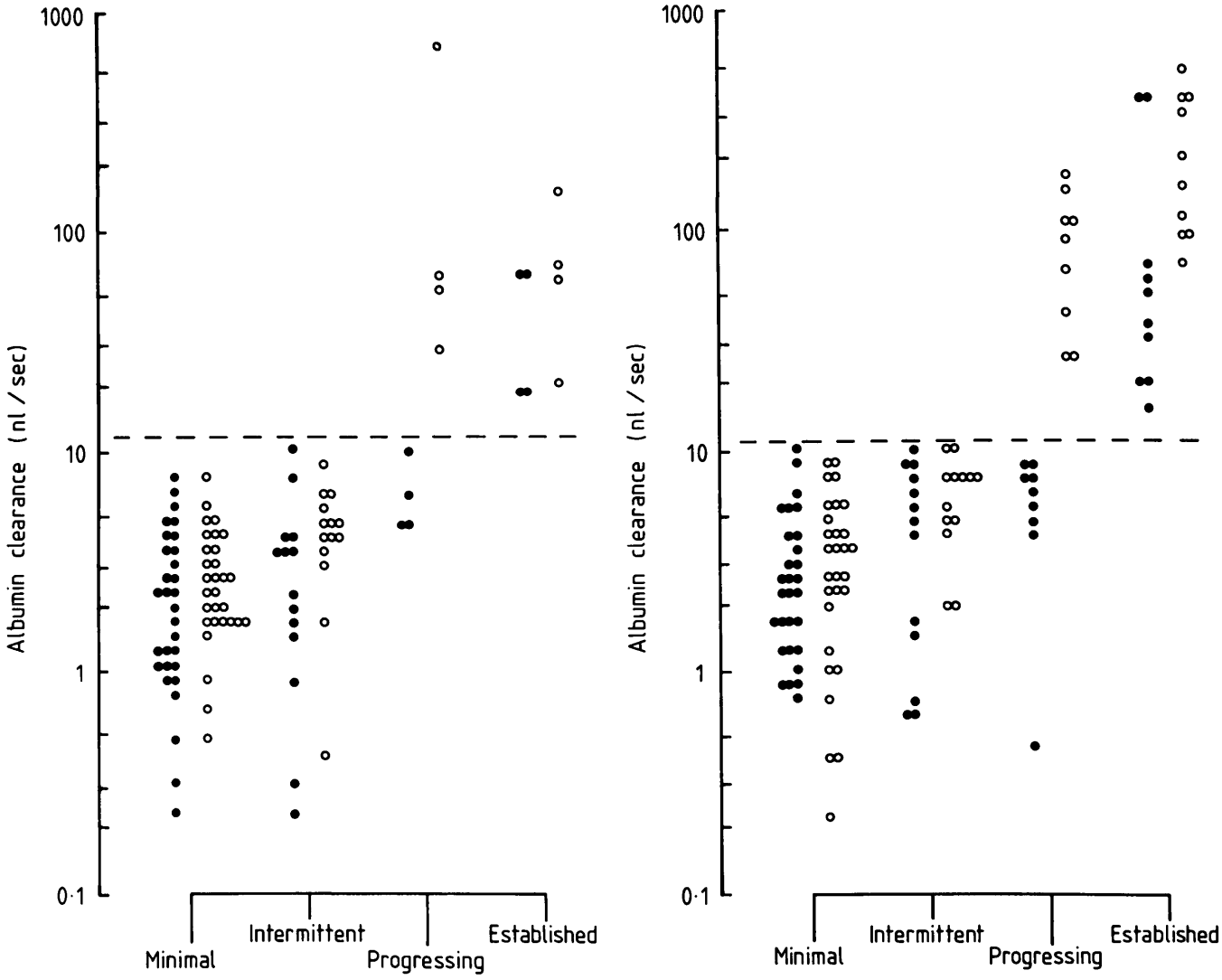

FIG. 5 ***Left*****: initial (●) and final (○) albumin clearances in type I diabetics represented on a logarithmic scale, with intervals indicating 0.2, 0.3, and 0.5 of each cycle.** ***Dashed line*** **represents twice upper limit of normal range, equal to lower limit of microalbuminuric range. Albumin clearance of 11 nl/s = albumin excretion rate of 30 μg/min.** ***Right*****: initial and final albumin clearances in type II diabetics.**

and IgG clearance (Figs. 2 and 3). The coefficients of variation of repeated measurements over several years of albumin, transferrin, and IgG clearances in individual subjects ranged from 60 to 110%. This was four- to eightfold higher than the coefficients of variation of the assays themselves.

The first and last measurements of albumin clearance in each subject are shown in Fig. 5. However, classification was based on the mean of the first three and last three measurements of albumin clearance to exclude the possibility that classification depended on a single transient elevation of albumin clearance. The intermittent and minimal proteinuria groups were similar when initial and final values were examined; however, they were significantly different when albumin clearance over the entire study period was examined (Table 2). Despite similar initial values for albumin clearance in the intermittent and progressing groups (Fig. 5), the progressing proteinuria group had much higher mean levels of albumin clearance than the intermittent proteinuria group (Table 2). Furthermore, a difference in mean protein clearances between the intermittent (INT) and progressing (PROG) groups was confirmed by analysis of transferrin clearance [type I: INT 8.9 (1.2), PROG 110 (1.8), $P < .05$; type II: INT 12.8 (1.2), PROG 29.9 (1.4), $P < .05$] and IgG clearance [type I: INT 7.7 (1.1), PROG 44.4 (1.4), $P < .01$; type II: INT 9.6 (1.1), PROG 16.7 (1.2), $P < .01$; geometric means are shown with SE in parentheses].

Clinical characteristics of proteinuria groups. In type I diabetics there was an increase in duration of diabetes from normal to intermittent to progressing to established proteinuria ($F = 4.2$, $P < .05$). This trend was not significant in

TABLE 2
Clinical characteristics according to pattern of proteinuria

	Proteinuria pattern			
	Minimal	Intermittent	Progressing	Established
Number of subjects	30 (29)	14 (13)	4 (9)	4 (10)
Mean albumin clearance (nl/s)	2.3 ⁑ 1.1 (3.2 ⁑ 1.1)	6.4 ⁑ 1.1 (11.5 ⁑ 1.2)*	56.5 ⁑ 1.6 (29.6 ⁑ 1.3)*	51.5 ⁑ 1.4 (191.4 ⁑ 1.3)*
Age at diagnosis (yr)	21 ± 2 (52 ± 2)	22 ± 4 (48 ± 2)	34 ± 3 (48 ± 3)†	24 ± 5 (46 ± 3)
Age at start of study (yr)	26 ± 3 (58 ± 2)	30 ± 5 (57 ± 2)	45 ± 2 (56 ± 2)†	44 ± 2 (55 ± 2)†
Disease duration at end of study (yr)	12.2 ± 1.3 (11.7 ± 1.3)	16.3 ± 3.2 (15.1 ± 2.7)	18.9 ± 1.6 (15.3 ± 2.9)†	27.7 ± 5.0 (16.4 ± 2.1)†
Duration of study (yr)	7.5 ± 0.4 (6.1 ± 0.5)	8.6 ± 0.6 (6.8 ± 0.6)	7.0 ± 1.1 (6.7 ± 0.7)	7.4 ± 1.1 (6.6 ± 0.9)
Number of observations per subject	19 ± 2 (19 ± 1)	29 ± 3 (21 ± 2)†	29 ± 6 (21 ± 3)	16 ± 5 (19 ± 2)
Sex (M/F)(n)	22/8 (13/16)	8/6 (10/3)	3/1 (5/4)	2/2 (8/2)

Means ± SE are shown for type I diabetics with results for type II diabetics in parentheses. Albumin clearance results are represented as geometric means (⁑ SE). Proteinuria patterns: minimal, all albumin clearance values <11 nl/s; intermittent, initial and final values <11 nl/s (at least 2 values >11 nl/s); progressing, initially <11 nl/s with last 3 values >11 nl/s; established, initial and final values >11 nl/s.
*$P < .05$ and †$P < .01$ compared with minimal proteinuria group.

type II diabetics ($F = 1.3$, NS). In type I and type II diabetics the intermittent and minimal proteinuria subjects had similar durations of disease (Table 2). Note that there was no significant difference in duration of follow-up between the four proteinuria groups in either type I or type II diabetics (Table 2). To further evaluate if duration of follow-up was a contributory factor to rises in specific protein clearances, stepwise multiple regression analysis was performed (22). This showed that there was no significant association between duration of follow-up and specific protein clearances (type I: albumin clearance, $F = 0.48$, NS; type II: albumin clearance, $F = 0.002$, NS). In type I diabetics, the number of observations in the intermittent proteinuria group was greater than in subjects with minimal proteinuria but similar to that in subjects with progressing proteinuria (Table 2).

Glycemic control, blood pressure, and renal function. Glycemic control, blood pressure levels, and renal function in subjects with the four proteinuria patterns are shown in Table 3. A comparison of HbA_1 levels in type I and type II diabetics with intermittent and minimal proteinuria disclosed no significant differences (Table 3). Similarly, analysis of fasting plasma glucose and 24-h urinary glucose levels performed on the same day as the collection of urine and plasma for determinations of renal function and specific protein clearances disclosed no significant differences among the four proteinuria groups in either type I or type II diabetics. There was no evidence of raised blood pressure in subjects with intermittent compared with minimal proteinuria. Type I diabetics with established proteinuria had increased systolic blood pressure over the study period compared with the minimal proteinuria group but had equivalent glycemic control.

Creatinine clearance results from the four groups are shown in Table 3. In type I diabetics, creatinine clearance decreased progressively from minimal to intermittent to progressing to established proteinuria ($F = 8.92$, $P < .01$, one-way analysis of variance). There was no such progressive decline in creatinine clearance in type II diabetics. In type I but not type II diabetics, subjects with progressing proteinuria had a faster rate of decline in renal function than subjects with minimal or intermittent proteinuria (Table 3).

DISCUSSION

This study describes the natural history of diabetic proteinuria over a mean period of 7 yr in type I and type II diabetics. Our results show that the time course of proteinuria in both types of diabetes is characterized by intermittent as well as

TABLE 3
Relationship of glycemic control, blood pressure, and renal function to proteinuria patterns

	Proteinuria pattern			
	Minimal	Intermittent	Progressing	Established
HbA_1 (%)	10.5 ± 0.3 (9.9 ± 0.3)	10.1 ± 0.2 (10.5 ± 0.5)	11.9 ± 1.2 (10.3 ± 0.5)	11.7 ± 1.0 (10.4 ± 0.6)
Systolic blood pressure (mmHg)	128 ± 2 (144 ± 3)	132 ± 4 (147 ± 3)	143 ± 9 (153 ± 4)	157 ± 7 (158 ± 8)*
Diastolic blood pressure (mmHg)	81 ± 1 (85 ± 1)	82 ± 2 (88 ± 2)	83 ± 3 (84 ± 3)	90 ± 3 (87 ± 2)
Creatinine clearance ($ml \cdot min^{-1} \cdot 1.73\ m^{-2}$)	102.5 ± 3.4 (85.4 ± 3.8)	91.8 ± 5.2 (94.3 ± 7.8)	65.0 ± 9.6 (86.7 ± 8.4)*	61.5 ± 10.2 (75.1 ± 9.6)
Creatinine clearance rate of decline ($ml \cdot min^{-1} \cdot yr^{-1}$)	2.1 ± 0.6 (0.7 ± 0.4)	2.3 ± 0.9 (1.8 ± 1.2)	3.6 ± 0.2 (1.1 ± 0.3)*	3.5 ± 1.3 (1.6 ± 0.6)

See Table 2 and text for number of subjects. Means ± SE are shown for type I diabetics with results for type II diabetics in parentheses. Proteinuria patterns: minimal, all albumin clearance values <11 nl/s; intermittent, initial and final values <11 nl/s (at least 2 values >11 nl/s); progressing, initially <77 nl/s with last 3 values >11 nl/s; established, initial and final values > 11 nl/s.
*$P < .05$.

progressive rises in albuminuria. Analysis of serial measurements in individual subjects indicated that intermittent rises in renal protein clearances into the microalbuminuric range (11–55 nl/s) are present in ~20% of diabetic subjects. Note that only 4 out of 52 type I diabetics had albumin clearances >11 nl/s (urinary albumin excretion rate of 30 μg/min) at the start of the study and only 4 more type I diabetics developed microalbuminuria during the study period. Therefore, at the end of the study, 44 of 52 type I diabetics did not have albumin clearances >11 nl/s. Similarly, in type II diabetics, most (42 of 61) had not developed microalbuminuria by the end of the study.

The lack of progression to overt Albustix-positive proteinuria (albumin clearance >55 nl/s) in this study may be related to multiple factors. A few type I diabetic subjects will develop diabetic nephropathy, which develops over many years with a median duration of 20 yr (24). The population evaluated in this study included many subjects with a duration of disease of <20 yr, and subjects were excluded if they had serum creatinine >0.2 mM, a level associated with irreversible progression of diabetic renal disease (25). Therefore, we concentrated on a group of diabetics who are either destined not to develop diabetic nephropathy or who are early in the course of this process. Only four type I diabetics had microalbuminuria at the start of the study, and thus, emphasis has been placed on the development of microalbuminuria rather than overt Albustix-positive proteinuria.

Because diabetic proteinuria evolves with time, the analysis in this study has emphasized changes in levels of proteinuria by following individual subjects in a longitudinal manner. This avoids the limitations of cross-sectional data analysis. Because diabetic nephropathy occurs in few diabetics, it was important to separate patients with no evidence of disease from those who developed microalbuminuria. Inclusion of all patients in one analysis would have reduced the possibility of detecting specific factors that may be associated with the development of microalbuminuria. This study has shown that microalbuminuria is associated with similar changes in the urinary excretion of transferrin and IgG, which is consistent with the glomerular origin of diabetic proteinuria (26). This phenomenon may be more appropriately termed microproteinuria.

The existence of intermittent proteinuria has been previously documented in short-term studies (8,9). By definition, intermittent proteinuria is associated with reversible episodes of elevated albumin clearance. The factors associated with the onset and disappearance of these episodes may determine the ultimate occurrence of overt diabetic nephropathy. In one previous study, serial observations were made in 23 type I diabetics over 6 yr (27). In that study the variability of proteinuria could be deduced from the data, but the authors did not comment on this. The entity of intermittent proteinuria is further complicated by the presence of a small group of diabetics who have been shown to revert to normal urinary albumin excretion rates after a phase of persistent proteinuria (2). These patients may have had intermittent proteinuria that had been incorrectly diagnosed as established diabetic nephropathy. A further follow-up of such patients is required to determine if intermittent proteinuria will ultimately result in overt nephropathy.

In our study, an examination of the time course of proteinuria in the progressing groups reveals episodes of intermittent proteinuria before the ultimate development of persistent micro- or macroproteinuria (Fig. 2). Intermittent microproteinuria may reflect a transitional phase in the development of diabetic nephropathy. The increase in mean duration of disease from minimal to intermittent to progressing proteinuria is consistent with this hypothesis (Table 2). However, there is a large overlap in duration of disease between the minimal and intermittent proteinuria groups, which raises the possibility that these patterns may differentiate subjects sensitive or resistant to the occurrence of clinically overt diabetic nephropathy. If this were so, then subjects with minimal proteinuria after 12 yr of disease would be ultimately protected from progression, and subjects with an intermittent proteinuria pattern would be at higher risk for the later development of overt proteinuria and renal failure. Shorter duration of follow-up in individual patients classified as having progressing proteinuria may result in a change in classification to intermittent proteinuria (Fig. 2). This is consistent with the hypothesis that a phase of intermittent microalbuminuria may precede persistent microalbuminuria and is analogous to the entity of intermittent Albustix-positive proteinuria that occurs before the onset of persistent macroproteinuria, as has been described previously (28). However, the similar duration of follow-up in all the proteinuria groups suggests that the classification in this study has not been biased by the length of the study (Table 2).

Transient hyperglycemia is associated with altered vascular permeability, which leads to proteinuria (8), but this has only been shown in subjects with poorly controlled diabetes and ketonuria (9). However, our results do not suggest that intermittent albuminuria is related to impaired glycemic control. Other potential causes of intermittent proteinuria such as severe or prolonged exercise (29), cardiac failure, severe essential hypertension (30), and urinary tract infection were not present. It is not likely that intermittent proteinuria can be explained by assay error, because assay errors were less than one-fifth of observed variations of protein clearance in the intermittent proteinuria group. Furthermore, increases in albumin clearance coincided with increases in the clearance of other proteins (Figs. 1–3).

Our study supports a link between proteinuria and renal function in type I but not type II diabetes. Creatinine clearance was reduced and rate of decline of creatinine clearance was increased in type I diabetics with progressing proteinuria, which was not seen in subjects with minimal or intermittent proteinuria (Table 3). No such relationship was evident in type II diabetics, suggesting that proteinuria in type II diabetes is not as closely coupled with diabetic nephropathy. This finding agrees with the less common occurrence of renal failure in type II diabetes (31) and is supported by the finding that microalbuminuria in type II diabetics may predict death from cardiovascular causes rather than renal failure (6,7).

Studies basing the prognosis of diabetics on two-point analysis of albuminuria have failed to recognize the possibility that microalbuminuria is often transient (3,4). The previous description of a subgroup of diabetics with persistent proteinuria reverting to normal albumin clearance (2) and the demonstration in our study of the frequent occurrence of intermittent proteinuria emphasize the importance of serial measurements in studying the natural history of diabetic nephropathy. The identification of a group of diabetics who develop intermittent microalbuminuria is of increasing significance because recent clinical studies have suggested that strict glycemic control is of minimal or no benefit in persistently microalbuminuric (32,33) or macroalbuminuric (34) patients. This intermittent microalbuminuric phase may precede persistent microalbuminuria, and it is possible that these subjects are the group in which intervention may be of therapeutic benefit.

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