Perspectives in Diabetes

Prediction of Clinical Diabetic Nephropathy in IDDM Patients

Alternatives to Microalbuminuria?

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This perspective deals with prediction of overt diabetic nephropathy in patients with insulin-dependent diabetes mellitus (IDDM). The role of elevated urinary albumin excretion rate (microalbuminuria) in predicting diabetic nephropathy has been emphasized by new follow-up studies. Development of severe kidney impairment was seen in a large percentage of patients with microalbuminuria, but with more intensive care for diabetic patients, this percentage may be falling. Herein, I analyzed alternatives to microalbuminuria in predicting kidney disease in diabetes. *1*) Parental predisposition to hypertension is not seen in all studies and therefore may not be a decisive factor, and it cannot be used in prediction of nephropathy. *2*) Prediabetic blood pressure may predict nephropathy in certain non-insulin-dependent diabetic patients, but elevated blood pressure seems to develop after early microalbuminuria and is likely to be an aggravating factor in established microalbuminuria in IDDM patients. *3*) At the clinical diagnosis of IDDM, diabetic nephropathy cannot be predicted. *4*) Glycemic control is poor in normoalbuminuric patients with later development of microalbuminuria, and multiple glycosylated hemoglobin measurements are therefore important. *5*) In diabetes, glomerular hyperfiltration is associated with late nephropathy, but it alone cannot be the decisive factor, because hyperfiltration in nondiabetic individuals does not produce kidney disease, according to new long-term follow-up studies. *6*) Studies of glomerular structure and ultrastructure have not yet documented predictive values for overt nephropathy, but further studies are in progress. *7*) Isolated blood pressure elevation without microabuminuria (probably representing essential hypertension in diabetes) has not been predictive. *8*) It is clear that elevation of serum creatinine is a very late and insensitive parameter, occurring only with pronounced proteinuria. Creatinine clearance is a poor index for glomerular filtration rate. Therefore, it can be concluded that microalbuminuria currently is the most simple and sensitive parameter for detection of the patient at risk of kidney disease in diabetes. The abnormality probably reflects an early renal lesion rather than being a susceptibility factor. Long-term follow-up of microalbuminuria is recommended for early detection of diabetic kidney disease in IDDM patients, and proposals regarding intervention are discussed. *Diabetes* 39:761-67, 1990

Measurement of urinary albumin excretion (UAE) rate in the normal and elevated ranges (the latter termed *microalbuminuria* in the absence of overt proteinuria) was introduced in the 1960s and early 1970s with radioimmunoassays or immunochemical techniques (1–3). However, the clinical significance of microalbuminuria as a predictor of overt nephropathy only became apparent after a long lag in the beginning of the 1980s (4–6). This concept now seems widely acknowledged from both theoretical and practical points of view (7). However, some leading groups studying diabetic nephrology in the United States long failed to accept the crucial clinical significance of microalbuminuria and incipient diabetic nephropathy and were inclined to rely on kidney biopsies in conjunction with ordinary kidney function tests such as creatinine clearance (8).

The concept of microalbuminuria is not at all sophisticated but reflects the insensitivity of the old-fashioned clinical test to detect an elevated UAE rate. When the mean normal UAE rate found in almost all studies is ~5 μg/min (range 2–15 μg/min) and the dipstick-positive level is ~150–200 μg/min (with normal urine flow), it is hardly surprising that excretion rates between these two ranges cannot be detected by the conventional test for proteinuria (9,10). We now have a much clearer picture of the spontaneous course of kidney disease in diabetes, at least in patients with insulin-dependent dia-

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betes mellitus (IDDM). Figure 1 is a compilation of published data on 20 patients from three studies, the only studies on the long-term follow-up of patients with exact measurement of glomerular filtration rate (GFR; constant-infusion technique with labeled iothalamate) and UAE (5,11,12). The mean ± SD follow-up in these studies was 12 ± 3 yr, and all patients developed diabetic nephropathy or UAE > 150 μg/min, and some developed end-stage kidney failure. GFR and UAE were not measured in all patients either initially or at follow-up, but at least one of them was always measured. Further new data (16 yr of follow-up) are discussed.

Even if persistent microalbuminuria is widely accepted as an early sign of diabetic kidney disease (7,9), it may be asked whether there are any alternatives when trying to predict diabetic nephropathy. Diabetic nephropathy is defined as clinical proteinuria of >0.5 g total protein excretion/24 h and is different from diabetic glomerulopathy, which is a pure histological diagnosis and not necessarily related to clinical kidney disease.

APPROACHES TO TERMINOLOGY

Two approaches are being used in the definition of microalbuminuria. The first approach is based on the range of UAE in healthy individuals compared with the level where dipstick tests or similar procedures become positive. In principle, microalbuminuria may be defined as the difference between these two levels (9). The upper level of the UAE rate in young healthy individuals in the resting position rarely exceeds 15 μg/min. In a recent Danish study, the upper 95% confidence interval in healthy individuals was found to be 20 μg/min (13), comparable to an American study (14). Therefore, a level above the UAE rate of 20 μg/min but below the dipstick-positive range (~200 μg/min, provided normal urine flow of 1 ml/min) could be used in the definition of microalbuminuria. In the American study, a level of 15–139 μg/min was used to designate microalbuminuria (14), which is lower than the European standard of 20–200 μg/min (9).

Another approach would be to consider the range that is predictive of late nephropathy. In fact, the two approaches

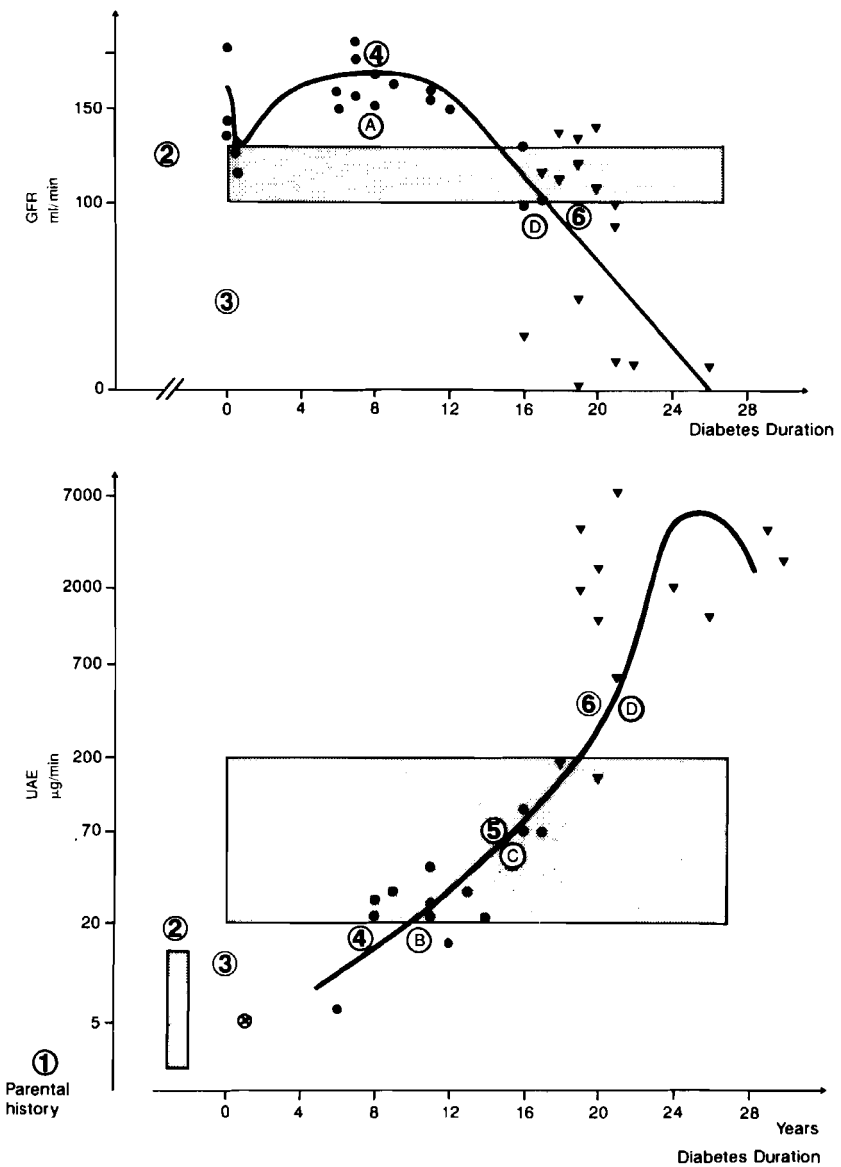

FIG 1. Outline of natural history of diabetic nephropathy in patients with insulin-dependent diabetes mellitus (IDDM, *n* = 20, all men) based on data from 3 papers (refs. 5,11,12) with *curved lines* as typical course. All patients developed diabetic nephropathy; 12 ± 3 yr were between 1st examination (●) and follow-up (▼). Intervention possibilities (*A–D*, see CONCLUSIONS) in various stages of diabetic nephropathy are noted. *Shaded area at top*, mean ± SD glomerular filtration rate (GFR) in healthy subjects. For technical reasons, fluctuation in urinary albumin excretion (UAE) is not depicted. Microalbuminuric range (*large shaded area at bottom*) is 20–200 μg/min, according to international consensus. It is not possible to predict malignant course from either parental history ① or from prediabetic course ②. Also, at clinical diagnosis of diabetes, complications cannot be predicted in IDDM patients ③. Practically all IDDM patients have normal UAE rates in first few years of diabetes (normal range, *vertical shaded bar at bottom*). Patients shown can be anticipated to be in poor metabolic control at least early in course as indicated by high level of GFR (>150 ml/min) ④ and increasing UAE rate ④. After ~7–14 yr of diabetes, microalbuminuria develops ⑤, and later, clinical nephropathy with proteinuria develops ⑥, typically after 18 yr of diabetes. Blood pressure rises, GFR starts to decline during incipient diabetic nephropathy with increasing microalbuminuria, and end-stage kidney failure is reached after ~25 yr of diabetes if intervention is not undertaken.

almost coincide in actual figures. The lower range predictive of diabetic nephropathy varies between 15 and 30 μg/min (4,5), although a very high level of 70 μg/min was reported in one study with 24-h collections and only a 6-yr follow-up (6). Based on these studies, a lower range of 20 μg/min has been proposed with an upper level of 200 μg/min, i.e., the dipstick-positive level (9). Compiling the two former studies, UAE rate of 20 μg/min clearly appears to be preferred (4,5). In the English study, only one patient showed a UAE rate between 20 and 31 μg/min (4), in contrast to eight patients in the Danish study (5).

Thus, if UAE is elevated but below the proteinuric range, the term microalbuminuria is used, regardless of the genesis of the elevated UAE rate. Very poor metabolic control, physical exercise, urinary tract infection, and considerable elevation of blood pressure due to essential hypertension in diabetes or cardiac decompensation are known to increase UAE (9). Of course, great care should be exercised to exclude such causes of microalbuminuria to avoid overdiagnosis, i.e., patients should be in good or fair metabolic control at examination. The level 20–200 μg/min is the microalbuminuric range, although a borderline range of 15–30 μg/min is preferred by some researchers (9,15).

Of course, it would be of benefit to rely on not only one abnormal parameter, e.g., microalbuminuria (which of course should be measured on several occasions), but also to consider a battery of tests that may be associated with development of subsequent overt kidney disease and other microvascular and macrovascular disease in diabetes (16). Are there alternatives in the prediction process, or are there parameters that may be used in conjunction with measurements for microalbuminuria? The following alternatives are discussed: parental history of hypertension; prediabetic level of blood pressure and other vascular abnormalities, e.g., hyperfiltration; the same abnormalities at clinical presentation of diabetes; glycemic control before the development of microalbuminuria; glomerular hyperfiltration in the course of diabetes; analysis of glomerular structure on kidney biopsy specimens; isolated blood pressure elevation; and serum creatinine or other indices of GFR.

POTENTIAL ALTERNATIVES TO MICROALBUMINURIA

Parental predisposition to hypertension and diabetic nephropathy. Genetic determinants of susceptibility for nephropathy have long been suspected (17), and it has been suggested that elevated parental blood pressure could be an independent marker of liability to hypertension conferring susceptibility to kidney disease if diabetes (or other kidney-damaging factors) were present. Potentially important data in favor of this hypothesis were presented by well-known researchers based on examination of parents of proteinuric diabetic patients compared with matched diabetic control subjects without kidney disease (18,19). It was reported that blood pressure was elevated in parents of proteinuric diabetic patients. Both groups also found significantly higher values for maximal velocity of Na^+-Li^+ countertransport in erythrocytes, an abnormality that is believed to be a marker of essential hypertension (19,20).

The same approach was taken in a Copenhagen study, in which the large number of required subjects (from a biostatistical point of view) was calculated before the start of the study (21). The results from this study are clear (21). There is no parental hypertension in diabetic patients with nephropathy in Copenhagen and no parental change in Na^+-Li^+ countertransport in erythrocytes as related to nephropathy. Therefore, it seems clear that parental disposition to hypertension (and associated abnormalities) may not be considered as the decisive factor, because it is not found in all populations.

Elevated blood pressure before diabetes onset. Knowler et al. (22) reported long-term follow-up data from studies of Pima Indians. In these special patients with non-insulin-dependent diabetes mellitus (NIDDM) found at a rather young age, it appeared that blood pressure before development of diabetes was an important factor for the development of later diabetic nephropathy. Abnormal prediabetic blood pressure occurred at a much higher rate in those with than without nephropathy (36 vs. 12%). Therefore, the researchers concluded that elevated blood pressure, at least in this population, is not entirely the result of kidney disease but may proceed or even contribute to development of nephropathy. Such studies are certainly difficult to conduct in IDDM patients, but it is quite clear that blood pressure in IDDM patients is not elevated 10 yr before development of nephropathy, as documented by Jensen et al. (23). Therefore, important differences seem to exist between IDDM and NIDDM, and early measurement of blood pressure (e.g., by population screening), even before the development of diabetes, does not seem to be important in the prediction of nephropathy, at least not in IDDM patients. In patients with NIDDM (outside the Pima population), elevated blood pressure is quite common, even at diagnosis of diabetes (24,25).

Can nephropathy be predicted at clinical diagnosis of diabetes? No evidence suggests that subsequent nephropathy can be predicted at clinical diagnosis of IDDM, when albumin excretion is normal after metabolic stabilization in practically all patients. There have been only a few studies, but so far, neither blood pressure elevation nor hyperfiltration can be used in the prediction process (12). On the other hand, note that diastolic blood pressure is low in IDDM patients with very long survival (26).

Glycemic control before development of incipient and overt nephropathy. The transition from normoalbuminuria to microalbuminuria is potentially a very important phase in the course of IDDM, and longitudinal studies revealed that patients developing microalbuminuria, before the microalbuminuric level is reached, already show elevation of UAE rate that is in the upper-normal range (27). Mathiesen et al. (27) also showed that if glycosylated hemoglobin (HbA_{1c}) is <7.5–8% (normal mean ± SD 5.5 ± 0.5%), the risk of developing microalbuminuria is very low in 4 yr of follow-up. On the other hand, there are many patients whose UAE rate remains totally normal, despite a long-standing and considerable elevation of HbA_{1c}. Although longer follow-up is needed, the study suggests that some patients seem to be protected against development of kidney abnormalities, but the crucial factor discriminating the two groups has not been identified. In the same study, blood pressure measured in the diabetes clinic was normal before the development of microalbuminuria but started to rise slowly a few years after microalbuminuria was established. This study suggests that the initial phase of microalbuminuria is much more closely

related to poor metabolic control than increased blood pressure. However, soon after the development of microalbuminuria, elevation of blood pressure was seen, and blood pressure increased a few percent per year (28). In patients with incipient nephropathy, progression is related not only to glycemic control but also to a rise in blood pressure (28). If HbA_{1c} is <7.5–8% and blood pressure is stable, the risk of progression is very low in 2 yr of follow-up (28).

Glomerular hyperfiltration. It was shown some years ago that patients with early glomerular hyperfiltration (and probably associated poor metabolic control) and diabetes duration of 3–6 yr had a great risk of subsequent nephropathy (11). In patients with early microalbuminuria, hyperfiltration was also a concomitant abnormality predictive of nephropathy, more so if associated with elevated blood pressure (5). In a multiple regression analysis, hyperfiltration appeared to be a powerful predictive parameter (29). The predictive value of hyperfiltration has not been found in all studies (30), which is not surprising considering the multifactorial nature of the disease.

However, a recent study showed that isolated glomerular hyperfiltration in nondiabetic subjects, such as found in individuals after uninephrectomy, is not associated with late nephropathy (31). On the contrary, these individuals maintained extremely high single-kidney GFRs and normal UAE rates despite decades of pronounced hyperfiltration. Obviously, hyperfiltration cannot be the sole factor in the pathogenesis of diabetic nephropathy. Instead, it is probably a modulating factor, possibly aggravating the course of kidney disease only if diabetes or other factors are present.

Recently, it was proposed that elevated erythrocyte Na^+-Li^+ countertransport may be used in the prediction of nephropathy very early in its course, before microalbuminuria develops. However, long-term follow-up studies are not available with this technique, but clearly this would be of major interest in future studies. Also, in most centers, measurement of GFR by any technique (but not creatinine clearance) may be more feasible than measurement of Na^+-Li^+ countertransport (32).

Glomerular structure. There are only a few studies dealing with glomerular structure in patients with microalbuminuria, but work is in progress in several centers. A Japanese study showed that light-microscopic changes correlate well with degree of UAE (33). Patients with microalbuminuria show changes intermediate between those in patients with overt proteinuria and those in normoalbuminuric patients with histological changes.

In a recent study with morphometric techniques, no structural differences (compared with normoalbuminuria) were reported in patients with microalbuminuria who did not have elevated blood pressure and had well-preserved creatinine clearance, used as crude index of GFR (14). A UAE level of 15–139 μg/min was used to designate microalbuminuria, and in most cases, UAE in these patients was low (15–28 μg/min) with the exception of two patients. According to earlier observations, patients with low-range microalbuminuria and only borderline increases in blood pressure showed a poor prognosis without intervention (5). With regard to these two articles, the following points are discussed (5,14).

Is there really no difference in kidney structure between the two groups in the American study, normoalbuminuric patients (group 1) and microalbuminuric patients without elevated blood pressure and/or low creatinine clearance (group 2) (14)? Subjects with microalbuminuria with these abnormalities (group 3) showed more advanced structural lesions. Indeed, there seems to be a tendency toward more severe structural lesions with increasing functional changes, at least considering basement membrane thickness. However, a few extremes may have disturbed statistical evaluation. With regard to mesangial volume expansion, there is complete overlap between the normoalbuminuric group and the group with microalbuminuria without elevation of blood pressure and no reduction in creatinine clearance. Only in those patients with microalbuminuria and some discrete elevated blood pressure or decreased creatinine clearance was there evidence of mesangial expansion. In this study, normal UAE says nothing about the absence of glomerulopathy. However, there is a huge variability in mesangial expansion, a factor of ~5, between the lowest and highest values in the normoalbuminuric group. With such a big variability, more precise measurements or methodologies may be needed. As discussed by the researchers, it is certainly also a possibility that expansion of the patient material would allow detection of differences between groups 1 and 2.

It should also be discussed whether the patients in these two studies actually are comparable. In fact, there seem to be considerable differences. First, patients in the Minneapolis group were recruited from a very special cohort of patients attending the University Clinic in Minneapolis for isolated pancreas transplantation. In the Danish study, patients were recruited from a general nonreferral diabetes clinic at a university hospital. There is also considerable variation with respect to duration of diabetes. Duration of diabetes was much longer in the Minneapolis study, and these patients may represent a special diabetic cohort with a better prognosis. If very slight or borderline microalbuminuria is first detected after 21 yr of diabetes, it will obviously not increase to the proteinuric level at the typical diabetes duration, i.e., 18 yr. Also, most patients in the Minneapolis group were women, who have a somewhat smaller risk of developing nephropathy. Also of importance is that patients with microalbuminuria in our experience do not show GFRs below the normal range (6), rather the contrary (5). Thus, the two patient cohorts are by no means comparable.

The researchers concluded that microalbuminuria is a powerful predictor of clinically apparent diabetic nephropathy when other features of nephropathy are already present. I would rather conclude, from our study, that microalbuminuria is associated with more advanced histological glomerulopathy compared with normoalbuminuria only when some elevation of blood pressure (or ongoing diuretic or antihypertensive treatment) and/or reduced creatinine clearance is seen in the microalbuminuric patient. Being cross-sectional, the study provides no information on prediction of future events, and the patients described are not comparable to those in previous studies that documented the predictive value of microalbuminuria.

In fact, the structural analysis used may not be sensitive enough to detect minute glomerular lesions in patients with early microalbuminuria, perhaps because insufficient material is available by kidney biopsy. It is also possible that no structural changes are present in early microalbuminuria,

but elevated UAE is still highly predictive of nephropathy, perhaps because subtle functional structural changes cannot be seen with crude electron microscopy. Therefore, electron-microscopic evaluation of biopsy specimens is currently of little help to clinicians. However, much more research in this area should be encouraged and is already ongoing.

In 1989, we did a 16-yr follow-up study on patients from a 1984 study (5). Figure 2 shows the long-term follow-up data on patients with microalbuminuria, some of whom had a very low UAE rate (15–40 μg/min). As can be seen, initial blood pressure increased with increasing severity of prognosis. In normoalbuminuric patients, initial mean ± SD systolic/diastolic blood pressure was 124 ± 7/80 ± 8 mmHg.

Isolated blood pressure elevation. Blood pressure is usually close to normal in patients with a normal UAE rate (34). However, a few patients may show elevated values comparable to a pattern seen in essential hypertensive patients. These are therefore likely to be patients with two diseases, i.e., diabetes mellitus with a normal UAE rate and essential hypertension. However, such diabetic individuals are few and play only a small role in the clinical follow-up of patients (34).

Serum creatinine or other indices of GFR. As mentioned, most IDDM patients with normal UAE rates show some degree of hyperfiltration. GFR starts to decline in the microalbuminuric range, probably around a UAE rate of 70 μg/min (5). Patients with overt proteinuria often still maintain GFR values in the normal range and thus normal serum creatinine (9). Therefore, serum creatinine is an insensitive parameter, and GFR measurement is recommended. On the other hand, longitudinal follow-up is important because, in this way, increases in serum creatinine can be detected (provided there is no change in extracellular volume, e.g., by diuretic treatment) also within the so-called normal reference range. There is general agreement that creatinine clearance is not valid for measurement of GFR.

CONCLUSIONS

It can be concluded that microalbuminuria is the most simple and sensitive parameter for early detection of risk of kidney disease in diabetic patients. The abnormality probably reflects early kidney lesions rather than being a susceptibility factor itself, but this has to be further clarified. Long-term follow-up, e.g., every 3 or 6 mo, is advisable. In this way, the rapid and the slow progressors can be identified (28). Of course, it is important to consider development of frank hypertension or a rise in blood pressure and to monitor glycosylated hemoglobin on multiple occasions. In fact, measurements of GFR by constant infusion or other exact techniques could also be important but may be difficult in some clinical settings, and many clinicians are often left with measurement of serum creatinine. In this case, it is important to follow increases within the normal range. Single-shot ra-

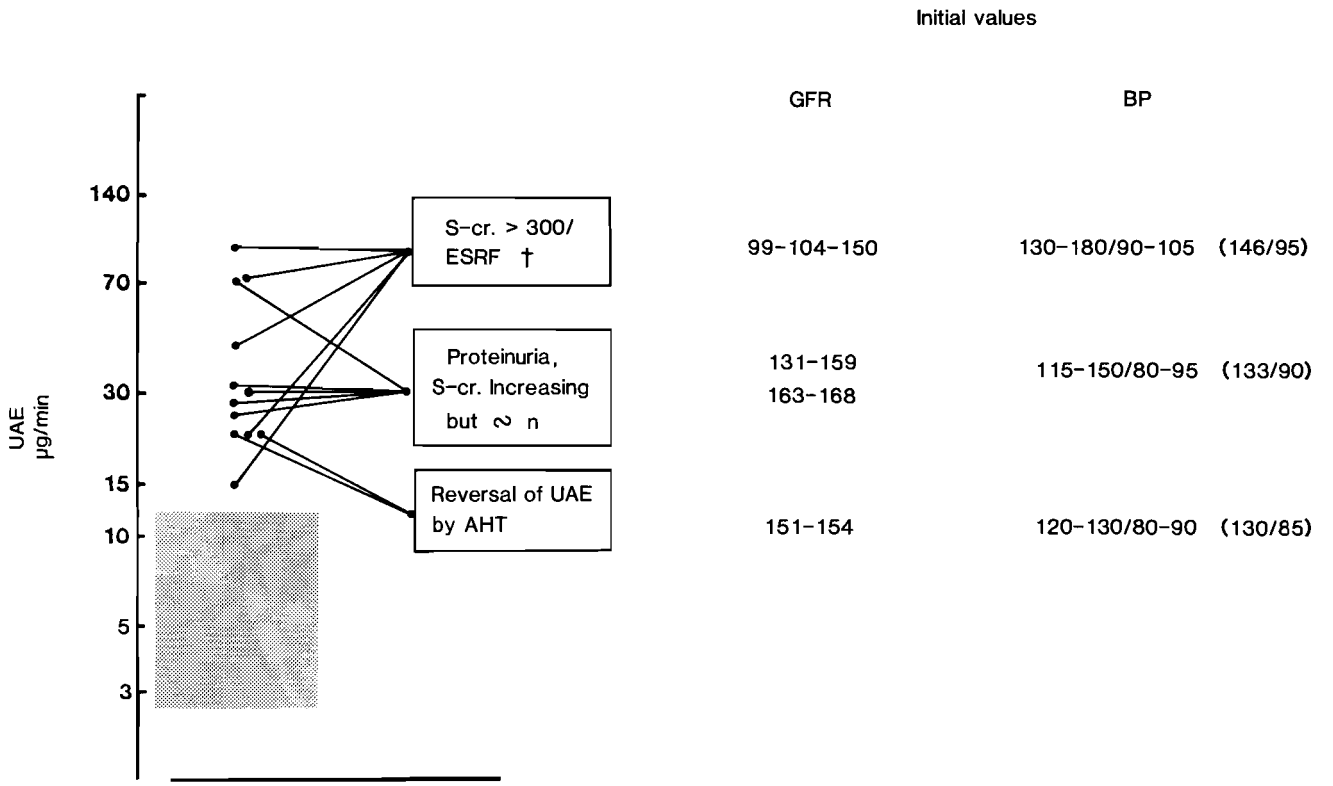

FIG. 2. Initial urinary albumin excretion (UAE) values (●) and subsequent progression in kidney disease found after 16 yr of follow-up (*lines*) of 12 patients (see ref. 5 for patient description). *Shaded area*, normal range of UAE in young healthy individuals. Five patients developed pronounced increase in serum creatinine (S-cr; μM), developed end-stage renal failure (ESRF), or died (†; *n* = 3). Five patients developed clinical proteinuria with S-cr still in normal (n) range but increasing (~n). Two patients showed decrease in UAE by antihypertensive treatment (AHT). Glomerular filtration rate (GFR; ml/min) was initially measured by constant-infusion technique with iothalamate as filtration marker. Initial blood pressure (BP; mmHg; mean values in parentheses) was highest in those with subsequent severe progression.

dioisotope plasma clearance is preferable for clinical use but is not used in all centers (35).

The curved lines in Fig. 1 depict the typical course of a patient developing diabetes at a young age. Note that there is considerable variability with respect to diabetes duration and end-stage kidney failure. The patient showed poor metabolic control as indicated by the high GFR (>150 ml/min) After duration of diabetes of ~10 yr, the patient developed microalbuminuria and later clinical nephropathy with proteinuria, typically occurring after 18 yr of diabetes. (The variability in UAE is for technical reasons not depicted in the figure.) Blood pressure rises and GFR starts to decline with increasing microalbuminuria, and end-stage kidney failure is reached after ~28 yr of diabetes if no intervention is undertaken.

Hyperfiltration is the earliest abnormality in kidney function in diabetes. So far, there is no clinical evidence that reduction of early hyperfiltration will ameliorate the course of kidney disease in diabetes. Note that hyperfiltration (Fig. 1*A*) may be reduced by nonglycemic intervention, e.g., a moderate reduction of protein intake (36), administration of aldose reductase inhibitors (37), or acute administration of a somatostatin analogue (38), inhibiting growth hormone and glucagon secretion. Also, optimized insulin treatment reduces hyperfiltration (39). Angiotensin converting enzyme inhibition may reduce high filtration fraction in these patients without an effect on GFR (40).

Otherwise, intervention is potentially possible as follows. Good glycemic control with HbA_{1c} levels <7.5–8% (Fig. 1*B*) is probably able to protect against development of microalbuminuria (27) and hyperfiltration (41). However, long-term follow-up studies are clearly needed (27). In the course of microalbuminuria or incipient diabetic nephropathy, UAE rate can be reduced by effective antihypertensive treatment (Fig. 1*C*) in patients with borderline elevation of blood pressure (42,43). Some evidence also suggests that GFR can be preserved by this treatment (42,43). Good metabolic control with HbA_{1c} <7.5–8% also stabilizes or reduces microalbuminuria with stable GFR (after initial slight reduction; 28). In overt diabetic nephropathy, proteinuria can be reduced, but more important, rate of decline of GFR can be considerably reduced by effective antihypertensive treatment, reducing blood pressure to a mean value of ~135/85 mm Hg (Fig. 1*D*; mean rate of decline of GFR decreased from 1.0 to ~0.3 ml · min^{-1} · mo^{-1}; 35,44). Reduction of protein intake is also able to reduce albuminuria and may inhibit progression of kidney disease in incipient and overt diabetic nephropathy (45).

With early and effective antihypertensive treatment, it can be anticipated from the described decrease in GFR (~0.3 ml · min^{-1} · mo^{-1}) that end-stage kidney failure may not be reached after 28 yr of diabetes but rather after 40–50 yr (46–48). Obviously, some patients may die before then from cardiovascular disease, and thus far, we have not observed patients during that many years of antihypertensive therapy. However, initial observations suggest that survival has improved greatly in proteinuric IDDM patients, probably due to early antihypertensive treatment (46).

STUDIES IN NIDDM AND OTHER DISEASES

This perspective does not discuss the nature and predictive value of UAE in NIDDM patients. In NIDDM patients, and also in the background population (49), microalbuminuria is clearly predictive of early mortality (12). It remains to be clarified whether microalbuminuria in these individuals is not so much a marker of kidney disease as a factor of susceptibility to early large-vessel disease, which mortality data suggest (49,50). A general review of the significance of microalbuminuria in nondiabetic subjects is given elsewhere (51). Also, I do not deal with development of experimental nephropathy in animals, and readers are referred to a review (52). Finally, it is clear that there is a steadily increasing interest within the field of diabetic nephropathy with respect to clarification of pathogenesis and early diagnosis and treatment (53–58).

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