Stable Glomerular Filtration Rate in Normotensive IDDM Patients With Stable Microalbuminuria

A 5-year prospective study

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OBJECTIVE — To investigate the long-term course of glomerular filtration rate (GFR) in IDDM patients with microalbuminuria in order to identify patients with stable or declining kidney function over a 5-year study.

RESEARCH DESIGN AND METHODS — Forty normotensive (129 ± 11/80 ± 8 mmHg) IDDM patients with persistent microalbuminuria (mean urinary albumin excretion [UAE] 84 mg/24 h [range 30–300]) were followed prospectively for 5 years of clinical examinations that included the measurement of GFR (^{51}Cr-labeled EDTA clearance) at least once a year. The mean GFR at baseline was 120 ± 18 ml · min^{-1} · 1.73 m^{-2}.

RESULTS — Using multiple regression analysis, the rate of decline in GFR was independently correlated to onset of diabetic nephropathy ($P < 0.001$) and systolic blood pressure (sBP) at baseline ($P < 0.05$). Increase in UAE was correlated to the mean HbA_{1c} during the observation period. Out of 40 patients, 14 progressed to diabetic nephropathy (UAE >300 mg/24 h). These patients had a significant reduction in GFR (mean −2.2 ± 3.8 ml · min^{-1} · year^{-1}; $P = 0.05$), while GFR remained stable in the remaining 26 patients with nonprogressive microalbuminuria (change in GFR 0.5 ± 2.1 ml · min^{-1} · year^{-1}; NS). The difference in the rate of decline of GFR was significant (mean 2.7 ml · min^{-1} · year^{-1}; $P < 0.05$).

CONCLUSIONS — Normotensive IDDM patients with nonprogressive microalbuminuria have a stable GFR. Progression of UAE to diabetic nephropathy heralds a progressive loss of kidney function. Efforts should be made to prevent the progression from microalbuminuria to diabetic nephropathy in every IDDM patient with microalbuminuria.

About 30–40% of patients with IDDM will develop diabetic nephropathy. The clinical syndrome is characterized by persistent proteinuria, rise in blood pressure, and decline in glomerular filtration rate (GFR), leading to end-stage renal failure. Elevated urinary albumin excretion (UAE) in the range 30–300 mg/24 h, so-called microalbuminuria, precedes the onset of nephropathy. Several intervention studies of patients with microalbuminuria have demonstrated that strict metabolic control (1,2) and ACE inhibition (3,4) can slow the progression from microalbuminuria to diabetic nephropathy. Whether this slowing of progression is associated with prolonged preservation of the GFR within the normal or supranormal range is unknown. The natural course of GFR in patients with microalbuminuria is only sparsely investigated (5).

The aim of our study is to evaluate the long-term course of GFR in IDDM patients with microalbuminuria in order to identify patients with stable or declining kidney function over a 5-year study.

RESEARCH DESIGN AND METHODS

— Forty normotensive IDDM patients with microalbuminuria (range 30–300 mg/24 h) were followed for 5 years as control patients in one of two clinical trials performed at the Steno Diabetes Center, Copenhagen, Denmark (1–3). All 23 control patients chosen from work by Mathiesen et al. (3) and 17 patients chosen from work by Feldt-Rasmussen et al. (1,2) were included, except one patient who developed anorexia nervosa during the study period. None of the patients received insulin pump treatment or ACE inhibitors. All patients gave informed consent, and the study was approved by the scientific ethics committee of Copenhagen County.

At baseline, all patients had at least two out of three consecutive urine samples with UAE 30–300 mg/24 h and an average of three or more blood pressure readings <160/95 mmHg (all except three patients had blood pressure <140/90). None of the patients were receiving diuretics or other antihypertensive treatment. The patients received two to four insulin injections daily; during the study, self-testing of glucose with adjustment of insulin dose was applied. The baseline clinical data of the patients are stated in Table 1.

Patients were seen prospectively in the outpatient clinic every 4 months. Two supine blood pressure recordings were performed with a mercury manometer, and two 24-h urine samples were collected for analysis of UAE. UAE was measured by radioimmunoassay in the patients from the captopril study (3) and measured with an enzyme-linked immunosorbent assay (ELISA) in the patients from the insulin pump study (1). Annually, GFR was determined with a single intravenous injection of 3.7 MBq ^{51}Cr-labeled EDTA by determining the radioactivity in blood samples taken at least 180–240 min after the injec-

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dBP, diastolic blood pressure; GFR, glomerular filtration rate; sBP, systolic blood pressure; UAE, urinary albumin excretion.

Table 1—*Clinical data at baseline and after 5-year follow-up of IDDM patients with persistent microalbuminuria later developing diabetic nephropathy and IDDM patients who remained microalbuminuric*

Status at follow-up	Nonprogressors Microalbuminuria	Progressors Nephropathy
n	26	14
Age (years)	30 (6)	30 (11)
Duration of diabetes (years)	17 (6)	17 (5)
UAE		
At baseline (mg/24 h)	61 (1.8)	151 (1.5)*
At follow-up (mg/24 h)	47 (2.4)	590 (1.9)
Blood pressure (mmHg)		
At baseline	127 (11)/80 (8)	124 (12)/80 (9)
At follow-up	127 (15)/76 (12)	134 (14)/86 (12)‡
HbA_{1c} (%)		
At baseline	8.4 (1.3)	9.2 (1.4)
Average during follow-up	8.3 (0.8)	9.2 (1.0)†
GFR		
At baseline (ml · min^{-1} · 1.73 m^{-2} per year)	122 (18)	115 (17)
Annual change (ml · min^{-1} · 1.73 m^{-2} per year)	0.46 (2.41)	−2.24 (3.8)†
Serum cholesterol		
At baseline (mmol/l)	4.82 (1.1)	5.33 (0.8)
Urinary sodium excretion		
Average during follow-up (mmol/24 h)	179 (44)	179 (67)
Urinary urea excretion		
Average during follow-up (mmol/24 h)	402 (102)	377 (155)

Data are means ± SD and UAE is geometric mean (tolerance factor). *$P < 0.001$, †$P < 0.01$, ‡$P < 0.05$ among the groups.

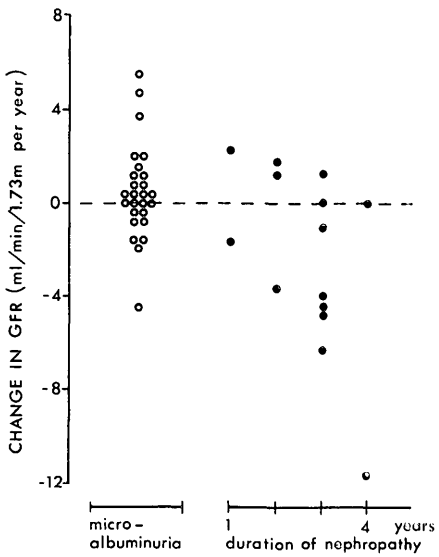

Figure 1—*Change in GFR in relation to onset of nephropathy in 40 IDDM patients. Patients with microalbuminuria during the whole 5-year observation period (○) and patients who developed nephropathy during the observation period (●).*

tion (1,3). Average GFR in normoalbuminuric IDDM patients are 122 ± 17 ml/min, and normal range for nondiabetic subjects is 70–130 ml/min. HbA_{1c} (normal range 4.1–6.1) was determined annually with conventional laboratory techniques (1,3). At least three of the 24-h urine samples collected during the observation period (0, 12, 24 months) were analyzed for sodium and urea concentrations by conventional techniques. Mean excretion values during the follow-up period were calculated for each patient. Total serum cholesterol was measured at baseline with conventional techniques. A detailed description of the methods was previously published (1,3).

Diabetic nephropathy was diagnosed clinically if persistent albuminuria developed in a patient with otherwise normal urine and no clinical or laboratory evidence of kidney or urinary tract disease other than diabetic glomerulosclerosis (3). At follow-up, persistent albuminuria was defined as a geometric mean UAE exceeding 300 mg/24 h, based on at least six consecutive urine collections during 6 months of observation. Antihypertensive treatment was initiated if blood pressure persistently exceeded 160/95 mmHg.

Progressors were defined as patients who developed diabetic nephropathy as defined above and nonprogressors defined as patients with UAE <300 mg/24 h during the follow-up period.

Results are expressed as means ± SD. Values for UAE were logarithmically transformed before analysis because of their positively skewed distribution and the geometric means with ranges given. The best polynomial fit for the time course of GFR was sought with analysis of variance. The best-fit was linear, and the slope of a fitted line to the data was measured by the regression coefficient estimated by least-squares. Correlations were calculated with stepwise multiple linear regression analysis, and *t* tests were used for comparisons of the change in GFR within and between the two groups (three analyses). In addition, *t* tests were used in Table 1 to help the reader (no conclusions from these *t* tests were drawn), and we have decided not to perform Bonferroni's adjustments for multiple comparisons. $P < 0.05$ was considered significant (two-tailed).

RESULTS — The rate of decline in GFR was independently correlated to progression of microalbuminuria to UAE >300 mg/24 h ($P < 0.001$) and systolic blood pressure (sBP) at baseline ($P < 0.05$), but it was not correlated to patient age and duration of diabetes or baseline values of UAE, diastolic blood pressure (dBP), GFR, HbA_{1c}, and intake of protein or salt during the observation period. The increase in UAE rate was independently correlated with mean HbA_{1c} during the observation period, but it was not correlated with baseline values of UAE, sBP, plasma cholesterol, GFR, or patient age and duration of diabetes, or correlated with the average of protein or salt during the study.

Out of 40 patients, 14 progressed to diabetic nephropathy during the 5-year observation period, and 26 patients had nonprogressive microalbuminuria defined as UAE <300 mg/24 h during the 5-year follow-up period. The baseline and follow-up clinical characteristics of the progressors and nonprogressors are given in Table 1. The patients who progressed to diabetic nephropathy had a significant reduction in GFR (−2.2 ± 3.8 ml · min^{-1} · $year^{-1}$; $P = 0.05$), while GFR remained stable in the 26 microalbuminuric patients (change in GFR 0.5 ± 2.1 ml · min^{-1} · $year^{-1}$; NS). The difference in the decline rate of GFR was significant (mean 2.7 ml/min; $P < 0.01$). The annual change in GFR was calculated for each patient and depicted in relation to onset of nephropathy (Fig. 1). Within a few

years after onset of nephropathy, a clinically significant decline in GFR was demonstrated. The nine patients who developed diabetic nephropathy during the initial 2 years of the 5-year observation period had a change in GFR of -3.5 ml · min^{-1} · year^{-1} (range -11 to 1). In patients who developed diabetic nephropathy, an increase in blood pressure was seen (Table 1). Seven patients initiated antihypertensive treatment, mainly with diuretics; five of these patients were found among the patients who progressed to nephropathy.

CONCLUSIONS — Our 5-year prospective study has demonstrated that progression from microalbuminuria to diabetic nephropathy is the best predictor of future loss of kidney function. IDDM patients with nonprogressing microalbuminuria have a stable GFR within the normal or supranormal range. Patients progressing to diabetic nephropathy start to lose kidney functions shortly after albumin excretion >300 mg/24 h.

Recently, it has been suggested that proteinuria is not simply a marker of the extent of glomerular damage, but proteinuria, per se, may contribute to glomerular damage (6). In a study of the natural history of diabetic nephropathy in IDDM patients, a positive correlation between the magnitude of albuminuria and the decline rate in GFR has been demonstrated (7). Reduction of albuminuria shortly after the start of long-term antihypertensive treatment predicts an attenuated fall in GFR in IDDM patients with diabetic nephropathy (8). In the present study, higher levels of UAE at baseline were associated with a progression to diabetic nephropathy. Only 1 out of 21 patients with basal values <100 mg/24 h progressed, while 13 out of 19 patients with basal values >100 mg/24 h progressed to diabetic nephropathy (Fig. 2). However, the figure demonstrates a linear relationship between baseline and follow-up values of logarithm transformed UAE, and no cutoff level at 100 mg/24 h could be demonstrated. Albumin excretion within the upper range of microalbuminuria is a poor prognostic sign.

Progression of microalbuminuria to UAE >300 mg/24 h and sBP at baseline was independently related to future decline in GFR. The mean decline in GFR was 3.5 ml · min^{-1} · year^{-1} in the patients who progressed to diabetic nephropathy during the initial 2 years of observation. Among the six patients with basal values of albumin >100 mg/24 h without progressing to nephropathy, three patients had a small increase, and another three had a small decline in GFR (median change -0.8 ml · min^{-1} · year^{-1}). This indicates that albumin excretion within the upper range of microalbuminuria does not lead to decline in GFR, unless the disease progresses to diabetic nephropathy.

In the discussion of whether ACE inhibition should be given to normotensive patients with microalbuminuria, it is wise to focus on the fact that the endpoints in the clinical trials dealing with ACE inhibition in these patients (3,4) has been the "development of UAE >300 mg/24 h." Using a hard endpoint, defined as decline in renal function leading to renal insufficiency, would be more clinically relevant. This paper suggests that UAE >300 mg/24 h can be regarded as a surrogate endpoint for the more clinically significant endpoint "onset of decline in GFR leading to renal insufficiency."

Poor metabolic control was independently associated with progression to diabetic nephropathy. One out of seven (14%) patients with mean HbA_{1c} <7.5% (versus six out of eight [75%] patients with mean HbA_{1c} >9.5%) during the 5-year observation period progressed to diabetic nephropathy. Our own group (9) and Krolewski et al. (10) have proposed a safe level of metabolic control (HbA_{1c} <7.5–8.1%) protecting against renal complications in IDDM patients. Only a tendency toward HbA_{1c} <7.5 as safe, regarding progression to diabetic nephropathy, was seen in this study.

The sBP at baseline was independently related to future decline in GFR. Only three patients had sBP >140 mmHg at baseline. This emphasizes the importance to focus on even slightly elevated systolic blood pressure in patients with microalbuminuria.

Hyperlipidemia has been shown to play a role in initiation and progression of glomerular injury in animal models. Bjorck et al. (11) have found a correlation between serum total cholesterol and rate of decline in GFR in IDDM patients with diabetic nephropathy. In our study, we found a tendency toward a higher level of serum cholesterol in patients with microalbuminuria progressing to diabetic nephropathy compared with patients with stable microalbuminuria.

In conclusion, normotensive IDDM patients with nonprogressive microalbuminuria have a stable GFR. Progression from microalbumnuria to diabetic nephropathy (values >300 mg/24 h) is a bad sign, indicative of loss of kidney function. Efforts should be made to prevent the progression from microalbuminuria to diabetic nephropathy in every single patient. Earlier studies have suggested that this can be obtained with strict metabolic control and/or ACE inhibition (1–4).

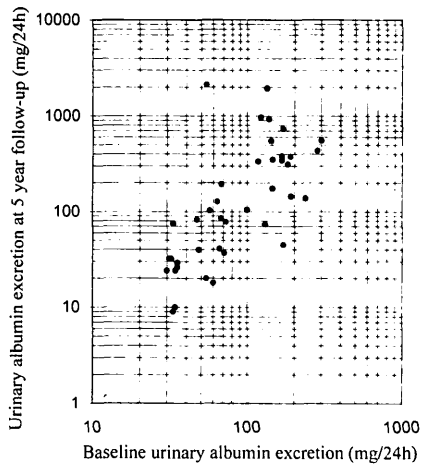

Figure 2—*UAE at 5-year follow-up in relation to UAE excretion at baseline in 40 IDDM patients with microalbuminuria at baseline.*

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