Glomerular Hyperfiltration in the Prediction of Nephropathy in IDDM

A 10-Year Follow-Up Study

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Glomerular hyperfiltration has been proposed as an independent risk factor for the development of diabetic nephropathy in patients with IDDM. In a case-controlled prospective study of IDDM patients without albuminuria, serial glomerular filtration rate (GFR) measurements were performed over an observation period of 10 years. A group of 25 IDDM patients (20 men, 5 women; initial age, 29 [17–49] years) with glomerular hyperfiltration (GFR >135 ml · min^{-1}· 1.73 m^{-2}) were matched for age, sex, and duration of diabetes with 25 IDDM patients (20 men, 5 women; initial age, 30 [17–48] years) with glomerular normofiltration (GFR 83–135 ml · min^{-1} · 1.73 m^{-2}). GFR, urinary albumin excretion rate (AER), blood pressure, and glycated hemoglobin were measured at baseline and at 5, 8, and 10 years. The two groups had similar entry levels of blood pressure, AER, and glycated hemoglobin. Metabolic control was similar in the two groups during follow-up. The final GFR remained higher in the group with hyperfiltration (122 [109–135] vs. 103 [95–111] ml · min^{-1} · 1.73 m^{-2}; P = 0.02) despite a nonsignificantly faster rate of fall of GFR compared with that of the control group (2.54 [1.20–3.88] vs. 1.50 [1.01–1.99] ml · min^{-1} · year^{-1}; P = 0.14). A similar number of patients in each group progressed to either microalbuminuria or macroalbuminuria (n = 4 vs. n = 3) or developed hypertension (blood pressure, >160/95 mmHg; n = 3 vs. n = 4). End-of-study AER was, however, higher in the group with hyperfiltration (geometric mean [95% CI]: 18.9 [11.3–31.6] vs. 11.0 [8.1–15.0]; P = 0.05), and baseline glomerular hyperfiltration was an independent determinant of end-of-study blood pressure (P = 0.04). The strongest predictors of end-of-study AER and blood pressure were their baseline values (P < 0.04 and P < 0.01, respectively). In conclusion, levels of AER and blood pressure are the main risk factors for renal outcome, while glomerular hyperfiltration appears to play a lesser role. *Diabetes* 45:1729–1733, 1996

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AER, albumin excretion rate; GFR, glomerular filtration rate.

Approximately 35% of patients with IDDM develop clinical nephropathy. Microalbuminuria is a predictor of clinical albuminuria, but significant glomerular pathology already exists in these patients compared with those with normal urinary albumin excretion rate (AER) (1). An earlier risk marker of progressive diabetic renal disease would enable timely intervention in an attempt to prevent structural damage. Disturbance of glomerular hemodynamics is an early event in IDDM, and glomerular hyperfiltration has been advocated as a determinant of progression to clinical nephropathy. In humans, however, the evidence remains controversial and partly based on retrospective studies (2–6). Animal data suggest that increased intraglomerular pressure, rather than glomerular hyperfiltration per se, is the injurious hemodynamic event that leads to segmental glomerulosclerosis (7–10). Between 1981 and 1983, we initiated a prospective case-control study to evaluate the renal outcome of a group of IDDM patients with glomerular hyperfiltration. The 5-year follow-up results were previously published (5), and we report here the findings of 10 years of follow-up.

RESEARCH DESIGN AND METHODS

Subjects. Between 1981 and 1983, all IDDM patients with duration of diabetes <20 years, no arterial hypertension (blood pressure ≤160/95 mmHg) or albuminuria (urinary AER >200 µg/min and/or urine dipstix positive), aged 16 to 60 years, and receiving no medication other than insulin who were attending the diabetes clinics of Guy's and Mayday hospitals were invited to take part in a screening program of glomerular filtration rate (GFR). A total of 108 patients accepted to participate and were screened. Twenty-six patients who were identified as having GFR above the upper limit of the normal range for our laboratory (83–135 ml · min^{-1} · 1.73 m^{-2}) (11) were individually matched for sex, age (± 1 year), and duration of diabetes (± 1 year) with patients randomly selected from the same cohort with normal GFR. All but five patients had an initial urinary AER <30 µg/min. Three patients with hyperfiltration had AERs of 80.6, 158, and 196 µg/min, and two with normal filtration had AERs of 52.1 and 36.2 µg/min. If blood pressure values >140/90 mmHg were considered abnormal, two patients with hyperfiltration and four with normal filtration would be classified as being hypertensive on entry into the study. Serial measurements of GFR, AER, blood pressure, and metabolic control were made at entry and after approximately 5, 8, and 10 years. The study was approved by the Guy's Hospital and Mayday Hospital Ethics Committees.

Methods. Patients arrived at a metabolic ward at 8:30 A.M. after having fasted from 10:00 P.M. the night before. They were asked to bring one 24-h urine collection for estimation of AER by a radioimmunoassay (12). They were weighed in light outdoor clothes without shoes, and height was recorded. Sitting blood pressure was measured twice from the right arm

(Korotkov phases I and V) to the nearest 2 mmHg after 10 min rest in the supine position, using a standard mercury sphygmomanometer. Over the 10-year follow-up period, three observers were responsible for data collection and worked to a standard methodology. An intravenous cannula was inserted and blood samples were withdrawn for measurement of glycated hemoglobin (HbA_1 by electroendosmosis, CIBA Corning Diagnostics, Halstead, Essex, U.K.; normal range in our laboratory 5.5–7.5%), plasma urea (by a Hitachi multichannel autoanalyzer, BCL, Lewes, U.K.), and creatinine by a Jaffe reaction rate method. Patients then had their normal injection of morning insulin 15 min before breakfast. One hour later, GFR was assessed by the single injection technique for ^{51}Cr-EDTA with 11-point sampling and multiple exponential analysis of the decay curve as described previously (13). GFR values were corrected to 1.73 m^2 using the baseline body surface area. All measurements taken over the 10-year observation period were made at a central laboratory in the Unit for Metabolic Medicine of Guy's Hospital using the same methodology. The endpoints for the study were the development of microalbuminuria (AER 30–200 μg/min) or macroalbuminuria (AER >200 μg/min) and the development of arterial hypertension, defined as blood pressure >160/95 mmHg or the requirement of antihypertensive medication. These outcomes had to be confirmed on two successive measurements. The rate of decline of GFR and final GFR were also analyzed.

Statistical analysis. Student's paired *t* test and Wilcoxon's rank-sum test were used for comparison of parametric and nonparametric values, respectively. The rate of change in GFR was calculated as the slope of the regression line of GFR versus time for each individual patient, as described previously (5). Univariate linear regression analysis was used for testing correlations between individual variables. Multivariate analysis evaluated the interactions of baseline and time-dependent variables on the outcome. Initial GFR and the category glomerular hyperfiltration, AER, mean blood pressure, and either initial or mean glycated hemoglobin over the study period were entered as independent variables. Final mean blood pressure and the category arterial hypertension, AER and the categories microalbuminuria and macroalbuminuria, and final GFR as well as the rate of decline of GFR were treated as dependent variables. Each group of patients was analyzed separately. AER values were log-transformed before analysis. A *P* value of <0.05 (two-tailed) was considered statistically significant. Results are reported as means or geometric means (95% CIs), unless otherwise stated.

RESULTS

Twenty-five of the matched pairs were available for follow-up, the patient with hyperfiltration of the remaining pair having emigrated soon after entry into the study. The baseline demographic and clinical data of the two groups are shown in Table 1. By the end of 1992, the groups with glomerular hyperfiltration and normal filtration had completed a follow-up period of 115 (109–121) and 114 (109–118) months, respectively, with a minimum of three GFR assessments for every patient. Seventy-five percent of patients had four GFR determinations. The reasons for failure to complete the fourth GFR measurement in the remaining 25% of patients were similar in both groups and included death, pregnancy, and nonattendance.

Albumin excretion rate. At the end of the study, mean AER was 18.9 (95% CI, 11.3–31.6) vs. 11.0 (8.1–15.0) (P = 0.05) for the groups with hyperfiltration and normal glomerular filtration, respectively. In the group with hyperfiltration, two of the three patients with microalbuminuria at baseline progressed to macroalbuminuria, while the third patient remained in the microalbuminuria range throughout the study. Among the 22 patients with normal AER at entry, one developed microalbuminuria and one macroalbuminuria. In the group with normal filtration, one of the two patients with microalbuminuria at entry developed macroalbuminuria, while the other remained in the microalbuminuria range. Of the remaining 23 patients with initial normoalbuminuria, one progressed to microalbuminuria and one to macroalbuminuria during the follow-up period. The differences in categorical changes between the two groups were not statistically significant.

TABLE 1
Baseline characteristics of 25 IDDM patients with glomerular hyperfiltration and 25 IDDM patients with normal GFR

	Hyperfiltration	Normal filtration
n (M/F)	25 (20/5)	25 (20/5)
Age (years)	29 (17–49)	30 (17–48)
Duration of diabetes (years)	8 (1–19)	8 (2–18)
GFR (ml · min^{-1} · 1.73 m^{-2})	152 (146–158)	117 (112–122)
AER (μg/min)*	9.7 (8.7–10.7)	7.1 (6.6–7.7)
HbA_1 (%)	9.6 (8.8–10.4)	10.3 (9.5–11.2)
sBP (mmHg)	116 (112–120)	119 (114–124)
dBP (mmHg)	75 (71–79)	79 (75–83)

Data are means or *geometric means (95% CI), except for age and duration of diabetes, where the values in brackets indicate range. sBP, systolic blood pressure; dBP, diastolic blood pressure.

Blood pressure. The end-of-study blood pressure was similar between the group with hyperfiltration and that with normal filtration, mean (95% CI): 123 (118–128)/78 (75–83) vs. 122 (116–128)/76 (72–80) mmHg, respectively, P = 0.53. Three patients from the group with hyperfiltration and four from that with normal filtration attained a blood pressure >160/95 mmHg or were treated with antihypertensive medications. These included the sole patient with hyperfiltration and two of the three patients with normal filtration who exhibited reduced GFR at the end of the study. Of the five patients with microalbuminuria at entry, one from each group developed hypertension.

GFR. The end-of-study mean (95% CI) GFR remained higher in the group with hyperfiltration compared with that in the group with normal filtration (122 [109-135] vs. 103 [95–111] ml · min^{-1} · 1.73 m^{-2}; P = 0.02) despite a moderately faster rate of decline in the former (2.54 [1.20–3.88] vs. 1.50 [1.01–1.99] ml · min^{-1} · $year^{-1}$; P = 0.14). In both groups, the final GFR was significantly lower than the baseline value (P < 0.01) (Fig. 1). In the group with hyperfiltration, GFR remained in the supranormal range (>135 ml · min^{-1} · 1.73 m^{-2}) in 4 patients, fell to normal in 20 patients, and fell to below normal in 1 patient (23 ml · min^{-1} · 1.73 m^{-2}) who was blind from diabetic retinopathy and had normoalbuminuria at baseline. He later received renal replacement therapy. Three patients in the group with normal filtration developed subnormal GFR (59, 74, and 71 ml · min^{-1} · 1.73 m^{-2}), two of whom had progressed to macroalbuminuria during the course of the study. There was no relationship between the rate of fall of GFR and disease duration in either group. Plasma urea and creatinine were normal at entry and end of study for all patients, with the exception of the patient with hyperfiltration whose GFR had fallen to 23 ml · min^{-1} · 1.73 m^{-2} (end of study creatinine 578 μmol/l; urea 17.5 mmol/l).

Metabolic control. Glycated hemoglobin levels were similar at baseline (Table 1) and fell to 8.8 (8.1–9.4%) in the group with hyperfiltration and 8.5 (7.9–9.1%) in the group with normal glomerular filtration by 5 years of follow-up (P < 0.05 and < 0.0001, respectively). They

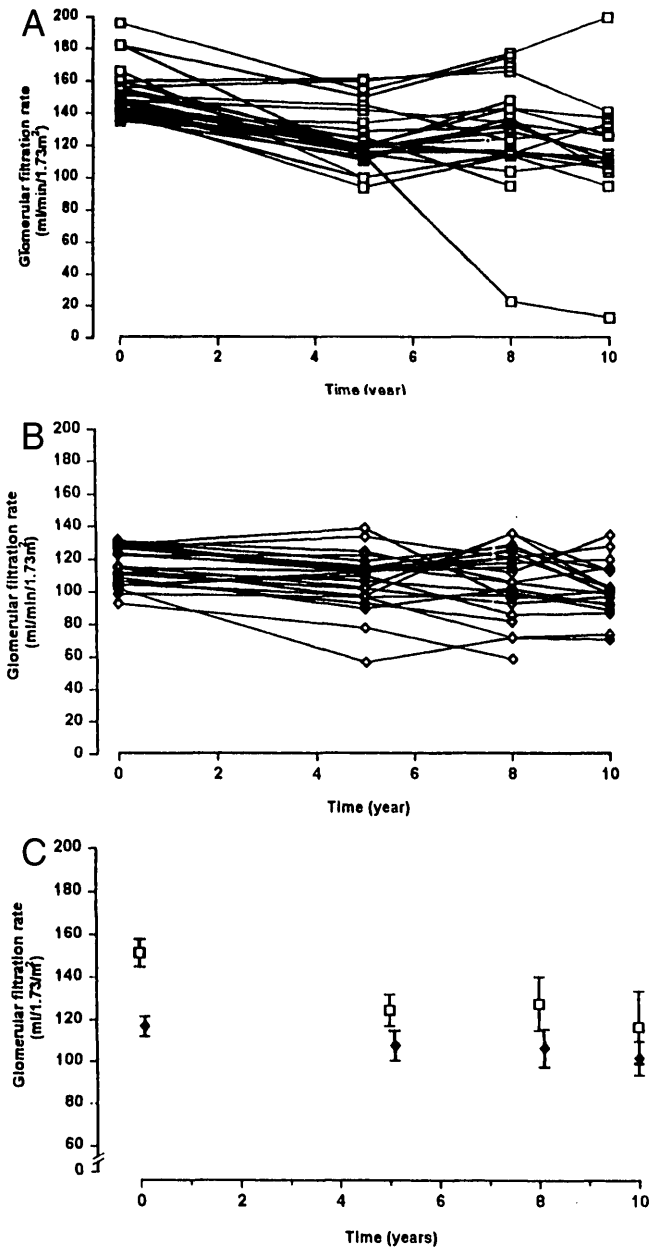

FIG. 1. GFRs (in milliliters per minute per 1.73 m^2) over time (years) in 25 IDDM patients with initial glomerular hyperfiltration (□; *A*) and in 25 IDDM patients with initial normal glomerular filtration (◇; *B*). Six patients in each group had their last assessment at the 8-year time point.

remained stable thereafter, and the average HbA_1 values from all assessment time points in each patient were similar for both groups: mean (95% CI) hyperfiltration versus normal filtration, 9.2 (8.7–9.8%) vs. 9.2 (8.7–9.3%). In this context, there was no relationship between the rate of decline of renal function and HbA_1 in either group.

Univariate correlations. In IDDM patients with glomerular hyperfiltration, baseline GFR correlated significantly with final blood pressure ($r = 0.46$, $P = 0.02$), but with no other outcome variables. Initial AER and initial blood pressure were significantly related to final AER ($r = 0.44$, $P = 0.03$) and final blood pressure ($r = 0.56$, $P = 0.01$), respectively. Neither initial nor average HbA_1 had significant influence on any of the outcome variables.

In IDDM patients with normal glomerular filtration, baseline GFR correlated significantly with both end-of-study GFR ($r = 0.80$, $P < 0.001$) and the rate of decline of GFR ($r = 0.49$, $P = 0.01$). As for the group with hyperfiltration, there was a significant correlation between initial AER and blood pressure with end-of-study AER ($r = 0.42$, $P = 0.04$) and blood pressure ($r = 0.46$, $P = 0.02$), respectively. Neither initial nor average HbA_1 showed any significant correlation with any of the outcome variables.

Multiple regression analysis. Baseline glomerular hyperfiltration was not correlated with end-of-study AER or the categorical outcomes of microalbuminuria or macroalbuminuria, but was a significant predictor of end-of-study blood pressure ($P = 0.04$) when baseline (rather than average) HbA_1 was entered in the model. End-of-study GFR and the rate of decline of GFR were not predicted by baseline glomerular hyperfiltration. End-of-study AER and blood pressure were independently predicted by their respective baseline AER ($P < 0.04$) and blood pressure ($P < 0.01$).

DISCUSSION

This study was designed to examine prospectively the role of glomerular hyperfiltration as an independent risk factor for the development of albuminuria and elevation of blood pressure in IDDM patients. Approximately 25% of patients exhibit a supranormal GFR even after their diabetes is under average control. Some authors have argued that such an increase in filtration function is deleterious to the kidney and therefore represents a risk factor for later development of overt nephropathy. We have failed to demonstrate any significant difference in renal morbidity in this group of diabetic patients with glomerular hyperfiltration compared with their counterparts with normal glomerular filtration over an observation period of 10 years. Overt clinical nephropathy, defined as an elevated urinary albumin excretion and/or arterial hypertension, occurred at similar frequencies in the groups with and without glomerular hyperfiltration (16 vs. 20%, respectively). Only one patient with hyperfiltration progressed to renal failure. By contrast, three patients in the group with baseline normal filtration attained a subnormal GFR, though none developed uremia.

Glomerular hyperfiltration is well documented in newly diagnosed IDDM patients and falls gradually after stabilization of blood glucose control (14). Adult Munich-Wistar rats made diabetic by streptozotocin and maintained at a moderate level of hyperglycemia by low-dose insulin injection have both whole-kidney and single-nephron GFRs ~40% above normal. This increase in glomerular filtration is accounted for, in part, by a rise in intraglomerular pressure, which is thought to be the major determinant of renal injury in this model (7–10). Correction of intraglomerular hypertension with persisting hyperfiltration prevents the subsequent focal segmental glomerulosclerosis in the diabetic animal (15). In humans, glomerular mesangial expansion is the lesion that correlates more closely with the clinical development of diabetic kidney disease (16), and yet glomerular hyperfiltration correlates poorly with either mesangial expansion or the loss of capillary filtration surface within a glomerulus (17).

Two separate longitudinal studies reported an association between glomerular hyperfiltration and the development of clinical nephropathy (2,3). The first study consisted of IDDM patients with microalbuminuria, and baseline urinary albumin excretion rate was not available for all patients in the second study. Microalbuminuria is an independent predictor of clinical albuminuria and may have acted as an important confounder. Furthermore, the role of long-term metabolic control was not assessed. In the present study, if a urinary AER of 20 μg/min were used as the cutoff point for the definition of microalbuminuria, as was the case in previous studies (2,3), there would be 19 and 21 patients from the groups with hyperfiltration and normal filtration, respectively, who had normoalbuminuria at baseline. However, the outcome would not change in that five of the patients with hyperfiltration and six of those with normal filtration developed raised AER during the course of the follow-up.

Lervang et al. (4) also failed to find an association between the development of increased urinary AER and early glomerular hyperfiltration in a 18-year retrospective follow-up study of 29 IDDM patients. A larger-scale prospective cohort study examined the predictive value of glomerular hyperfiltration in 64 of 75 Swedish adolescent diabetic patients followed for 8 years (6). Hyperfiltration was defined as a GFR >125 ml · min^{-1} · 1.73 m^{-2}. The authors found initial glomerular hyperfiltration to be a significant predictor of progression to micro- or macroalbuminuria, with a positive predictive value of ~50%. The patients in the study were young (mean age 17 years), with an average disease duration of 12 years and poor metabolic control (mean HbA_{1c} 12%) at entry. There are aspects of this study that suggest that this was an unusual group of patients. A very large proportion (45 of 64, i.e., 70%) of the study population had a baseline GFR above their quoted upper limit of normal of 125 ml · min^{-1} · 1.73 m^{-2}. A high rate of progression from normoalbuminuria to micro- or macroalbuminuria was reported, with a cumulative frequency of ~30% over 8 years. This corresponds to an annual rate of 4%, a value considerably higher than published annual incidence rates, which range between 1 and 2% (20,21).

In the present study, if only the patients with baseline normoalbuminuria (AER <30 μg/min) are considered, a cumulative frequency for progression to microalbuminuria and persistent clinical albuminuria of 14% over 10 years was observed, a value consistent with recent observational studies (19,20). In the Swedish study, there was no association between elevated urinary AER and increases in blood pressure, now a well-described uniform finding by other authors (20,21). In our study, the patients were older, had a shorter duration of diabetes, and were in better and more stable metabolic control, and it is possible that these differences could, in part, account for the different findings.

Although we found no differences between the groups in categorical changes of AER and blood pressure, the group with hyperfiltration had a mean final AER higher than that of the group with normal glomerular filtration, and glomerular hyperfiltration was a weak but independent significant predictor of end-of-study blood pressure. The clinical significance of these observations needs to be confirmed by longer follow-ups. The group of patients with initial hyperfiltration exhibited a moderately faster rate of fall of GFR, but all except one patient attained a normal or supranormal final GFR. The strongest predictors of final urinary albumin excretion and final blood pressure were their initial values. That the actual level of AER, within the normal range, is predictive of the progression to microalbuminuria has been uniformly confirmed in all recently reported longitudinal studies (19–21). Therefore, it appears that the interaction between urinary AER and blood pressure is paramount in determining renal outcome, while glomerular hyperfiltration, per se, seems to play a lesser role.

Although the present study is the second largest and the longest prospective investigation of the prognostic value of glomerular hyperfiltration in IDDM patients, it could be argued that a higher number of events (and thus a larger sample size) would be required to detect a smaller effect of raised GFR on the development of micro- or macroalbuminuria and hypertension. Despite this limitation, the present data demonstrate that, given comparable blood glucose control, other factors, namely AER and blood pressure, are more important predictors of renal outcome than is glomerular hyperfiltration.

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