Five-Year Prospective Study of Glomerular Filtration Rate and Albumin Excretion Rate in Normofiltering and Hyperfiltering Normoalbuminuric NIDDM Patients

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OBJECTIVE — To evaluate the evolution of glomerular filtration rate (GFR) and albumin excretion rate (AER) of normofiltering (NF) and hyperfiltering (HF) normoalbuminuric NIDDM patients.

RESEARCH DESIGN AND METHODS — A longitudinal study of 32 normoalbuminuric (AER <20 μg/min) NIDDM patients and 20 age-, sex-, and BMI-matched normal individuals was done. Subjects had their GFR (^{51}Cr-labeled EDTA single-injection method) measured at entry and after 40 and 60 months. At entry, 13 NIDDM patients had GFR values above the upper limit of the normal range in our laboratory (>137 ml · min^{-1} · 1.73 m^{-2}) and were considered as HF. In NIDDM patients, the 24-h AER (radioimmunoassay), HbA_{1c}, urinary urea, and mean arterial blood pressure (MBP) were analyzed at entry and after 40 and 60 months.

RESULTS — There was a significant decline of GFR in NIDDM patients and normal subjects at 60 months. The decline was significantly greater in HF patients (−0.61 ml · min^{-1} · month^{-1}; P = 0.001) than in NF (−0, 18) and control subjects (−0, 14); the rate of change in NF and control subjects was the same (P > 0.05). In stepwise multiple regression analysis, with GFR decline as the dependent variable and GFR and AER at baseline, age and change in MBP, change in urinary urea, change in HbA_{1c}, and change in therapy as independent variables, only baseline GFR (R^2 = 0.19, P = 0.002) and age (R^2 = 0.31, P = 0.048) were significantly related to the outcome. At 60 months, AER raised >20 μg/min in three HF and in four NF patients. In logistic regression analysis, only higher initial AER (although still in the normal range; P = 0.037) and an increase in urinary urea (P = 0.021) were significantly related to the later development of microalbuminuria.

CONCLUSIONS — The GFR of normoalbuminuric NIDDM patients declines significantly over 60 months. This decline is associated to baseline GFR and age. HF NIDDM patients show a faster decline in GFR than NF patients, whose GFR falls at a rate that is compatible with the age-related change observed in normal control subjects. The development of microalbuminuria is related to higher baseline AER and to increases in urinary urea and is similar in NF (4 of 19) and HF (3 of 13) NIDDM patients (P > 0.05).

Glomerular hyperfiltration is a well-described finding in both IDDM (1) and NIDDM patients (2,3). In IDDM, there is a suggestion that a raised glomerular filtration rate (GFR) is an independent predictor of diabetic nephropathy (4). Other studies in IDDM are still in course (5–7). There are few data concerning the evolution of GFR and its determinants in NIDDM patients without nephropathy. Therefore, the aim of the present study was to describe the course of GFR and the albumin excretion rate (AER) of normoalbuminuric NIDDM patients over a mean period of 60 months.

RESEARCH DESIGN AND METHODS

— Between January 1988 and December 1989, 64 NIDDM patients (World Health Organization criteria) attending the outpatient clinic of the university hospital were identified as normoalbuminuric (AER <20 μg/min). They were screened out of a population of consecutive attenders during a screening program of renal abnormalities in NIDDM patients. In 15 of these 64 patients, the GFR values were above the upper normal limit for this age range in our laboratory (137 ml · min^{-1} · 1.73 m^{-2}), and they were classified as hyperfiltering (HF) (3); 13 of these patients were available for follow-up. Of the remaining 49 patients with GFRs within the normal limits (normofiltering [NF]), 19 were randomly selected to be followed. In our original cross-sectional study, 44 subjects served as a control group (3); 20 of these were randomly selected to have their GFR measured at entry and after 60 months. All subjects gave informed consent.

At entry and at 40 and 60 months, patients were submitted to a complete clinical examination. Height and weight (light clothes without shoes) were measured, and BMI was calculated. Blood pressure was measured twice in the sitting position after a 10-min rest with a standard 12.5-cm cuff mercury sphygmomanometer (phases I-V). Hypertension was defined as a blood pressure >140 × 90 mmHg or any value if antihypertensive drugs were being used. Mean blood pressure was calculated as diastolic pressure plus one-third pulse pressure. The presence of retinopathy (any grade) was assessed by fundus examination performed by the ophthalmologist after mydriasis. Peripheral neuropathy was considered whenever vibratory perception was diminished (tuning fork test). All patients

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AER, albumin excretion rate; CV, coefficient of variation; GFR, glomerular filtration rate; HF, hyperfiltering; MBP, mean blood pressure; NF, normofiltering.

Table 1—*Baseline clinical features of NIDDM patients and control subjects*

	NF	HF	Control group
n	19	13	20
Age (years)	53 ± 7 (44–67)	53 ± 6 (43–63)	50 ± 7 (41–61)
Sex (M/F)	10/9	9/4	9/11
BMI (kg/m^2)	25 ± 3 (19–30)	25 ± 2 (21–28)	25 ± 2 (22–28)
MBP (mmHg)	98.5 ± 13.4 (71–126)	98.7 ± 12.6 (80–120)	89.2 ± 9.4 (75–107)
Diabetes duration (years)	6.3 ± 5.4 (1–20)	7.5 ± 4.8 (3–16)	—
Treatment (diet/oral agents/insulin)	8/8/3	4/7/2	—
Retinopathy	3	4	—
Peripheral neuropathy	3	0	—
Autonomic neuropathy	3	1	—
Macrovascular disease	1	1	—

Data are means ± SD (range) or number of cases. All *P* values are nonsignificant.

were given five autonomic cardiovascular tests according to Ewing and Clarke (8), and autonomic neuropathy was diagnosed in the occurrence of two abnormal tests. Macroangiopathy was diagnosed if history and/or evidence of peripheral arterial, cerebrovascular, or coronary heart disease were present.

GFR and AER were measured at baseline and after 40 and 60 months of follow-up. The changes of GFR were calculated as the difference between 40- or 60-month and baseline values divided by the time of follow-up in months. At 40 months, 26 patients were examined, and 29 patients were examined at 60 months. Before 60 months, two HF patients suffered myocardial infarction (one died, and the other developed severe heart failure) and were analyzed only at 40 months. One NF patient declined to attend the 60-month review. Six patients did not reply to the 40-month recall and were only seen at 60 months.

At entry, 12 patients were treated with diet alone, 15 were on oral agents, and 5 were on insulin. Seven patients initially on diet alone were started on oral agents, and seven patients originally on oral agents were changed to insulin during the study.

HbA_{1c} was measured by ion-exchange chromatography (normal range: 6.5–8.5%), cholesterol and triglycerides by an enzymatic method, and urea by a kinetic reaction.

The GFR was measured by the ^{51}Cr-EDTA single injection method (coefficient of variation [CV] = 12%) and calculated as a monoexponential function of the plasma disappearance curve according to Chantler and Barratt (9).

The AER was determined in 24-h timed sterile urine samples by radioimmunoassay (DPC, Los Angeles, CA; inter- and intra-assay CV = 2.3 and 2.8%) in three occasions at least 2 weeks apart. The log-transformed values were used for calculations. Microalbuminuria was defined as an AER of 20–200 μg/min.

Comparisons were performed using the appropriate tests. The one-sample *t* test was used to evaluate differences from zero. Stepwise multiple regression analyses were carried out to study the relative contributions of different independent variables to the outcome change in GFR. Logistic regression analysis was used to examine the importance of several parameters on the categorical variable microalbuminuria at 60 months. *P* values <0.05 were considered to be statistically significant. Results are expressed as means ± SD unless otherwise stated.

RESULTS — Baseline clinical features of NIDDM patients and control subjects are presented in Table 1. There were no differences between NF, HF, and control subjects in terms of age and sex. BMI and MBP were similar at baseline and did not change during the study. Known duration of diabetes did not differ in NF and HF patients. Six patients (five NF, one HF) were initially hypertensive; a further NF patient became hypertensive during the observation.

The prevalence of chronic complications was similar in the groups initially and did not change along the study.

The kind of treatment used for the diabetes control was not different between NF and HF patients at baseline and at 60 months (Fisher's exact test, $P > 0.05$).

The change in GFR was not significant at 40 months in either NF (-0.09 ± 0.64 ml · min^{-1} · month^{-1}) or HF patients (-0.15 ± 0.38; one-sample *t* test, $P > 0.05$).

At 60 months, the decline in GFR was significant in both the patients and the control group. The decline was significantly faster in HF patients (-0.61 ± 0.20 ml · min^{-1} · month^{-1}) than in NF patients (-0.18 ± 0.28) or control subjects (-0.14 ± 0.19); the declines in GFR of NF and control subjects were not different (Kruskal-Wallis analysis of variance, $P < 0.001$ for HF). The average rate of change of GFR in the 40–60 months' interval was also higher in HF patients in comparison with NF patients (-1.13 ± 0.83 vs. -0.45 ± 1.06 ml · min^{-1} · month^{-1}, $P = 0.037$).

HbA_{1c} remained similar in NIDDM patients. In the HF group, HbA_{1c} values were 10.3 ± 1.9, 10.3 ± 2.9, and 10.8 ± 1.8%, respectively at baseline, 40, and 60 months; in the NF group, they were 9.6 ± 1.7, 8.9 ± 2.3, and 10.3 ± 3.5%. Urinary urea did not change in the HF group, with mean values of 24 g/24 h at baseline and 40 months, and 25 g/24 h at 60 months. In the NF group, urinary urea raised significantly from 21 g/24 h at baseline to 26 g/24 h at 40 months ($P = 0.035$) and returned to 24 g/24 h at 60 months. Baseline and 60 month values were not different ($P > 0.05$).

In stepwise multiple regression analysis with the decline in GFR of NIDDM patients as the dependent variable and the baseline GFR and AER, age, diabetes duration, and change in MBP,

Table 2—*Baseline clinical and laboratory features of normoalbuminuric and microalbuminuric patients at follow-up*

	Normoalbuminuric	Microalbuminuric
n	25	7
Age (years)	52 ± 6 (43–66)	56 ± 8 (44–67)
Sex (M/F)	14/11	5/2
BMI (kg/m^2)	25 ± 3 (19–29)	26 ± 3 (23–30)
MBP (mmHg)	98.2 ± 12.5 (71–120)	99.6 ± 15.0 (80–126)
Diabetes duration (years)	7.1 ± 4.9 (1–20)	5.4 ± 5.0 (1–18)
GFR (ml · min^{-1} · 1.73 m^{-2})	128.9 ± 21.8 (73.9–170.1)	122.6 ± 22.3 (100.9–158.6)
AER (μg/min)	3.4 (0.2–11.0)	6.8 (2.7–19.0)*
FPG (mmol/l)	10.4 ± 3.7 (4.4–18.8)	11.1 ± 5.2 (5.2–17.7)
Urinary urea (g/24 h)	23 ± 6 (13–37)	20 ± 6 (10–27)
Cholesterol (mmol/l)	5.35 ± 1.00 (3.62–8.17)	6.20 ± 1.90 (3.95–9.74)
HDL (mmol/l)	1.3 ± 0.3 (0.8–2.3)	1.3 ± 0.4 (0.9–1.8)
Triglycerides (mmol/l)	1.8 ± 1.3 (0.4–4.8)	3.1 ± 2.3 (0.5–6.7)

Data are means ± SD (ranges) or number of cases and AER as geometric means (ranges). *P = 0.04.

urinary urea, HbA_{1c}, and therapy as the independent variables, significant relationships for the changes in GFR were noted only with baseline GFR (R^2 = 0.19, P = 0.002) and age (R^2 = 0.31, P = 0.048).

Four NF and three HF patients became microalbuminuric (Fisher's exact test, $P > 0.05$). In univariate analysis, only the initial logAER could differentiate patients who later developed microalbuminuria (n = 7; geometric mean of AER at follow-up = 31.7 μg/min, range: 22.6–68.0) from those who remained normoalbuminuric (n = 25; geometric mean = 5.1 μg/min, range: 1.9–16.6; Student's t test, P = 0.04; Table 2). This observation was confirmed when logistic regression analysis was performed relating initial AER, baseline GFR, diabetes duration, age, and change in urinary urea, HbA_{1c}, and MBP to development of microalbuminuria. Baseline AER was significantly related to the development of persistent microalbuminuria (P = 0.037). Change in urinary urea was also significant in the model (P = 0.021).

CONCLUSIONS— In this prospective study, we observed after a 60-month follow-up a significant decline in GFR in both NIDDM patients and the control group. The decline was significantly faster in HF patients than in NF patients or control subjects. In our NF and HF NIDDM patients, the observed decline in GFR was similar to that reported in prospective studies in nonproteinuric IDDM patients (5–7). The change in GFR in NF patients was similar to that recently reported in normoalbuminuric NIDDM patients (10). The similar change in renal function in patients with initially normal GFR and in the control group is probably related to the aging process. Our previous experience corroborates this observation; we found a negative correlation between GFR and age (r = −0.37, P = 0.008) in NIDDM patients (3). Cross-sectional studies in normal subjects have described a reduction in GFR of 0.6 ml · min^{-1} · year^{-1} after the age 40 (11), and of 1 ml · min^{-1} · year^{-1} after the age 50 (12). In this study, we found a reduction of GFR of 1.68 ml · min^{-1} · year^{-1} in normal individuals. This value is greater than previously described in the above mentioned cross-sectional studies (11,12) but is similar to that of a longitudinal study that observed a slope of −0.73 ml · min^{-1} · year^{-1} for ages 45–54 and of −1.64 ml · min^{-1} · year^{-1} for ages 55–64 (13). Therefore, in HF patients, the average rate of decline in GFR (7.3 ml · min^{-1} · year^{-}) was significantly greater than would be expected from the aging process only.

The decline in GFR seen in our patients could not be attributed to changes in metabolic control or protein intake, factors known to influence GFR levels (14,15), because change in HbA_{1c} and urinary urea excretion failed to reach significance in the regression model.

In a recent prospective study of NIDDM patients, Nielsen et al. (10) observed that the baseline systolic blood pressure was a determining factor for the rate of decline of GFR. In multivariate analysis, our data do not allow us to confirm an effect of either baseline or change in blood pressure.

In a stepwise multiple linear regression analysis, the only variables significantly associated to the rate of reduction in GFR were the initial GFR and age, suggesting that higher baseline GFR levels and advanced age (in a minor degree) could be related to a faster decline in renal function (though follow-up GFR levels remained in the normal range).

The observed reduction in GFR cannot be attributed entirely to the regression to the mean phenomenon. If the baseline values were used only to classify the patients as HF or NF and the slope of GFR was analyzed in the 40–60 months interval, the decline of GFR was still greater in HF patients.

The incidence of microalbuminuria at follow-up was comparable between HF and NF patients. A longitudinal study in NIDDM patients reported a similar 39.1% (9 of 23) incidence of microalbuminuria over a mean period of 3.4 years (10). This is not different from our finding of 21.8% (7 of 32) (χ^2, $P > 0.05$). In the same study, patients who subsequently developed microalbuminuria had initially higher AER, just as in our group. In IDDM patients, higher baseline AERs have also been found to be a risk factor for the later appearance of microalbuminuria (16). Change in urinary urea was also associated with the development of microalbuminuria. Although acute loads of protein intake can increase the fractional clearance of albumin in humans (17), this finding has to be further clarified.

In conclusion, this study demonstrates that the GFR of normoalbuminuric NIDDM patients presents a decline over a 60-month period that is associated with the baseline GFR and age; the decline in GFR is faster in HF NIDDM patients, and this is not necessarily associated with higher incidence rates of microalbuminuria after 60 months. A higher baseline AER and increases in urinary urea are predictive of microalbuminuria at 60 months.

A longer follow-up is needed to evaluate the implications of initial hyperfiltration and faster decline of GFR in these patients to define if the glomerular hyperfiltration is a time-limited phase or

if it indeed represents an early phase of diabetic nephropathy.

References

1. Mogensen CE: Glomerular filtration rate and renal plasma flow in long-term juvenile diabetics without proteinuria. *Br Med J* 2:257–259, 1972
2. Vora JP, Dolben J, Dean JD, Thomas D, Williams J, Owens DR, Peters JR: Renal haemodynamics in newly presenting non-insulin dependent diabetes mellitus. *Kidney Int* 41:829–835, 1992
3. Silveiro SP, Friedman R, Gross JL: Glomerular hyperfiltration in NIDDM patients without overt proteinuria. *Diabetes Care* 16:115–119, 1993
4. Rudberg S, Persson B, Dahlquist G: Increased glomerular filtration rate as a predictor of diabetic nephropathy: an 8-year prospective study. *Kidney Int* 41:822–828, 1992
5. Jones SL, Wiseman MJ, Viberti GC: Glomerular hyperfiltration as a risk factor for diabetic nephropathy: five-year report of a prospective study. *Diabetologia* 34:59–60, 1991
6. Azevedo MJ, Gross JL: Follow-up of glomerular hyperfiltration in normoalbuminuric type 1 (insulin-dependent) diabetic patients (Letter). *Diabetologia* 34: 611, 1991
7. Bognetti E, Meschi F, Bonfanti R, Gianolli L, Chiumello G: Decrease of glomerular hyperfiltration in short-term diabetic adolescents without microalbuminuria. *Diabetes Care* 16:120–124, 1993
8. Ewing DJ, Clarke BF: Autonomic neuropathy: its diagnosis and prognosis. *Clin Endocrinol Metab* 15:855–858, 1986
9. Chantler C, Barratt TM: Estimation of glomerular filtration rate from plasma clearance of 51-Chromium Edetic Acid. *Arch Dis Child* 47:613–617, 1972
10. Nielsen S, Schmitz A, Rehling M, Mogensen CE: Systolic blood pressure relates to the rate of decline of glomerular filtration rate in type II diabetes. *Diabetes Care* 16:1427–1432, 1993
11. Gross JL, Friedman R, Azevedo MJ, Silveiro SP, Pecis M: Effect of age and sex on glomerular filtration rate measured by ^{51}Cr-EDTA. *Brazilian J Med Biol Res* 25: 129–134, 1992
12. Granerus G, Aurell M: Reference values for ^{51}Cr-EDTA clearance as a measure of glomerular filtration rate. *Scand J Clin Lab Invest* 41:611–616, 1981
13. Rowe JW, Andres R, Tobin JD, Norris AH, Shock NW: The effect of age on creatinine clearance in men: a cross-sectional and longitudinal study. *J Gerontology* 31:155–163, 1976
14. Rudberg S, Dahlquist G, Aperia A, Persson B: Reduction of protein intake decreases glomerular filtration rate in young type 1 (insulin-dependent) diabetic patients mainly in hyperfiltering patients. *Diabetologia* 31:878–883, 1988
15. Vora JP, Dolben J, Williams JD, Peters JR, Owens DR: Impact of initial treatment on renal function in newly-diagnosed type 2 (non-insulin-dependent) diabetes mellitus. *Diabetologia* 36: 734–740, 1993
16. Microalbuminuria Collaborative Study Group, United Kingdom: Risk factors for development of microalbuminuria in insulin-dependent diabetic patients: a cohort study. *Br Med J* 306:1235–1239, 1993
17. Viberti GC, Bognetti E, Wiseman MJ, Dodds R, Gross JL, Keen H: Effect of protein-restricted diet on renal response to a meat meal in humans. *Am J Physiol* 253: F388–F393, 1987