Glomerular Filtration Rate, Urinary Albumin Excretion Rate, and Blood Pressure Changes in Normoalbuminuric Normotensive Type 1 Diabetic Patients

An 8-year follow-up study

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OBJECTIVE — To analyze the changes in glomerular filtration rate (GFR), urinary albumin excretion rate (UAER), and blood pressure (BP) levels in a cohort of normoalbuminuric and normotensive type 1 diabetic patients.

RESEARCH DESIGN AND METHODS — This is an 8.4 ± 2.1–year prospective study of 33 normotensive normoalbuminuric (24-h UAER <20 μg/min) type 1 diabetic patients. UAER (radioimmunoassay), GFR (^{51}Cr-EDTA single-injection technique), and GHb (ion-exchange chromatography) were measured at baseline and at 1- to 2-year intervals.

RESULTS — The GFR decreased (137.6 ± 16.5 to 116.4 ± 21.3 ml · min^{-1} · 1.73 m^{-2} $P < 0.05$) during the follow-up period. GFR reduction (-0.20 ± 0.29 ml · min^{-1} · month^{-1}; $P < 0.05$) was associated with baseline GFR and mean GHb ($R^2 = 0.30$; $\beta = 0.072$; $F = 6.54$; $P = 0.004$). UAER was higher at the end of the study (3.7–7.1 μg/min; $P = 0.017$). Microalbuminuria was observed in two patients, while macroalbuminuria was observed in one. No changes in UAER were observed when these three patients were excluded from the analysis. Mean blood pressure (MBP) increased during the study (85.8 ± 9.7 to 99.6 ± 11.6 mmHg; $P < 0.001$). MBP at the end of the study was associated with age and GFR at baseline ($R^2 = 0.39$; $\beta = 0.074$; $F = 9.64$; $P = 0.001$).

CONCLUSIONS — In this cohort of normoalbuminuric normotensive type 1 diabetic patients, GFR decreased and BP levels increased during the follow-up period. The predictors for the GFR change were baseline GFR level and metabolic control. For end-of-study MBP, the predictor was baseline GFR level.

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Diabetic nephropathy (DN) occurs in only 30–40% of type 1 diabetic patients. The risk factors for DN have not been completely elucidated. Poor metabolic control is an important risk factor (1), although there are patients who do not develop renal disease despite having suboptimal glucose levels for long periods. Such susceptibility to DN could be explained by genetic predisposition. Epidemiological and familial studies contain evidence to support the idea that genetic factors have a substantial role in the pathogenesis of DN (2,3). This genetic susceptibility to DN could be related to a genetic predisposition to hypertension (4,5).

Increased glomerular filtration rate (GFR) has also been considered a risk factor for the development of DN in type 1 diabetic patients. Still, the few available prospective studies with a long follow-up period analyzing the role of GFR levels in the development of DN in normoalbuminuric type 1 diabetic patients are controversial (6,7). Thus, the aim of the present study was to prospectively analyze the changes in GFR, urinary albumin excretion rate (UAER), and blood pressure (BP) levels in a cohort of normoalbuminuric normotensive type 1 diabetic patients.

RESEARCH DESIGN AND METHODS

Subjects and methods

This is an 8.4 ± 2.1–year (range 4.1–11.2) prospective study with a cohort of normoalbuminuric normotensive type 1 diabetic patients. The definition of type 1 diabetes was based on World Health Organization criteria (8), i.e., age <40 years at onset of diabetes, a previous episode of ketoacidosis or documented ketonuria, and obligatory use of insulin for life maintenance. There were 33 patients (20 men; age 31.8 ± 6.6 years [range 22.4–48.7]; BMI 22.2 ± 2.4 kg/m^2 [range 15.9–29.6], and diabetes duration 6.5 ± 4.6 years [range 1.5–24.2]) selected from 71 type 1 diabetic patients attending the diabetes outpatient clinic at Hospital de Clínicas de Porto Alegre according to the following inclusion criteria: diabetes duration >1 year; >18 years of age; office ambulatory BP <140/90 mmHg; normal maximal exercise electrocardiogram; absence of renal diseases and of autonomic

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Abbreviations: BP, blood pressure; CV, coefficient of variation; DN, diabetic nephropathy; GFR, glomerular filtration rate; MBP, mean blood pressure; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; UAER, urinary albumin excretion rate.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

neuropathy (more than one abnormal result of five cardiovascular autonomic reflex tests) (9); and normoalbuminuria (24-h UAER <20 μg/min) upon measurement on at least two different occasions, 3 months apart, on sterile urine. There were 26 patients who fulfilled the inclusion criteria and agreed to participate in the study in the period from 1986 to 1989, and another 16 patients were enrolled in the period from 1990 to 1992. Nine patients were excluded from the final analysis for the following reasons: six patients were evaluated only at baseline; two patients died after a short follow-up period of 12 months (one patient died of ketoacidosis and one drowned); and one patient did not return for further evaluation after 24 months. The patients who were excluded did not differ from the 33 patients included in the study in terms of age (28.4 ± 7.1 years), sex distribution (four men), diabetes duration (4.4 ± 3.6 years), GFR values (130.4 ± 32.2 ml · min^{-1} · 1.73 m^{-2}), and proportion of hyperfiltering patients (four patients) (all $P > 0.10$). Informed consent was obtained from all patients, and the protocol was approved by the ethics committee of the hospital.

At baseline, patients were evaluated for history of hypertension in first-degree relatives and for smoking habits (smokers were defined as those who smoked at the time of the study, and ex-smokers as those having smoked for ≥1 year and who had quit ≥1 year ago), and had a complete clinical examination. Office auscultatory BP was measured twice with the patient in the sitting position after a 10-min rest, to the nearest 2 mmHg, with a standard 12.5-cm cuff mercury sphygmomanometer (Korotkov phases I and V). The presence of retinopathy was assessed by fundus examination after mydriasis by an ophthalmologist and graded in the following manner: *1*) no sign of diabetic retinopathy; *2*) mild nonproliferative diabetic retinopathy (NPDR) (microaneurysms plus mild-to-moderate retinal hemorrhages or hard exudates); *3*) moderate NPDR (microaneurysm plus any of the following: cotton-wool spots, mild intraretinal microvascular abnormalities or venous beading, or severe retinal hemorrhages); or *4*) proliferative diabetic retinopathy (PDR). Peripheral neuropathy was diagnosed whenever vibratory perception or lower-limb reflexes were diminished along with the presence of compatible symptoms. At the end of the study, microalbuminuria was defined as an UAER of 20–200 μg/min and macroalbuminuria as an UAER >200 μg/min on at least two of three 24-h sterile urine samples (10). Patients were conventionally treated with one (n = 10) or two (n = 22) daily subcutaneous insulin injections, except for one patient who took four injections per day. Apart from insulin, two patients received levothyroxine for primary hypothyroidism, and three female patients used oral contraceptives for short periods during the follow-up. The usual protein intake, assessed by 24-h urinary urea measurements, was 1.4 ± 0.4 g/kg body weight. During the follow-up period, the patients were regularly seen (two or three times a year) by the investigators, and metabolic control indexes were measured. At intervals of 1.7 ± 1.0 years, GFR and 24-h UAER were measured and patients underwent a complete clinical evaluation. Each patient was evaluated 5.7 ± 2.6 times (2–11), except for one patient, who was evaluated only twice, with an interval of 8.3 years between the two evaluations.

The GFR was measured using the ^{51}Cr-EDTA single injection technique (coefficient of variation [CV] = 11.2%) (11,12). The reference GFR range in our laboratory was 94.6–134 ml · min^{-1} · 1.73 m^{-2} (11). Glomerular hyperfiltration was defined as GFR >134 ml · min^{-1} · 1.73 m^{-2}. At least two or three GFR measurements were required to classify patients as hyperfiltering or normofiltering. UAER was determined by radioimmunoassay (DPC, Los Angeles, CA; inter- and intra-assay CV = 2.3 and 2.8%, respectively). Glucose was measured by the glucose-oxidase method, GHb by a micro-column chromatography (HbA_1, Labtest Diagnostica, MG, Brazil; normal range 5.3–8.0%), creatinine by Jaffe's reaction, urinary urea by a kinetic reaction, and cholesterol and triglycerides by a colorimetric method.

Statistical analysis

Student's t test, Fisher's exact test, or the χ^2 test, and Wilcoxon's signed-rank test or Mann-Whitney U test were used for comparison of parametric and nonparametric variables. The changes in GFR, mean blood pressure (MBP) levels, and UAER (log-transformed) over time were analyzed by a regression line determined for each patient, and the mean slopes (expressed as b, i.e., mean change) were then calculated. Multiple regression analyses (backward method) were performed using changes in UAER, MBP, and GFR, as well as end-of-study MBP, as dependent variables. The results were expressed as means ± standard deviation or as geometric means and ranges for UAER values. P values <0.05 (two-tailed) were considered to be statistically significant.

RESULTS — At baseline, 19 patients had a familial history of hypertension, 10 patients were smokers, 9 were ex-smokers, and 6 had evidence of diabetic retinopathy (mild NPDR in 4, and PDR in 2). Only four patients had a diabetes duration of >10 years (12.5, 12.5, 17.0, and 24.2 years). There were no cases of either peripheral vascular disease or sensitive peripheral symmetric neuropathy. One patient died (ketoacidosis) after 6 years of follow-up. The other clinical and laboratory characteristics of the patients at baseline and at the end of the study are shown in Table 1 and Fig. 1. At the end of the study, an increase in MBP, urinary urea, and UAER was observed. On the other hand, GFR and GHb levels decreased. The lipid profile did not change.

There were 21 patients who had glomerular hyperfiltration at baseline (GFR = 154.8 ± 16.5; 134.3–187.8 ml · min^{-1} · 1.73 m^{-2}) and 12 patients who had normal GFR (107.5 ± 15.7; 84.9–128.6 ml · min^{-1} · 1.73 m^{-2}). A significant GFR reduction at the end of the study was observed only in hyperfiltering patients (154.8 ± 16.5 to 123.1 ± 21.0 ml · min^{-1} · 1.73 m^{-2}; mean GFR change = −0.26 ± 0.24 ml · min^{-1} · month^{-1}; $P < 0.05$). Among the 21 hyperfiltering patients, GFR became normal in 14 and remained elevated in 7. Including all patients, GFR diminished during the study (mean GFR change −0.20 ± 0.29 ml · min^{-1} · month^{-1}; $P < 0.05$). A multiple regression analysis was performed, with mean GFR change as the dependent variable and baseline MBP, GFR, and UAER, and mean GHb during the study as independent variables. The GFR reduction during the study was associated with baseline GFR and mean GHb ($R^2 = 0.32$; $\beta = 0.072$; $F = 6.54$; $P = 0.004$).

Three patients developed DN: two developed microalbuminuria and one developed macroalbuminuria. The incidence density and cumulative incidence of DN were 1.1 cases per 100 patient-years and 9.1%, respectively. Patients with and without DN at the end of the study did not differ at baseline regarding age, sex, BMI, smoking habit, diabetes duration, familial history of hypertension, BP levels, GHb levels, lipid profile, GFR, and UAER. At the end of the study, these three patients

Table 1—*Baseline and end-of-study characteristics of 33 type 1 diabetic patients*

	Baseline	End of study	*P* value
Blood pressure (mmHg)			
Systolic	112.3 ± 12.8 (80–134)	128.1 ± 15.3 (100–160)	<0.001
Diastolic	72.3 ± 9.7 (52–88)	84.4 ± 11.1 (60–108)	<0.001
Glycohemoglobin (%)	9.9 ± 2.0 (5.0–13.3)	8.2 ± 1.6 (5.2–14.1)	<0.001
Cholesterol (mg/dl)	179.6 ± 48.7 (87–295)	186.4 ± 37.8 (134–274)	0.431
Triglycerides (mg/dl)	78.1 ± 35.8 (40–183)	82.4 ± 35.5 (45–200)	0.585
Urinary urea (g/24 h)	19.3 ± 9.8 (10.0–34.8)	25.0 ± 10.3 (6.0–47.0)	0.003
GFR (ml · min^{-1} · 1.73 m^{-2})	137.6 ± 28.0 (84.9–187.8)	116.4 ± 21.3 (68.9–164.9)	<0.001
UAER (μg/min)	3.7 (0.1–17.5)	7.1 (0.5–1,190)	0.017

Data are means ± SD (range) or geometric mean (range).

showed an improvement in metabolic control (GHb: 11.4 ± 0.5 vs. 8.03 ± 0.7%; P = 0.03), an increase in MBP levels (82.5 ± 2.9 vs. 101.3 ± 2.1 mmHg; P = 0.001), and a decrease in GFR (156.5 ± 10.5 vs. 118.8 ± 16.4 ml · min^{-1} · 1.73m^{-2}; P = 0.02). The mean UAER for all patients was higher at the end of the study (3.7 vs. 7.1 μg/min; P = 0.017). Also, the increase in UAER during the study was significant (mean log UAER change = 0.0024 μg · min^{-1} · month^{-1}; P = 0.038). When the three patients with DN were excluded from the analysis, the increase in UAER was not significant. These three patients had glomerular hyperfiltration at baseline. Taking into account the 33 patients, the increase in UAER during the study was observed only in patients with hyperfiltration (mean log UAER change = 0.0029 μg · min^{-1} · month^{-1}; $P < 0.05$) when compared with patients with normal GFR. UAER was not different for patients with (3.9 [0.1–17.5] μg/min) or without (3.4 [0.5–17.4] μg/min) glomerular hyperfiltration at baseline. In a multiple regression analysis including all patients, none of the analyzed independent variables (UAER, GFR, MBP, and diabetes duration) was associated with mean UAER change.

Seven patients developed hypertension, and the incidence density was 2.6 cases per 100 patient-years, which corresponds to a cumulative incidence of 21.2%. Hypertension was diagnosed at the end of the study in five patients. Two patients developed hypertension before the end of the study. In one patient, an increased BP level (150/80 mmHg) was detected 1 year before the last evaluation, and only nonpharmacological measures were prescribed. In the other one, a BP level of 124/96 mmHg was observed 3 years after the patient started the study. This patient's increased BP levels, however, were not sustained in the subsequent visits, until 3 months before the end of the study, when hydroclorothiazide 25 mg/day was prescribed. MBP increased at the end of the follow-up period (85.8 ± 9.7 to 99.6 ± 11.6 mmHg; mean MBP change = 1.7 ± 2.0 mmHg/year; $P < 0.05$). This increase was observed even after the seven patients who developed hypertension were excluded

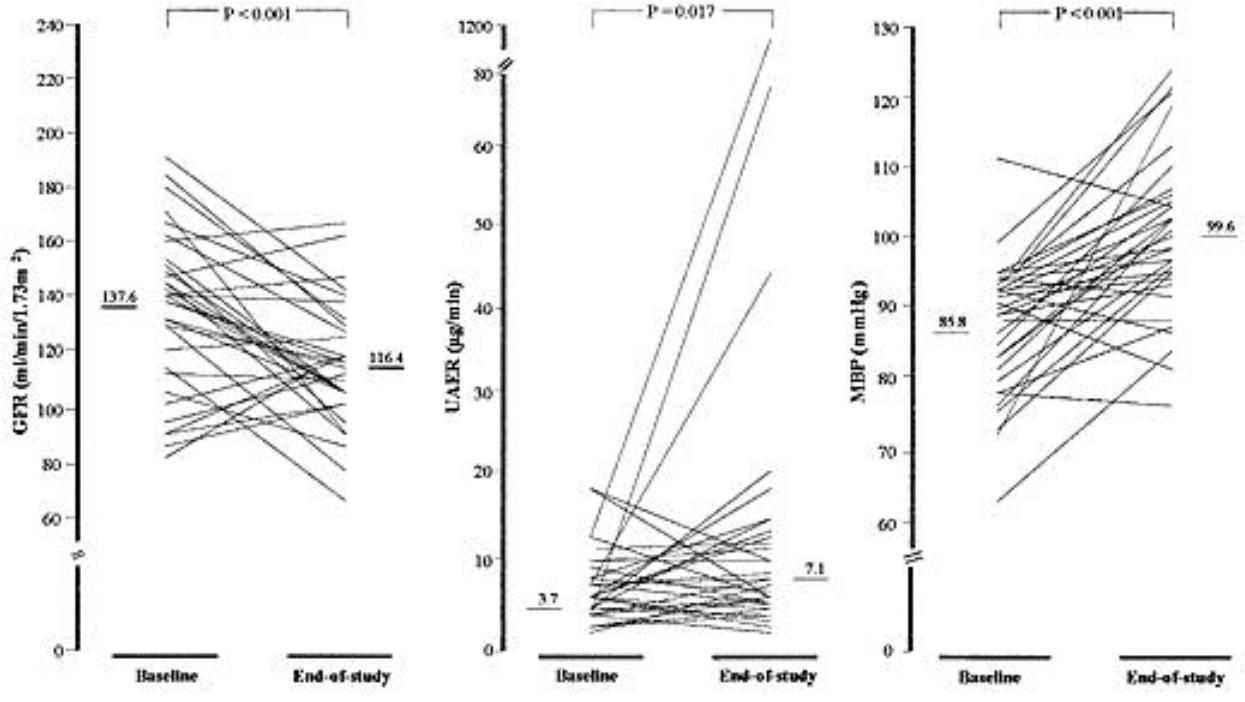

Figure 1—*GFR, UAER, and MBP at baseline and at the end of the study. Horizontal bars indicate mean or geometric mean for UAER values.*

from the analysis. The increase in MBP occurred in patients both with hyperfiltration and with normal GFR. In a multiple linear regression analysis that took into account all patients, the mean MBP change (dependent variable) was associated with baseline MBP and age (R^2 = 0.46; β = 0;001; F = 12.98; $P < 0.001$). Family history of hypertension, GFR, and UAER at baseline were eliminated from the model. When the end-of-study MBP was considered as the dependent variable, however, it was significantly associated with age and GFR at baseline (R^2 = 0.39; β = 0.074; F = 9.64; P = 0.001). MBP and UAER at baseline were eliminated from the model.

There were no cases of progression of baseline retinopathy to more advanced stages. By the end of the follow-up period, another five patients had developed mild NPDR.

CONCLUSIONS — This cohort of normoalbuminuric type 1 diabetic patients showed a decrease in GFR and an increase in UAER and MBP levels. Changes in GFR and UAER were more pronounced in hyperfiltering patients. The faster decline of GFR in hyperfiltering patients had already been observed in our previous 4-year prospective study (13) and was also observed in other studies (7,14). In this cohort, the decrease in GFR was observed despite an increase in protein consumption, as measured by urinary urea, and despite the fact that high protein intake is usually associated with higher GFR (15). The meaning of the observed GFR decline probably does not represent a deterioration of renal function, but rather a normalization of high levels of GFR. The GFR decline can be explained in part by the improvement in metabolic control observed in these patients during the follow-up period. Reduction of plasma glucose levels caused GFR to become almost normal in normoalbuminuric hyperfiltering patients (16).

Only three patients developed DN. This cumulative incidence of DN (9.1%) is similar to what was found in other observational studies (7,17–19). The small number of individuals with this end point limits the analysis of possible risk factors. It is interesting to note, however, that these patients progressed to renal disease irrespective of the observed improvement in metabolic control. In this study, GFR was not a significant risk factor for DN. However, we cannot disregard the role of increased GFR in the development of DN, because the increase in UAER was observed only in hyperfiltering patients, and the three patients with DN at follow-up had glomerular hyperfiltration at baseline. Furthermore, end-of-study BP levels were significantly associated with higher baseline GFR. This observation is relevant because hypertension (a surrogate end point) has been considered the main factor related to genetic predisposition and to further development of DN (4,5). We had previously observed high-normal BP levels in hyperfiltering type 1 diabetic patients (20). Recently, we were able to confirm an association between BP abnormalities and glomerular hyperfiltration in normoalbuminuric type 1 diabetic patients (21). Therefore, we can hypothesize that an interaction between abnormalities of BP patterns and glomerular hemodynamics could increase one's susceptibility to DN.

Only two other prospective studies with similar follow-up analyzed the role of glomerular hyperfiltration as a risk factor for the development of DN (6,7). The results of the study by Yip et al. (7) were very similar to ours. Likewise, in that study, glomerular hyperfiltration was not a significant risk factor for micro- and macroalbuminuria, but it was an independent determinant of MBP at the end of the study. On the other hand, in the study by Rudberg et al. (6), glomerular hyperfiltration was a strong risk factor for DN. However, we have to consider that in the Rudberg et al. study, the patients were younger, the metabolic control was worse, and the cutoff value for the definition of hyperfiltration was lower than in our study.

In our cohort, baseline UAER was neither a risk factor for DN, as was the case in other studies (6,7,17), nor was it associated with further increase in BP levels. Values of UAER >8–10 μg/min have been considered an early predictive factor for the development of DN in type 1 (17) and type 2 diabetic patients (14). In our study, however, baseline UAER was much lower (<4 μg/min), suggesting that those patients who were susceptible to the development of DN were in such early stages of renal involvement that UAER could not predict the later onset of renal lesions.

One characteristic of the sample that might be a limitation of this study is the high proportion of patients with a family history of hypertension. This probably occurred by chance, because when the patients were selected, we did not take into account any factor that could lead to this association. Another aspect to be considered is that 21 of our 33 patients had increased levels of GFR at baseline. This proportion of hyperfiltering patients was similar to that reported by other prospective studies that analyzed the role of GFR in the development of DN in cohorts of type 1 diabetic patients (6,22). Nevertheless, other authors reported that only 25–40% of type 1 diabetic patients have glomerular hyperfiltration (23).

In conclusion, in this cohort of normoalbuminuric normotensive type 1 diabetic patients, GFR decreased and BP levels increased during the follow-up period. The predictors for GFR change were baseline GFR level and metabolic control. For end-of-study MBP, the predictor was baseline GFR level.

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