

Systolic Blood Pressure Relates to the Rate of Decline of Glomerular Filtration Rate in Type II Diabetes

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OBJECTIVE— To relate deterioration in kidney function to some potential cardiovascular risk factors in type II diabetic patients.

RESEARCH DESIGN AND METHODS— Twenty-four normoalbuminuric and 13 microalbuminuric patients completed a 3.4-yr prospective observational study. Glomerular filtration rate, urinary albumin excretion rate, blood pressure, glycemic control, and lipids were measured on entry and at the end of the study. Of the patients, 19 normoalbuminuric and 8 microalbuminuric (73%) patients had no history of antihypertensive treatment.

RESULTS— The glomerular filtration rate was significantly reduced during the follow-up period ($-1.34 \pm 0.54 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ [mean \pm SE], $P < 0.02$). The rate of decline varied considerably in normoalbuminuric and microalbuminuric patients (from -13.5 to 4.3 and from -7.0 to $4.2 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ per year, respectively) but was on average not accelerated in normoalbuminuric or microalbuminuric patients (-1.3 ± 0.7 and $-1.5 \pm 0.8 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ per year, respectively). Significant correlations were observed between the glomerular filtration rate fall rate and initial systolic blood pressure ($r = -0.47$, $P < 0.01$; patients without antihypertensive treatment: $r = -0.42$, $P = 0.03$) but not diastolic blood pressure. In a stepwise multiple linear regression analysis, baseline systolic blood pressure significantly determined the fall rate of the glomerular filtration rate (regression coefficient = -0.050 , SE = 0.018 , $P = 0.011$; patients without antihypertensive treatment: regression coefficient = -0.047 , SE = 0.021 , $P = 0.030$).

CONCLUSIONS— In these type II diabetic patients neither normoalbuminuria nor microalbuminuria are at an average associated with an accelerated decline in kidney function. Still, systolic blood pressure is a determining factor for the rate of decline in the glomerular filtration rate. A longer follow-up time with consecutive glomerular filtration rate measurements are needed to determine the long-term implications of normoalbuminuria and microalbuminuria on kidney function in type II diabetic patients.

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Received for publication 22 December 1992 and accepted in revised form 22 July 1993.

Type I diabetes, insulin-dependent diabetes mellitus; type II diabetes, non-insulin-dependent diabetes mellitus; UAE, urinary albumin excretion; CVD, cardiovascular disease; GFR, glomerular filtration rate; AHT, antihypertensive treatment; RIA, radioimmunoassay; HPLC, high-performance liquid chromatography; CV, coefficient of variation; ANOVA, analysis of variance; TG, triglyceride; HDL, high-density lipoprotein; BP, blood pressure; sBP, systolic blood pressure; dBp, diastolic blood pressure; BMI, body mass index.

Impaired renal function is a well-described and serious complication in type I diabetes (1), and microalbuminuria (UAE rate from 20 to 200 $\mu\text{g}/\text{min}$) is considered a strong predictor of overt clinical nephropathy (2–5). In type II diabetes end-stage renal failure develops in a much smaller percentage of patients; morbidity and mortality, at least in Western Europe, is primarily caused by CVD and strokes. Microalbuminuria predicts the development of persistent proteinuria (UAE $>200 \mu\text{g}/\text{min}$) and especially premature mortality in type II diabetic patients (6–8). However, little is known about the rate of decline in renal function (GFR) and the relation to potential risk factors such as hypertension, glycemic control, or lipids.

We prospectively followed renal function in a group of 55 middle-aged and elderly type II diabetic patients without clinically overt proteinuria and evaluated the relation of some potential risk factors to the rate decline in kidney function.

RESEARCH DESIGN AND

METHODS— During a 2-yr period (1986–1988) 55 nonproteinuric, type II diabetic patients, 37 with normoalbuminuria (UAE $<20 \mu\text{g}/\text{min}$) and 18 with microalbuminuria, from the outpatient clinic were identified from hospital records and invited to participate in the study. Additional entrance criteria were: current age between 45 and 70 yr, age at diagnosis of diabetes ≥ 45 yr, known diabetes duration >3 mo, antidiabetic treatment by diet or oral hypoglycaemic agents, and no known major disease (including severe oedema and kidney disease). Of the patients, 11 (8 normoalbuminuric and 3 microalbuminuric) could not or refused re-examination (2 patients [1 normoalbuminuric and 1 microalbuminuric] because of severe CVD and mental disability). Moreover, 1 normoalbuminuric patient was excluded because of massive heart failure, and 6 patients (4 normoalbuminuric and 2 microalbumin-

Table 1—Clinical characteristics of type II diabetic patients

	Normoalbuminuria	Microalbuminuria
n	24	13
Sex (M/F)	13/11	10/3
Age (yr)	62 (53–69)	64 (57–69)
Diabetes duration (yr)	7.0 (1–16)	6.5 (0–18)
BMI (kg/m ²)*	28.6 ± 1.0	28.1 ± 1.0
Retinopathy (n)		
Normal	17	8
Background	7	3
Proliferative	0	2
Follow-up period (yr)	3.4 (2.1–4.8)	3.5 (2.6–4.5)

Data are means (range), except for BMI, which is mean ± SE.

uric) had died. Causes of death for these patients, as recorded from hospital records and death certificates, were myocardial infarction (2 normoalbuminuric and 1 microalbuminuric), carcinoma of the lung and the liver (1 normoalbuminuric and 1 microalbuminuric), and acute gangrenous cholecystitis (1 normoalbuminuric). None of the 18 excluded patients had uremia or were known to have proteinuria as evaluated from hospital records. A total of 37 patients (24 normoalbuminuric and 13 microalbuminuric) were re-examined after 3.4 yr (2.1–4.8 yr) (Table 1).

GFR was measured by the plasma clearance of ⁵¹Cr-EDTA (single-shot procedure) and corrected to 1.73 m² body surface (9). UAE was measured by RIA (10) and assessed as the mean of two 24-h urine samples. Blood samples were taken after an overnight fast, and plasma glucose was measured by a glucose oxidase technique. Two HPLC methods for GHb (HbA_{1c}) were used (11,12). The interassay CVs were 5 and 2%, respectively. Serum C-peptide was measured by an RIA kit (Inc. Star Corp. Minneapolis, MN). Serum cholesterol was measured by continuous-flow analysis (13), serum TGs by an enzymatic technique (14), serum HDL cholesterol by a Dextran Sulfate-Mg²⁺ precipitation procedure (15), and serum creatinine by a modified Jaffe's reaction (16), and all

were adapted to the Technicon CHEM 1(R) analyzer (Cherrytown, NY).

Because AHT may modulate albuminuria in nonproteinuric type II diabetic patients (17–20), separate evaluations were performed in the subgroup of 27 (73%) (19 normoalbuminuric and 8 microalbuminuric) patients without a history of AHT and/or diuretic therapy. BP was measured in the sitting position after 15 min of rest using a conventional sphygmomanometer with phase V for the diastolic value.

Statistical analysis

Data are presented as mean ± SE, except for UAE, which has been log (10) transformed before further processing caused by the positively skewed distribution and are therefore given as the geometric mean × / ÷ antilog SE. Time-related changes between groups were compared by repeated-measures of ANOVA. For baseline comparisons between normoalbuminuric and microalbuminuric patients, Students *t* test and the Mann-Whitney two-sample test were used. Stepwise multiple regression analysis and correlations were performed by linear regression analysis.

RESULTS— The results are summarized in Table 2. The mean GFR for all patients was moderately reduced during the study ($-1.34 \pm 0.54 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73$

m^{-2} per year, $P < 0.02$). One normoalbuminuric patient showed an excessive reduction in GFR ($-13.5 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ per year) without signs of other disease likely to modify kidney function. The GFR fall rate in the remaining 23 normoalbuminuric patients was 0.7 ± 0.3 ($-4.4 - 4.3$) $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ per year. As calculations and statistical comparisons were not significantly affected whether included or not, this patient was not excluded from the study, except from the multiple linear regression models. In 3 microalbuminuric patients (57, 67, and 68 yr of age), baseline GFR was $< 70 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ (64.9, 58.8, and 67.7 $\text{ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$, respectively). At follow-up, UAE had regressed in 2 of these patients, while urine collection was unsuccessful in the third. The GFR fall rate (-2.6 , -7.0 , and $-1.4 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ per year) and other measurements were comparable with those of the remaining patients.

Figure 1 shows UAE at the two examinations. Proteinuria developed in 3 patients, who all initially had a high level of microalbuminuria. Follow-up urine collections were unsuccessful in 2 patients (1 normoalbuminuric and 1 microalbuminuric). Of 23 initially normoalbuminuric patients, 9 (39.1%) developed microalbuminuria. They had significantly higher initial UAE levels than the remaining 14 patients ($10.1 \times / \div 1.1$ vs. $5.3 \times / \div 1.1 \mu\text{g}/\text{min}$, $P < 0.005$). Except for a longer follow-up time than in patients who did not develop microalbuminuria (3.9 ± 0.3 vs. 3.0 ± 0.2 yr, $P < 0.05$), no further clinical or laboratory differences between the groups were observed. No significant correlations to the rise in UAE were observed in the normoalbuminuric and microalbuminuric groups or in both groups taken together. Comparing patients with a rise in UAE with those with a decline, as well as comparing patients with a rise of $> 30\%$ with the remainder, revealed no difference in clinical and biochemical characteristics. Mean (of initial and follow-up) values of UAE and sBP correlated significantly

Table 2—Kidney function, BP, glycemic control, and lipids in type II diabetic patients

	Normoalbuminuria (n = 24)		Microalbuminuria (n = 13)	
	Initial	Follow-up	Initial	Follow-up
GFR (ml · min ⁻¹ · 1.73 m ⁻²)	93.2 ± 2.4	89.1 ± 3.2	95.1 ± 6.0	91.0 ± 6.4
UAE (μg/min)*	6.8 ×/÷ 1.1	11.4 ×/÷ 1.2†	59.1 ×/÷ 1.2‡	67.0 ×/÷ 1.5‡
BP (mmHg)	148/82 ± 4/2	155/80 ± 6/2	162/84 ± 7/3	160/83 ± 6/3
P-glucose (mM)	8.4 ± 0.5	9.9 ± 0.5	8.3 ± 0.6	9.2 ± 0.8
HbA _{1c} (%)	7.4 ± 0.3	8.0 ± 0.3	7.6 ± 0.4	8.3 ± 0.5
C-peptide (ng/ml)	2.9 ± 0.2	1.9 ± 0.2†	3.6 ± 0.5	2.1 ± 0.2†
Serum cholesterol (mM)	6.7 ± 0.3	6.3 ± 0.3	6.4 ± 0.3	6.2 ± 0.2
Serum TGs (mM)	2.23 ± 0.29	2.24 ± 0.28	3.13 ± 0.77	2.35 ± 0.37
Serum HDL cholesterol (mM)	1.03 ± 0.09	1.18 ± 0.06	1.09 ± 0.07	1.13 ± 0.08
GFR fall rate (ml · min ⁻¹ · 1.73 m ⁻² per year)	-1.3 ± 0.7 (-13.5-4.3)		-1.5 ± 0.8 (-7.0-4.2)	
Rise in UAE (%/yr)	16 ± 4		3 ± 8	
Antidiabetic treatment (n)				
Diet	5	3	3	2
Oral hyperglycemic agents	19	18	10	11
Insulin	0	3	0	0
Receiving antihypertensive treatment (n)	3	5	4	5

Data are means ± SE.

*UAE values are geometric mean ×/÷ SE.

†Significantly different from initial ($P < 0.05$).

‡Significantly different from n ($P < 0.05$).

($r = 0.34$, $P < 0.05$). Patients with and without retinopathy showed no difference in GFR fall rate or rise in UAE. Changes in BP did not correlate to the rise in UAE.

The GFR fall rate correlated sig-

nificantly with the initial (and the mean of initial and follow-up) sBP as shown in Fig. 2. This correlation was also statistically significant in normoalbuminuric patients alone ($r = -0.50$, $P = 0.01$)

but not in microalbuminuric patients alone ($r = -0.49$, $P = 0.09$), probably attributable to the small number of patients. No correlations were found between the rate of decline in GFR and age, diabetes duration, follow-up time, BMI, HbA_{1c}, lipids, baseline GFR, or UAE. Moreover, neither changes in BP nor a rise in UAE were correlated to changes in GFR. A stepwise multiple linear regression analysis including baseline values of the risk factors listed in Table 3 showed that initial sBP significantly determines the rate of decline in GFR. A subset of variables was selected for the final model (21). Because of a close interrelationship between sBP and DBP and between follow-up time and HDL cholesterol, these variables were also entered separately in the analysis. However, the overall results were unaltered. During the stepwise analysis HDL cholesterol was not considered significant.

In 27 (73%) patients (19 normoalbuminuric and 8 microalbuminu-

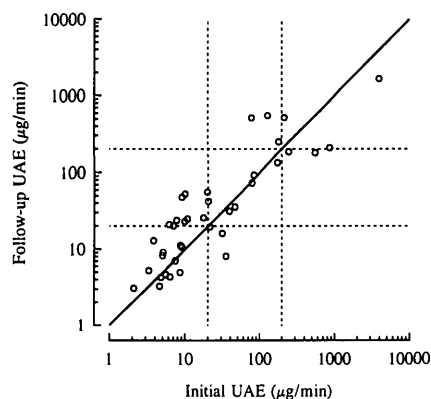


Figure 1—UAE rate in normo- and microalbuminuric patients at the initial and follow-up examinations (lower microalbuminuric level and identity line indicated).

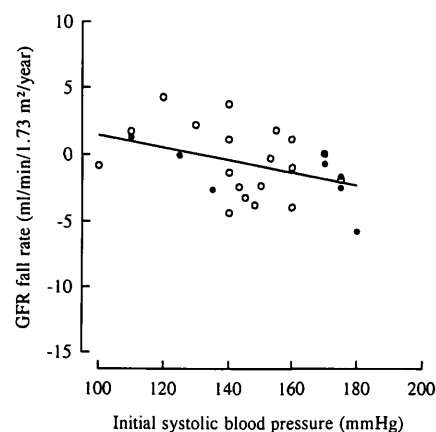


Figure 2—The fall rate in GFR as related to the initial sBP in 37 normo-(○) and microalbuminuric (●) patients ($r = -0.47$, $P < 0.01$).

Table 3—Results of a multiple linear regression analysis

Risk factor	Original model			Final model		
	Regression coefficient	SE	P value	Regression coefficient	SE	P value
Age	0.003	0.206	NS	E*	—	—
Diabetes duration	−0.061	0.192	NS	E*	—	—
Follow-up time	0.122	0.099	NS	0.103	0.060	NS
GFR	0.028	0.044	NS	0.015	0.031	NS
UAE	−0.187	1.464	NS	E*	—	—
sBP	−0.118	0.594	NS (0.06)	−0.099	0.032	0.0038
dBP	0.105	0.092	NS	0.086	0.061	NS
HbA _{1c}	32.53	45.60	NS	23.95	36.00	NS
C-peptide	−0.467	0.567	NS	−0.352	0.361	NS
Cholesterol	0.139	0.685	NS	E*	—	—
TGs	0.182	0.723	NS	E*	—	—
HDL cholesterol	3.579	2.542	NS	3.349	1.531	0.037
BMI	−0.047	0.169	NS	E*	—	—

Models are after multivariate subset selection.

*E, eliminated variable.

ric) without AHT, the fall rate of GFR correlated significantly with the initial sBP ($r = -0.42$, $P = 0.03$). Again, a multiple regression analysis, revealed initial sBP as the single significant determinant of GFR fall rate (regression coefficient = -0.047 , SE = 0.021 , $P = 0.03$). The rise in UAE did not correlate to the fall rate of GFR or sBP, whereas mean values of UAE and sBP correlated significantly ($r = 0.43$, $P < 0.03$). Again, changes in BP did not correlate to changes in GFR or UAE.

CONCLUSIONS— In this 3.4-yr (mean) follow-up study, we found that the rate of decline in GFR in microalbuminuric type II diabetic patients was not significantly accelerated as compared with normoalbuminuric patients. The fall rate was similar to that reported in healthy, nondiabetic individuals ($\sim 1.0 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ per year) (22). However, the changes in GFR varied considerably among individuals. Clearly, conclusions about a true linear fall rate will be, in part, speculative as only two measurements have been conducted for each patient. Consideration of selective

mortality as a possible source of bias should be remembered. The deaths of these patients might have been promoted by alterations in kidney function; the exact rate of decline in GFR could be underestimated. In our material, none of the 18 eliminated patients suffered from uremia or were known to have overt proteinuria. Although patients who progressed from normoalbuminuria to microalbuminuria had significantly higher initial UAE levels and a slightly longer follow-up time, take cautions about the conclusions that can be drawn from these data. Similar UAE levels could be expected if day-to-day variability was studied.

The pathogenetical relationship between elevated BP and renal disease in type II diabetes is difficult to establish. The time of diabetes onset is often unknown, and some 40–50% of the patients receive AHT at the time of diagnosis (23). Furthermore, insulin resistance and hyperinsulinemia may lead to hypertension through a variety of mechanisms (24–28). In our study, sBP tended to be higher in microalbuminuric than in normoalbuminuric patients, although not statistically sig-

nificant. A significant correlation between initial sBP and the fall rate in GFR, irrespective of AHT or diuretic treatment, was noticed. Thus, the sBP level serves as a predictor of the degree of future GFR decreases, but a cause-relationship cannot be elucidated. Baba et al. (29) found that the fall rate in GFR correlated to sBP in proteinuric type II diabetic patients. Long-term AHT of microalbuminuric and proteinuric type II diabetic patients with hypertension reduces UAE without affecting renal function (18–20). We observed a significant correlation between sBP and UAE in patients without a history of AHT or diuretic treatment. Cross-sectional studies are not consistent on the relationship between BP and UAE in type II diabetes, but some reports have shown positive correlations (8,30–33).

Glycemic control was not related to the falling rates of GFR or UAE levels. Serum C-peptide decreased significantly during the study, probably caused by a reduced secretory capacity of insulin developed over the years. Long-term improved glycemic control can retard the GFR fall rate and the rise in UAE in type I diabetic patients (34,35). So far, no such evidence exists in type II diabetes.

Moreover our patients were characterized by normal levels of serum cholesterol and serum HDL cholesterol and slightly elevated serum TG levels; no correlation was observed to the GFR fall rate or rise in UAE. Abnormalities in lipoprotein metabolism has been proposed as a potentially nephrotoxic factor (36,37). So far, randomized long-term clinical trials of lipid-lowering therapy in type II diabetic patients has not shown any effect on kidney function (38).

During a mean follow-up period of 3.4 yr, we found that the average fall rate in GFR in a group of normoalbuminuric and microalbuminuric patients was not different from healthy, nondiabetic individuals but varied considerably among individuals. A longer follow-up time, including successive measurements, is needed to determine the long-term implications of normoalbuminuria and microalbuminuria on kidney function. The observation that sBP relates significantly to the fall rate in GFR—before overt proteinuria is evident and before GFR is subnormal—supports the notion that systolic hypertension, and not renal hypertension, is a risk factor developing independently from renal impairment. AHT may be a tool in future attempts to reduce cardiovascular/renal lesions in type II diabetic patients with an elevated UAE rate.

Acknowledgments—We wish to thank Merete Moller for excellent technical assistance.

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